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Clinical and Molecular-Metabolic Phase II Trial of Perifosine for Recurrent/Progressive Malignant Gliomas

MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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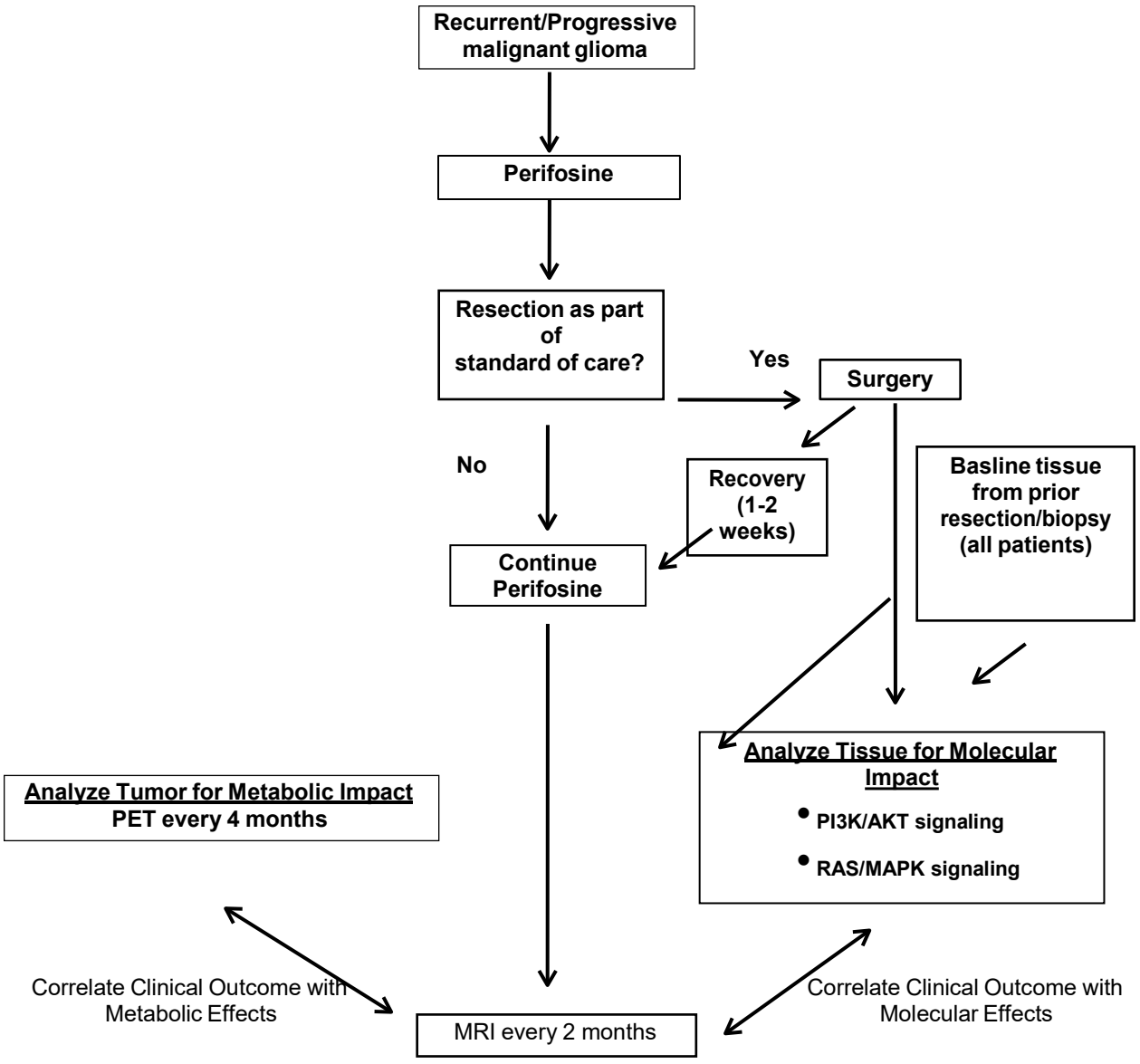
1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This is a phase II study of the small molecule inhibitor perifosine (NSC 639966, D21266, KRX-0401) in the treatment of patients with recurrent glioblastoma multiforme (GBM) and other recurrent malignant gliomas. The sponsor of this study is Keryx, as well as AOI pharmaceuticals and OCOG, which are subsidiaries of Keryx. The goal of the phase II study is to determine efficacy as measured by the progression-free survival rate after 6 months of treatment. Secondary goals include determination of molecular and metabolic effects of perifosine by tissue analysis and PET imaging. In addition, when cytoreductive surgery is recommended as part of the standard of care at study entry, patients will be considered for a "surgical arm." In this case, patients will receive perifosine for 5-10 days before surgery during which tumor will be aliquoted both for diagnostic purposes and for molecular effects of the drug in vivo and for analysis of drug penetration into tumor tissue. A schema is shown on the following page.


Recurrent/Progressive malignant glioma
Perifosine
Resection as part of standard of care?
Yes
Surgery
No
Recovery (1-2 weeks)
Basline tissue from prior resection/biopsy (all patients)
Continue Perifosine
Analyze Tissue for Molecular Impact
PI3K/AKT signaling
RAS/MAPK signaling
Analyze Tumor for Metabolic Impact
PET every 4 months
Correlate Clinical Outcome with Metabolic Effects
MRI every 2 months
Correlate Clinical Outcome with Molecular Effects

2.1 OBJECTIVES AND SCIENTIFIC AIMS

- Primary aim:
  - Determine the efficacy of perifosine in patients with recurrent/progressive GBMs not taking EIAEDs as measured by 6mPFS.

- Secondary aims
  - Determine molecular effects of perifosine on AKT, RAS, and proliferation in malignant gliomas by analysis of resected tissue in patients on the surgical substudy.
  - Determine metabolic effects of perifosine on malignant gliomas by PET imaging.
  - Identify molecular features that predict perifosine response.

3.0 BACKGROUND AND RATIONALE

3.1 *Malignant gliomas*

The most common cancer arising from the brain is the glioblastoma multiforme (GBM). It is also the most aggressive subtype among the gliomas, a collection of tumors including astrocytomas and oligodendrogliomas. While the extent of surgical resection is an important prognostic factor [1, 2], malignant gliomas are diffusely infiltrative tumors; hence, all locally directed therapy (surgery, radiotherapy) inherently palliative. Such tumors are also relentlessly progressive with the most aggressive forms carrying a dismal prognosis. For example, the median survival of patients with GBM is approximately 1 year. Chemotherapy, typically temozolomide, is usually given either during radiotherapy (and continued afterward) or following radiotherapy, and a recent multinational study demonstrated a modest survival benefit of 2.5 months relative to radiotherapy alone [2]. However, only 10.7% of patients were progression-free and only 26.5% of patients were alive 2 years following diagnosis [2]. Recurrent disease following radiotherapy is commonly refractory to treatment, with a 6mPFS following carmustine (BCNU) of only 17.5% in a recent study [3]. Therefore, while systemic chemotherapy improves the outcome for some patients, long term disease control presently remains elusive. Novel agents that inhibit the key molecular pathways driving glioma growth need evaluation in malignant gliomas.

3.2 *Perifosine (NSC 639966, D21266, KRX-0401)*

Alkylphospholipids represent a new class of lipid-related compounds that exhibit promising anticancer activity and a different spectrum of toxicity than conventional cytotoxic agents. Perifosine (1,1-dimethyl-4 [[(octadecyloxy) hydroxyphosphinyl]oxy]-piperidinium inner salt) is a synthetic, substituted heterocyclic alkylphospholipid, structurally related to miltefosine (NSC 60558, D-18506). The anti-tumor activity of miltefosine was initially evaluated in the 1980s, and it is licensed in Europe as a topical application for the treatment of patients with cutaneous metastases from breast cancer. It is also used in an oral formulation to treat leishmaniasis. Because the only major toxicities of miltefosine are gastrointestinal --and this was thought be a local rather than a central effect of the drug, numerous analogues were developed to see if a less toxic analogue could be identified. Perifosine was identified as a potentially active and better tolerated analog of miltefosine. Its spectrum of activity across the NCI 60 cell line screen was very similar to miltefosine (Pearson correlation coefficient = 0.817). Both miltefosine and perifosine had very unique patterns of *in vitro* cell growth inhibition that are distinctly different from most cytotoxic agents. Perifosine has been shown to be more active and better tolerated than miltefosine in preclinical models [4]. Perifosine exhibited marked activity in animal and human tumor cell lines resistant to standard chemotherapeutic agents with relative sparing of normal cells, including macrophages, bone marrow cells and normal glial cells in a glioblastoma model.

Alkylphospholipids are known to affect tumor cell proliferation, differentiation, invasion, and metastasis. These compounds are absorbed directly into cell membranes where they accumulate (reviewed in [5]). Although there is considerable evidence that the plasma membrane is the primary site of action, alkylphospholipids may be widely distributed throughout the cytoplasm and possibly within the nucleus. [6, 7]

3.3 *Perifosine Mechanism of Action*

Perifosine has been shown to inhibit or otherwise modify signaling through a number of different signal transduction pathways including PI3K/AKT, RAS/MAPK which are of particular interest because these pathways are active in the majority of malignant gliomas and combined activation of these pathways induce GBMs in mice [8].

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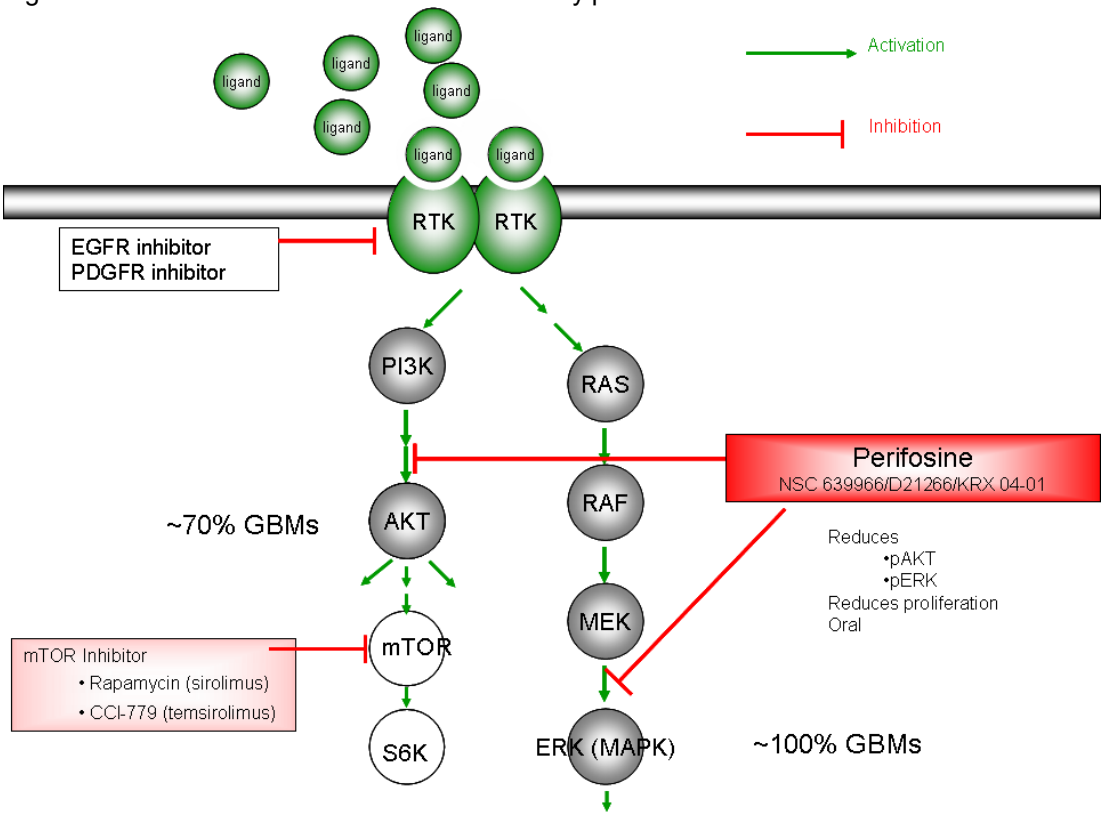
Figure 1: RAS and AKT cascades are inhibited by perifosine.



Approximately 70% of GBMs exhibit activated AKT [8, 9], typically through loss of the tumor suppressor PTEN[10-12] which normally represses AKT activation (figure 1). Modeling by Dr. Holland here at MSKCC and others has also demonstrated that *PTEN* loss is functionally equivalent to AKT activation[13], and that either *PTEN* loss or activated AKT can combine with RAS activation to induce GBMs[8, 13]. One downstream effector of AKT is the mammalian target of rapamycin (mTOR); however, treatment with mTOR inhibitors such as with rapamycin (sirolimus) or CCI-779 (temsirolimus) [14] for recurrent high grade gliomas have not shown response or survival rates that are markedly superior to those observed with traditional chemotherapies such as temozolomide[2, 15-17] or BCNU [3]. One potential explanation is that mTOR inhibitors affect only a subset of the pathways activated by AKT. Therefore, inhibition of AKT itself may be more effective as an anti-cancer treatment. In addition, rapamycin and its analogs also are associated with severe toxicity in some patients, including thrombocytopenia and hyperlipidemia, limiting their use. Other direct inhibitors of AKT have been too toxic for clinical use. By contrast, perifosine has been used with limited toxicity in humans (below).

3.4 *Pre-clinical studies*

3.4.1 In vitro

Prior to stimulation of the PI3K/AKT pathway, AKT is localized in the cellular cytoplasm. Following stimulation and activation of PI3K, AKT is recruited to the cell membrane, where it then localizes. Since the long alkyl chain of the alkylphosphocholines can insert into the outer leaflet of the plasma membrane and since these agents use lipids, such as those found in cellular membranes, as substrates, it seemed plausible that perifosine might inhibit a transduction pathway component known to be dependent for its activity on membrane localization.

Investigators at the US National Cancer Institute (NCI) first studied the effects of perifosine on AKT using a prostate cell line, PC-3, which is known to have a mutated, non-functional PTEN and thus to have constitutively activated AKT. [7] Their results demonstrated that very small doses of perifosine (5μM) blocked phosphorylation of AKT but did not decrease the total amount of AKT present in the cell. These effects occurred within 30 minutes of exposure to perifosine, suggesting this was an initial event rather than a secondary phenomenon due to perifosine effects elsewhere in the cell. When perifosine was removed, substantial recovery of AKT phosphorylation began within one hour, also suggesting that perifosine's effects are specific and not the result of general detergent effects. Perifosine also blocked the effects of insulin, EGF (epidermal growth factor), PDGF (platelet derived growth factor) and other ligands known to stimulate AKT activation. By contrast, perifosine did not affect growth factor-mediated PI3K activation. Finally, the investigators showed that perifosine blocked the localization of AKT to the cell membrane, consistent with the observation that PI3K activation was not affected but AKT phosphorylation was clearly diminished, and with the initial hypothesis that led to the initiation of these studies.

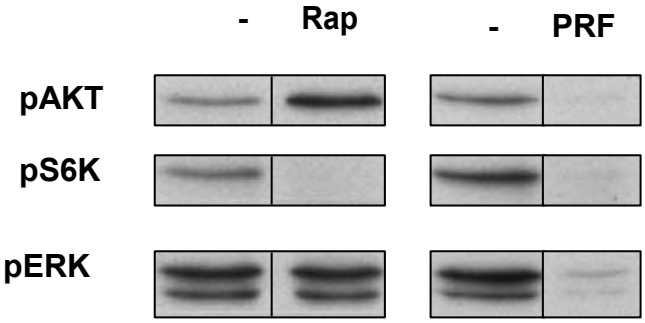
Investigators at the Netherlands Cancer Institute in Amsterdam obtained similar results using the epithelial cell line A431 and HeLa. [6] Three alkylphosphocholines, including both miltefosine and perifosine, were evaluated, and all appeared to inhibit AKT in a dose-dependent fashion. The alkylphosphocholines also blocked stimulation of AKT activity by insulin.

These effects on AKT were accomplished with perifosine levels that inhibit the growth of tumor cells *in vitro* and that can be achieved in the clinic.

Preclinical studies undertaken mainly by Dr. Holland's lab at MSKCC have also demonstrated that perifosine is a potent inhibitor of AKT signaling in glia *in vitro*. In addition, perifosine (PRF) inhibits the RAS cascade (reduced pERK) in glia, an effect not achieved by the mTOR inhibitor rapamycin

(Rap). The dual inhibition of AKT and RAS signaling by PRF is a major theoretical advantage over agents that inhibit only one but not both cascades, especially because these cascades are activated in ~70% and ~100% of GBMs, respectively. Furthermore, forced activation of both cascades in mice is sufficient to induce GBMs [8]. Therefore, combined inhibition of both cascades with one agent such as PRF may offer significant therapeutic advantage over mTOR inhibitors and over agents that inhibit only AKT or RAS.

Figure 2: PRF inhibits both AKT and RAS (exhibited by diminished pERK); Rap inhibits only mTOR (exhibited by diminished pS6K) in cultured glia.



The activity of perifosine has been evaluated in numerous other human and murine cell lines. Cell lines demonstrating the greatest sensitivity to perifosine included KB (larynx), LNCaP (prostate), MAI-PaCa-2 (pancreas), DLD-1 (colon), and SK-HEP-1 (liver) (IC50 1.0 – 4.9 µg/mL) (Perifosine Investigator's Brochure 2003). In a soft agar tumor stem cell assay, the human KB (squamous) and murine L1210 (leukemia) cell lines were the most sensitive. In the methylene blue exclusion assay, the five most sensitive lines were: KB (squamous mouth), LU 65A (lung), LNCaP (prostate), PC-1 (lung) and Hep-2 (larynx) with IC50 values of 0.8 – 3.4 µg/mL. In the SRB/metabolic capacity assay, KM12 (colon), PC3 (prostate), M14 (melanoma), HOP-92 (lung) and SF295 (CNS) cancer cell lines were the most sensitive with IC50 values of 0.2 – 3.1 µg/mL. The majority of cell lines (in all assays) were more sensitive to perifosine than to miltefosine. Compared with leukemic cells, normal mouse bone marrow cells were shown to be relatively insensitive to perifosine *in vitro.*

3.4.2 Animal studies

The *in vivo* activity of perifosine has been evaluated via oral dosing in various schedules in several transplanted tumors, as well as in the dimethylbenzanthracene (DMBA) induced mammary tumor model of the rat.

Two tumors resistant to conventional cytotoxics but sensitive to perifosine were the KB tumor (squamous cell) and AsPC-1 (human pancreatic carcinoma). *In vivo*, single oral doses of 511 mg/kg completely inhibited the growth of subcutaneously transplanted KB squamous cell tumors. When smaller doses (203 or 300 mg/kg) were administered twice at 7 day intervals, complete remissions lasting >63 days were achieved. Other xenografts in nude mice that responded well to perifosine included the Hep-2 laryngeal, R3327 rat prostate, SAS tongue, SC115 mouse breast and HCT-8 colon tumor. Perifosine was extremely active in the Sprague-Dawley rat model of dimethylbenzanthracene (DMBA) induced mammary tumors. Daily oral treatment using 21.5 mg/kg for 5 weeks led to complete regressions of tumors. Notably, complete regressions over the entire study period were also achieved by combining a high initial dose of 68.1 mg/kg followed by lower daily doses of 2.15 mg/kg over 20 days, whereas neither the loading dose nor low maintenance doses alone exhibited significant ant-tumor activity. Even large (4-8 grams), established DMBA induced mammary tumors responded to daily doses of 14.7 to 68.1 mg/kg over 28 days, with a persistent effect for more than 20 days after cessation of treatment.

Preclinical studies of perifosine given as a single oral dose (10 mg/kg) demonstrated near complete absorption, with an absolute bioavailability of 81% and 95% in male and female rats (Perifosine Investigator's Brochure, 2003). For doses ranging from 1 to 50 mg/kg, maximum plasma concentration (C_{max}) values ranged from 0.34 to 10.5 μg/mL. Time to achieve C_{max} was reached at a median of 16 to 32 hours following administration of perifosine. It should be noted however that while there was an approximately linear increase in C_{max} from 1 to 10 mg/kg, a 5-fold increase in dose from 10 to 50 mg/kg led only to a 3-fold increase in C_{max}. The volume of distribution (Vd) was twice the physical body volume, and the terminal half-life ($t_{1/2}$) was 120.5 – 171.4 hours.

A study of [^{14}C] excretion (urine, feces) in the rat after an oral dose of [^{14}C] perifosine at 10 and 50 mg/kg revealed the following proportions of renal and fecal excretion:

Table 1

Dose (mg/kg)	Excretion in Urine	Excretion in Feces
10	<24 hr 1.0%, 360 hr 20.4 %	<24 hr 24.6 %, 360 hr 42.9%
50	<24 hr 1.2% 48 hr 2.4% 72 hr 3.6%	<24 hr 22%, 48 hr 48.5%, 72 hr 52.6 %

In vitro binding of perifosine to human serum albumin or α1-acid glycoprotein ranged from 92 to 98% (Perifosine Investigator's Brochure, 2003). No concentration dependence of protein binding was observed, suggesting a high binding capacity of the plasma proteins for perifosine.

3.4.2.1 Activity in mouse gliomas

Perifosine has been shown to cross the blood/brain barrier in the mouse as the Holland lab also demonstrated that PRF also causes reductions in mouse glioma cell proliferation ($p<0.005$), as measured by MIB-1 (Ki67) labeling commonly used in human gliomas as shown in figure 4.

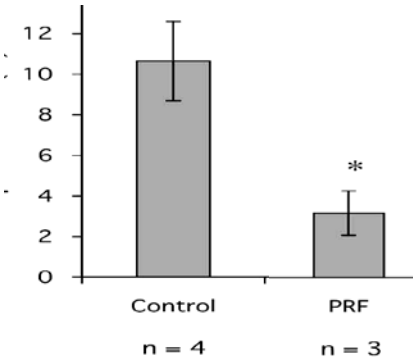


Fig 4: Ki-67$^+$ cells (%)=MIB1

3.4.3 Preclinical Toxicity

In a subchronic toxicity study in rats, dose dependent toxicities were observed in the kidneys, gastrointestinal tract, skin, mammary glands, pituitary, hematopoietic tissue, spleen, ovaries, male genital tract, and eyes (Perifosine Investigator's Brochure, 2003). Effects on the hematopoietic tissue were characterized by an increase in cellularity for the bone marrow and an increased extramedullary hematopoiesis. Histopathologic changes seen in other tissues included evidence of chronic nephropathy, atrophy of hair follicles, atrophy of mammary glands, reduction of follicular development in the ovaries, degeneration of the germinal epithelium of the testes,

atrophy/inactivation of prostate and seminal vesicles, secondary hypertrophy of the Leydig cells in the testes, and hypertrophy/hyperplasia of mucosal epithelium cells in stomach and small intestine. All toxicities, except those in the male genital tract and eyes, were reversible within 13 weeks. Most significant and not clearly reversible were ophthalmologic lesions, specifically, retinal degeneration and cataract formation. This toxicity was seen in rat but not in dog toxicity studies. Clinical chemistry revealed reversible increases in CK, BUN, SGOT, SGPT and reversible decrease of red blood cell parameters, total cholesterol, triglycerides, inorganic phosphorus and albumin and total protein.

In dogs, decreased food consumption, anorexia, diarrhea and vomiting were noted. Clinical chemistry revealed reduced glucose levels in the group receiving the highest dose. All changes were reversible during a 6-week recovery period. Histopathologically, minimal to mild degeneration of proximal tubular cells of the kidneys were found in male animals.

The no adverse effect level (NOAEL) was estimated to be < 2.15 mg/kg (12.9 mg/m^2) in rats and 2.15 mg/kg (43 mg/m^2) in dogs.

3.5 *Perifosine Clinical Data*

Several Phase I and II studies of perifosine in humans have been completed and others are on-going in which patients experienced tumor regressions and/or disease stabilization. The safety profile of perifosine is distinctly different from that of most cytotoxic agents. It causes dose-related nausea, vomiting, diarrhea and fatigue. The gastrointestinal symptoms are thought to arise primarily because of direct interactions between perifosine and the gut. Responding patients have been treated with months to more than a year with almost no symptoms at all. It does not cause myelosuppression, alopecia, or rash. In phase I studies it has been administered using a variety of schedules including daily, weekly, or daily after an induction dose. Responses have been seen with both the daily and weekly regimens. The half-life of the drug exceeds 100 hours.

In preclinical models, higher doses have been shown to be more effective than lower doses. The clinical responses observed thus far have been at lower doses in patients who have experienced no toxicity. Therefore, MTD may not be required and a lower dose may actually be superior clinically.

3.5.1 Clinical Results: European Phase I Trials

Asta Medica/Zentaris sponsored three European phase I trials of perifosine evaluating weekly and daily dosing, as well as an enteric-coated formulation.

Study D-21266-3040

This was a phase I study of escalating doses of perifosine given on a weekly schedule. Thirty-six patients were treated in sequential cohorts at dose levels of 100, 200, 350, 450, 600 and 800 mg/week. At 350 mg weekly, grade 3 vomiting occurred in the first two patients. These patients responded to antiemetic prophylaxis with tropisetron, alizaprid, and dexamethasone, and all subsequent patients received antiemetic prophylaxis. Among 7 patients treated at the maximum dose of 800 mg/wk all taken together at one time, grade 2 nausea and vomiting of residual perifosine tablets and grade 4 diarrhea occurred. In addition to nausea, vomiting and diarrhea the following grade 1/2 events were reported to be likely caused by the drug: gastritis, erythematous rash, abdominal pain, fatigue, bradycardia, increased sweating and arthralgia. Preliminary data from analyzed plasma samples of patients receiving perifosine in the dose range of 100 to 600 mg indicated a dose-linearity of C_{max} and of the area under the concentration time curve (AUC) in this dose range. However, at 800 mg/week, the dose-AUC and C_{max} proportionality was reduced. Cmax and $t_{1/2}$ values ranged from 8 – 25 hours and 96 – 225 hours, respectively (Perifosine Investigator's Brochure, 2003). After repeated dosing a slight accumulation of perifosine was seen, which is in accordance with the relatively prolonged terminal $t_{1/2}$ of the agent. Perifosine was not detectable in the patients' urine.

Gastrointestinal toxicities for this protocol are summarized in the following table:

Table 2
Number of patients exhibiting nausea, vomiting, and diarrhea during the once-weekly oral treatment with perifosine (data from study D-21266-3040)

Dose Level [mg/wk]	No. of Patients Treated	Total no. of doses (min-max)	Maximum intensity (CTC grade) during any treatment course													
			Nausea				Vomiting					Diarrhea				
			0	I	II	III	0	I	II	III	IV	0	I	II	III	IV
100	6	40 (2 - 15)	2	1	1	2	3	1	1	1	-	4	1	1	-	-
200	6	51 (5 - 16)	2	3	1	-	4	1	1	-	-	3	3	-	-	-
350	6	37 (4 - 8)	3	1	2	-	4	1	-	1	-	4	1	1	-	-
450	3	28 (5 - 16)	-	1	2	-	1	2	-	-	-	2	-	1	-	-
600	8	39 (2 - 14)	2	3	2	1	2	4	2	-	-	-	4	3	-	1
800	7	25 (2-6)	2	2	3	-	3	2	2	-	-	3	2	1	-	1

Efficacy was not a primary end point of this phase I study; however, indicator lesions were evaluated every 8 weeks, if possible. Patient diagnoses included NSCLC (7 patients), melanoma (4), colorectal carcinoma (4), head and neck cancer (5), sarcoma (4), mesothelioma (2), hepatocellular carcinoma (1), esophageal carcinoma (2), SCLC (1), corpus carcinoma (1), bladder (1), breast (1), renal (1) and CUP syndrome (2). No change for at least 8 weeks in the size of indicator lesions was found in 6/36 patients. All of these patients were stable for 15-16 week. The number of patients with stable disease, the total number with each tumor type along with the dose administered to the patients with stable disease were:
salivary gland 1/1 pt., 100 mg/wk
mesothelioma 2/2 pts., 100 and 600 mg/wk
hepatocellular carcinoma 1/1 pts., 200 mg/wk
NSCLC 2/7 pts., 200 and 450 mg/wk

D-21266-3079
In the second phase I study, 22 patients received perifosine at escalating doses of 50-350 mg daily for 21 days in every 28 day cycle. Fatigue (43%), nausea (52%), vomiting (38%) and diarrhea (43%) were the most frequent toxicities experienced by patients on this study. The maximum tolerated dose on this study was 200 mg/day. Three of six patients treated at 250 mg/day and the one patient treated at 350 mg/day had intolerable fatigue and/or gastro-intestinal toxicity. No patients treated at 150 mg/day experienced grade 3 or 4 toxicity. [18]

The gastrointestinal toxicities experienced in this protocol are summarized in the following table:

Table 3
Number of patients with nausea, vomiting, diarrhea during daily oral treatment with perifosine (data from study D-21266-3079)

Dose level [mg/day]	No. of Patients Treated	Total no. of doses (min-max)	Maximum intensity (CTC grade) during any treatment course		
			Nausea	Vomiting	Diarrhea
50	4	7 (1-2)	[redacted]		
100	3	5 (1-2)			
150	3	6 (2)			
200	5	12 (1-4)			
250	6	11 (1-5)			
350	1	1			

Efficacy is not a primary end point of this phase I study; however, indicator lesions were evaluated every 8 weeks, if possible. Patient diagnoses included pancreatic carcinoma (1 patient), ocular melanoma (1), colorectal carcinoma (11), Ovarian carcinoma (1), bladder (1), hepatocellular carcinoma (1), esophageal carcinoma (1), and adenocarcinoma of unknown primary (5). No change in the size of indicator lesions was found in 2/22 patients two months after start of treatment. These patients were treated for the following tumor indications:
hepatocellular carcinoma (1/1 pts., 200 mg/day)
melanoma (1/4 pts., 250 mg/day)

D-21266-3087

An enteric-coated formulation was evaluated on a weekly study in the trial. Thirteen patients were recruited. The enteric coating did not improve the tolerability of the oral administration of perifosine and reduced its bioavailability.

The gastrointestinal toxicities experienced by the patients are summarized in the following table:

Table 4
Number of patients with nausea, vomiting, diarrhea during once weekly oral treatment with enteric-coated perifosine (data from study D-21266-3087)

Dose level [mg/wk]	No. of patients treated	Total no. of doses (min - max)	Maximum intensity (CTC grade) during any treatment course													
			Nausea				Vomiting					Diarrhea				
			0	I	II	III	0	I	II	III	IV	0	I	II	III	IV
200	4	17 (1 - 8)	2	-	2	-	2	1	1	-	-	2	2	-	-	-
350	6	63 (5 – 16)	-	4	1	1	-	3	3	-	-	2	1	2	1	-
450	3	12 (2 - 8)	1	1	1	-	1	2	-	-	-	1	2	-	-	-

Patients with the following diagnoses were recruited: lung (2 patients), breast (2), colorectal carcinoma (1), sarcoma (2), renal (2), cervical carcinoma (1), esophageal carcinoma (1), ovarian (1) and pancreas (1). One patient with chondrosarcoma treated at 350 mg/weekly achieved a partial response. No change in the size of indicator lesions was found in 2/13 patients (both patients had breast carcinomas) two months after start of treatment. (Perifosine investigators Brochure 2003) The response in the chondrosarcoma patient was ongoing at 6 months.

3.5.2 Clinical Results: US Phase I Trials

The Division of Cancer Treatment and Diagnosis, National Cancer Institute sponsored two phase I trials of perifosine evaluating a loading dose followed by daily maintenance dose schedule. A loading dose/daily maintenance schedule was proposed due to improved efficacy in several preclinical cancer models with this schedule and the fact that daily doses alone required some days (and possible more than a week) to reach steady state plasma levels. A loading dose could potentially achieve active anti-tumor serum concentrations followed by tolerable daily maintenance dosing. Since both preclinical studies and the earlier phase I studies had suggested that increases in plasma levels were not linear after a threshold that might be about 400 mg, the loading dose was fractionated and administered every 6 hours to improve bioavailability and decrease C_{max}. It was also anticipated that by lowering C_{max} toxicities such as emesis might be decreased. In both studies, patients received antiemetic prophylaxis with dexamethasone and 5HT3 antagonist before initial loading dose. Similar to the results from the Asta Medica-sponsored studies, the most frequently observed toxicities in NCI sponsored phase I studies were gastrointestinal (nausea, vomiting, diarrhea) and fatigue. Chronic nausea among patients receiving perifosine appears to resolve approximately 48 hours following discontinuation of therapy. In contrast, fatigue may persist for weeks after therapy has ended.

Phase I evaluation of the "Intermittent Schedule" at the NCI

The first trial examined a loading dose on day 1 followed by a maintenance dose schedule for 20 days in patients with solid tumors repeated every 28 days. (Because of the 7 day intervals without drug, this has been referred to as the "intermittent schedule.") In an attempt to minimize nausea, doses were administered with meals or, with maintenance doses, at bedtime. In addition, prior to the initial loading dose, patients were given granisetron, metoclopramide, diphenhydramine, and dexamethasone as antiemetic prophylaxis. Thirty-one patients were treated on this study. Gastrointestinal toxicities were dose limiting. Dose limiting nausea and vomiting despite antiemetic prophylaxis occurred with loading doses of 1200-1500 mg. Grade 3 arthralgias and arthritis in the form of gout or pseudo-gout were seen in two patients taking perifosine 200 mg/day. One patient with a history of gout had reappearance of gout and one patient without a prior history had an episode of pseudogout. One patient with a history of hyperuricemia, had grade 2 episodes of gout. Persistent grade 2 nausea and vomiting despite antiemetics and fatigue occurred with a maintenance dose of 200 mg/day. The maximum tolerated dose (MTD) and recommended phase II dose (RP2D) were established as: Cycle 1: 900/150 mg loading/maintenance dose and for

subsequent cycles: 300/150 mg loading/maintenance dose ([19]). The day 1 loading dose was divided into 2 equal doses of 450 mg taken with food, 6 hours apart on day 1. Among 11 patients treated at the MTD/RP2D, no patients experienced grade 3-4 dose limiting events during the loading dose or maintenance dose periods in the first cycle. Only one other grade 3 toxicity, infection without neutropenia, felt to be probably due to the drug was recorded at dose level III. Grade 1-2 fatigue occurred in 8/11 patients and grade 2 gastrointestinal toxicity was intermittent and tolerable.

Gastrointestinal toxicities experienced on this trial are summarized in the following table:

Table 5
NCI Trial I - A Phase I Trial of Oral Perifosine with Different Loading/ Maintenance Doses using the "Intermittent Schedule" in Patients with Refractory Neoplasms

Dose Level [mg/wk]	Dosage - Cycle 1 (Loading / Maintenance)	Patients Treated	Maximum intensity (CTC grade) during any treatment course											
			Nausea				Vomiting				Diarrhea			
			0	I	II	III	0	I	II	III	0	I	II	III
I	300 mg/50 mg	3		2				1				1	1	
II	600 mg/100 mg	2		2				1	1			1	1	
IIA	600 mg/200 mg	1		1				1				1		
III	900 mg/150 mg	11		4	6			4	4			4	2	2
IV	1200 mg/200 mg	11		5	5			4	4			6	2	2
V	1500 mg/250 mg	3			2	1			2	1			2	1

Patient diagnoses included head/neck (1 patient), esophagus (1), colon (6), pancreas (2), non-small cell lung (1), urethra (1), melanoma (2), sarcoma (3), breast (1), prostate (10) and renal cell (2). No clinical responses have been observed; however, four patients with stable disease have been reported (duration 167-750 days, 3 patients with hormone refractory prostate carcinoma and one with melanoma).

Phase I evaluation of the "Continuous Schedule" at the University of Wisconsin

The second NCI sponsored phase I trial evaluated a loading dose followed by a continuous maintenance dose schedule in 42 patients with advanced cancer. The loading dose was only given in course one, and maintenance dosing continued without a scheduled break (hence the name "continuous schedule"). Cohorts of patients received loading/maintenance doses ranging from 400/50 – 1200/150 mg. In this study, loading doses were split into 4-8 equal doses

given at 6 hour intervals. Patients received dexamethasone and dolasetron mesylate prior to each dose during the loading period with lorazepam and prochlorperazine prn. Reported severe toxicities for this trial include anorexia, fatigue, dehydration, nausea/vomiting, constipation, diarrhea, elevated liver function tests, and decreased hemoglobin. The MTD and recommended phase II dose for this schedule was 900 mg loading dose (divided into 6 equal doses of 150 mg taken with food q 6 hourly) followed by 100 mg daily maintenance. Among 14 patients treated at the MTD, there were 4 grade 3 events (fatigue in 2 patients, nausea in 1 and vomiting in 1 patient). Subsequently a review of the pharmacokinetics for this study revealed that there was only a minimal increase in plasma concentration between dose level 3 and dose level 4. For this reason the actual doses used in subsequent phase II studies were a loading dose of 600 mg (150 x 4) and a maintenance dose of 100 mg. Among the 12 patients treated at dose level 2 there were 3 patients who experienced grade 3 fatigue and 1 patient with grade 3 nausea. There were no additional grade 3 toxicities recorded as probably due to the drug.

The gastrointestinal toxicities experienced on this protocol are summarized in the following table:

Table 6
NCI Trial II - A Phase I Trial of Perifosine with Different Loading/Maintenance Doses using the "Continuous Schedule" in Patients with Advanced Cancer

Dose Level	Dosage - Cycle 1 (Loading / Maintenance)	Patients Treated	Maximum intensity (CTC grade) during any treatment course											
			Nausea				Vomiting				Diarrhea			
			0	I	II	III	0	I	II	III	0	I	II	III
I	400 mg/50 mg	3		3								3		
II	600 mg/50 mg	7		3	3			3	2			3	1	1
III	600 mg/100 mg	12		6	2	1		3	2			6	3	
IV	900 mg/100 mg	14		7	3	1		3	2	1		3	3	
V	900 mg/150 mg	6		4	1			4	0			2	3	

Patient diagnoses included pancreatic carcinoma (1 patient), sarcoma (5), colorectal carcinoma (19), ovarian carcinoma (2), renal cell (6), lung cancer (4), esophageal carcinoma (1), breast (1), cervical (1), glioblastoma (1) and tonsilar (1). One partial response in a patient with uterine sarcoma was reported. The responder received 18 cycles of therapy on study and has since been followed for 17 months without significant progression. Seven patients

had stable disease lasting greater than 2 cycles (renal cell carcinoma – 2; sarcoma – 2; colon carcinoma – 2; ovarian carcinoma – 1). [20]

In the phase II program initiated by the National Cancer Institute trials were conducted with both the intermittent and continuous regimens. Preliminary analysis showed that there was greater toxicity associated with the intermittent than the continuous regimen.

Table 7
Toxicity seen in phase II trials conducted by the NCI using either the 'Intermittent' or 'Continuous' Regimens. (See definitions above)

		Regimen	
		Intermittent	Continuous
Number of patients with toxicity data available		87	57
Frequency of:		Percent	Percent
Nausea:	Grade 2	36	9
	Grade 3	8	2
Diarrhea:	Grade 2	28	4
	Grade 3	11	2
Vomiting:	Grade 2	45	11
	Grade 3	5	2

One additional response has been seen in a patient with sarcoma. This occurred in a patient with extra-skeletal myxoid sarcoma who received 10 cycles of therapy on study. [21]

Perifosine 201

AOI Pharmaceuticals is currently undertaking a phase I/II trial of perifosine in non-small cell lung cancer. In this study patients receive weekly doses in which the total dose is divided into 300 mg doses delivered at least 4 hours apart. Dosing began at 900 mg (300 mg x 3) and was escalated to 1800 mg (300 mg x 6). A dose limiting toxicity was defined as a grade 3 or 4 gastrointestinal toxicity or nausea and/or vomiting lasting more than 48 hours. Two patients at 1800 mg experienced grade 3 diarrhea, and 1500 mg was the maximum tolerated dose. The GI toxicities encountered in the initial 3 cohorts of patients are described in the following table. The table reflects the first week of therapy only.

Table 8
AOI Trial 201 - A Phase I Trial of Perifosine Administered Weekly in Patients with Metastatic Lung Cancer

Dose Level	Dosage - Cycle 1 (Loading / Maintenance)	Patients Treated	Maximum intensity (CTC grade) during any treatment course											
			Nausea				Vomiting				Diarrhea			
			0	I	II	III	0	I	II	III	0	I	II	III
I	300 mg x 3 weekly	5	1	3	1		4	1			2	3		
II	300 mg x 4 weekly	3	2		1		3				1	1	1	
III	300 mg x 5 weekly	5		4	1		1	4			0	3	1	1
IV	300 mg x 6 weekly	4	1	2	1		1	3			0	2		2

3.5.3 Pharmacokinetics

The pharmacokinetic data from each of the phase I studies is summarized in the table below.

Table 9

Study	Dose Range	Parameter	Median Plasma Values (μM)
Study D-21266-3040	100-800 mg/week	Peak Concentration	1.59 – 7.97
		Concentration day 7	0.34 – 2.05
Study D-21266-3079	50 – 350 mg/day	Peak Concentration	3.89 – 14.58
		Concentration Day 22	3.49 – 12.24
Study D-21266-3087	200- 450 mg/week	Peak Concentration	1.51 – 2.42
	(enteric coated)	Steady State Trough	0.54 – 2.00
Intermittent	300/50 – 1500/200	Concentration Day 22	6.87 – 22.31
Continuous	400/50 – 900/150	Concentration Day 2	9.29 - 15.14
		Steady State Concentration	7.23 – 14.36

The phase I pharmacokinetic studies showed that plasma concentrations similar to the IC_{50} values obtained for many cell lines in *in-vitro* studies could be obtained using each of the regimens with the exception of the enteric coated tablet. When doses above 300 mg were administered at a single time, the pharmacokinetics were not linear. Two patients on the phase I studies responded: one patient on the study that utilized the enteric coated tablets (D-21266-3087) had serum values ranging from 2.78 – 6.29 μM and one patient on the continuous regimen had steady state levels of 12.78 ± 2.23 μM.

3.5.4 Results of Phase II conducted by NCI

The results of three of the nine NCI phase II studies have been presented at national and international meetings. None has yet been published in a full report.

A multicenter Phase II Consortium organized by the Mayo Clinic and lead by Howard Bailey of the University of Wisconsin evaluated the continuous regimen in 23 patients with soft tissue sarcomas. The results were reported at the EORTC-NCI-AACR meeting on Molecular Targets and Cancer Therapeutics. The median age of the patients was 53 (range 24-77). Eight were male and 15 female. Thirteen had an ECOG performance status of 0 and 10 had a PS=1. Twenty patients had received prior chemotherapy, and 5 patients (22%) had liver metastases. Grade 3 toxicities definitely or probably related to the drug included fatigue in 2 patients and diarrhea, anorexia and/or dehydration, each in 1 patient. One patient had a partial response and five patients were stable for 84-229 days. The responder was a 58-year-old man with an extra-skeletal myxoid chondrosarcoma. The primary lesion on the thigh had been treated 8 years previously, and metastases to the lung and the lymph nodes had been identified 22 months prior to starting perifosine. The patient had previously been treated with surgery, radiotherapy and chemotherapy consisting of gemcitabine and cisplatin. He had not responded to the chemotherapy. The patient received 10 months of perifosine therapy (600 mg loading dose and 100 mg/day continuously). He had grade 1 nausea and diarrhea on cycle 1 only and no toxicities of any type after that point. The primary endpoint of the study was 6 month progression-free survival. In addition to the responder, two other patients (one with a myxoid sarcoma and one with a desmoid tumor) had disease stabilization for more than six months.

Nineteen patients with head and neck cancers were enrolled in a phase II trial conducted by a consortium of hospitals in Chicago, and results from this study were presented at the Third Chicago International Symposium on Malignancies of the Chest and Head and Neck. The patients had a median age 59 (range 46-81; 15 were male and 4 female. Five had an ECOG performance status of 0 and the remainder had a status of 1. Thirteen of these patients had received prior chemotherapy and 12 had prior radiotherapy. The continuous regimen was used with a starting dose of 600 mg in 4 divided doses followed by a daily dose of 100mg. The investigators reported that administration by gastrostomy tube was feasible. Grade 3 toxicities described in their presentation included pain in one patient and hypercalcemia in another. Seventeen patients were evaluable for response. There were no objective responses but one patient had stable disease for 4 cycles.

The only phase II trial of breast cancer enrolled 18 (17 evaluable) patients. This trial was presented at the 2005 San Antonio Breast Cancer Symposium before the study was officially closed. In this trial the intermittent regimen was used. The patients' median age was 52 (range 28-69). There was 1 male patient. The ECOG performance status was 0 for 10, 1 for 6, and 2 for 1 patient. Eight patients had tumors that were ER/PR positive, but none had HER2/*neu* positive tumors. This was a heavily pre-treated population. Sixteen patients had received prior systemic therapy including neoadjuvant or adjuvant chemotherapy in 11, a single chemotherapy regimen for metastatic disease in 5 patients, and two prior chemotherapy regimens for metastases in 9. Fifteen patients had previously received an anthracycline and 11 a prior taxane. Drug related toxicities included Grade 3 diarrhea (2 patients), vomiting (2 patients), nausea (1 patient) and fatigue (1 patient). One patient had a mixed response after 2 cycles and 2 patients were stable for 4 months. The mixed response occurred in a patient with extensive disease involving multiple organs. At the end of 2 cycles some lesions had shrunk while others had remained stable or increased. Although this patient had experienced no major toxicities, she refused further treatment for unspecified reasons.

3.5.5 Description of the responders in previous phase I/II trials

Three patients have had clearly documented partial responses on earlier perifosine trials.

Patient # 1 (D 21266-3079) was a 66 year old with a chondrosarcoma with a primary in the Xiphoid. The patient had local recurrences treated surgically at 4 and 10 months. At 10 months distant metastases were also documented. Previous chemotherapy included 2 cycles of Adriamycin, cisplatin and ifosfamide. The patient received 24 weeks of enteric-coated perifosine at a dose of 350 mg per week and was then taken off study due to non-compliance. The plasma perifosine levels ranged from 2.78 – 6.29 μM. Only minimal toxicity was observed until week 22 when the patient had grade 3 nausea and vomiting along with grade 2 fatigue from weeks 20-24. The sum of products of lesions in the lung and sternum decreased from 28.56 at on-study to 9.39 at the conclusion of treatment.

Patient # 2 (Phase I trial of continuous regimen) was a 50 year old with a leiomyosarcoma with a primary in the uterus. She developed distant metastases at 4 years with lesions in the scalp, lung, retroperitoneum and bone. She had previously received two cycles of adriamycin and dacarbazine as well as strontium for bone metastases. The patient received a loading dose

of 600 mg and then continuous daily perifosine at 50 mg/day for 504 days. The patient was taken off study at that time due to patient refusal for further therapy. The patient experienced absolutely no toxicity while on study. The patient had disease in both lungs as well as an infrasplenic mass. The measurements on the patient's disease were scored by 3 independent observers. At the time the patient went off study the average decrease in measurements was scored as 62% (range 53 – 70%). The patient remains in partial remission after 3 years.

Patient # 3 (Mayo Clinic phase II trial) was a 58 year old with an extra-skeletal myxoid chondrosarcoma with a primary on the thigh. The patient's disease was metastatic to the lung and the lymph nodes. The patient was previously treated with surgery, radiotherapy and chemotherapy consisting of gemcitabine and cisplatin. The patient was treated with 10 cycles of therapy (600 mg loading dose and 100 mg/day continuously) and had grade 1 nausea and diarrhea on cycle 1 only

3.6 *Potential impact on metabolism by hepatic enzyme inducing antiepileptic drugs (EIAEDs)*

There is increasing evidence that brain tumor patients receiving enzyme-inducing anti-epileptic drugs (EIAEDs) have markedly altered pharmacokinetics, resulting in accelerated drug metabolism. This may result in decreased levels of certain chemotherapeutic agents when administered at conventional doses. Failure to achieve adequate plasma levels of such agents may account for the lack of efficacy in past brain tumor trials.

Perifosine is a potential substrate for the cytochrome P450 system, and the escalating concentrations of perifosine were tested for inhibition of the liver microsomal cytochrome P450 system in vitro (table 10). Enzyme activities associated with CYPlA2 (7-ethoxyresorufin 0-deethylation), CYP2A6 (coumarin 7-hydroxylation), CYP2B6 (S-mephenytoin N-demethylation), CYP2C9 (tolbutamide methyl-hydroxylation), CYP2C19 (S-mephenytoin 4'-hydroxylation), CYP2D6 (dextromethorphan 0-demethylation), CYP2E1 (chlorzoxazone 6-hydroxylation) and CYP3A415 (testosterone 6P-hydroxylation) were determined using enzyme-specific probe compounds incubated with pooled human liver microsomal samples.

In the presence of perifosine, a moderate inhibitory effect was observed on CYP2A6 activity (50%), and a slight inhibitory effect on CYP3A4 activity (29%), in both cases only at the highest concentration (100 yM). No inhibitory effect was observed on CYP2C19 activity by perifosine at any of the concentrations tested.

Enzyme activities associated with CYPIA2 (7-ethoxyresorufin 0-deethylation), CYP2B6 (S-mephenytoin Ndemethylation), CYP2C9 (tolbutamide methyl-hydroxylation), CYP2D6 (dextromethorphan 0-demethylation), and CYPZEI (chlorzoxazone 6-hydroxylation) were not inhibited by perifosine at any of the concentrations (0.25 - 100 μM).

Perifosine	Percentage of Activity Remaining							
Conc (μM)	CYP1A2	CYP2A6	CYP2B6	CYP2C9	CYP2C19	CYP2D6	CYP2E1	CYP3A4/5
0.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
0.25	96.4	97.7	100.1	101.3	98.4	96.0	99.8	102.2
1	101.2	101.2	100.7	96.6	96.8	94.1	100.4	101.3
5	100.8	90.8	100.1	95.7	102.0	98.5	95.8	103.0
10	98.8	94.7	98.0	95.3	97.6	95.9	95.0	97.0
25	99.9	88.9	100.8	96.0	103.1	98.5	96.5	94.5
50	97.8	88.7	101.0	95.8	113.9	94.3	89.1	98.4
100	113.6	46.1	99.9	98.0	106.4	88.1	86.0	71.3

Table 10: The Effect of Perifosine on CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 AND CYP3SA4/5 Activities in Pooled Human Liver Microsomes

These data suggest that patients taking EIAEDs may have increased drug metabolism and a higher MTD than patients who are not taking EIAEDs. Therefore, to avoid the possibility of effects of EIAEDs on the metabolism of perifosine, and vice-versa, only patients not taking EIAEDs will be eligible for this trial as has become common in trials of novel agents for malignant glioma. (See Appendix 20.2 for a list of EIAED drugs).

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

Only patients not taking EIAEDs will be considered for this study. If patients were previously on EIAEDs that have been discontinued, patients must have been off the agent for at least 2 weeks prior to registration. For patients who need to start an AED or the AED needs to be changed, it is strongly recommended that all efforts should be made to use a non-EIAED. If another non-EIAED cannot be used, the PI or co-PI should be notified immediately. Questions regarding these requirements should be discussed with PI or co-PI.

Surgery

In addition, if cytoreductive surgery is recommended as part of the standard of care for tumor recurrence, all patients will be considered for the "surgical

arm" of the trial. In this case, patients will receive perifosine for 5-10 days before surgery during which tumor will be aliquoted both for diagnostic purposes and for molecular and pharmacokinetic analyses. Ideally, tissue will be available from a prior surgical resection for intra-patient comparison. Following recovery from surgery, patients will restart perifosine until either tumor progression (as determined by brain imaging with CT or MRI every 2 months) or toxicity. All patients will be followed for overall survival after discontinuing perifosine.
Biologic impact will also be determined by periodic FDG-PET imaging (see below).

4.1.1 Patients will also be stratified as follows:

Histology at Registration:

GBM/Gliosarcoma (GBM/GS)
Anaplastic Astrocytoma (AA)
Anaplastic Oligodendroglioma (AO)
Anaplastic Mixed Glioma (AMG)

Pre-operative Candidate: Yes or No

Measurable/Evaluable disease: Yes or No

4.2 Intervention

Following a diagnosis of tumor recurrence or progression, all patients will receive perifosine monotherapy until toxicity, progression, or death. Brain imaging (MRI/CT) will be performed at baseline and every 2 months (standard of care). FDG-PET imaging will be performed at baseline, after 1-2 weeks of therapy, and every 4 months to assist with interpretation of tumor response. MR Spectroscopy and MR Perfusion may also be performed with every MRI to assist with interpretation of tumor response. Patients on the surgical arm trial will resume perifosine after recovering from surgery and continue until toxicity, progression, or death.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

Perifosine (NSC # 639966; IND # 69,383)

Chemical Name: 1,1-dimethyl-4-[[(octadecyloxy)hydroxyphosphinyl]oxy]-piperidinium inner salt

Other Names:	Octadecylphosphopiperidine (OPP), D-21266, KRX-0401
Molecular Formula:	C25H52NO4P
M.W.:	461.66 g/mol
CAS No.:	157716-52-4
How Supplied:	Perifosine is supplied as a film-coated tablet containing 50 mg of active ingredient.
Storage:	Store closed containers at room temperature (20-25 ° C). Perifosine is hygroscopic, so containers must be kept closed and dry. Perifosine tablets must be dispensed in the original container.
Stability:	Stability testing program ongoing. Perifosine has a demonstrated shelf stability of at least 3 years.
Route of Administration:	Oral with meals unless otherwise specified.
Potential Drug Interactions:	None reported.
Availability:	Perifosine is an investigational agent supplied to investigators by AOI Pharmaceuticals.
Agent Accountability:	The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of all agents received from AOI Pharmaceuticals using the Drug Accountability Record Form.

6.1 CRITERIA FOR SUBJECT ELIGIBILITY

6.2 Inclusion Criteria

- Patients must have shown unequivocal evidence for tumor progression by MRI or CT scan.

- Patients must be on a stable or decreasing dose of corticosteroids for a minimum of 5 days before the baseline MRI and FDG-PET scans.

- Patients must have failed prior radiation therapy.

- Patients with prior therapy that included interstitial brachytherapy or stereotactic radiosurgery (including gamma-knife or cyber-knife) must have confirmation of true progressive disease rather than radiation necrosis based upon either PET or Thallium scanning, and/or MR spectroscopy, and/or MR Perfusion, and/or surgical documentation of disease.

- All patients must sign an informed consent indicating that they are aware of the investigational nature of this study. Patients must have signed an authorization for the release of their protected health information.

- Age > 18 years old, and with a life expectancy > 8 weeks.

- Karnofsky Performance Status ≥ 50%

- Patients must have recovered from all acute toxicities from prior therapies. At least 28 days must have elapsed since prior radiation. At least 28 days must have elapsed since prior therapy directed at VEGF/VEGFR such as bevacizumab (Avastin), VEGF-Trap, or AZD2171 In addition, the baseline MRI (with MR Perfusion if possible) and brain FDG-PET scans for this study must also be performed at least 28 days after discontinuation of prior therapy directed at VEGFR. Any questions regarding the definition of anti-VEGF/VEGFR therapy must be discussed with the PI or co-PI.

- Patients must have adequate bone marrow function (WBC > 3,000/µl, ANC > 1,500/mm^3, platelet count of > 100,000/mm^3, and hemoglobin > 10 gm/dl), adequate liver function (SGOT and bilirubin < 2.5 times ULN), and adequate renal function (creatinine < 1.5 mg/dL before starting therapy. These tests must be performed within 2 weeks prior to treatment initiation. Eligibility level for hemoglobin may be reached by transfusion.

- Baseline MRI (with MR Perfusion if possible) must be performed within 2 weeks prior to treatment initiation. It also must be performed at least 28 days after discontinuation of prior therapy directed at VEGF/VEGFR such as bevacizumab (Avastin), VEGF-Trap, or AZD2171. Any questions regarding the definition of anti-VEGF/VEGFR therapy should be discussed with the PI or co-PI.

- Baseline FDG-PET (dedicated study of the brain) must be performed within 2 weeks prior to treatment initiation. It also must be performed at least 28 days after discontinuation of prior therapy directed at VEGF/VEGFR such as bevacizumab (Avastin), VEGF-Trap, or AZD2171. Any questions regarding the definition of anti-VEGF/VEGFR therapy should be discussed with the PI or co-PI.

- There is no limitation on the number of prior relapses or prior therapies.

- Patients must agree to practice adequate contraception. Women of childbearing potential must have a negative B-HCG pregnancy test documented within 7 days prior to registration. Women must not be breast feeding.

- If cytoreductive surgery is planned for tumor recurrence at the time of enrollment, such patients are eligible for the surgical arm, taking perifosine for 5-10 days pre-operatively and then continuing perifosine after recovering from the effects of surgery.

- Measurable disease is not required for eligibility in patients who recently underwent resection as long as the following conditions are met as applicable:

    - Progression of disease led to the surgery
    - Gliadel wafers were not placed during the most recent surgery
    - Neither convection enhanced delivery nor catheters for infusion of chemotherapy were used during the most recent surgery
    - Radioactive seeds were not placed during the most recent surgery
    - The histology of the most recent surgery documented recurrent/persistent/progressive malignant glioma

    Note, however, that patients who are eligible for surgery because of progressive disease may be considered for the surgical arm.

- Any adult patient with a recurrent/progressive malignant glioma is eligible. Patients will be eligible if the original histology was low-grade glioma and a subsequent histological diagnosis of a high grade (malignant) glioma is made.

6.2 Subject Exclusion Criteria

- Patients must not be taking EIAEDs. If patients were previously on EIAEDs that have been discontinued, patients must have been off the agent for at least 2 weeks prior to registration.

- Patients must not have any significant medical illnesses or other history that in the investigator's opinion cannot be adequately controlled with appropriate therapy or would compromise the patient's ability to tolerate this therapy.

- Patients with a history of any other cancer (except non-melanoma skin cancer or carcinoma in-situ of the cervix), unless in complete remission and off of all therapy for that disease for a minimum of 3 years are ineligible.

- Patients must not have active infection or serious intercurrent medical illness.

- HIV-Positive patients receiving combination anti-retroviral therapy are excluded from the study due to possible retro-viral drug interactions.

- Patients must not have any disease that will obscure toxicity or dangerously alter drug metabolism.

- **Surgical arm only:** Patients must not have received prior therapy with signal transduction inhibitors (including but not limited to ZD1839/gefitinib/Iressa, OSI-774/erlotinib/Tarceva, rapamycin/sirolimus, CCI-779/temsirolimus, STI-571/imatinib/Gleevec, bevacizumab/Avastin, VEGF-Trap, AZD2171, sorafinib, sunitinib). Any questions about the eligibility based on prior treatments should be discussed with the PI or co-PI.

7.0 RECRUITMENT PLAN

Patients will be recruited from the neurology and neuro-surgery services at MSKCC. All patients will be seen by a neuro-oncology attending. All patients entered in the protocol will give written informed consent. There are no gender or racial restrictions.

8.1 PRETREATMENT EVALUATION

The following studies are required within two weeks prior to starting perifosine:

- Complete history and physical exam including neurologic exam and KPS.
- Height and weight.
- CBC including WBC differential and platelet count.

- Comprehensive chemistry panel.
- Uric Acid
- Contrast enhanced MRI (with MR Perfusion if possible) of the brain. The same type of scan, i.e., MRI or CT, should be used throughout the period of protocol treatment for tumor measurement. Patients unable to undergo an MRI will undergo contrast enhanced CT scans. It also must be performed at least 28 days after discontinuation of prior therapy directed at VEGF/VEGFR such as bevacizumab (Avastin), VEGF-Trap, or AZD2171. Any questions regarding the definition of anti-VEGF/VEGFR therapy should be discussed with the PI or co-PI.
- **Brain FDG-PET:** It also must be performed at least 28 days after discontinuation of prior therapy directed at VEGF/VEGFR such as bevacizumab (Avastin), VEGF-Trap, or AZD2171. Any questions regarding the definition of anti-VEGF/VEGFR therapy should be discussed with the PI or co-PI.
- **All brain PET scans must be performed on MSKCC scanners for adequate ability to compare scans over time.**
- For patients with histologically documented malignant gliomas who will receive perifosine for their 2nd or greater relapse, the date that the most recent therapy was started will be recorded and used to calculate the time to the prior relapse for comparison with time to progression on perifosine (intrapatient comparison).

9.1 TREATMENT/INTERVENTION PLAN

Dosing will be continuous, and for the purpose of this trial a cycle will be defined as 28 days.

9.2 Dosing

Perifosine will be given as a 600 mg loading dose on day 1. The loading dose will be divided into 4 equal doses of 150 mg each. The first 3 doses should be given with food in the adult day hospital to allow intravenous antiemetic prophylaxis, and 4th dose at bedtime at home. The interval between doses of perifosine should be no less than 4 hours. On day 2, patients will start the maintenance dose of 100 mg daily at bedtime at home.

9.3 Pharmacokinetics/drug concentration in tumor tissue (all patients)

In addition to baseline serum, all patients will have weekly serum drawn during weeks 2-4. Patients in surgical arm of the trial will have blood drawn at baseline and during surgery to determine the concentration of perifosine in serum at the time of surgery. Tissue will also be collected for determination of the concentration of perifosine in tumor tissue relative to simultaneously collected serum. The date and time of blood collection should be recorded. In addition, the date and time of the most recent dose of pre-surgical perifosine should be recorded.

9.4 Treatment modifications (all patients)

For grade 1 perifosine related adverse events, treatment with perifosine will not be interrupted.

For grade 2 perifosine related adverse events

For nausea, vomiting and diarrhea, maintain dosing with symptomatic treatment. The dose of perifosine may be repeated if emesis occurs within 30 minutes of taking the tablet(s) OR all the tablets are seen in the emesis.

For persistent nausea, vomiting or diarrhea, or other persistent grade 2 adverse events despite symptomatic treatment, the daily dose will be reduced by 50 mg.

For grade 3 or 4 perifosine related adverse events

Hold perifosine and re-evaluate the patient at least weekly until toxicity improves to < grade 2 (grade 0 or 1).

If the toxicity resolves in 7 days or less, maintenance (daily) perifosine should be restarted but the daily dose will be reduced by 50 mg.

If the toxicity resolves in 8-14 days, the patient will take another loading dose before reinitiating daily maintenance but the load will by reduced by 200 mg to 400 mg and the maintenance will be reduced to 50 mg. The loading dose will be divided into 4 equal doses of 100 mg each. The first 3 doses should be given with food in the adult day hospital to allow intravenous antiemetic prophylaxis, and 4th dose at bedtime at home. The interval between doses of perifosine should be no less than 4 hours.

If toxicity does not resolve within 14 days, the patient will be withdrawn from the study.

9.5 Treatment Schedule for patients participating in the Pre-operative study:

Patients who are candidates for surgical resection of recurrent disease will be considered for a pre-operative study to evaluate biological/tissue correlates. Patients who choose to participate in this component of the study must have a brain MRI (with MR Perfusion if possible) performed within 14 days of taking pre-operative perifosine. Patients unable to undergo MRI will have CT scans. A brain FDG-PET scan must also be performed within 14 days of taking pre-operative perifosine. The drug will be administered for 5-10 days prior to the

surgery. The last dose will be given the night before surgery. Patients on the surgical arm will also undergo a pre-operative FDG-PET following at least 5 days of perifosine and before surgery to correlate metabolic and tissue effects during treatment.

Day of Surgery: Prior to the surgical procedure, tissue freezer vials should be labeled with the patient's protocol study identifier number(s). Additionally, a thermos with liquid nitrogen (preferably), or if not possible, an ice bucket with dry ice should be prepared. All attempts will be made to obtain specimens immediately adjacent to the areas of resection taken for "permanent sections" in order to optimize the likelihood that the tumor seen on permanent sections is representative of that taken for analysis. Once the pathologist has made a diagnosis of "tumor" on frozen section at the time of surgical resection, the tumor tissue should be divided into 50 – 100mg pieces.

At the time of surgery 10ml of blood will be collected for pharmacodynamic analysis.

Following surgery: A post-operative MRI/CT scan should be done no later than 96 hours from surgery. Once patients have recovered from the effects of surgery and demonstrated wound healing, they will restart perifosine (load and maintenance). Patients are not required to have residual disease to continue perifosine. Treatment with perifosine post-operatively should start a minimum of 7 days after surgery. If more than 14 days have passed since the post-operative MRI was performed, new baseline brain MRI (with MR Perfusion if possible) and brain FDG-PET sans must be performed.

9.6 Supportive Care Guidelines (all patients)

9.6.1 Antiemetic prophylaxis

Patients are to be instructed that perifosine is to be taken with food. Patients will maintain a daily patient treatment diary to track when they take each dose of perifosine and return the diary to the clinic each week along with any remaining medication. The pills should remain intact and should not be split unless a gastrostomy tube is being used.

All patients should have antiemetic medications prescribed and administered as needed, and adjusted during the cycle at the discretion of the treating investigator.

Patients should receive an oral or IV prophylactic antiemetic regimen. The regimen to be used is at the discretion of the treating investigator.

Premedication with a 5HT3 blocker with dexamethasone is recommended.

9.6.2 Diarrhea Management

All patients should be instructed to take loperamide at the earliest signs of diarrhea and/or abdominal cramping after beginning study medication. This can include (a) loose stool, (b) the occurrence of 1 to 2 more bowel movements than usual in 1 day, or (c) an unusually high volume of stool.

Loperamide should be dosed in the following manner: 4 mg at the first onset of diarrhea, then 2 mg every 2 hours around the clock until diarrhea free for at least 12 hours. Patients may take 4 mg every 4 hours during the night.

Additional antidiarrheal measures may be used at the discretion of the treating physician as warranted by the patient's condition.

9.6.3 Hyperuricemia Prophylaxis

Prior to beginning perifosine, all patients should be questioned about a history of hyperuricemia and/or gout. Patients with a known history of hyperuricemia and/or gout should receive prophylactic treatment with allopurinol 300 mg po daily. If severe gout does occur or uric acid levels increase, the dose of allopurinol should be increased at physician discretion.

9.6.4 G-CSF Administration

Routine prophylactic use of G-CSF is not permitted. However, therapeutic use in patients with serious neutropenic complications, such as sepsis, may be considered at the investigator's discretion

9.6.5 Other Concomitant Medications

Therapies considered necessary for the well being of the patient may be given at the discretion of the investigator. Other concomitant medications should be avoided except for analgesics, chronic treatments for concomitant medical conditions, or agents required for life-threatening medical problems. All concomitant medications must be recorded.

9.6.6 Other Anticancer or Experimental Therapies

No other anticancer therapy (including chemotherapy, radiation, hormonal treatment or immunotherapy) of any kind is permitted during the study period.

No other drug under investigation may be used concomitantly with the study drug.

9.6.7 Surgery

If neurosurgical management is required for reasons not due to tumor progression, these procedures must be documented, including the indications for surgery, the surgical operative note and pathology report.

9.6.8 Corticosteroids should be used in the smallest dose to control symptoms of cerebral edema and mass effect, and discontinued if possible.

Anti-seizure medications should be used as indicated. However, only patients not taking EIAEDs are eligible to enroll on this trial. Patients who were previously on a non-EIAED and need to change anticonvulsants should be started on another non-EIAED if at all possible. No delays in treatment would be required. Patients who were previously on no anticonvulsants should be treated with non-EIAEDs if at all possible. If for unavoidable clinical reasons (severe allergies, toxicities etc.) a patient is started on an EIAED, he/she should immediately be started on another non-EIAED and the EIAED should be tapered and discontinued as quickly as possible. The patient may continue the current treatment dose while a non- EIAED is re-started because an EIAED will likely increase metabolism of perifosine, reducing rather than increasing any potential anti-tumor effect and therefore any efficacy bias introduced would be negative rather than positive.

Patients who were previously on a non-EIAED and need to permanently change anticonvulsant, but who cannot change to another non-EIAED may continue the current treatment dose for the next 2 weeks while an EIAED is started. FOLLOWING THIS PERIOD, THE SUBSEQUENT TREATMENT DOSE MUST BE DISCUSSED WITH THE PI OR CO-PI. Treatment may be allowed to continue if the patient is felt to be deriving clinical benefit. In some cases this dose may be higher than the previously used dose.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

10.1 Clinical

History and physical examination (including vital signs, weight and KPS) will be performed at each clinic visit. Patients will have a follow up physical exam 1 week after the patient starts treatment and every first week of each subsequent cycle (4 week period).

A diary should be completed by the patient each week to score duration and severity of gastrointestinal side effects. Patients will also maintain a weekly patient treatment diary to track doses of perifosine taken at home and return the diary to the clinic each week.

10.2 Laboratory

A CBC with differential and serum chemistry will be performed 1 week after the patient starts treatment, and every first week of each subsequent cycle.

- Albumin
- Alkaline phosphatase
- Total bilirubin
- Bicarbonate
- BUN
- Calcium
- Chloride
- Creatinine
- Glucose
- LDH
- Phosphorus
- Potassium
- total protein
- SGOT [AST], SGPT [ALT]
- Sodium
- Uric acid
- Magnesium

Serum pregnancy test should be obtained within 72 hours prior to the initiation of therapy for women of childbearing potential.

10.3 Imaging and Molecular Studies

Patients not on the surgical arm will undergo imaging evaluation with brain MRI (with MR Perfusion and MR spectroscopy if possible) at baseline and every 8 weeks Patients unable to undergo MRI will have CT scans. Patients will also undergo FDG-PET imaging of the brain (at MSKCC) at baseline and every 16 weeks (4 cycles) to assist with interpretation of MRI. Patients will also undergo a brain FDG-PET scan after 1-2 weeks of therapy at MSKCC to investigate potential metabolic effects of perifosine and to explore early FDG-PET as a predictor of response by clinical and radiographic evaluations performed later.

Patients on the surgical arm will undergo baseline imaging evaluation with brain MRI (with MR Perfusion and MR Spectroscopy if possible) and FDG-PET at MSKCC no more than 2 weeks before pre-operative perifosine. Patients on the surgical arm will also undergo a pre-operative FDG-PET at MSKCC following at least 5 days of perifosine and before surgery to correlate metabolic and tissue effects during treatment. After surgery, a brain MRI must also be performed no more than 2 weeks before initiation of post-operative perifosine. It is expected that in most cases, the post-operative MRI (performed within 96 hours after surgery) will suffice and function as the new baseline scan before initiation of post-operative perifosine. Patients unable to undergo MRI will have CT scans. FDG-PET does not need to be repeated post-operatively before re-initiating perifosine. Patients will then undergo brain MRI every 8 weeks (with MR Perfusion if possible) and brain FDG-PET every 16 weeks (4 cycles) at MSKCC to assist with interpretation of MRI.

Fifteen unstained paraffin slides and 100 mg of flash frozen tissue will be used to evaluate the effect of perifosine on PI3K/AKT and RAS/MAPK signaling, the effect on proliferation, and other molecular effects. In addition, 100 mg of flash frozen tissue and one tube of serum will be collected for pharmacokinetic analysis.

All patients: The brain MRI, MR Perfusion, MR Spectroscopy and FDG-PET scans will be used for clinical care and be billed to insurance/patient with the exception of the FDG-PET performed after 1-2 weeks of therapy which is research in nature.. In addition, such scans will be used to determine effects of perifosine on tumor blood flow and metabolism.

If available, 15 unstained paraffin slides and flash frozen tissue will be obtained from the surgery closest to initiation of this clinical trial. These will be used to evaluate molecular markers that could predict glioma sensitivity to perifosine such as a PI3K/AKT activity, RAS/MAPK activity, proliferation rate, and somatic mutations of potential oncogenes or tumor suppressor genes in tumor cell DNA.

Dr. Eric Holland and members of his laboratory will conduct analyses of baseline tumor tissue for abnormalities of the RAS, AKT, and other signal transduction cascades that may predict tumor sensitivity to perifosine. Dr. Holland will also conduct analyses of tissue resected during treatment with perifosine (surgical arm of the study) to determine the effects of perifosine on signaling.

Jill M. Kolesar, Pharm. D. at the University of Wisconsin will conduct PK and tissue drug concentration analyses. AOI Pharmaceuticals subcontracted Dr. Kolesar to perform such assays. Please see section 20.3 for instructions on shipping tissue/serum to Dr. Kolesar.

(Remainder of this page intentionally left blank.)

	All assessments should be obtained prior to the first dose of perifosine in each week unless otherwise specified														
	Pre-Study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13	Off Study[c]
Perifosine administration[a]		X	X	X	X	X	X	X	X	X	X	X	X	X	
Informed consent	X														
Demographics	X														
Medical history	X														
Concurrent meds	X														
Physical exam	X		X			X				X				X[f]	
Vital signs	X		X			X				X				X[f]	
Height	X														
Weight	X		X			X				X				X[f]	
Performance status	X		X			X				X				X[f]	
CBC (w/diff, plts[f])	X		X			X				X				X[f]	
Serum chemistry[b]	X[d]		X			X				X				X[d]	
Serum pregnancy[e]	X														
Adverse event evaluation	X	X ----------													X
Patient Diaries	X	X ----------													X
Tumor measurements	X	Tumor measurements are repeated every 8 weeks. Documentation (radiological) must be provided for patients removed from study for progressive disease.													X[c]

a: Perifosine: Dose, route, schedule as assigned.
b: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, uric acid, magnesium.
c: Off-study evaluation. It is preferable that two consecutive measurements taken to document progressive disease if the patient is removed from study for this reason.
d: Assessments to continue at least every 12 weeks while patient is on study.
e: Within 72 hours prior to initiation of therapy for women of childbearing potential only.
f: Assessments to continue at least every 4 weeks while patient is on study.

11.1 Toxicities/side effects

The most common toxicities associate with perifosine are nausea, vomiting, and diarrhea. NCI CTC version 3.0 will be used to grade all toxicity.

Reported Adverse Events and Potential Risks:

- Constitutional Symptoms: fatigue (lethargy, malaise, asthenia)
- Gastrointestinal: anorexia, dehydration, flatulence, diarrhea, nausea, vomiting

The following events were reported in two or fewer of the patients treated on the NCI sponsored phase I trial:

- Pulmonary: hiccoughs (hiccups, singultus)
- Renal/Genitourinary: increased creatinine
- Hepatic: increased alkaline phosphatase, increased GGT

Also reported on the NCI phase I perifosine trials and occurring in two or fewer patients with the relationship to perifosine still undetermined:

- Blood/Bone Marrow: decreased hemoglobin
- Constitutional Symptoms: fever, sweating, weight loss
- Dermatology/Skin: mild skin reaction
- Gastrointestinal: mucositis, dyspepsia/heartburn
- Neurology: lightheadedness
- Ocular/Visual: eye symptoms, specifically blurred vision, photophobia and cataract formation
- Pain: abdominal pain, headache, arthritis, arthralgia
- Genitourinary: hyperuricemia

Also from animal data:

- Dose dependent kidney and eye events (retinal degeneration and cataracts)

If hematologic toxicity grade 3 or higher occurs patients may be treated with appropriate growth factors.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

The primary efficacy endpoint will be progression free survival (PFS) at six months from registration. For this and for all other time to event analyses, if a patient is NOT registered on the pre-operative portion of the study (surgical arm), the start date for calculation of time to event will be the date of first study drug administration. For this and for all other time to event analysis, if a patient IS enrolled on the pre-operative portion of the study (surgical arm), the start date for calculation of time to event will be the date of the first post-operative study drug administration.

Objective status should be measured and recorded although this is not the primary endpoint. The following definitions will be used based on standard criteria for malignant glioma trials [23]:

Measurable Disease: Bidimensionally measurable lesions with clearly defined margins by CT or MRI scan.

Evaluable Disease: Unidimensionally measurable lesions, masses with margins not clearly defined.

Non-Evaluable Disease: Not Applicable for response evaluation

Objective Status, To Be Recorded at Each Evaluation: If there are too many measurable lesions to measure at each evaluation, choose the largest two to be followed before a patient is entered on study. The remaining lesions will be considered evaluable for the purpose of objective status determination. Unless progression is observed, objective status can only be determined when ALL measurable and evaluable sites and lesions are assessed.

Complete Response (CR): Complete disappearance of all measurable and evaluable disease. No new lesions. No evidence of non-evaluable disease. All measurable, evaluable and non-evaluable lesions and sites must be assessed using the same techniques as baseline. Patients must be on no steroids.

Partial Response (PR): Greater than or equal to 50% decrease under baseline in the sum of products of perpendicular diameters of all measurable lesions. No progression of evaluable disease. No new lesions. All measurable and evaluable lesions and sites must be assessed using the same techniques as baseline. *The steroid dose at the time of the scan evaluation should be no greater than the maximum dose used in the first 8 weeks from initiation of therapy.*

Partial Response, Non-Measurable (PRNM): Not applicable.

Stable/No Response: Does not qualify for CR, PR, or progression. All measurable and evaluable sites must be assessed using the same techniques as baseline. The steroid dose at the time of the scan evaluation should be no greater than the maximum dose used in the first 8 weeks from initiation of therapy.

Progression: 25% increase in the sum of products of all measurable lesions over smallest sum observed (over baseline if no decrease) using the same techniques as baseline, OR clear worsening of any evaluable disease, OR appearance of any new lesion/site, OR clear clinical worsening or failure to return for evaluation due to death or deteriorating condition (unless clearly unrelated to this cancer).

Unknown: Progression has not been documented and one or more measurable or evaluable sites have not been assessed.

Best Response: This will be calculated from the sequence of objective statuses.

For patients with all disease sites assessed every evaluation period, the best response will be defined as the best objective status. If the response does not persist at the next regular scheduled MRI, the response will still be recorded based on the prior scan, but will be designated as a non-sustained response. If the response is sustained, e. g. still present on the subsequent MRI, it will be recorded as a sustained response, lasting until the time of tumor progression. Best response is unknown if the patient does not qualify for a best response or increasing disease and if all objective status determinations before progression are unknown.

Criteria permitting uni-dimensional response measurement have recently been adopted and published by an international consensus committee, Response Evaluation Criteria In Solid Tumors Group (RECIST). In order to ensure comparability of data from this trial with data from earlier trials, this trial will retain the traditional evaluation definition above as primary. However, RECIST criteria that can be collected, will be used for secondary evaluation.

Neurological Exam: Although not used for determining response, it is useful to evaluate improvement in the neurologic exam, (as compared to the baseline assessment), that should coincide with objective measurement of tumor size.

+2	Definitely better
+1	Possibly better
0	Unchanged
-1	Possibly worse
-2	Definitely worse

Performance Status: Patients will be graded according to Karnofsky Performance Status (see Appendix 20.1).

Time to Treatment Failure: From the treatment start date to the date of first observation of progressive disease, non-reversible neurologic progression or permanently increased steroid requirement (applies to stable disease only), death due to any cause, or early discontinuation of treatment. If a patient is NOT registered on the pre-operative portion of the study (surgical arm), the start date for calculation of time to event will be the date of first study drug administration. If a patient IS enrolled on the pre-operative portion of the study (surgical arm), the start date for calculation of time to event will be the date of the

first post-operative study drug administration. As an exploratory evaluation of other means to demonstrate clinical efficicacy, the time to treatment failure in comparison to time to the most recent progression for prior relapse will also be calculated for each patient; in this manner, each patient serves as his/her own control and an increase in the time to treatment failure relative to the most recent progression may also suggest clinical activity of the drug.

Time to Death: From the treatment start date to date of death due to any cause. If a patient is NOT registered on the pre-operative portion of the study (surgical arm), the start date for calculation of time to event will be the date of first study drug administration. If a patient IS enrolled on the pre-operative portion of the study (surgical arm), the start date for calculation of time to event will be the date of the first post-operative study drug administration.

13.1 CRITERIA FOR REMOVAL FROM STUDY

All patients may continue therapy unless disease progression, death, or dose limiting toxicity is documented. The cause of death should be recorded.

The following events may be considered sufficient reason for discontinuing treatment with the study medication

- Serious toxicity due to the study drug graded according to the NCI Common Terminology Criteria for Adverse Events v3.0 [22]
- Conditions requiring therapeutic intervention not permitted by the protocol
- Unacceptable toxicity in the opinion of the patient or investigator even if not specifically defined elsewhere
- Personal preference by the patient for any reason
- Subject non-compliance with the defined treatment plan
- Medical or psychiatric illness or social environment which in the investigator's judgment renders the patient incapable of further therapy.
- Any other situation where, in the opinion of the investigator, continued participation in the study would not be in the best interest of the patient
- Treatment delay due to toxicity greater than 14 days
- Pregnancy
- Disease progression

All reasons for discontinuation of treatment must be documented in the flow sheets.

14.0 BIOSTATISTICS

The historical values for comparison are from a database of 225 GBM patients enrolled in 8 previous phase II studies (in which none of the treatments were considered particularly effective.[24] In this database, the 6 month PFS was 15% for GBM. The 6 month PFS for patients treated with BCNU for recurrence/progression was 17.5%.[3] Therefore, we would expect 6 month PFS to be less than 20%.

We will utilize a Simon two-stage design in which the primary endpoint is the progression rate at 6 months. All patients will be followed for 6 months and progression or death due to disease will be considered an event. Assuming a 6 month progression free survival rate of 20% is considered promising, a 6 month progression free survival rate of 5% is considered not promising, and the probabilities of a type I error (falsely accepting a non-promising therapy) and type II error (falsely rejecting a promising therapy) are set at 0.10 and 0.10, respectively. In the first stage of this design, 12 patients with GBM will be accrued. If at least 1 patient with GBM does not progress at the 6 month time among these 12 patients, then an additional 25 patients with GBM (for a total of 37) will be accrued to the second stage, otherwise the trial will be terminated. Note that enrollment of patients with both GBM and non-GBM malignant gliomas will continue while the first 12 patients with GBM are followed for PFS. However, if 0 of these first 12 reach 6mPFS, then enrollment will terminate; in that event, any patients still on trial with any histology may continue until progression or death at the discretion of the treating physician. At the end of the trial, if 3 or less patients with GBM are progression free at 6 months, the study will be declared negative. This design yields at least a 0.90 probability of a positive result if the true response rate is at least 20% and yields a 0.90 probability of a negative result if the true response rate is 5%.

Up to 20 patients with anaplastic glioma and evaluable disease at study entry (i.e., did not undergo gross total resection as the most recent therapy prior to registration) will be accrued. Endpoints such as response, one-year survival probability, overall survival and progression-free survival will be computed in order to gain preliminary data for these other malignant glioma subtypes. However, the historical controls for patients with anaplastic glioma are less well defined than for GBM; therefore, only patients with GBM will be included in analyses of efficacy and the two-stage design will be applied only to the GBM cohort.

<u>Surgical arm</u>
In order to obtain specimens for study of the tissue pharmacokinetics of perifosine in tumors, as well as the molecular effects of perifosine in tumor tissue, we plan to accrue subjects to a preoperative treatment arm. There is no upper bound on the number of patients that can be entered into this substudy. However, if the study reaches the total enrollment and fewer than 10 patients have entered this substudy, the trial will be kept open to accrue at least 10 surgical arm patients. Note, the study will only be kept open if

the drug is considered promising (defined above) after either the first stage enrolling 12 patients with GBM or complete accrual of the total cohort of 37 patients with GBM. Any additional patients enrolled through this mechanism will be included in the primary analysis of efficacy (6mPFS) and the total cohort will be increased from 37 patients with GBM to a maximum of 47 patients with GBM (37 + 10 additional surgical patients in the unlikely circumstance that none of the initial 37 patients are enrolled on the surgical arm). Therefore, the maximum enrollment is up to 57 patients (37 with GBM, not on surgical substudy; up to 10 additional patients with anaplastic glioma; up to 10 additional patients on surgical stubstudy if not already accrued).

Although patients on the surgical substudy will have resections of tumor at the initiation of treatment, the natural history of recurrent GBM strongly supports the concept that nearly all patients will have tumor progression by 6 months if no further treatment or ineffective treatment is provided post-operatively. For example, a review of patients with recurrent GBM treated for first relapse at the MD Anderson Cancer Center also supports the concept that gross total resection does not impact on 6-month PFS rate. During the time from of 2001-2003, 220 patients were treated at MD Anderson for first relapse or progression of GBM. There was no difference in 6-month PFS between those patients who had a gross total resection at relapse compared with all other patients. Hence, we plan to combine data from patients on and not on the surgical substudy in efficacy analyses.

Molecular and Metabolic Correlates

Pre-treatment tissue will be used for exploration of molecular predictors of tumor sensitivity to perifosine (all patients). Tissue resected during perifosine treatment (surgical arm) will be used to explore effects of the agent on PI3K/AKT and RAS/MAPK signaling as well as proliferation and other pathways.

FDG-PET and MR Perfusion studies will be used for clinical care with the exception of the FDG-PET performed after 1-2 weeks of therapy.. However, they will also be used for exploration of perifosine effects on tumor metabolism and blood flow. To ensure adequate comparability of scans, all FDG-PET scans must be performed at MSKCC.

The analysis of biological correlate data has the overall goal of providing increased understanding of the nature of the response to perifosine. The amount of data available for the various measures is uncertain. Information may also be limited by the impact of intervening treatment between the most recent surgery and initiation of perifosine. The nature of the analyses and the strength of the conclusions from these laboratory studies depend not only on the amount of data available, but also on the nature of patient response to therapy. If the response is not favorable, the data may be used to better understand the reason for the failure. In addition, new assays may become available between the opening of this study and the collection and analysis of tumor tissue. Thus,

it is difficult to prespecify the nature of the analyses and the list assays here is a general guide rather than all inclusive.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

The following person(s) can obtain informed consent:

- Thomas Kaley, MD
- Lisa DeAngelis, MD
- Igor Gavrilovic, MD
- Adilia Hormigo, MD
- Craig Nolan, MD
- Jerome Posner, MD
- Eugenie Obbens, MD
- Antonio Omuro, MD
- Ingo Mellinghoff, MD
- Xi Chen, MD

Confirm with electronic medical record that the patient has received the Notice of Privacy Practice. This must be obtained before the eligibility confirmation and obtaining of the research informed consent.

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain written informed consent, by following procedures defined in section entitled Informed Consent Procedures.

All patients must be registered through the Protocol-Patient Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at (646) 735-8000. The PPR fax numbers are (646) 735-0008 and (646) 735-0003. Registrations can be phoned in or faxed. The completed signature page of the informed consent form, the completed signature page of the Research Authorization and a completed Eligibility Checklist must be faxed to the PPR.

During the registration process registering individuals will be required to answer specific eligibility questions and provide the following information:

Registering Individual	[Last, First Name]
Notice of Privacy Status	[Yes, No, N/A]

MSKCC IRB Protocol#
Attending of Record (if applicable) [Last, First Name]
Consenting Professional [Last, First Name]
Informed Consent Date
Patient's Full Name [Last, First Name]
Patient MRN

16.1 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team.

The data collected for this study will be entered into a secure database. Source documentation will be available to support the computerized patient record.

16.2 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extext and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address thenew policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: *http://mskweb2.mskcc.org/irb/index.htm*

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.0 PROTECTION OF HUMAN SUBJECTS

17.1 Privacy

It is the responsibility of the Research Staff to ensure that protocol patients have received the Center's Notice of Privacy Practices. If the subject has not already done so, MSK personnel must try to obtain acknowledgment before the patient participates in this study.

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board.

17.2 Serious Adverse Event (SAE) Reporting

Any SAE must be reported to the IRB as soon as possible but no later than 5 calendar days. The IRB requires a Clinical Research Database (CRDB) AE report to be delivered to the Institutional SAE Manager (307 East 63rd Street, 1st Floor) containing the following information:

Fields populated from the CRDB:

- Subject's name

- Medical record number
- Disease/histology (if applicable)
- Protocol number

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following information:
  - A explanation of how the AE was handled
  - A description of the subject's condition
  - Indication if the subject remains on the study
  - If an amendment will need to be made to the protocol and/or consent form

The PI's signature and the date it was signed are required on the completed report.

All serious adverse events will also be reported to AOI. This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences.

These reports should be sent by FAX or E-MAIL to the Online Collaborative Oncology Group (OCOG), which is a subsidiary of AOI Pharmaceuticals:

Online Collaborative Oncology Group
1355 Lynnfield, Suite 245
Memphis, TN 38119

By FAX: (901)-869-3842, within 24 hours of receipt by investigator. FAX transmission should include Subject Number, Study Title, Study Number and name of Principal Investigator.

By E-MAIL: ocogtrials@ocog.net, within 24 hours of receipt by investigator. E-Mail transmission should include Subject Number, Study Title, Study Number and name of Principal Investigator.

17.2.1 Relationship between the adverse event and the study drug

The Investigator must also assess the relationship of any adverse event to the use of study drug, based on available information, using the following guidelines:

Unlikely - no temporal association, or the cause of the event has been identified, or the drug cannot be implicated.
Possibly - temporal association, but other etiologies are likely to be the cause; however, involvement of the drug cannot be excluded.
Probably - temporal association, other etiologies are possible, but unlikely.

17.2.2 Definition of Adverse Event

Adverse events are illnesses, signs, or symptoms that appear or worsen during the course of a study. Adverse events occurring in association with study drug administration, whether believed by the investigator to be related or unrelated to the drug should be recorded on the case report form. When the investigator is confident of the diagnosis, he should group together as a single illness all related signs, symptoms, and abnormal laboratory results, e.g. cough; rhinitis, and sneezing can be reported as "upper respiratory infection."

Abnormal laboratory results should be noted on the case report form if they are associated with an overdose, require or prolong inpatient hospitalization or are otherwise considered significant by the investigator.

17.2.3 Definition of Serious Adverse Event

A serious adverse event is one that meets any of the following criteria:

- life-threatening (all grade 4 events except myelosuppression, nausea, emesis, and hyperglycemia) or fatal
- substantial or permanent disability
- requires or prolongs inpatient hospitalization (this does not include hospitalization for elective treatment or emergency room visits)
- cancer (2° malignancy)
- a congenital anomaly in the offspring of a patient who received trial medication
- an event resulting from an overdose (overdoses without clinical sequelae are not serious adverse events)
- an event (not mentioned in a-f) that may jeopardize the patient or may require intervention to prevent one of the outcomes listed above.

18.1 INFORMED CONSENT PROCEDURES

All patients must provide written informed consent prior to registration and treatment. Those physicians authorized to obtain informed consent are listed on the title page of this document.

18.2 Research Authorization: Procedures for obtaining Research Authorization: Before any protocol-specific procedures are carried out, investigators and/or designated staff will fully explain the details of the protocol, study procedures, and the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must sign the Research Authorization component of the informed consent form. The Research Authorization requires a separate set of signatures from the patient. The original signed documents will become part of the patient's medical record, and each patient will receive a copy of the signed documents.

19.0 REFERENCE(S)

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20.1 APPENDICES

20.2 Karnofsky Performance Status, Neurological Function, and Mental Status

Patient's performance status will be graded according to the following scale:

Karnofsky Performance Status

KPS 100 Normal; no complaints; no evidence of disease
KPS 90 Able to carry on normal activity; minor signs or symptoms of disease
KPS 80 Normal activity with effort; some sign or symptoms of disease
KPS 70 Cares for self; unable to carry on normal activity or do active work
KPS 60 Requires occasional assistance, but is able to care for most personal needs
KPS 50 Requires considerable assistance and frequent medical care
KPS 40 Disabled; requires special care and assistance
KPS 30 Severely disabled; hospitalization is indicated, although death not imminent
KPS 20 Very sick; hospitalization necessary; active support treatment is necessary
KPS 10 Moribund; fatal processes progressing rapidly
KPS 0 Dead

20.3 EIAEDs and Non-EIAEDs

EIAEDs:
Carbamazipine (Tegretol, Tegretol XR, Carbatrol)
Oxcarbazepine (Trileptal)
Phenytoin (Dilantin, Phenytek)
Fosphenytoin (Cerebyx)
Phenobarbital
Primidone (Mysoline)

Non-EIAEDs:
Valproic acid (Depakote, Depakene)
Gabapentin (Neurontin)
Lamotrigine (Lamictil)
Topriamate (Topamax)
Tiagabine (Gabatril)
Zonisamide (Zonegran)
Levatriacetam (Keppra)
Clonazepam (Klonopin)
Clonozam (Frisium)

20.4 Handling and Shipping of Serum and Tissue for Perifosine Measurement:

A. Serum

At each time point, heparinized blood is collected into a plastic vacutainer to minimize adhesion of perifosine. Plasma is separated by centrifugation and stored in polypropylene cryovials at -70°C until assayed. Perifosine in plasma is measured by a validated reversed phase liquid chromatography/electrospray mass spectrometry method by Jill M. Kolesar, Pharm.D at the University of Wisconsin, Comprehensive Cancer Center who has been subcontracted by AOI Pharmaceuticals to perform these analyses. An LC/MS analytical method used in NCI sponsored phase I trials (Woo EW, Messmann R, Sausville EA, Figg WD. Quantitative determination of perifosine, a novel alkylphosphocholine anticancer agent, in human plasma by reversed-phase liquid chromatography-electrospray mass spectrometry. J Chromatogr B Biomed Sci Appl. 2001 Aug 15;759(2):247-57), is currently available for plasma samples at the Univ. of Wisconsin, and will be used for this study. The pharmacokinetic characteristics of perifosine in patients will be evaluated using WinNonlin modeling software.

Sample processing and handling outline:

1) A pharmacokinetic sample will be obtained from each patient, at the times outlined. One sodium heparin 10cc green top with >7ml of blood will be obtained and shipped to the Jill M. Kolesar, Pharm.D at the University of Wisconsin for further analysis.

2) Pharmacokinetic samples will be obtained in association with perifosine administration at pretreatment, and weekly during weeks 2-4.

3) Peripheral blood is to be drawn into heparinized vacutainer (green top) provided in the sample collection kit. The Patient's initials, time sample obtained, date sample was obtained should be recorded on each green top tube.

4) Within 20 minutes of collection, centrifuge the blood samples at 900g for 15 minutes (or use the local laboratory Standard Operating Procedure) to separate plasma.

5) For each sample collected, pipet duplicate aliquots of plasma, 2 ml each, in polypropylene cryovials (Nunc) provided in the sample collection kit. Aliquot 1 is the sample and aliquot 2 is the duplicate.

6) Place the appropriate labels, included in the sample collection kit, onto the tubes and freeze at -70°C until shipped.

7) Sample Shipping:

- Samples are to be shipped overnight in sufficient dry ice to keep samples frozen using the airbill and shipping box provided in the kit.

- Please place all 6 nunc sample tubes into the plastic bag provided. Do not ship samples and duplicates in the same box. Save the duplicates and ship them with your next patient.

- Place the patient flowsheets in a separate plastic bag and then place it in the shipping box.

- Please contact the central lab before shipping samples
  Amy Dresen (608) 263-5369 or
  Jill Kolesar (608) 262-5549

- The laboratory is open to receive samples Monday through Friday. NOTE: **DO NOT ship samples on Thursdays, Fridays or on days prior to holidays.**

- Ship to: **Jill M. Kolesar, Pharm.D**
  Analytical Instrumentation Laboratory for Pharmacokinetics, Pharmacodynamics and Pharmacogenetics (3P)
  University of Wisconsin
  Comprehensive Cancer Center Room K6/570
  600 Highland Avenue
  Madison, WI 53792-5669

B. Tumor tissue Perifosine Assay

IMPORTANT NOTE: THESE INSTUCTIONS PERTAIN *ONLY* TO THE DETERMINATION OF PERIFOSINE CONCENTRATION IN TISSUE THAT WILL BE PERFORMED BY JILL M. KOLESAR, PHARM. D. AT THE UNIVERSITY OF WISCONSIN.
A SEPARATE ALIQUOT OF TISSUE FLASH FROZEN IN LIQUID NITROGEN SHOULD BE STORED AT -*70 DEGREES CECLIUS* AT MSKCC FOR MOLECULAR ANALYSIS OF THE EFFECTS OF PERIFOSINE THAT WILL BE PERFORMED BY DR. ERIC HOLLAND.

To determine intracellular perifosine levels, samples will be drawn under the same conditions and timepoints as for pharmacokinetics studies. Tissues without processing will be frozen at **-70^{O} C** until shipment. Specimens will be shipped to:

University of Wisconsin Comprehensive Cancer Center 3P Lab
600 Highland Ave K6/571 CSC
Madison, WI 53792
608-263-5369
Attn: Amy Dresen

20.4. Supportive Care Guidelines for Controlling Side Effects Associated with the Administration of Perifosine

REMINDERS

Patients should take all medication with food, and not on an empty stomach.
Pills should remain intact and should not be crushed *except* to administer via g-tube.

NAUSEA AND VOMITING

Loading dose schedule

- Patients should divide the loading dose of perifosine into 150mg every 6 hours until the total loading dose is administered. Please note that administering the total dose could take longer than 24 hours, but it must be taken within a 48-hour period.
- 5HT3 antagonist—such as, but not limited to, ondansetron and granisetron—can be administered every 12 hours on the day of therapy and every 12 hours for 24 hours *after* the day of therapy.
- Dexamethasone 4mg po in conjunction with the 5HT3 antagonist *unless otherwise contraindicated*.

If the above steps are ineffective, the frequency of the 5HT3 antagonist can be increased.

- Metoclopramide 5mg Q.I.D. can be added if needed.
- If the nausea could be related to anticipation, the use of lorazepam can be initiated.
- Patients should have some medication on hand for breakthrough nausea—such as promethazine or prochlorperazine.

If nausea and/or vomiting remains uncontrollable after following the recommendations listed above, the perifosine dose can be reduced as detailed in the Dose Modifications section of the relevant perifosine protocol(s).

Daily dosing schedule

- Patients should take medication *at bedtime* – with food and not on an empty stomach.
- Although the use of prophylactic antiemetics should not be necessary for patients on daily dosing, they should have antiemetics on hand—such as promethazine or prochlorperazine—if they do encounter nausea and/or vomiting. If these antiemetics are not effective, the treating physician may escalate the antiemetics to the ones listed above for the loading dose.

If nausea and/or vomiting continue after following the recommendations above, dose reductions can be initiated in accordance to the Dose Modifications section of the relevant perifosine protocol(s).

DIARRHEA

For both Loading and Daily Dose Schedules

At the first sign of change in stool or bowel function initiate recommendations

- Imodium 4mg at the first onset of diarrhea.
- Repeat Imodium 2mg every 2 hours until diarrhea subsides for 12 hours.
- Patients can take Imodium 4mg every 4 hours during the night to minimize interruption of sleep.
- Drink plenty of fluids.
- Avoid foods and liquids that can aggravate diarrhea—such as dairy products, seeds, nuts, etc..
- The treating physician may use other antidiarrhea medications at his/her discretion.

For diarrhea that cannot be controlled by following these recommendations, refer to the Dose Modification section of the relevant perifosine protocol(s).

GOUT AND/OR HYPERURICEMIA

For both Loading and Daily Dose Schedules

- All patients should be asked about the possible prior history of gout or hyperuricemia.
- Patients with prior history of gout or elevated uric acid levels should receive allopurinol 300mg by mouth daily for prophylaxis.
- The treating physician may increase the dose of allopurinol or change medications at his/her discretion as warranted by the individual patient's status.

NOTE ABOUT THIS INFORMATION

- Treating physicians may use other agents at their discretion.
- These recommendations are based on current information obtained from clinical studies—that have either been completed or are underway—examining the efficacy and safety of perifosine.