Clinical Review for NDA 19-880 Supplement SE8-019

Executive Summary

I. Recommendations

A. Recommendation on Approvability

The Division of Oncology Drug Products (DODP), Center for Drug Evaluation and Research (CDER), FDA does not recommend addition of any information based on the pediatric studies conducted to the label.

The phase 1 study (CA124001), which enrolled patients to a combined regimen of carboplatin and irinotecan, also included the collection of pharmacokinetic data. However, because this was a combination study, it is difficult to reach definitive conclusions regarding pharmacokinetics and dosing for carboplatin based on the results of this study. Limitations included exclusion of a number of patients from the analysis due to lack of evaluable sampling and dosing errors. See also review by Dr. Bhattaram for further details.

The phase 2 study (CA124002), which allocated patients to carboplatin / irinotecan or irinotecan alone in a non-comparative fashion with each arm divided into two strata (CNS tumors versus non-CNS tumors), again provides data which are difficult to interpret. No pharmacokinetic data was collected in this study. Furthermore, the lack of a carboplatin alone arm and lack of a formal comparative design makes it difficult to draw any definitive conclusions regarding the activity of carboplatin. Responses were seen in only a few patients, whether on the irinotecan or combination arm. Response duration was also difficult to interpret. Another complicating factor in interpretation of both activity and safety was the prior exposure to carboplatin or cisplatin in a majority of patients.

From a safety perspective, the adverse events (AE's) observed were consistent with those previously observed and described in the respective carboplatin and irinotecan labels. Diarrhea, which was observed uniformly and with numerically comparable frequencies in all of the treatment arms of CA124002, is a well recognized AE associated with irinotecan use. Neurologic AE reports such as seizures and neuropathy were numerically more common in the CNS tumor groups as would be expected given the nature of the underlying disease. Hematologic toxicities of anemia, neutropenia and thrombocytopenia appeared to occur more commonly in the combination treatment groups compared to irinotecan alone. This finding is not surprising given the known myelosuppressive effect of either drug.

In summary, the response rates which can be attributed to carboplatin are not high enough to justify a treatment indication for carboplatin nor low enough to exclude the possibility that

carboplatin has meaningful activity in these diseases, the safety data provide no new information for the label, and the pharmacokinetic (PK) data are not conclusive.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

No new phase 4 commitments are contemplated.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

The applicant has submitted two clinical studies in pediatric patients with relapsed/refractory solid tumors with this supplemental NDA. The studies are described briefly as follows:

CA124001 was a dose finding study which enrolled 28 patients aged 1-21 with refractory solid tumors. The primary objective was to determine the maximum tolerated dose of carboplatin when administered in combination with irinotecan. Secondary objectives included evaluation of the safety profile and dose-limiting toxicity, determination of plasma pharmacokinetics of carboplatin and irinotecan, and evaluation of preliminary evidence of anti-tumor activity of the combination using objective response rate.

CA124002 was a study of carboplatin/irinotecan or irinotecan alone in pediatric patients with relapsed/refractory solid tumors. Patients were evaluated in CNS or non-CNS primary tumor strata. The primary endpoint was objective response rate. There was no formal comparative analysis of irinotecan alone versus the combination planned as part of the study design. Further evaluation of the safety of carboplatin was a secondary endpoint of the study. The chemotherapy administration schedules were as follows. Treatment was administered on a 21-day cycle in both arms.

<u>Treatment A</u>

Carboplatin: AUC 4 mg/ml.min as a 50-minute infusion on day 1, preceding the irinotecan
(b)(4)---------- :
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Irinotecan: 12 mg/m^2/day as a 60-minute IV infusion x 10 days

<u>Treatment B</u>

Irinotecan: 20 mg/m^2/day as a 60-minute IV infusion x 10 days

A total of 151 patients were enrolled. The distribution of patients in each of the two treatment arms and between the CNS and non-CNS strata are outlined in Table 1 below.

Table 1 : CA124002 Distribution of Patients

CNS Tumor Treatment A	CNS Tumor Treatment B	Non-CNS Tumor Treatment A	Non-CNS Tumor Treatment B
N = 28	N = 28	N = 47	N = 48

B. Efficacy

In the phase 1 study CA124001, objective response rate was a secondary endpoint. A total of 4 responses were observed. One patient with medulloblastoma had a complete response. Three patients were documented to have partial responses, one with medulloblastoma, one with lymphoepithelial carcinoma, and one with neuroblastoma. Observance of responses in medulloblastoma is consistent with previous clinical experience, where medulloblastoma is one childhood brain tumor known to be responsive to chemotherapy regimens. These observed responses were of limited duration, with relapse/progression documented about 2 months after observation of a response

Objective response rate was the primary endpoint of CA124002. Table 2 outlines the response rate in each of the two arms by stratum (CNS versus non-CNS primary). Table 3 outlines the individual diagnoses for responders.

Table 2 : Response Rates in CA124002

	CNS tumor Treatment A (N=28)	CNS tumor Treatment B (N=28)	Non-CNS tumor Treatment A (N=47)	Non-CNS tumor Treatment B (N=48)
CR + PR	4	3	3	6
Response Rate (%)	14	11	6	13
(95% Confidence Interval)	(4-33)	(2-28)	(1-18)	(5-25)

Table 3 : Diagnosis in Individual Responders in CA124002

Treatment A CNS Tumor / Response	Treatment B CNS Tumor / Response	Treatment A non-CNS Tumor / Response	Treatment B non-CNS Tumor / response
Glioblastoma Multiforme/ PR Astrocytoma / PR Brainstem / PR Pineoblastoma / CR	Medulloblastoma / PR Medulloblastoma / PR Medulloblastoma / PR	Desmoplastic small round cell / PR Undifferentiated epithelial / PR Soft tissue sarcoma / PR	Neuroblastoma / CR Rhabdomyosarcoma/ PR Neuroblastoma / PR PNET / PR Hepatoblastoma / PR Rhabdomyosarcoma CR

There were a limited number of responses observed across treatment arms.
Although the addition of carboplatin to irinotecan (treatment A) does not numerically Increase the response rate when added to irinotecan alone(in fact, the irinotecan alone response rate in the non-CNS stratum is numerically higher than that with the combination), it is difficult to quantify the contribution of carboplatin to anti-tumor activity given the lack of a comparative statistical design and lack of a carboplatin single-agent comparator.

Responses ranged in duration from 1 month to 5 months.One patient with pineoblastoma who received therapy with carboplatin+irinotecan had a CR which was documented for over 5 months and one patient with rhabdomyosarcoma who was treated with irinotecan alone had a response which was documented for 4.7 months. Aside from the small number of patients in each cohort and lack of a formal comparative design for the combination versus irinotecan alone, nine of the 16 patients with a response were censored for response duration at last tumor assessment date, making it difficult to draw any conclusions regarding response duration in either arm as a whole or as a comparison between the two arms.

C. Safety

1. Adequacy of safety testing

CA124001 was a dose finding study with determination of a maximum tolerated dose (MTD) as its primary objective. As described above, this study enrolled 28 patients ranging in age from 1 – 21 years who were treated with a carboplatin / irinotecan

combination. Due to the toxicity encountered at the –2a dose level (carboplatin AUC 5 mg/mL.min and irinotecan 12 mg/m^2/day), the carboplatin AUC 4 mg/mL.min and irinotecan 12 mg/m^2/day dose level was identified as the maximum tolerated dose. This dose level was expanded to 13 patients. Table 4 outlines the dose ranges evaluated, the number of patients enrolled at each level, and the nature of adverse events observed.

Table 4 : CA124001 DLT at Cycle 1 Dose

Initial Dose Level (carboplatin AUC/irinotecan mg/m^2/day)	Number of Patients	Number Experiencing Cycle 1 DLTs	Cycle 1 DLTs And Grade (GR)
4 / 18	6	2	GR3 Diarrhea, ileus, dehydration, epistaxis
4 / 15	6	3	GR4 abdominal pain, prolonged neutropenia, thrombocytopenia GR3 hemorrhage, catheter infection Greater than 2-week delay in retreatment
4 / 12	13	1	GR3 bone pain GR4
5 / 12	3	3	GR3 diarrhea, abdominal pain > 2 platelet transfusions in 7 days > 2 week delay in retreatment

The safety database also consisted of 151 patients enrolled to CA124002. Of these, 75 were treated with the combination of irinotecan plus carboplatin, and 76 were treated with irinotecan alone. Duration of therapy ranged from one cycle to 10 cycles. Table 5 summarizes number of treatment cycles by treatment arm and tumor group.

Table 5 : Treatment Cycles per Patient on CA124002

	Treatment A ; CNS Tumors	Treatment B ; CNS Tumors	Treatment A ; non-CNS	Treatment B ; non-CNS
Median	4.5	4	2.5	3
Min – Max	1-9	1-10	1-9	1-9

Within each stratum, the median number of therapy cycles was similar for both treatment arms. However, within each stratum, patients with CNS tumors had a slightly greater number of median cycles of therapy than non-CNS tumors.

Over 50% of patients had at least one dose delay due to carboplatin or irinotecan. Approximately 10% of patients across the 4 individual treatment groups required at least 1 dose reduction for irinotecan. As a whole, approximately 60% of treatment cycles given to patients on the combination arm were delayed, compared with 27% of cycles given to patients receiving irinotecan alone.

2. Serious side effects

Serious adverse events are discussed in the context of the CA124002 study results. As expected given the known adverse events (AEs) associated with carboplatin and irinotecan, hematologic toxicity including anemia, thrombocytopenia, or neutropenia was observed. Adverse events previously associated with irinotecan included diarrhea and other gastrointestinal toxicities. Adverse events previously associated with carboplatin included nausea, vomiting and neuropathy. All patients experienced adverse events, and the majority experienced at least one grade 3 or 4 AE during the study. The most commonly observed and clinically relevant grade 3 / 4 AE's are discussed below. As discussed above, the limited number of patients in each treatment group makes it difficult to draw any conclusions regarding comparisons between CNS and non-CNS patients or between treatment A and treatment B.

a. Gastrointestinal : Diarrhea, Vomiting

Grade 3 / 4 diarrhea appeared to occur with comparable frequency in both irinotecan alone and combination treatment groups, reflecting the prior known association of diarrhea with irinotecan administration. However, diarrhea did occur more frequently in CNS tumor patients than non-CNS tumor patients. The frequency of grade 3 / 4 diarrhea across the four treatment groups was as follows : CNS treatment A 32%, CNS treatment B 30%, non-CNS treatment A 9%, non-CNS treatment B 11%.

Although vomiting of any grade was reported in over 60% of patients on CA124002, grade 3 / 4 vomiting was reported in less than 5% of patients in most treatment groups, except the CNS treatment B group, where 5 patients (19%) were reported to have a grade 3/ 4 vomiting AE.

b. Neurologic: Motor Neuropathy, Seizures

Motor neuropathy was more commonly reported in CNS than in non-CNS treatment groups, possibly reflecting underlying disease. The frequency of grade 3 / 4 motor neuropathy across treatment groups was CNS treatment A 18%, CNS treatment B 22%, non-CNS treatment A 7%, non-CNS treatment B 4%. The incidence of seizures exhibited

a similar pattern, with 18%-19% of CNS tumor patients experiencing a seizure compared with 6% or less of non-CNS tumor patients.

c. Infection / Febrile Neutropenia

Infection and febrile neutropenia appeared to occur slightly more commonly in the combination (treatment A) groups than with irinotecan alone, although the differences are not large enough for a definitive judgement. When evaluating febrile neutropenia alone, the differences between combination and irinotecan alone treatment groups are more pronounced: CNS treatment A 21%, CNS treatment B 7%, non-CNS treatment A 17%, non-CNS treatment B 2%.

d. Hematologic AE's : Neutropenia, Anemia, Thrombocytopenia

As expected, these appeared to occur more commonly in the carboplatin/irinotecan treatment groups than with irinotecan alone. The frequencies of grade 3 / 4 hematologic AE's across treatment groups are as follows in Table 6.

Table 6 : Grade 3 / 4 Hematologic AEs in CA124002

Hematologic AE	CNS Tumor Treatment A %	CNS Tumor Treatment B %	Non-CNS Tumor Treatment A %	Non-CNS Tumor Treatment B %
Hemoglobin	57	15	45	25
Neutrophils (ANC)	82	52	78	30
Platelets	68	7	56	4

These differences are noteworthy, especially for neutropenia, where G-CSF use was required in patients receiving combination therapy but only suggested for patients receiving irinotecan alone.

3. Drug-drug interactions

Cautions relevant to drug interactions already outlined in the carboplatin label include the following: 'The renal effects of nephrotoxic compounds may be potentiated by PARAPLATIN'

No changes are proposed or recommended.

4. Warnings

Warnings pertaining to bone marrow suppression, vomiting, neurologic effects, renal toxicity, and anaphylactic reactions and their treatment are outlined in the carboplatin label. No additions are proposed or recommended.

D. Dosing

The dosing guidelines in the current labeling provide for a mg/m^2 dosing approach when determining dosing. The guidelines also describe determination of dosing using mathematical formulae such as the Calvert formula based on the patient's pre-existing renal function.

The clinical pharmacology and biopharmaceutics review executive summary described the limitations of the pharmacokinetic data from CA124001 and its analysis as follows. The pharmacokinetic analysis of the data was inconclusive. Due to lack of an adequate number of samples, data from 25-30% of the patients were discarded as they could not be utilized in the non-compartmental pharmacokinetic analysis methodology. The reviewer tried to provide a summary of the pharmacokinetic information from previous reviews in the division. No clear interpretation could be made based on the information available. Hence, the current study should be treated as inconclusive.

Due to these limitations and the limitations of the clinical data as described above, no additional dosing guidelines are recommended to be added to the label.

E. Special Populations

1. Pediatrics

See above. Both Ca124001 and 124002 were conducted in children ages 1 – 21 years of age.

2. Elderly

The current label describes the experience in elderly patients with ovarian cancer as follows :

"Of the 789 patients in initial treatment combination therapy studies (NCIC and SWOG), 395 patients were treated with carboplatin in combination with cyclophosphamide. Of these, 141 were over 65 years of age and 22 were 75 years or older. In these trials, age was not a prognostic factor for survival. In terms of safety, elderly patients treated with carboplatin were more likely to develop severe thrombocytopenia than younger patients. In a combined database of 1942 patients (414 were ≥65 years of age) that received single-agent carboplatin for different tumor types, a similar incidence of adverse events was seen in patients 65 years and older and in patients less than 65. Other reported clinical experience has not identified differences in responses between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Because renal function is often decreased in the elderly, renal function should be considered in the selection of PARAPLATIN dosage"

No patients over the age of 21 were enrolled to either of the two clinical studies submitted to this sNDA. No additional wording regarding use in the elderly was proposed nor is any recommended.

2. Renal or Hepatic Impairment

Warnings regarding potential hepatic or renal toxicity are outlined in the current labeling. As discussed above, the current labeling includes dosing guidelines based on mathematical formulae which take into account pre-existing renal function. No changes were proposed by the sponsor nor are any recommended.

4. Gender / Ethnicity / Specific Age Distribution

The demographics of the 28 patients enrolled to CA124001 can be summarized as follows. There were 17 males and 11 females enrolled. Patients' age range was from 1 to 21 years. Ten patients were age 4 years or younger, 6 were between 5 and 10 years of age, and 12 patients were age 11 years or older. Eighteen patients were listed as white (including hispanic) 6 as black, and 4 as other.

The demographics of patients enrolled to CA124002 are summarized in table 7 below.

Table 7 : Gender, Race and Age on CA124002

Demographic	**CNS Tumor Treatment A N = 28**	**CNS Tumor Treatment B N = 28**	**Non-CNS Tumor Treatment A N = 47**	**Non-CNS Tumor Treatment B N = 48**
Gender				
Male	13	18	32	24
Female	15	10	15	24
Race				
White	21	23	28	29
Black	1	2	5	5
Asian	1	1	2	4
Other	5	2	12	0
Age (years)				
Median	8.5	12	14	10
Range	1-17	2-19	1-20	1-21

5. Pregnancy

Carboplatin injection should not be used in pregnant women. The drug is currently labeled as pregnancy class D, due to its teratogenic effects.

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/s/

Ramzi Dagher
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