

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 ($< 4 \times 10^9/L$) 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 P2Y₁₂ 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		Clopidogrel	
	n (%)	n (%)	n (%)	n (%)
all	87 (1.29)	60 (0.89)		
colon cancer	10 (0.15)	2 (0.03)	metastases to bone	1 (0.01)
gastric cancer	6 (0.09)	7 (0.1)	metastases to liver	1 (0.01)
prostate cancer	6 (0.09)	7 (0.1)	nasal neoplasm	1 (0.01)
breast cancer	4 (0.06)	1 (0.01)	oesophageal adenocarcinoma	1 (0.01)
adenocarcinoma	2 (0.03)	0 (0)	oesophageal cancer metastatic	1 (0.01)
bladder cancer	2 (0.03)	4 (0.06)	oesophageal carcinoma	1 (0.01)
brain cancer	2 (0.03)	1 (0.01)	ovarian neoplasm	1 (0.01)
clear cell cancer of kidney	2 (0.03)	0 (0)	pancreatic carcinoma	1 (0.01)
lung neoplasm malignant	2 (0.03)	2 (0.03)	papillary thyroid cancer	1 (0.01)
lung squamous cell carcinoma	2 (0.03)	1 (0.01)	papilloma	1 (0.01)
metastases to lung	2 (0.03)	0 (0)	peripheral t-cell lymphoma	1 (0.01)
metastatic neoplasm	2 (0.03)	0 (0)	pituitary tumour benign	1 (0.01)
non-small cell lung cancer	2 (0.03)	2 (0.03)	prostatic adenoma	1 (0.01)
prostate cancer metastatic	2 (0.03)	1 (0.01)	rectal cancer	1 (0.01)
renal neoplasm	2 (0.03)	0 (0)	rectal neoplasm	1 (0.01)
squamous cell carcinoma	2 (0.03)	1 (0.01)	renal cell carcinoma	1 (0.01)
acute myeloid leukaemia	1 (0.01)	0 (0)	salivary gland neoplasm	1 (0.01)
adenoma benign	1 (0.01)	0 (0)	sarcoma	1 (0.01)
basal cell carcinoma	1 (0.01)	1 (0.01)	small cell lung cancer	1 (0.01)
benign lung neoplasm	1 (0.01)	0 (0)	thyroid cancer	1 (0.01)
bladder neoplasm	1 (0.01)	1 (0.01)	transitional cell carcinoma	1 (0.01)
bladder papilloma	1 (0.01)	0 (0)	uterine leiomyoma	1 (0.01)
bone neoplasm	1 (0.01)	0 (0)	adenocarcinoma pancreas	0 (0)
bronchial carcinoma	1 (0.01)	2 (0.03)	adrenal neoplasm	0 (0)
cervix carcinoma	1 (0.01)	0 (0)	bladder transitional cell carcinoma	0 (0)
chronic lymphocytic leukaemia	1 (0.01)	0 (0)	carcinoid tumour pulmonary	0 (0)
colon adenoma	1 (0.01)	1 (0.01)	chronic myeloid leukaemia	0 (0)
colon neoplasm	1 (0.01)	0 (0)	colon cancer metastatic	0 (0)
colorectal cancer	1 (0.01)	0 (0)	gastric neoplasm	0 (0)
gallbladder cancer	1 (0.01)	0 (0)	hepatic cancer metastatic	0 (0)
gastrointestinal carcinoma	1 (0.01)	2 (0.03)	hepatic neoplasm	0 (0)
gastrointestinal tract adenoma	1 (0.01)	0 (0)	lymphocytic leukaemia	0 (0)
haemangioma	1 (0.01)	0 (0)	malignant melanoma	0 (0)
lung adenocarcinoma	1 (0.01)	0 (0)	metastases to adrenals	0 (0)
lung neoplasm	1 (0.01)	1 (0.01)	myelodysplastic syndrome	0 (0)
malignant ascites	1 (0.01)	0 (0)	non-hodgkin's lymphoma	0 (0)
mesothelioma malignant	1 (0.01)	0 (0)	small cell lung cancer metastatic	0 (0)
			thymoma	0 (0)

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

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

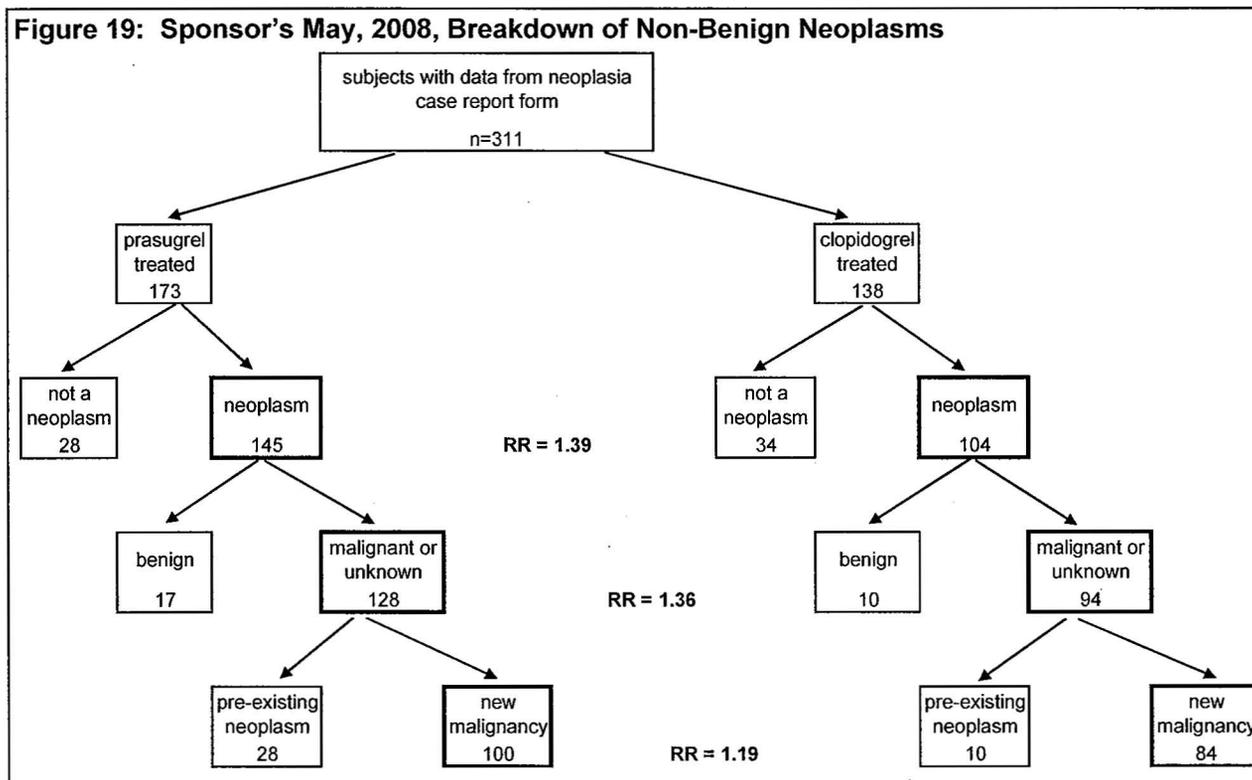


Table 18: Sponsor's May 9, 2008, Analysis of New, Non-Benign Neoplasms

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

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

Ascertainment Bias:

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

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

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

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

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