Practically speaking, the increased frequency of CABG-related TIMI major bleeding with prasugrel is principally a cause for concern in the setting of urgent CABG, where there is no opportunity to stop the drug. The review team concluded that use of prasugrel should be discouraged when coronary anatomy is unknown and CABG is a possibility. For elective CABG, it seems reasonable to discontinue prasugrel 7 days prior to surgery.

Table 15: CABG-Related TIMI Major or Minor Bleeding Events: Days from Last Dose of Study Drug to CABG

Days from last dose to CABG	Prasugrel			Clopidogrel		
	N	n	%	N	n	%
0	12	1	8.3	22	1	4.5
1	17	6	35.3	12	0	0
2	4	2	50	11	1	9.1
3	12	3	25	15	1	6.7
4	8	1	12.5	14	1	7.1
5	30	3	10	30	2	6.7
6	18	2	11.1	21	0	0
7	24	3	12.5	25	0	0
8	13	1	7.7	10	0	0
9	8	0	0	9	2	22.2
10	10	2	20	5	0	0
11	5	0	0	2	0	0
12	3	0	0	1	0	0
13	1	1	100	2	0	0
14-27	9	0	0	11	0	0
28	1	1	100	1	0	0
29-60	4	0	0	3	0	0
61-341	6	1	16.7	5	0	0

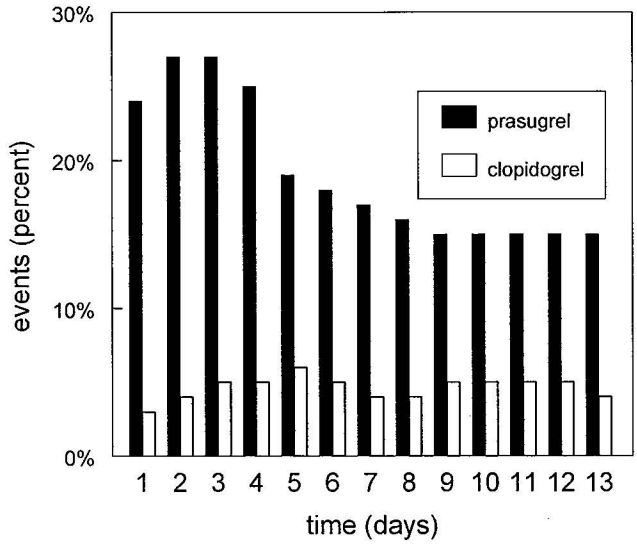
N = numbers of subjects who underwent CABG
N = numbers of bleedin events

In summary, the review team concluded that the risk of bleeding is clearly higher with prasugrel, and specific information is merited in labeling for:

- patients ≥ 75 years of age (here the greater risk is for fatal and life-threatening bleeding)
- patients with a prior history of a transient ischemic attack or cerebrovascular accident (contraindication)
- patients who undergo CABG, or by extension, probably any surgical procedure

This information appropriate for labeling for patients of low weight is still under discussion.

Figure 18: Cumulative Frequency of TIMI Major or Minor CABG-Related Bleeding, by Day of Discontinuation Prior to Surgery



7.4.14. Non-Hemorrhagic Serious Adverse Events

Respiratory failure, hypotension, colon cancer, and atrial flutter were statistically significantly higher in subjects treated with prasugrel compared to subjects treated with clopidogrel:

- Respiratory failure: 0.22% prasugrel versus 0.09% clopidogrel; p = 0.050
- Hypotension: 0.21% prasugrel versus 0.06% clopidogrel; p = 0.019
- Atrial flutter: 0.18% prasugrel versus 0.06% clopidogrel; p = 0.046

Several of the events of respiratory failure occurred in the setting of TIMI bleeding.

The incidence of cardiac failure was statistically significantly lower in subjects treated with prasugrel than clopidogrel, possibly a dividend from decreasing the frequency of MI.

Clopidogrel carries a warning for thrombotic thrombocytopenia purpura (TTP), which has been reported rarely in association with the drug, and has been fatal in some cases. In the prasugrel development program, there were no reported cases of TTP in prasugrel-treated subjects, versus one case in a clopidogrel-treated subject.

Fifteen (0.22%) subjects in the prasugrel treatment group developed abnormal hepatic function, 8 (0.12%) had abnormal hepatic function reported as a serious adverse event, and 8 (0.12%) developed ALT > 3X ULN and total bilirubin > 1.5X ULN. These compare to 18 (0.27%), 15 (0.22%), and 4 (0.06%) subjects, respectively, in the clopidogrel treatment group. Clopidogrel's labeling does not contain any specific warning or precaution for hepatotoxicity, and based on these data, none seems appropriate for prasugrel.

Twenty-four prasugrel-treated (0.36%) and clopidogrel-treated (0.36%) subjects had allergic reactions reported as serious adverse events. Four (0.06%) prasugrel subjects and 3 (0.04%) clopidogrel subjects had angioedema reported as a serious adverse event. One of the

prasugrel subjects was also receiving an angiotensin converting enzyme inhibitor, begun 5 days earlier.

No adverse events of pancytopenia were reported in any subjects in the development program. Anemia was reported in 2.2% and 2.0% of subjects treated with prasugrel and clopidogrel, respectively. Leukopenia (< 4 x 10^9/L) was reported in 2.8% and 3.5% of prasugrel- and clopidogrel-treated subjects, respectively. There were 4 reported cases (0.06%) of neutropenia in the prasugrel treatment group, compared with 21 cases (0.31%) in the clopidogrel treatment group. The reported frequency of thrombocytopenia was similar between the prasugrel and clopidogrel groups (0.3%). In most of the cases of thrombocytopenia, subjects were also receiving a GPIIb/IIIa inhibitor.

Pyrexia and increased tendency to bruise were reported in at least 1% of prasugrel subjects and the incidence of these adverse events was significantly higher than that in the clopidogrel treatment group. Fever may have been related to bleeding. The sponsor found that subjects treated with prasugrel who had a bleeding event were twice as likely to have fever compared to subjects treated with clopidogrel who had a bleeding event.

7.4.15. Cancer

Proportionally greater numbers of cancers were reported in subjects in the prasugrel treatment group, and much attention was paid to this issue by the Division of Cardiovascular and Renal Products clinical (Dr. K. Hicks) and secondary (Dr. T. Marciniak) reviewers, as well as consultants from the Division of Drug Oncology Products (B. Mann) and the Division of Epidemiology, Office of Surveillance and Epidemiology (Dr. D. Wysowski).

Non-Clinical, *In Vitro*

Review of the literature finds very little evidence suggesting that prasugrel, clopidogrel, or modulation of the $P2Y_{12}$ receptor would have important effects on genotoxicity, tumorigenesis, tumor promotion, metastasis, or angiogenesis.

Non-Clinical, *In Vivo*

To briefly recapitulate the results of the 2-year rodent carcinogenicity studies, the rat data do not suggest increased rates of either benign or malignant neoplasms (see section **Error! Reference source not found.** for details). In the mouse, at high exposures, there was a statistically significant dose-response relationship for hepatocellular adenoma. There was also a non-statistically significant trend in favor of increased hepatocellular carcinomas at the highest dose (300 mg/kg/day). Dr. Marciniak, the Medical Team Leader, expressed concern regarding the findings, in particular the trend for a dose-response in liver carcinomas. He also expressed concern regarding excess cases of lung cancer and intestinal cancer in the prasugrel groups with suggestions of dose-response relationships.

The Pharmacology/Toxicology review team and the Executive Carcinogenicity Advisory Committee opined that there was no evidence of a prasugrel-associated increase in malignant tumors in either species (hepatic or extra-hepatic), and found the results reassuring. Based on classical definitions, they opined that prasugrel is neither a "complete carcinogen" nor a "cancer promoter."

Clinical

The sponsor's original tabulation of treatment-emergent serious adverse events, system organ class (SOC) "neoplasms benign, malignant and unspecified (including cysts and polyps)," is

shown in Table 16, as adapted from Table TAAL 14.99. The corresponding tabulation of non-serious adverse events is provided in Table 17, adapted from Table TAAL 14.92.

Colorectal Cancer: The sponsor found 19 colorectal neoplasms in the prasugrel group and 8 in the clopidogrel group (RR=2.4), but found reassurance in the fact that half of cases in the prasugrel group were discovered as a result of an antecedent GI bleed.

Breast Cancer: The sponsor counted 5 cases of breast cancer in the prasugrel group, versus 1 in the clopidogrel group (RR=5.0), but the relatively short time frame between initiation of study drug and diagnosis, for at least some of the cases, assuaged the sponsor's concern.

Lung Cancer: There were 8 and 2 lung cancers reported as adverse events in the prasugrel and clopidogrel groups, respectively (RR=4.0). However, when "lung neoplasms" were added to the cancers, the respective numbers were 12 and 10. The sponsor determined, therefore, that the numbers of subjects with lung neoplasm were not different between treatment groups.

Prostate Cancer: Sixteen subjects in the prasugrel group and 9 in the clopidogrel group experienced an adverse event for prostate cancer or adenoma (RR=1.8). The sponsor took reassurance from the fact that in half of the 16 neoplasms in the prasugrel group, the diagnosis was made within 6 months of starting the study drug, ergo; they considered these unlikely to represent new cancers.

The sponsor was dismissive of these findings in their original summary interpretation:

> "Cases of malignancy were reported at a frequency that was higher in the prasugrel than in the clopidogrel group. In some cases, such as prostate cancer, this appears to be a coincidental finding since about half of the cases were reported within 6 months of starting drug. In the case of colon cancer, they were often discovered during a diagnostic procedure following a bleed. In summary, there is no evidence that use of prasugrel is associated with a higher risk of cancer."

Division's Analyses:
The sponsor's initial description and analysis of cancer adverse events was difficult to interpret: 1) the distinction between pre-existing neoplasms and treatment-emergent neoplasms was not always clear; 2) there was little attempt to categorize neoplasms as malignant or non-malignant; and 3) there was little emphasis on categorization of cancers by organ or organ system.

With respect to distinguishing pre-existing from treatment-emergent neoplasms, the case report forms (CRFs) used in TAAL included a "Pre-Existing Conditions" form that was used to "list all ongoing medical conditions at the time of study entry/screening." Confusion arose for two reasons: 1) Each pre-existing condition was recorded as an "event" and given an "event code" numerically continuous with treatment-emergent adverse events recorded on the "Study Adverse Events" CRFs. At times, investigators inadvertently assigned treatment-emergent adverse events to numbers previously allocated to pre-existing conditions, which caused confusion (at times, a pre-existing condition was simply replaced by an adverse event; and 2) There were inconsistencies in recording pre-existing neoplasms, presumably because of investigators' difficulty in deciding whether a prior cancer was "ongoing" if it was not an active medical problem. Finally, for patients in the throes of an acute coronary event, understandably little attention was given to obtaining specific historical information regarding prior cancers.

Table 16: Treatment Emergent Serious Adverse Events from TALL, SOC "Neoplasms, benign, malignant and unspecified..."

Neoplasm as serious adverse event (from TAAL Table 14.99)	Prasugrel n (%)	Clopidogrel n (%)
all	87 (1.29)	60 (0.89)
colon cancer	10 (0.15)	2 (0.03)
gastric cancer	6 (0.09)	7 (0.1)
prostate cancer	6 (0.09)	7 (0.1)
breast cancer	4 (0.06)	1 (0.01)
adenocarcinoma	2 (0.03)	0 (0)
bladder cancer	2 (0.03)	4 (0.06)
brain cancer	2 (0.03)	1 (0.01)
clear cell cancer of kidney	2 (0.03)	0 (0)
lung neoplasm malignant	2 (0.03)	2 (0.03)
lung squamous cell carcinoma	2 (0.03)	1 (0.01)
metastases to lung	2 (0.03)	0 (0)
metastatic neoplasm	2 (0.03)	0 (0)
non-small cell lung cancer	2 (0.03)	2 (0.03)
prostate cancer metastatic	2 (0.03)	1 (0.01)
renal neoplasm	2 (0.03)	0 (0)
squamous cell carcinoma	2 (0.03)	1 (0.01)
acute myeloid leukaemia	1 (0.01)	0 (0)
adenoma benign	1 (0.01)	0 (0)
basal cell carcinoma	1 (0.01)	1 (0.01)
benign lung neoplasm	1 (0.01)	0 (0)
bladder neoplasm	1 (0.01)	1 (0.01)
bladder papilloma	1 (0.01)	0 (0)
bone neoplasm	1 (0.01)	0 (0)
bronchial carcinoma	1 (0.01)	2 (0.03)
cervix carcinoma	1 (0.01)	0 (0)
chronic lymphocytic leukaemia	1 (0.01)	0 (0)
colon adenoma	1 (0.01)	1 (0.01)
colon neoplasm	1 (0.01)	0 (0)
colorectal cancer	1 (0.01)	0 (0)
gallbladder cancer	1 (0.01)	0 (0)
gastrointestinal carcinoma	1 (0.01)	2 (0.03)
gastrointestinal tract adenoma	1 (0.01)	0 (0)
haemangioma	1 (0.01)	0 (0)
lung adenocarcinoma	1 (0.01)	0 (0)
lung neoplasm	1 (0.01)	1 (0.01)
malignant ascites	1 (0.01)	0 (0)
mesothelioma malignant	1 (0.01)	0 (0)
metastases to bone	1 (0.01)	2 (0.03)
metastases to liver	1 (0.01)	1 (0.01)
nasal neoplasm	1 (0.01)	0 (0)
oesophageal adenocarcinoma	1 (0.01)	0 (0)
oesophageal cancer metastatic	1 (0.01)	0 (0)
oesophageal carcinoma	1 (0.01)	3 (0.04)
ovarian neoplasm	1 (0.01)	0 (0)
pancreatic carcinoma	1 (0.01)	1 (0.01)
papillary thyroid cancer	1 (0.01)	0 (0)
papilloma	1 (0.01)	0 (0)
peripheral t-cell lymphoma	1 (0.01)	0 (0)
pituitary tumour benign	1 (0.01)	0 (0)
prostatic adenoma	1 (0.01)	0 (0)
rectal cancer	1 (0.01)	0 (0)
rectal neoplasm	1 (0.01)	0 (0)
renal cell carcinoma	1 (0.01)	2 (0.03)
salivary gland neoplasm	1 (0.01)	0 (0)
sarcoma	1 (0.01)	0 (0)
small cell lung cancer	1 (0.01)	3 (0.04)
thyroid cancer	1 (0.01)	0 (0)
transitional cell carcinoma	1 (0.01)	0 (0)
uterine leiomyoma	1 (0.01)	0 (0)
adenocarcinoma pancreas	0 (0)	1 (0.01)
adrenal neoplasm	0 (0)	1 (0.01)
bladder transitional cell carcinoma	0 (0)	1 (0.01)
carcinoid tumour pulmonary	0 (0)	1 (0.01)
chronic myeloid leukaemia	0 (0)	1 (0.01)
colon cancer metastatic	0 (0)	1 (0.01)
gastric neoplasm	0 (0)	1 (0.01)
hepatic cancer metastatic	0 (0)	1 (0.01)
hepatic neoplasm	0 (0)	1 (0.01)
lymphocytic leukaemia	0 (0)	1 (0.01)
malignant melanoma	0 (0)	1 (0.01)
metastases to adrenals	0 (0)	1 (0.01)
myelodysplastic syndrome	0 (0)	1 (0.01)
non-hodgkin's lymphoma	0 (0)	2 (0.03)
small cell lung cancer metastatic	0 (0)	1 (0.01)
thymoma	0 (0)	1 (0.01)

Division's Concerns: The Division expressed its concerns regarding excess neoplasia in the prasugrel group in early communications with the sponsor. The sponsor espoused the view that the observed difference between the prasugrel and clopidogrel groups was due to ascertainment bias, because of increased bleeding associated with prasugrel compared to clopidogrel.

This possibility seemed plausible on its face, and the relative risks of neoplasia and bleeding were quantitatively similar. The Division re-analyzed the cases, excluding cancers where a hemorrhagic adverse event preceded the cancer *in the same organ system as the cancer*, i.e., hemoptysis for lung cancer, hematuria for genitourinary (GU) cancers, GI bleeds for GI cancers, and dysfunctional uterine bleeding for gynecologic cancers. The Division's analysis showed that the between-group difference in neoplasms largely persisted (results not shown).

Table 17: Treatment Emergent Adverse Events from TAAL, SOC "Neoplasms, benign, malignant and unspecified..."

Neoplasm as adverse event (from TAAL Table 14.92)	Prasugrel	Clopidogrel
	n (%)	n (%)
all	153 (2.27)	123 (1.83)
prostate cancer	16 (0.24)	7 (0.1)
colon cancer	11 (0.16)	2 (0.03)
lung neoplasm malignant	8 (0.12)	2 (0.03)
gastric cancer	6 (0.09)	8 (0.12)
bladder cancer	5 (0.07)	4 (0.06)
breast cancer	5 (0.07)	1 (0.01)
squamous cell carcinoma	5 (0.07)	5 (0.07)
lung neoplasm	4 (0.06)	8 (0.12)
prostatic adenoma	4 (0.06)	0 (0)
skin papilloma	4 (0.06)	1 (0.01)
colon adenoma	3 (0.04)	3 (0.04)
malignant melanoma	3 (0.04)	3 (0.04)
metastases to lung	3 (0.04)	0 (0)
metastatic neoplasm	3 (0.04)	1 (0.01)
renal neoplasm	3 (0.04)	1 (0.01)
skin cancer	3 (0.04)	4 (0.06)
adenocarcinoma	2 (0.03)	1 (0.01)
basal cell carcinoma	2 (0.03)	5 (0.07)
biliary neoplasm	2 (0.03)	1 (0.01)
brain neoplasm	2 (0.03)	1 (0.01)
chronic lymphocytic leukaemia	2 (0.03)	1 (0.01)
clear cell carcinoma of the kidney	2 (0.03)	0 (0)
gastric neoplasm	2 (0.03)	1 (0.01)
lung squamous cell carcinoma	2 (0.03)	1 (0.01)
metastasis	2 (0.03)	0 (0)
mycosis fungoides	2 (0.03)	1 (0.01)
non-small cell lung cancer	2 (0.03)	2 (0.03)
ovarian neoplasm	2 (0.03)	0 (0)
prostate cancer metastatic	2 (0.03)	1 (0.01)
thyroid neoplasm	2 (0.03)	2 (0.03)
acrochordon	1 (0.01)	1 (0.01)
acute myeloid leukaemia	1 (0.01)	0 (0)
adenoma benign	1 (0.01)	1 (0.01)
adrenal adenoma	1 (0.01)	0 (0)
benign lung neoplasm	1 (0.01)	0 (0)
bladder neoplasm	1 (0.01)	3 (0.04)
bladder papilloma	1 (0.01)	0 (0)
bladder squamous cell carcinoma	1 (0.01)	0 (0)
bladder transitional cell carcinoma	1 (0.01)	0 (0)
bone neoplasm	1 (0.01)	0 (0)
bone neoplasm malignant	1 (0.01)	0 (0)
breast cancer recurrent	1 (0.01)	0 (0)
bronchial carcinoma	1 (0.01)	2 (0.03)
cardiac neoplasm	1 (0.01)	0 (0)
cervix carcinoma	1 (0.01)	0 (0)
colon neoplasm	1 (0.01)	0 (0)
colorectal cancer	1 (0.01)	0 (0)
fibroadenoma of breast	1 (0.01)	0 (0)
gallbladder cancer	1 (0.01)	0 (0)
gastrointestinal carcinoma	1 (0.01)	2 (0.03)
gastrointestinal tract adenoma	1 (0.01)	0 (0)
haemangioma	1 (0.01)	0 (0)
hepatic neoplasm	1 (0.01)	1 (0.01)
lipoma	1 (0.01)	1 (0.01)
lung adenocarcinoma	1 (0.01)	0 (0)
lymphoma	1 (0.01)	1 (0.01)
malignant ascites	1 (0.01)	0 (0)
meso helioma malignant	1 (0.01)	0 (0)
metastases to bone	1 (0.01)	2 (0.03)
metastases to liver	1 (0.01)	1 (0.01)
metastases to lymph nodes	1 (0.01)	0 (0)
multiple myeloma	1 (0.01)	0 (0)
nasal cavity cancer	1 (0.01)	0 (0)
nasal neoplasm	1 (0.01)	1 (0.01)
oesophageal adenocarcinoma	1 (0.01)	0 (0)
oesophageal cancer metastatic	1 (0.01)	0 (0)
oesophageal carcinoma	1 (0.01)	3 (0.04)
oesophageal neoplasm	1 (0.01)	0 (0)
pancreatic carcinoma	1 (0.01)	1 (0.01)
papillary thyroid cancer	1 (0.01)	0 (0)
papilloma	1 (0.01)	1 (0.01)
peripheral T-cell lymphoma	1 (0.01)	0 (0)
pituitary tumour	1 (0.01)	0 (0)
pituitary tumour benign	1 (0.01)	0 (0)
rectal cancer	1 (0.01)	0 (0)
rectal neoplasm	1 (0.01)	1 (0.01)
renal cell carcinoma	1 (0.01)	3 (0.04)
salivary gland neoplasm	1 (0.01)	1 (0.01)
sarcoma	1 (0.01)	0 (0)
small cell lung cancer	1 (0.01)	3 (0.04)
thyroid cancer	1 (0.01)	0 (0)
transitional cell carcinoma	1 (0.01)	0 (0)
uterine leiomyoma	1 (0.01)	2 (0.03)
xanthoma	1 (0.01)	0 (0)
adenocarcinoma pancreas	0 (0)	1 (0.01)
adrenal neoplasm	0 (0)	1 (0.01)
bladder transitional cell carcinoma	0 (0)	1 (0.01)
carcinoid tumour pulmonary	0 (0)	1 (0.01)
chronic myeloid leukaemia	0 (0)	1 (0.01)
colon cancer metastatic	0 (0)	1 (0.01)
fibrous histiocytoma	0 (0)	1 (0.01)
haemangioma of liver	0 (0)	1 (0.01)
hepatic cancer metastatic	0 (0)	1 (0.01)
hypergammaglobulinaemia benign	0 (0)	1 (0.01)
monoclonal	0 (0)	1 (0.01)
laryngeal cancer	0 (0)	1 (0.01)
lentigo	0 (0)	1 (0.01)
lung carcinoma cell type	0 (0)	1 (0.01)
unspecified recurrent	0 (0)	1 (0.01)
lymphocytic leukaemia	0 (0)	1 (0.01)
melanocytic naevus	0 (0)	1 (0.01)
metastases to adrenals	0 (0)	1 (0.01)
myelodysplastic syndrome	0 (0)	1 (0.01)
myeloproliferative disorder	0 (0)	1 (0.01)
nasopharyngeal neoplasm benign	0 (0)	1 (0.01)
neoplasm	0 (0)	1 (0.01)
neoplasm malignant	0 (0)	1 (0.01)
non-hodgkin's lymphoma	0 (0)	2 (0.03)
ocular neoplasm	0 (0)	1 (0.01)
osteoma cutis	0 (0)	2 (0.03)
pyogenic granuloma	0 (0)	1 (0.01)
rectal adenoma	0 (0)	1 (0.01)
seborrhoeic keratosis	0 (0)	1 (0.01)
small cell lung cancer metastatic	0 (0)	1 (0.01)
squamous cell carcinoma of skin	0 (0)	2 (0.03)
thymoma	0 (0)	1 (0.01)
tongue neoplasm malignant	0 (0)	1 (0.01)

The Division sought additional information from the sponsor, to clarify diagnoses and malignancy status for cases where it was not clear, to distinguish new from pre-existing cancers, to collect investigators' assessment of symptoms, signs, and laboratory studies that led to diagnoses of cancer, and to collect information on long-term vital status. The sponsor developed "Neoplasia" CRFs to capture this information, and sent clinical monitors to the sites to oversee collection of the data. The sites were to complete the CRFs and provide all available source documents supporting the data.

The sponsor provided a regulatory response on 9 May, 2008, wherein they identified 313 subjects reported as having experienced an adverse event within the "Neoplasms Benign, Malignant, and Unspecified" SOC, either as 1) a newly diagnosed adverse event, or 2) a pre-existing condition that increased in severity during the conduct of the trial.[4] There were 175 prasugrel-treated subjects and 138 clopidogrel-treated subjects who had experienced one or more of these events during the study. Figure 19 and Table 18 show the sponsor's breakdown of non-benign neoplasms, according to their 9 May 2008 submission. (These analyses focus on "non-benign" tumors, including neoplasms characterized as malignant or "unknown.") Once the benign and pre-existing neoplasms were subtracted, the RR was 1.19.

The distribution of tumor types was typical of the patient population, and 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 cancer cases in these categories for prasugrel and clopidogrel were 10 versus 7, 4 versus 1, 18 versus 14, and 20 versus 11, respectively (Table 18). 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.

During the ensuing months, there was much discussion regarding these cases, both internally within the Division/Office, and between the Agency and the sponsor. The sponsor submitted a "Neoplasm White Paper," on September 19, 2008, in response to the Division's ongoing concerns.

Ultimately, there was fair agreement between the Agency and sponsor on categorization of neoplasms in terms of: 1) whether there was substantial evidence of neoplasia; 2) whether a given neoplasm was benign, malignant, or indeterminate; and 3) whether a neoplasm was pre-existing or newly discovered. There was general recognition that newly discovered tumors were in all likelihood extant at the time of study entry, and that the duration of the study was not sufficient to detect tumors that were truly "new;" i.e., that might have arisen as a result of carcinogenesis. Thus, the Division and sponsor agreed that the concern is tumor stimulation, and not carcinogenicity.

Two issues have been contentious: 1) the extent to which ascertainment bias played a role in creating the imbalance in malignancies, and 2) whether or not non-melanomatous skin cancers should be considered in the analyses. Non-melanomatous skin cancers have less clinical importance than other solid tumors, and were reported in excess in the clopidogrel group. When they are included in these analyses, the difference between treatment groups is unimpressive (RR = 1.19). Conversely, when non-melanomatous skin cancers are omitted from

[4] Two subjects were not included, because the sponsor was not able to obtain additional information from the site. Both subjects has been in the prasugrel treatment group, and one was diagnosed with a new "papillary urothelial carcinoma."

Figure 19: Sponsor's May, 2008, Breakdown of Non-Benign Neoplasms

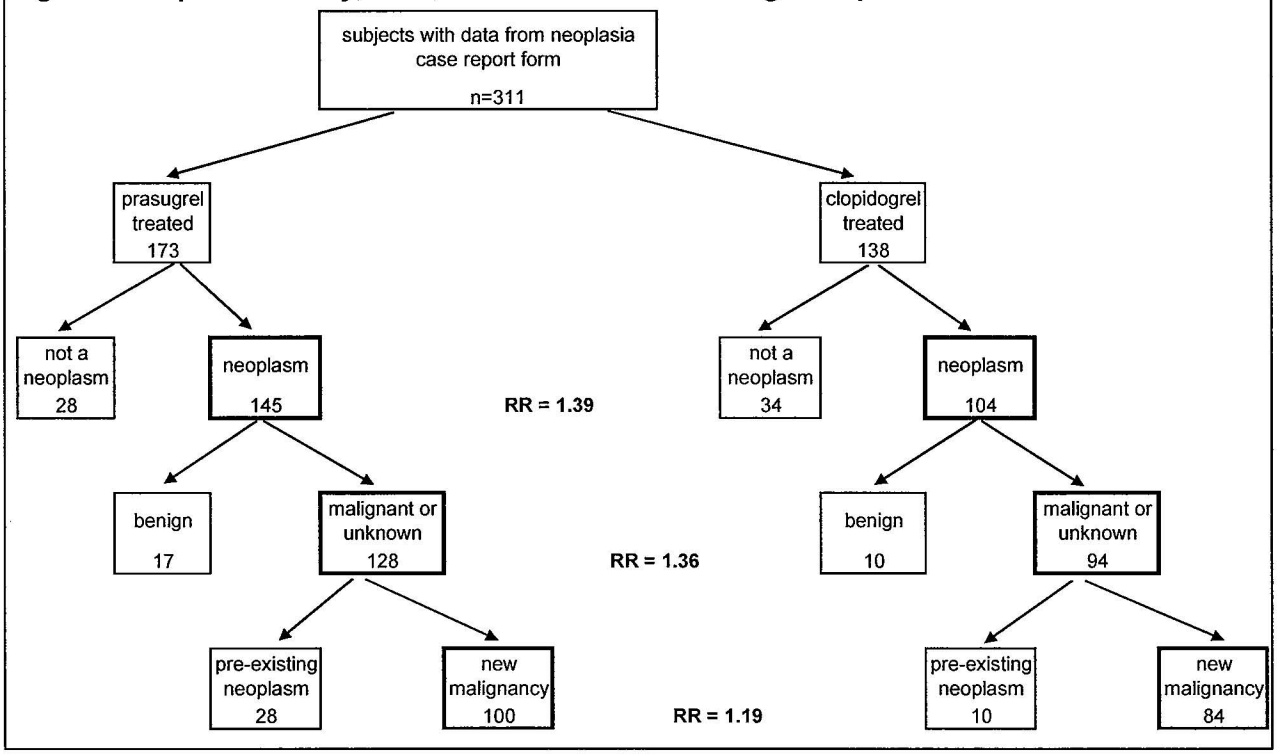


Table 18: Sponsor's May 9, 2008, Analysis of New, Non-Benign Neoplasms

neoplasm location	prasugrel n=6741	clopidogrel n=6716
brain	0	1
eye	0	1
oral cavity and pharynx	1	2
breast	4	1
lung and bronchus	18	14
other respiratory/thoracic	1	0
any GI site	35	25
colorectal, stomach, esophagus	31	21
colorectal	20	11
esophagus	4	3
stomach	7	7
pancreas	2	3
liver	0	1
gallbladder/biliary	2	0
any GU site	20	19
kidney	5	4
bladder	5	8
prostate	10	7
gynecologic	2	1
malignant melanoma	3	2
non-melanomatous skin	6	12
endocrine	2	0
any hematologic	4	4
leukemia	2	1
lymphoma	2	2
other hematologic	0	1
metastasis unknown primary	3	0
other unknown primary	0	1
unknown	1	1
all	**100**	**84**