

**CLINICAL SUMMARY DOCUMENT**  
**FOR THE**  
**ONCOLOGIC DRUGS ADVISORY COMMITTEE**

**CAMPTOSAR + 5-FU/LV FOR FIRST-LINE  
TREATMENT OF METASTATIC COLORECTAL CANCER:  
A POST-MARKETING RE-EVALUATION OF SAFETY**

Isagani M. Chico, MD  
Donna J. Griebel, MD  
Division of Oncology Drug Products

November 2001

In April 2000, Camptosar was approved for first line treatment of metastatic colorectal carcinoma. The approval was based on a significant survival advantage demonstrated in the CPT-11+5FU/LV treatment arms of two randomized controlled trials, Study 0038 and Study V303. Study 0038 (U.S.) was a three-arm trial comparing CPT-11+ 5FU/LV weekly x 4 (bolus, Saltz Regimen), 5FU/LV daily x 5 (Mayo Clinic Regimen), and single agent CPT-11. Study V303 compared two infusional regimens of 5FU/LV, each in combination with CPT-11, to the same infusional regimens without CPT-11.

A year later, in April 2001, a prespecified interim analysis of a North Central Cancer Treatment Group (NCCTG) trial, N9741, found a disproportionately high number of early deaths (deaths within 60 days of starting treatment on study) in the Saltz regimen control arm compared to two oxaliplatin combination regimens (4.8% on the Saltz arm vs. 1.8% on each of the oxaliplatin combination arms). This finding led to an unplanned interim safety analysis of a Cancer and Leukemia Group B (CALGB) adjuvant trial, C89803, that compared adjuvant treatment with the Saltz regimen to the weekly 5FU/LV Roswell Park regimen. A higher early death rate on the Saltz regimen was again observed (2.2% vs. 0.8% on the Roswell Park regimen arm). Based on these interim analyses, one unplanned, accrual to the NCCTG trial was temporarily suspended until the trial was redesigned, and the CALGB study was permanently closed to new accrual.

In response to the findings of these two interim analyses, P&U funded a panel organized by Theradex to review patient records of the early deaths in the cooperative group trials. The review panel was charged with assigning attribution for death, reviewing the patients' management, reviewing chemotherapy administration and adherence to the protocol dose modification guidelines, and identifying patient characteristics associated with increased risk of death on the Saltz arm. The results of that review and the recommendations of the panel were published in the Journal of Clinical Oncology in September 2001.<sup>i</sup>

The review panel found that the deaths on the Saltz arms of these studies also occurred earlier than on the control arm – median time to death 29 days (n=29) vs. 47 days (n=5) on the Roswell Park comparator arm of the adjuvant trial. They found that the primary cause of drug-related death was a combination of chemotherapy-induced diarrhea, neutropenia, fever, and consequent dehydration and electrolyte abnormalities. In addition, a number of patients had fatal vascular events (both arterial and venous). These vascular events were considered to be potentially treatment-related, but a specific pharmacological basis for causality was not proposed. The panel was unable to clearly define a high-risk patient profile, although they suggested that older patients might be at higher risk for death on the Saltz regimen. Poor performance status was not clearly associated with risk of death. They did not find problems related to adherence to protocol guidelines for treatment/dose modification, but did note that there were isolated

dosing errors and reported that antibiotic use was often “delayed”, “prematurely discontinued”, or “inappropriately selected” in a number of patients, possibly contributing to their deaths.

The panel made the following recommendations based upon their review:

1. Health care providers should be made more aware of the gastrointestinal and vascular syndromes associated with CPT-11+5FU/LV bolus regimen.
2. Patient monitoring should be heightened in frequency (i.e., weekly assessment at least in the first cycle of treatment), with closer follow-up for signs of dehydration and allowance should be made for resolution of gastrointestinal and hematologic toxicity syndromes. They suggested that older individuals should be followed “especially closely.”
3. Supportive care of patients treated with the Saltz regimen should be heightened; including adding an oral fluoroquinolone to the management of diarrhea, hospitalizing patients if diarrhea persists >48 hours and initiating antibiotics during hospitalization if the patient has prolonged diarrhea, even with an adequate neutrophil count.
4. Specific recommendations for modifying dosing were not given by the panel. However, treatment related recommendations included; requiring that diarrhea and abdominal cramps resolve for at least 24 hours before resuming treatment, and that pre-treatment CBC’s should be performed no more than 48 hours before scheduled treatment. The panel suggested that dose modification criteria should incorporate toxicity grade and duration, the need for supportive care after the prior dose, and the interval since resolution of toxicity.

A “Dear Health Care Provider” letter to notify physicians of the findings in the cooperative group trial was distributed by P&U in May 2001. The recommendations of the review panel were available to the public in September. In response to these reports, there have been proposals made for altering the Saltz regimen, including reducing the starting dose by 20% and changing the schedule to incorporate a week of rest after the second week of treatment.. The NCCTG trial was changed to incorporate treatment interruption for grade 2 toxicity and to increase the dose reduction for grade 3 toxicity to two dose levels. The guidelines for administering the Saltz bolus regimen that are currently found in the product label are those followed in the randomized, controlled trial that served as the basis for the approval of this regimen, Study 0038. Whether these newly proposed changes will adequately improve safety while retaining the efficacy of the Saltz regimen will be unknown without prospective study.

The patient safety issues raised by the findings of the cooperative group trials must be examined carefully, and any proposals to address these issues deserve serious consideration. The purpose of this advisory committee meeting is to critically evaluate the observations of early deaths in the cooperative group trials in light of the more

extensive and mature data sets from the trials that were the basis of Camptosar's approval for first line treatment of colorectal cancer, and consider the most appropriate regulatory action that should be taken to respond to these findings. The potential alternatives from a regulatory standpoint include no action, modification of the label to incorporate measures to enhance supportive care, modification of the Saltz regimen's administration schedule and/or dose modification scheme in the label, or removal of the Saltz regimen from the label. The product label includes an alternative administration schedule of the CPT-11+5FU/LV combination, an infusional biweekly schedule called the Doulliard regimen, that was used in one of the first line indication licensing trials. If available data justify removal of the Saltz regimen from the product label, this infusional regimen would still remain as an approved treatment regimen for first line treatment of metastatic disease. The GI Intergroup Executive Committee met earlier this fall and concluded that this infusional combination regimen should be the regimen used for future Intergroup investigations.

The following sections summarize the FDA's review of the findings of the cooperative group trials in the context of the two licensing studies that were the basis of Camptosar's approval for first line treatment of colorectal carcinoma.

### **FDA Review of Early Deaths on the Cooperative Group Trials**

The FDA reviewed the records of the 29 patients who died in the cooperative group trials and was unable to identify characteristics that placed patients at high risk for early death with the Saltz regimen. There was a slight preponderance of females and patients greater than 65 years of age in this group. (The current Camptosar label states in the Pharmacokinetics in Special Populations section that no change in starting dose is recommended for geriatric patients receiving the weekly dosage schedule, and the Geriatric Use subsection of the Warnings section states that patients greater than 65 years of age should be closely monitored because of a greater risk of late diarrhea in this population.) Only 2/29 had a performance status greater than 1. FDA review concurred with the findings that most deaths occurred within 4 weeks of starting treatment. Most patients received two full doses of chemotherapy before it was either terminated or modified, and 14 of the 29 had no dose modification up to the time of their death. Five of the patients who met criteria for dose reduction were not given appropriately reduced doses. The fact that so many patients were treated at full dose on a weekly regimen up to the events that led to their death suggests that once the adverse events occur, there is little opportunity to alter the course with dose modification.

## **FDA Analysis of Early Deaths in the Licensing trials 0038 and V303**

Unlike the NCCTG and the CALGB trials, the rate of death within 60 days of starting treatment in the Saltz regimen arm (bolus CPT-11+5FU/LV) of licensing study 0038 was similar to the corresponding control arm. The rate of death within 60 days of starting therapy in the Saltz regimen arm of 0038 is actually higher than observed on the Saltz regimen arms of the cooperative group trials. The median time to death in patients who died within 60 days in both arms of Study 0038 was similar to that in the cooperative group trials, 28 days. (see Table 7, FDA full report)

The Camptosar product label reports that the rate of deaths within 30 days of any treatment on study was 9% in the Saltz regimen arm of Study 0038 and 4% in the Douillard arm of Study V303. These percentages are higher than the rates presented as deaths within 60 days of starting treatment in these studies. It has been argued that inclusion of an “early deaths” analysis in the product label would have provided some context for evaluating the rates observed in the cooperative group trial interim analyses. Deaths are analyzed within the context of an NDA submission and review as deaths that occur within 30 days of drug administration throughout the entire study. This is considered a valid and meaningful method of comparison because the full data set from the trial is analyzed and the temporal relationship with drug administration implies the drug’s potential role in the death, while avoiding the bias introduced by assigning causality.. Reporting deaths within 60 days of starting therapy conveys information regarding the prevalence and severity of early, acute toxicity. Early deaths raise questions about the appropriateness of starting dose and the management of toxicity, both from a supportive care and a dose modification standpoint. The licensing trial datasets were queried with these questions in mind and the findings are discussed below.

### **Reanalysis of Camptosar Licensing Trials for First-Line Treatment of Metastatic Colorectal Cancer**

There are two administration schedules of CPT-11+5FU/LV approved for the first-line treatment of metastatic colorectal carcinoma, the Saltz regimen and the Douillard regimen. The safety profiles of both approved first line treatment regimens were reviewed. Differences between the two administration schedules observed in the cross-study comparisons presented could be secondary to unrecognized differences in the patient populations. Although the study populations appeared similar, Study V303 enrolled fewer patients with performance status 2 and allowed enrollment of patients with a history of radiotherapy.

A combination of GI and hematologic syndromes was observed in most patients who died within 60 days of starting treatment with both the Saltz regimen and the 5-FU/LV control in Study 0038. The predominance of GI+Heme/Infectious syndromes (60% for Saltz in Study 0038 ) is similar to that observed in the cooperative group trials.

The incidence of Grade 3/4 diarrhea and mucositis in the overall populations of the CPT-11+5FU/LV arms was similar between Study 0038 and V303. Grade 3 or 4 neutropenia was higher on the Saltz regimen, but neutropenic fever was only slightly higher. Considering all cycles, the incidence of fever with neutropenia was higher with the Saltz regimen (16%) compared to the Douillard regimen (5.5%). Grade 3 and 4 vomiting was more common on the Saltz regimen. The overall incidence of arterial and venous thromboembolic events was similar between the Saltz and Douillard regimens. The rate of discontinuations due to adverse events between patients treated with the Saltz and Douillard regimens was relatively similar.

A majority of the patients require dose reductions in both arms of Study 0038. (see Table 16, full report) There is a sharp drop (about 27%) in the proportion of patients treated with full doses of the Saltz regimen between the second and third week of the first cycle. Only 47% of patients received full-dose therapy by the second cycle. The survival advantage associated with the Saltz regimen was demonstrated despite significant reductions in doses.

In Study V303, there was a more gradual decline in the proportion of patients treated at full doses in both treatment arms. (see Table 19, full report) More than 85% of patients received full doses at the second cycle and 80% at the third. The much higher proportion of patients treated with full doses in this study compared to Study 0038 may indicate better patient tolerance of the higher biweekly dose of Camptosar and infusional 5-FU regimen utilized in this study. There was a somewhat higher proportion of deaths in the first 60 days after starting treatment in Study 0038 compared to V303, but unidentified differences in patient characteristics or supportive care measures could have contributed to these apparent differences across studies.

The preponderance of early deaths and the marked dose reductions necessary within one cycle on Study 0038 argue that the starting dose and/or dose modification guidelines for the Saltz regimen should be modified. The major dose change recommended by the Theradex panel was to hold treatment for grade 2 diarrhea or abdominal cramping. P&U has proposed to change the dose modification guidelines in the product label to recommend holding treatment for either grade 2 diarrhea or neutropenia. If the protocol for Study 0038 had required a treatment hold for Grade 2 toxicity, over half (8/15) of the patients who died within 60 days of starting treatment on the Saltz regimen in that study would have been impacted. A total of 45 (20%) patients on the Saltz arm of 0038 (analysis includes all patients, not just those died within 60

days of starting treatment) initially presented with a Grade 2 event that became worse upon continuous treatment. This group of patients would have been affected by the proposed dose modification change. On the other hand, 47 (21%) patients who initially presented with a grade 2 event did not worsen with continuous treatment. The dose intensity in this group of patients would have been affected adversely had this dose modification been followed. The sponsor's labeling proposal retains the current label's instructions to resume treatment in subsequent cycles at full doses in patients who experienced grade 2 toxicity, despite the new plan to reduce within-cycle weekly doses for within-cycle toxicity.

The current product label states that for grade 3 toxicity the dose should be held until resolution to at least grade 2 and then resumed with a one dose level reduction. The proposed label changes submitted by P&U retain the one dose level reduction, but now require toxicity to resolve to at least grade 1 before resuming treatment. For Grade 3 adverse events, some ongoing studies have proposed a reduction of TWO dose levels. Of the 225 patients treated in the Saltz regimen arm of Study 0038, 81 (36%) presented with a Grade 3 or 4 event initially. These events clustered between the third and fourth weeks of the first cycle.

The use of quinolones as prophylactic treatment once grade 4 or persistent diarrhea was observed was specified in Study V303, but not in Study 0038. It is difficult to infer from the licensing trials' database whether use of antibiotics prevented life threatening sepsis or infections. Quinolones were used in both studies. The Theradex panel recommended quinolone use for persistent diarrhea, diarrhea accompanied by fever, or prophylaxis if ANC<500, and P&U has incorporated those recommendations in the proposed product label changes. P&U has added that "antibiotic support" should be started in patients who develop ileus, and in keeping with the panel recommendations has proposed that the label state that patients should be provided with a prescription for oral fluoroquinolone (a 7 day course) when they start treatment, to use as needed.

## **SUMMARY OF ISSUES**

A disproportionate number of early deaths on the Saltz regimen arms of two cooperative group studies prompted those trials to be placed on clinical hold and has led to serious re-evaluation of the safety of this approved regimen. The data monitoring committees that performed the interim analyses of the cooperative group trials were not evaluating a mature data set, and one of the interim analyses performed was not a prespecified analysis. When the early death data from these analyses are compared to mortality data from the licensing trial, the absolute death rates and events that preceded deaths on the Saltz arms appear similar to those observed in the licensing trial. These observations are made with the caveat that there are inherent flaws in performing cross study comparisons. The within study comparison of the early death rate associated with the

Saltz regimen in the licensing trial was similar to its 5FU/LV control arm, whereas the within study comparisons in the cooperative group trials found that early deaths on the Saltz arms occurred at a disproportionately higher rate than the controls.

A panel of colorectal cancer experts who reviewed the patients' records from these cooperative group trials has proposed changes in the use of the Saltz regimen to enhance its safety. Others have proposed altering the regimen's doses and schedule. The pattern of early dose modification in a substantial portion of the patients treated with the Saltz regimen in licensing Study 0038 suggests that its starting dose may be high. The sponsor has proposed labeling changes that retain the starting dose and administration schedule, but employs more aggressive dose modification in response to observed toxicity. It is unclear whether these changes will affect the efficacy of the regimen, an issue that not only impacts the ability of an altered Saltz regimen to serve as a control arm in efficacy trials, but more importantly, challenges the safety of retaining the regimen in the product label without adequate supportive data.

The Douillard regimen (continuous infusion) is also approved in the United States. Review of the adverse events and patterns of dose modification in the licensing study indicate that this regimen might have a more acceptable safety profile compared to the Saltz regimen, but there has been no "head to head" comparison of the two regimens to fully support this. The GI Intergroup Executive Committee members have recently recommended that the Douillard regimen be used by the group in future studies that utilize a CPT-11+5FU/LV arm.

Labeling modifications that affect a regimen's administration should ideally be prospectively studied to evaluate their impact on safety and efficacy. Study designs that could clearly demonstrate safety and efficacy of a "modified" version of the Saltz regimen need to be discussed, as concern has been raised over the practicality of enrolling the large numbers of patients required to demonstrate noninferiority of a modified Saltz regimen in terms of survival. In the meantime, the Agency must determine the most appropriate regulatory response to address the current safety concerns. This decision hinges on whether the safety concerns raised by the cooperative group interim analyses are valid. If the ODAC believes that they are, then the committee will need to consider to what extent the label should be modified to adequately protect the safety of cancer patients.

---

<sup>i</sup> Rothenberg M, Meropol N, Poplin E, Van Cutsem E, Wadler S. JCO, Vol 19, No. 18, 2001: 3801-3807.