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 common, non-specific symptom not usually suspicious of cancer, 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 treatment-emergent solid cancer AEs 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 for new malignancies becomes nominally non-statistically significant (relative risk 1.31, p = 0.066), while it remains statistically significant for treatment-emergent malignancy AEs (relative risk 1.46, p = 0.005). See also my discussion of problems with skin cancers that follows the COMMENT below.

Finally, the vast majority of the reconciliation discussions concerned whether the malignancy was "new", not whether the patient had suffered a serious, malignancy-related event. I show how the different classifications (investigator, reviewer, reconciled) affect new solid cancer and treatment-emergent solid cancer AEs in Table 12.

Table 12: Comparison of Reviewer's and Reconciled 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
treatment-emergent solid cancer AEs (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 concerning. For treatment-emergent solid cancer AEs there is virtually no change, the relative risks among the three different classifications are remarkably similar, and the p values all have two zeroes after the decimal points. Because none of the solid cancers presenting as clinical problems in TAAL were really new, the treatment-emergent cancer AE rates are the best measures of the promoter potential of prasugrel. I believe these statistics still document a serious potential problem for prasugrel.

Non-melanoma Skin Cancers

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.

- *Some carcinogens cause skin cancers and some skin tumors are sensitive to some promoters.* But most carcinogens are site-specific, as a perusal of the Carcinogenic Potency Database will confirm. (Carcinogenic_Potency_Project 2008) Ideally we would like to know in advance exactly what cancers a carcinogen or promoter affects. In the case of prasugrel we can look to the animal data for some hints—which is what I did.

- *Skin would be a good signal tumor to detect tumor promotion because skin is an active mitotic organ and skin tumors are likely to have a lower probability of providing false negatives.* No data are presented to support these assertions. Because skin cancers are not as serious as other cancers and are usually handled without hospitalizations, reporting of them is more erratic than for other cancers. (Karagas 1994) Skin cancer data are noisy and may mask real effects.

- *Recent assessment of the role of drugs in cancer promotion include melanotic and nonmelanotic skin cancers (ezetimibe/Vytorin – Peto et al, 2008)* For ezetimibe there are no pre-clinical studies suggesting sites to examine, so inclusion of skin is reasonable. However, it may also illustrate my contention that skin cancer data are noisy because the greatest difference in rates in the one study (SEAS) in which more cancers were reported in the ezetimibe group was for skin cancers, and the difference for skin cancer rates favors ezetimibe in the other studies. (Peto, Emberson et al. 2008) Regardless, a signal of

increased cancers with or without skin cancers is highly concerning. The ezetimibe SEAS data are of low concern only because there are other large trials with ezetimibe that do not show increased cancer rates. Prasugrel, too, needs other large trials (or at least one) not showing increased cancer rates.

The sponsor neglects to mention two other arguments favoring the exclusion of skin cancers:

- There is a strong precedent for analyzing skin cancers separately in FDA-approved labels. Labels for four biologics (Cimzia, Enbrel, Humira, and Remicaide) discuss malignancies (excluding non-melanoma skin cancer) or non-cutaneous solid malignancies. While these biologics are all TNF alpha blockers, apparently some FDA staff judged it appropriate and scientific to make the mistake of excluding non-melanoma skin cancers four times.

- There are unique ascertainment problems for non-melanoma skin cancers. Non-melanoma skin cancers are typically diagnosed and excised in physicians' offices, while other malignancies typically involve hospitalizations. Because non-melanoma skin cancers do not typically involve hospitalizations and are not life-threatening, they are not SAEs, may not even be recorded as AEs, or the only AEs recorded may be procedure AEs. The latter problem can be confirmed with the TAAL experience: Seven new malignancies, all skin cancers, were reported only as excisions and not as neoplasms under the Medra neoplasm system organ class (SOC), as listed in Table 13.

Table 13: New Malignancies with Excision AEs Not in Neoplasm SOC in TAAL

group	day	investigator term
Clopidogrel	175	removal of basal cell carcinoma on nose
Prasugrel	373	skin cancer lesion removal
Prasugrel	172	excision skin cancer of the forehead
Prasugrel	174	right temple skin cancer remvoed
Prasugrel	387	basal cell removed from back
Prasugrel	231	skin cancer on nose removal
Prasugrel	268	cancer on nose that was removed

Note that all but one of the new malignancies reported as excisions rather than as neoplasms were in the prasugrel group. We classified these cases as malignancies and, in fact, all but one (the "basal cell removed from back") were included by the sponsor in the 313 cases of concern mentioned by the sponsor in their "Cardiovascular and Renal Drugs Advisory Committee Briefing Document" (see **Reconciliation of Cancers with Sponsor**, second paragraph, above) and for which the sponsor submitted case report forms on March 21, 2008. Despite that fact, the sponsor tabulated in their briefing document and presented at the Advisory Committee meeting only cases in the neoplasm SOC, ignoring the cases in Table 13.

The problem regarding identifying skin cancers is worse than Table 13 implies. Some excisions are reported only as a "lesion" removed or excised or biopsied as shown in Table 14.

Table 14: Ambiguous Lesion Removal and Biopsy AEs in TAAL

rx	day	investigator term
Clopidogrel	183	biopsy and excision skin lesion (r) forearm
Clopidogrel	326	lesion nose removed
Clopidogrel	136	scalp lesion removal
Prasugrel	268	skin biopsy
Prasugrel	89	skin biopsy
Prasugrel	383	lesion removed from neck
Prasugrel	111	excision of facial skin lesion
Prasugrel	14	removal of 2 skin lesions on chest
Prasugrel	69	skin lesion resection
Prasugrel	270	removal of skin lesion

Note that the majority of the ambiguous lesion removal AEs were in the prasugrel group. The above ambiguities plus one additional "radiation burn" (one prasugrel case in Table 14 also had a "radiation burn" AE for a total of two cases) and one missing path report for a villous adenoma, all in prasugrel patients, leaves 9 remaining ambiguities for prasugrel vs. 3 for clopidogrel, so most likely any of the current cancer statistics (FDA and sponsor) underestimate the cancer risks for prasugrel.

Counting the new skin cancers in Table 13 (but not the ambiguous lesion removals in Table 14), I tally 14 new skin cancers for clopidogrel and 15 for prasugrel. However, I also tally 2 squamous cell carcinomas (site not reported) for clopidogrel and 1 for prasugrel. Because the latter are most likely skin cancers, the final tallies are 16 new skin cancers in each group. The skin cancers are evenly distributed, so including them dilutes the significance of the striking non-skin cancer findings but does not make the non-skin cancer findings ignorable. The rates of patients with new malignancies, including skin cancers, is about 1.6 per cent for prasugrel and 1.2 per cent for clopidogrel, for a relative risk of about 1.3.

COMMENT: I believe I have excellent justification for excluding skin cancers. Furthermore, if non-melanoma skin cancers are counted correctly, they are evenly balanced between the two treatment groups in TAAL. There is no cancer site for which clopidogrel has more than one excess malignancy than prasugrel.

I can not provide any justification for analyzing skin cancers in TAAL but excluding the cases in Table 13. Presenting statistics on new malignancies without including these cases is misleading. I am dismayed that, despite about a year having passed since we identified increased cancer rates as a problem in TAAL and the sponsor insisted that skin cancers be counted, we do not have answers regarding whether the lesions listed in Table 14 are malignancies.

Cancer and Bleeding

Bleeding reporting is complicated because there were three sources for capturing bleeds: (1) the adverse event CRFs; (2) the bleeding endpoint CRFs; and (3) Clinical Endpoint Committee (CEC) added bleeds that are not recorded on the AE or bleeding endpoint CRFs but were mentioned on other documents provided to the CEC. For the following analyses I have used the data for 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, 54% of the prasugrel and 41% of the clopidogrel patients had a preceding bleed of any type. About 33% 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 15.

Table 15: New Solid Cancers and Site-Specific Prior Bleeds in TAAL

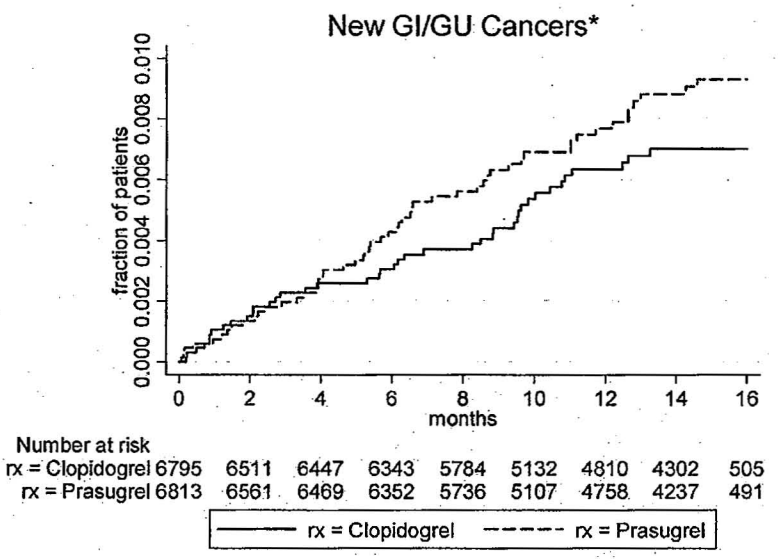
	new cancers		# with prior site specific bleed		% with prior site specific bleed	
	clopidogrel	prasugrel	clopidogrel	prasugrel	clopidogrel	prasugrel
breast	1	4	0	0	0%	0%
colorectal	10	22	6	12	60%	55%
gi*	20	33	11	16	55%	49%
lung	12	15	0	2	0%	13%
kidney/bladder	11	12	7	5	64%	42%
cervix/uterus	1	1	1	1	100%	100%

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

COMMENT: For the site (colorectal) with the largest difference in cancers and the one the sponsor argues that the difference is due to a detection bias, there is no difference in preceding site-specific bleeding. For kidney and bladder the prior bleeding also leans towards clopidogrel. 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. Regardless, demonstrating more bleeding prior to cancer detection is not very reassuring: I would expect cancers stimulated to grow would bleed more readily, so we can not be certain that more bleeding is due to cancer promotion, e.g., increased angiogenesis, or platelet inhibition or both. The appropriate criterion for whether a cancer is serious is not whether it is preceded by bleeding but whether it is followed by serious consequences, e.g., death. The excess prasugrel cancers are serious by this latter, vital criterion.

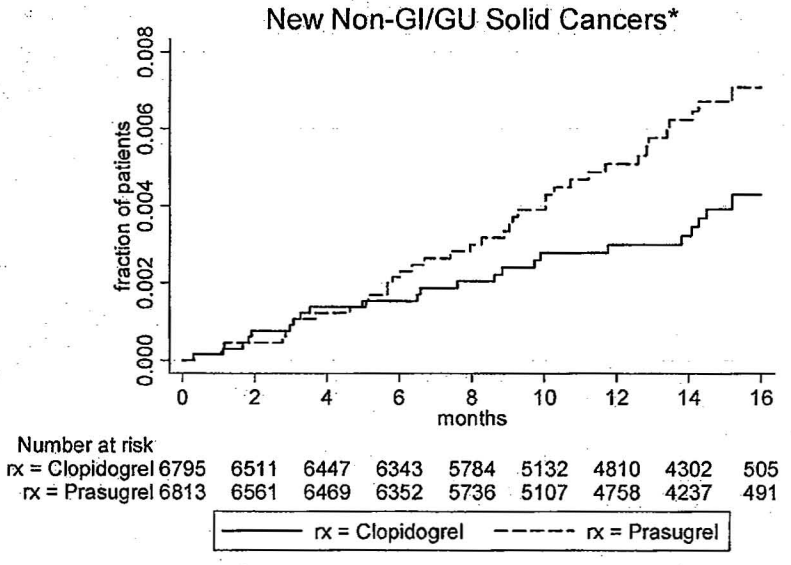
To explore further the hypothesis of ascertainment bias due to bleeding, I examined the incidence curves for cancers that commonly present with bleeding. I show the K-M incident plot for GI/GU cancers in Figure 7, for non-GI/GU cancers in Figure 8, for GI cancers alone in Figure 9, and for GU cancers alone in Figure 10. (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.) For comparison, I show the bleeding rates by month in TAAL in Figure 11.

Figure 7: K-M Incidence Plot for New GI/GU Cancers in TAAL



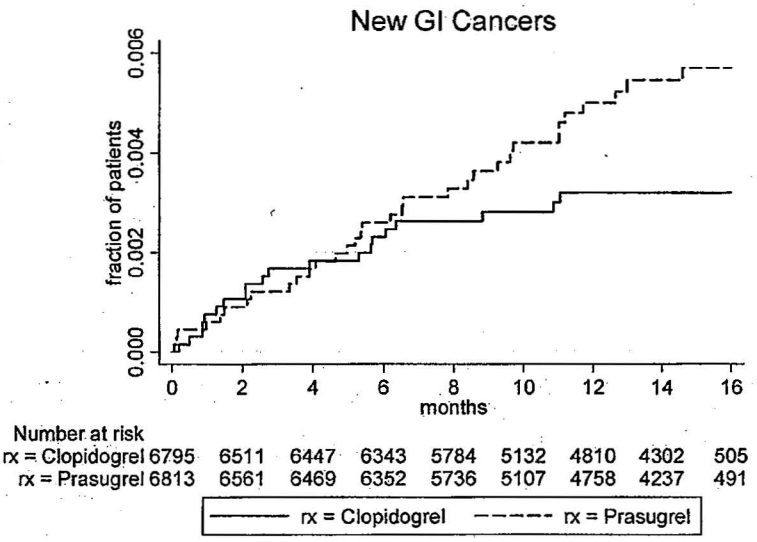
*ovarian, testicular, hepatic, GB, and pancreatic cancers excluded; p = 0.18 by log rank

Figure 8: K-M Incidence Plot for New Non-GI/GU Solid Cancers in TAAL



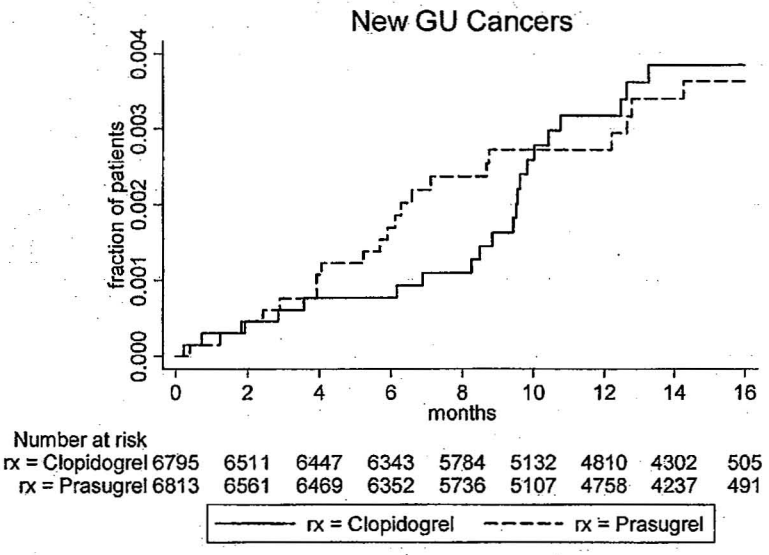
*excluding non-melanoma skin cancers and brain tumors; p = 0.053 by log rank

Figure 9: K-M Incidence Plot for New GI Solid Cancers in TAAL



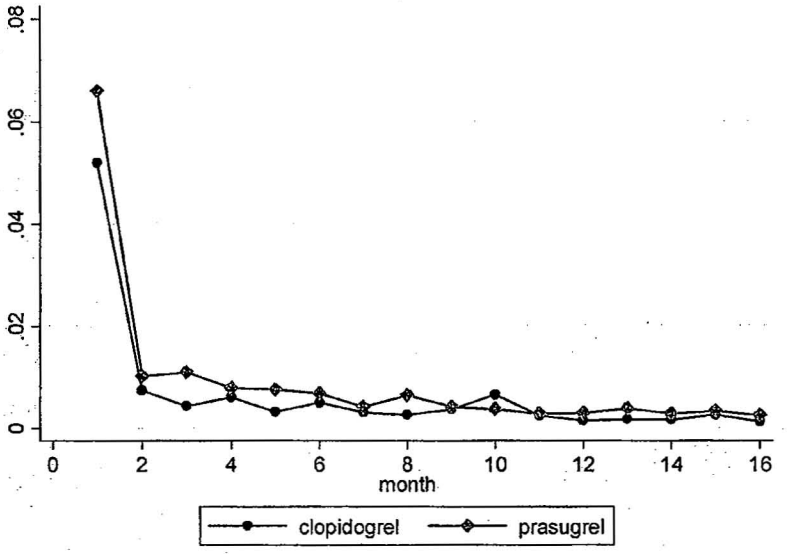
p = 0.074 by log rank

Figure 10: K-M Incidence Plot for New GU Cancers in TAAL



p = 0.99 by log rank

Figure 11: Bleeding Event Rates by Treatment and Month in TAAL



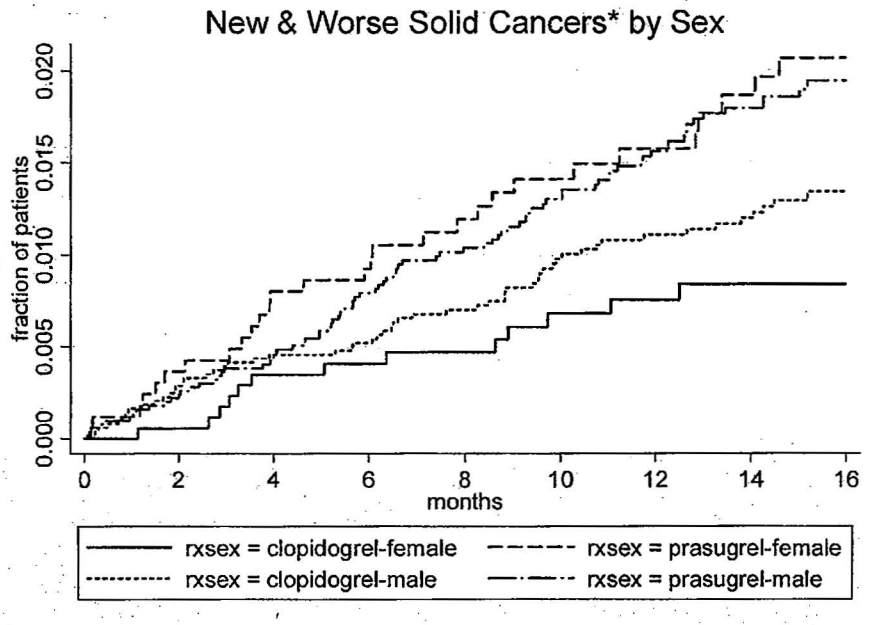
COMMENT: The site-specific incidence plots for GI/GU cancers diverge at four months and then almost converge at about 12 months. However, they do not diverge early when many bleeding events occur (as shown in Figure 11.*) Non-GI/GU cancers show a continuing divergence as do GI cancers, leaving only GU cancers for which the ascertainment bias due to bleeding remains plausible. Both the incidence plots for GI solid cancers (Figure 9) and for non-GI/GU cancers (Figure 8) suggest that the diagnosis rates for non-GU cancers were higher in the first four months than later, particularly for clopidogrel. I would speculate that this difference is due to the increased surveillance initially due to the hospitalization for the ACS event.*

Other Cancer Issues

Cancer and Gender

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 treatment-emergent solid cancer AE by sex in Figure 12. Note that TAAL patients were predominantly male (74%).

Figure 12: K-M Incidence Plot for Treatment-Emergent Solid Cancer AEs (Excluding Skin and Brain) by Sex in TAAL



*excluding non-melanoma skin cancers and brain tumors

COMMENT: There is some variation in treatment-emergent cancer AE rates by sex, with females on clopidogrel having the lowest rate and females on prasugrel having the highest. However, for each sex cancer rates are higher with prasugrel. I attribute the variations to the smaller numbers of female patients in TAAL.

Early Cancers

There is no biologic plausibility for cancers diagnosed shortly after randomization to be causally 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 biologically implausible incident cancers. I show the effects of varying early cancer diagnosis exclusions in Table 16.

Table 16: New Solid Cancers (excluding Non-Melanoma Skin and Brain) in TAAL Excluding Early Diagnoses

cutoff	clopidogrel	prasugrel	RR*	p†
none	64	92	1.44	0.024
>7 days	62	89	1.44	0.027
>14 days	60	87	1.45	0.025
> 30 days	56	86	1.54	0.011

*RR = relative risk prasugrel/clopidogrel; † 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.

Cancer by Region

The sponsor has also argued that the cancer results are inconsistent in subgroups, e.g., by country. I have classified the geographic sources of patients into four regions (US, Eastern and Western Europe, and other) yielding reasonable number of patients in each region. I show the rates of new solid cancers by region in Table 17.

Table 17: Rates of New Solid Cancers by Region in TAAL

Region	Patients		New solid cancers	
	Clopidogrel	Prasugrel	Clopidogrel	Prasugrel
E Europe	1,665	1,657	0.8%	1.4%
Other	1,342	1,342	0.7%	1.3%
US	2,020	2,039	1.0%	1.4%
W Europe	1,768	1,775	1.1%	1.2%
Total	6,795	6,813	0.9%	1.4%

COMMENT: New solid cancer rates with prasugrel are higher in all regions, with only Western Europe showing a small effect size. The US, the region of greatest interest to us, shows rates very similar to the entire study. Overall the variations in this table are consistent with random subgroup variations. I did not find convincing evidence for subgroup inconsistencies either by region or by sex.

Clopidogrel and Cancer

Because an excellent and critical question is whether carcinogenicity could be a class effect, I also examined the data we have available for large outcome trials using clopidogrel. For reference I have summarized the study features in Table 18.

Table 18: Clopidogrel Studies

Study	Population	Aspirin	Median age	n	Median months
CAPRIE	high CV risk	325 control	63	19,185	20
CREDO	PCI	325 then 81-325	61	2,116	12
CURE	ACS NSTEMI	75-325	65	12,562	9
CHARISMA	high CV risk	75-162	64	15,603	28

Note that CAPRIE used aspirin only in the control group, while the other studies involved adding clopidogrel to background aspirin at dosages selected by the investigators. CURE and CREDO are the smaller studies with more limited follow-up, so I will summarize briefly their findings but present CAPRIE and CHARISMA in more detail.

In CURE there was a slight excess of solid cancers (48 vs. 42) with clopidogrel due to higher rates of colorectal (16 vs. 8) and lung (12 vs. 7) but slightly higher rates for breast, prostate,