**DDOP OODP Consult**

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| **Consult requested by:** | Division of Cardiovascular and Renal Products |
| **IND:** | 063449 |
| **NDA:** | 022307 |
| **Date logged in:** | Mar 26 2008 |
| **Desired Completion Date:** | Apr 23 2008 |
| **Medical officer:** | Bhupinder S Mann MBBS |
| **Team Leader:** | John R Johnson MD<br>Patricia Cortazar MD (Acting) |
| **Review Completion** | Apr 24 2008 |

**Background:**

Div of Cardiovascular and Renal Products has consulted DDOP to address carcinogenic potential of prasugrel.

- Preclinical Studies:
  - The rat study was negative for drug-related tumors.
  - The mouse study was positive for hepatocellular adenomas in both sexes.
- Clinical Study:
  - DCVRP ongoing review of the pivotal study comparing prasugrel and clopidogrel demonstrates a statistically significant difference in new cancer diagnoses in the prasugrel treatment arm. "At 4 months, the time to event curves seem to diverge between the prasugrel treatment group and clopidogrel treatment group ($p = 0.0431$). Further analysis suggests that cancers in women drive this difference ($p = 0.0053$)."
- The sponsor has argued that the observed difference in cancer diagnoses stems from an ascertainment bias—there is a higher incidence of bleeding events in the prasugrel arm leading to investigations of the patients and discovering of cancers.

**DDOP has been requested to address the following specific questions:**

1. Do you agree that there is a statistically significant difference in the development of new malignancies in Study TAAL between the prasugrel and clopidogrel treatment groups?
2. Do you agree that cancers in women are driving this statistically significant difference?
3. Do you believe that prasugrel is a "promoter"?
4. There were a number of patients who had a history of cancer and developed worsening cancer in Study TAAL. Please comment on whether or not you believe this worsening of cancer (or development of metastatic disease) was related to the study drug, underlying malignancy, or both.
5. Please advise us on recommendations we can make to the sponsor regarding additional analyses (or studies) to be performed to further evaluate the possible carcinogenicity of prasugrel.

**For DDOP responses to above questions and comments go to page 19.**

**Relevant Details from the Request for Consultation**

COMMENTS / SPECIAL INSTRUCTIONS (FROM DCVRP TO DDOP) :

"We would appreciate your input on NDA 22,307, Prasugrel, a priority review on a new molecular entity to be used in the treatment of patients with acute coronary syndrome. Prasugrel is a prodrug, and the active metabolite is R-138727. The pharmacological action of Prasugrel results from covalent and irreversible binding of R-138727 to the P2Y12 platelet adenosine disphosphate (ADP) receptor."

"At the Executive CAC Meeting on 2/26/2008, the rat study was thought to be negative for drug-related tumors. The mouse study was positive for hepatocellular adenomas in both sexes."

"Our review of Study TAAL demonstrates a statistically significant difference in new neoplasias that develop in the prasugrel treatment arm. At 4 months, the time to event curves seem to diverge between the prasugrel treatment group and clopidogrel treatment group ($p = 0.0431$). Further analysis suggests that cancers in women drive this difference ($p = 0.0053$)."

"The sponsor argues that these new cancers were identified if a patient had any bleeding TEAE (for example, the sponsor looked at patients who may have had a puncture site bleed and then went on to develop cancer). However, we did a bleeding analysis and removed all patients who had a bleed in a particular organ system before they developed cancer in that particular organ system as well as removed anyone who was diagnosed with cancer in the first 14 days of the study. We found a highly significant difference ($p=0.0218$) in subjects who developed a new cancer > 14 days in the study who had no prior bleed in the particular organ system that subsequently developed cancer."

"We are concerned that prasugrel may be a "promoter"."

"We request a response by April 23, 2008, if possible, or as soon as you can reasonably provide us with a response."

"Please be aware of the following dates:
April 26, 2008: medical officer review due
May 26, 2008: CDTL secondary review due
June 26, 2008: Action date for this priority review"

**Relevant excerpt from the NDA submission:**

## *2.7.4.2.1.4.4. Uncommon, Relevant Treatment-Emergent Adverse Events of Special Interest*

### 2.7.4.2.1.4.4.1. Malignancies

**Colon cancer** was an uncommon TEAE **(0.17% with prasugrel, 0.03% with clopidogrel)** in the primary safety database that occurred with **a statistically significant higher incidence (p=.013)** in the all ACS subjects treated with prasugrel when compared to clopidogrel during the while at risk period. Thus, further analysis was conducted for the full study duration utilizing a broader group of PTs: rectal neoplasm, rectal cancer, colorectal cancer, colon neoplasm, colon cancer, and colon cancer metastatic.

**Nineteen (19)** TEAEs related to the above terms were found **in the prasugrel group** versus **8 in the clopidogrel group**. Of the 19 reports from the prasugrel group, **10 were diagnosed as a result of a diagnostic procedure following a GI bleed.** Another 4 had an AE temporally associated with the diagnosis (vomiting and weight loss, anemia [2], abdominal pain and chronic appendicitis), and another 5 had no AE that might have precipitated a diagnostic procedure of the GI tract. **The diagnosis of this type of malignancy was done in a similar proportion of subjects treated with clopidogrel (5 out of 8) as the result of a GI bleed (Appendix Section 2.7.4.7.2.5.13.5.1).**

On the basis of these findings, it is concluded that **colon cancer was diagnosed more often in subjects treated with prasugrel due to a higher rate of bleeding associated with this therapy.**

Malignancies of the **lung, breast**, and **prostate** were also further evaluated (Appendix Section 2.7.4.7.2.5.13.5) with **no evidence that the use of prasugrel is associated with a higher risk of cancer.**

**DDOP Review**

Division of Cardiovascular and Renal Products is concerned that prasugrel may be carcinogenic.

This concern was prompted by the pre-clinical carcinogenicity studies and preliminary estimates of cancer event rates in TRITON, the pivotal trial for the indication of the treatment of acute coronary syndromes with percutaneous coronary interventions. The review of TRITON is still in progress.

**Preclinical Evidence for Carcinogenicity**

The NDA submission has two two-year carcinogenicity studies: in mice and in rat.

- Each study has 55 animals per dosing and control groups
- The dosages are lower in the rat study because of a lower tolerability limit in rats compared to mice:
  - Mice dosages: 30, 100, and 300 mg/kg
  - Rat dosages were 10, 30, and 100 mg/kg

The positive carcinogenicity findings are predominantly in the mouse study.

- Distributions of neoplasms (benign and malignant) by sex, site and dosing groups are shown in Table 1.
- Distributions of neoplasms (benign and malignant) by dosing groups for both sexes combined are shown in Table 2.

***Reviewer Comments:*** *Methodology and conduct of the above preclinical studies is standard and acceptable.*

**Table 1: Neoplasms with Frequency > 4 by Site, Sex, and Dosing Group in the Prasugrel Mouse Carcinogenicity Study (NOTE: All Group Sizes Were 55)**

| Group | Female | | | | Male | | | |
|---|---|---|---|---|---|---|---|---|
| | Control | 30 | 100 | 300 | Control | 30 | 100 | 300 |
| Harderian gland | 5 | 3 | 7 | 6 | 5 | 8 | 2 | 2 |
| Intestinal cancer | 0 | 2 | 2 | 1 | 1 | 0 | 0 | 2 |
| Liver adenoma | 5 | 5 | 20 | 39 | 20 | 11 | 26 | 44 |
| Liver carcinoma | 1 | 4 | 2 | 5 | 11 | 12 | 13 | 16 |
| Liver cancer* | 2 | 6 | 3 | 5 | 11 | 15 | 14 | 17 |
| Liver hemangioma | 1 | 2 | 0 | 0 | 6 | 3 | 1 | 1 |
| Lung adenoma | 1 | 2 | 4 | 3 | 5 | 5 | 5 | 6 |
| Lung cancer | 2 | 2 | 1 | 2 | 3 | 3 | 8 | 4 |
| Lymphorecticular ca | 19 | 24 | 20 | 16 | 5 | 12 | 4 | 6 |
| Pituitary adenoma | 2 | 3 | 4 | 3 | 1 | 0 | 0 | 0 |
| Skin benign | 2 | 0 | 0 | 1 | 2 | 0 | 0 | 1 |
| Skin cancer | 4 | 1 | 2 | 2 | 0 | 0 | 1 | 0 |
| Spleen sarcoma | 1 | 3 | 0 | 1 | 0 | 0 | 1 | 0 |
| Spleen hemangioma | 2 | 3 | 0 | 1 | 4 | 0 | 1 | 0 |
| Uterus neoplasm† | 1 | 3 | 3 | 2 | 0 | 0 | 0 | 0 |

*including hemangiosarcoma, hepatoblastoma; †one carcinoma in 30 mg/kg group, the rest polyps

**Table 2: Neoplasms with Frequency > 4 by Site and Dosing Group in the Prasugrel Mouse Carcinogenicity Study**

| Group | Control | 30 | 100 | 300 |
|---|---|---|---|---|
| Harderian gland | 10 | 11 | 9 | 8 |
| Intestinal cancer | 1 | 2 | 2 | 3 |
| Liver adenoma | 25 | 16 | 46 | 83 |
| Liver carcinoma | 12 | 16 | 15 | 21 |
| Liver cancer* | 13 | 21 | 17 | 22 |
| Liver hemangioma | 7 | 5 | 1 | 1 |
| Lung adenoma | 6 | 7 | 9 | 9 |
| Lung cancer | 5 | 5 | 9 | 6 |
| Lymphorecticular ca | 24 | 36 | 24 | 22 |
| Pituitary adenoma | 3 | 3 | 4 | 3 |
| Skin benign | 4 | 0 | 0 | 2 |
| Skin cancer | 4 | 1 | 3 | 2 |
| Spleen sarcoma | 1 | 3 | 1 | 1 |
| Spleen hemangioma | 6 | 3 | 1 | 1 |
| Uterus neoplasm† | 1 | 3 | 3 | 2 |

*including hemangiosarcoma, hepatoblastoma; †one carcinoma in 30 mg/kg group, the rest polyps

***Reviewer Comments:*** *The incidence of spontaneous cancers appears high. Incidence of some cancers in the control group is observed equal to or higher than the incidence observed in the 30 mg dose group. A dose response may exist for liver adenomas ± for liver carcinoma and cancer.* Two other hepatic histologic findings "worth noting" are shown in Table 3.

**Table 3: Other Hepatic Histologic Findings in the Prasugrel Mouse Carcinogenicity Study**

| Group | Female | | | | Male | | | |
|---|---|---|---|---|---|---|---|---|
| | Control | 30 | 100 | 300 | Control | 30 | 100 | 300 |
| Central hypertrophy | 0 | 0 | 0 | 0 | 0 | 0 | 9 | 22 |
| Altered cell focus, eosinophilic | 6 | 6 | 18 | 36 | 9 | 17 | 23 | 24 |

Prasugrel is an enzyme inducer and in mice prasugrel produces an increase in liver size. The central hepatocytic hypertrophy seen in the male mice at the higher dosages (mild to moderate at the 100 mg/kg dosage and moderate in 7 mice at the 300 mg/kg dosage) is attributed to this enzyme induction.

"The significance of the altered cell focus requires more explanation. We have included below an abstract that provides background on the interpretation of altered cell foci in two-year carcinogenicity studies.

"Maronpot, R. R., T. Harada, et al. (1989). "Documenting foci of hepatocellular alteration in two-year carcinogenicity studies: current practices of the National Toxicology Program." Toxicol Pathol **17**(4 Pt 1): 675-83; discussion 683-4.

> "Altered hepatocellular foci (AHF) can be reliably identified in hematoxylin and eosin (H&E)-stained sections of liver from interim and final sacrifice intervals in 2-yr carcinogenicity studies in rats. While most AHF can be categorized on the basis of a defined set of descriptive terms, viz., basophilic, eosinophilic, clear vacuolated, and mixed foci, exposure to hepatocarcinogenic agents may induce unique types of AHF which should be distinguished from those that occur more commonly. It is proposed that unique treatment-associated AHF be classified as atypical AHF and that they be completely described in the pathology narrative accompanying the study. Since profound changes in the number and size of AHF have been documented in Fischer 344 rats with mononuclear cell leukemia, it is recommended that liver focus data from leukemic animals be censored in assessing potential effects of treatment on AHF. At the present time, there are insufficient data to allow routine use of AHF in regulatory decision-making in the absence of a liver tumor response. However, such data may form part of weight-of-evidence considerations used by regulatory bodies when accompanied by a concomitant liver tumor response.

**Prasugrel Rat Carcinogenicity Study**

The prasugrel rat carcinogenicity study does not show an increased rate of liver adenomas:

- There is no increase in the incidence of cancers with prasugrel, either by site or in total
- Lower rates are seen for large granular lymphocytic leukemia and mesothelioma

"The one finding consistent with the mice study findings is a higher rate of uterine neoplasms (due to high rates of polyps) in the prasugrel groups as also shown in Table 4."

***DDOP Reviewer Comments:*** *The incidence of uterine neoplasms in mouse study in the control, 30, 100, and 300 mg is 1, 3, 3, and 2 cases, respectively.*

***DCVRP Comments:*** *"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."*

**Clinical Study**

TRITON (or TAAL) was a large, international, multicenter, randomized, double-blind, active-controlled (vs. clopidogrel) of prasugrel in patients with Acute Coronary Syndrome undergoing Percutaneous Coronary Intervention.

- Labeled regimen for clopidogrel (300 mg loading, 75 mg maintenance) was compared to prasugrel 600 mg loading, 10 mg maintenance
- 13,608 patients were randomized 1:1 and followed for 6-15 months

**Table 4: Numbers of New First Cancers by Site and Treatment in TRITON**

| | clopidogrel | prasugrel |
|---|---|---|
| patients | 6,696 | 6,682 |
| bladder | 8 | 7 |
| breast | 1 | 5 |
| cervix | 0 | 1 |
| colorectal | 8 | 19 |
| esophagus | 2 | 5 |
| gall bladder | 0 | 2 |
| gi | 1 | 0 |
| head & neck | 2 | 2 |
| kidney | 4 | 4 |
| leukemia | 2 | 1 |
| liver | 1 | 0 |
| lung | 13 | 21 |
| lymphoma | 2 | 2 |
| melanoma | 3 | 3 |
| mesothelioma | 0 | 1 |
| myelodys | 1 | 2 |
| ovary | 0 | 1 |
| pancreas | 3 | 2 |
| prostate | 8 | 10 |
| sarcoma | 0 | 2 |
| stomach | 7 | 6 |
| thyroid | 0 | 1 |
| unknown/other | 2 | 7 |
| uterus | 1 | 0 |
| all nonskin/ nonbrain | 69 | 104 |
| brain | 0 | 2 (pituitary) |
| skin | 14 | 10 |
| squamous | 4 | 5 |

**DCVRP reviewer notes the following:**

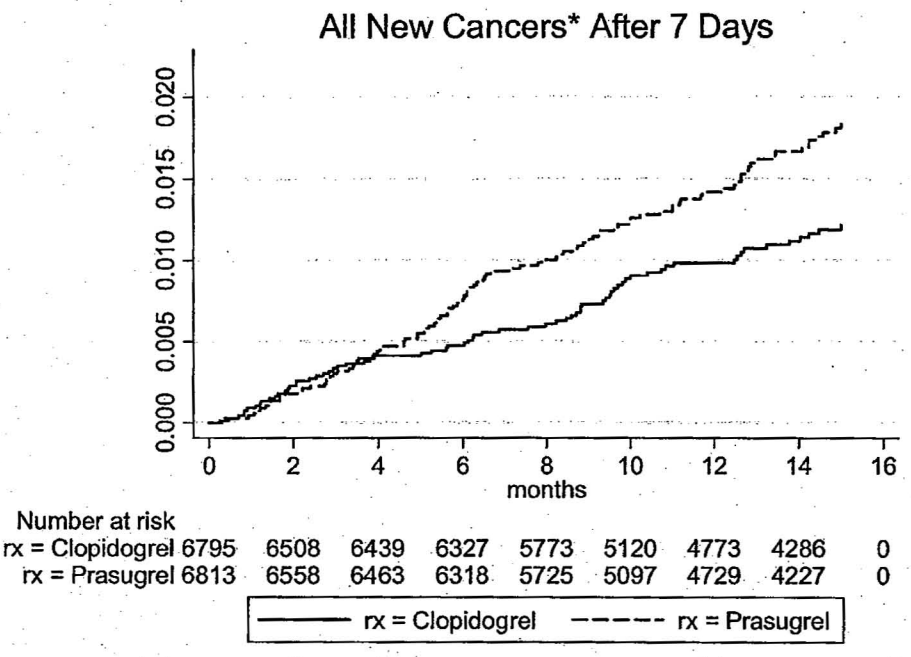
(In the following analyses, "all cancers" means all malignancies excluding non-melanoma skin cancers and brain tumors.)
(Text in "quotes" is DCVRP text. Underlining is by the DDOP reviewer.)

"The following analyses are still preliminary because there are issues with the completeness of the data. Some adverse events are tersely recorded as "LUNG MASS" and we do not yet have the details on all potential cancer cases. The recording of AEs was also different than most other sponsor's submissions: The AE file is also used for recording diseases present at baseline. If the baseline disease changes, then the investigator was supposed to record another AE, referencing the same AE number (AEID), and noting the change in severity. However, investigators appeared to have entered baseline diseases as later AEs erratically regardless of a change. Sorting out new cancers has been difficult and we are awaiting the submission of complete CRFs for all potential cancer cases. Because tumor findings were sometimes noted at screening but the cancer may not have been worked up or diagnosed until after enrollment, we have performed most analyses excluding cancers diagnosed during days 0 to 7—there were 16 cancers (9 prasugrel, 7 clopidogrel) diagnosed during the first seven days. The seven day cutoff is arbitrary, but varying it or eliminating it does not change the results substantially."

"The finding that attracted our attention initially was the increased rate of all cancers, particularly the solid tumors. We show the Kaplan-Meier (K-M) incidence plots by treatment for all new first cancers (excluding skin and brain tumors) in TRITON in Figure 1. We show the breakdown for new cancers by site and treatment in Table 7. What is striking to us is the divergence of the K-M all cancer incidence plots at four months with continuing divergence through the duration of the study. 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 differences favoring clopidogrel for any sites, suggesting the differences are not random occurrences."

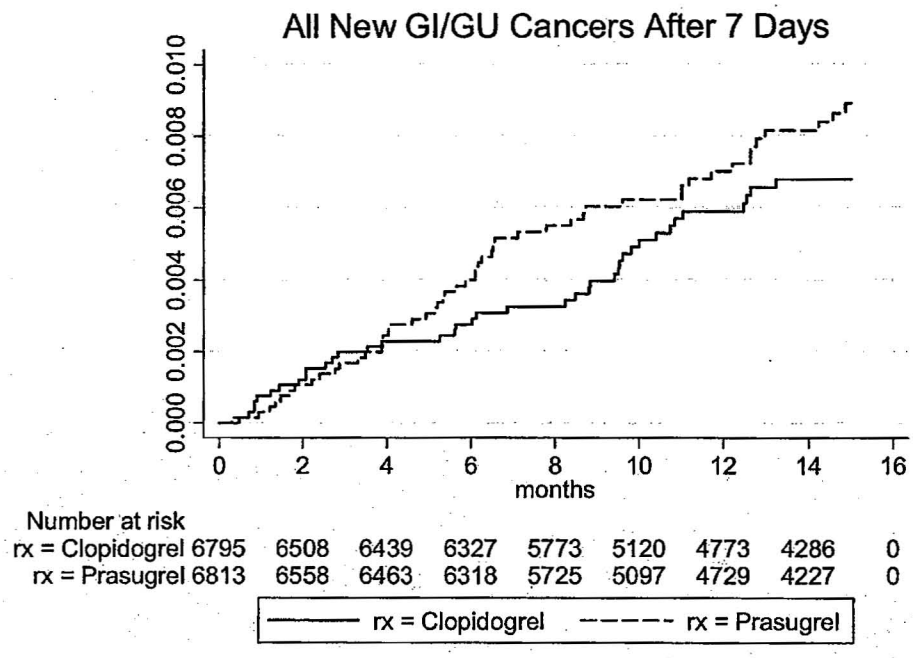
"The sponsor has argued that the differences may be due to an ascertainment bias: Prasugrel causes more bleeding than clopidogrel at the dosages used in TRITON, so the sponsor hypothesizes that prasugrel caused earlier bleeding of existing cancers leading to increased rates of detection. They hypothesize this effect particularly for gastrointestinal (GI) and genitourinary (GU) cancers. They have presented some tables and graphs suggesting that the incidence of new neoplasms (including benign) is different only for GI/GU neoplasms and that the incidence of malignancies is the same if patients with hemorrhagic AEs are excluded. While we have not had the time yet to duplicate or verify their results, we have done the following relevant analyses: We show the K-M incident plot for GI/GU cancers in Figure 2, for non-GI/GU cancers in Figure 3, for GI cancers alone in Figure 4, and for GU cancers alone in Figure 5. (For these analyses we have not counted ovarian cancer as a GU cancer or pancreas, gall bladder, or liver cancers as GI cancers because they do not usually present by bleeding.) There is a suggestion that GI/GU cancers diverge at four months and then may converge at about 12 months. However, they do not diverge early when many bleeding events occur (as shown in Figure 6) and 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."

**Figure 1: Kaplan-Meier (K-M) Incidence Plot for All New Cancers (Excluding Skin and Brain) Diagnosed After 7 Days in TRITON**



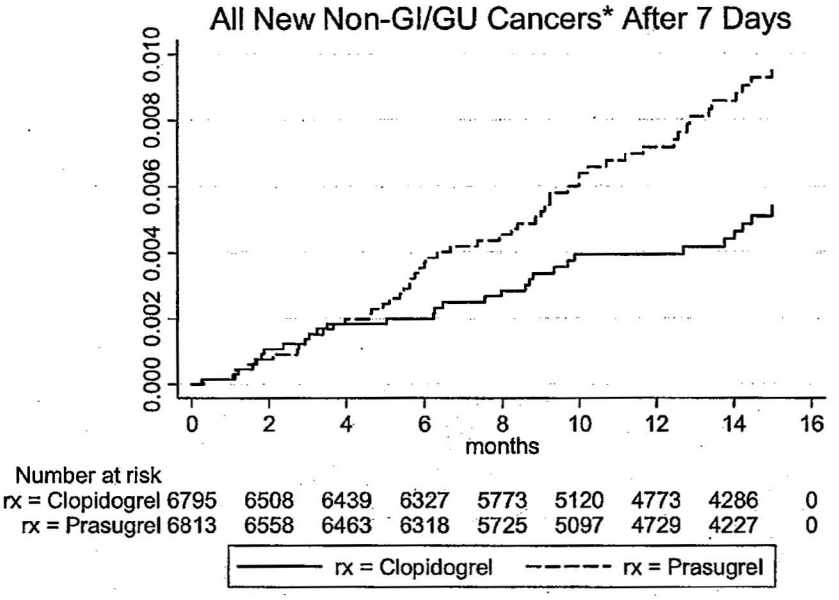

*excluding non-melanoma skin cancers and brain tumors; p = 0.008 by log rank

**Figure 2: K-M Incidence Plot for New GI/GU Cancers Diagnosed After 7 Days in TRITON**



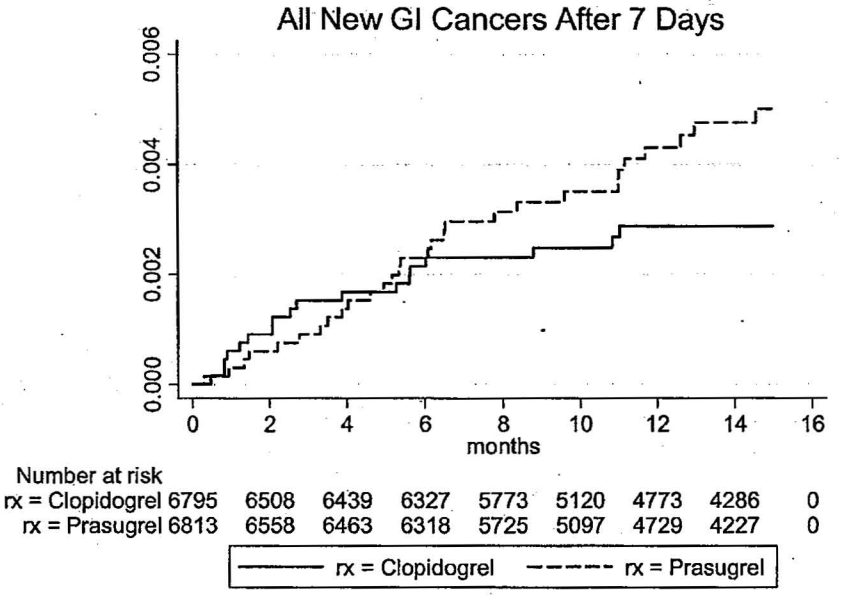

p = 0.2 by log rank

**Figure 3: K-M Incidence Plot for New Non-GI/GU Cancers Diagnosed After 7 Days in TRITON**



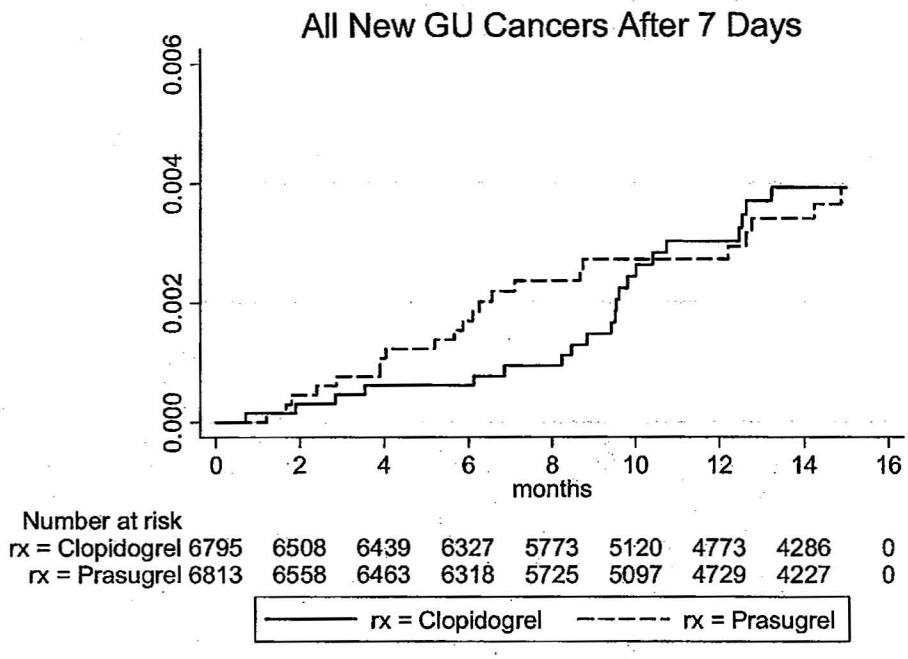

* excluding non-melanoma skin cancers and brain tumors; p = 0.01 by log rank

**Figure 4: K-M Incidence Plot for New GI Cancers Diagnosed After 7 Days in TRITON**




p = 0.11 by log rank

**Figure 5: K-M Incidence Plot for New GU Cancers Diagnosed After 7 Days in TRITON**




p = 0.9 by log rank