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ORIGINAL REPORT

Double-Blind Phase III Randomized Trial of the Antiprogestin Agent Mifepristone in the Treatment of Unresectable Meningioma: SWOG S9005

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ABSTRACT

Purpose
Progesterone receptors are expressed in approximately 70% of meningiomas. Mifepristone is an oral antiprogestational agent reported to have modest activity in a phase II study. This multicenter, prospective, randomized, placebo-controlled phase III trial conducted by SWOG was planned to define the role of mifepristone in the treatment of unresectable meningioma.

Patients and Methods
Eligible patients were randomly assigned to receive either mifepristone or placebo for 2 years unless disease progressed. Patients who were stable or responding to protocol therapy after 2 years had the option to continue with the same blinded therapy. Serial follow-up allowed assessment of efficacy and toxicity. Time to treatment failure and overall survival were ascertained for all randomly assigned patients. On progression, patients receiving placebo could cross over and receive active drug.

Results
Among 164 eligible patients, 80 were randomly assigned to mifepristone and 84 to placebo. Twenty-four patients (30%) were able to complete 2 years of mifepristone without disease progression, adverse effects, or other reasons for discontinuation. Twenty-eight patients (33%) in the placebo arm completed the 2-year study. There was no statistical difference between the arms in terms of failure-free or overall survival.

Conclusion
Long-term administration of mifepristone was well tolerated but had no impact on patients with unresectable meningioma.

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INTRODUCTION

Meningiomas are the most common of all neurologic tumors, accounting for 35.8% of all brain tumors and representing 53.8% of nonmalignant tumors.[1] Approximately 70% to 80% of meningiomas are benign (WHO grade 1), 20% to 30% are atypical or borderline (grade 2), and 1% to 2% are malignant (grade 3).[2] For the latter, 2-, 5-, and 10-year survival rates are 76%, 65.4%, and 57.2%, respectively.[1] Approach to the majority of patient cases is observation, but a small subset can involve invasive or symptomatic disease. These patients are managed by surgical resection or radiosurgery; there are no systemic curative therapies.[3] Symptomatic or recurrent meningiomas that are not operable may be lethal. There is epidemiologic evidence of association between meningioma, pregnancy, and breast cancer, suggesting hormonal regulation of tumor growth.[4,5]

Progesterone receptors are expressed in approximately 70% of meningiomas.[4] Although the nature and function of these receptors might be different than those expressed in breast cancer,[6] the presence of progesterone receptors might provide a potential therapeutic target for growth inhibition of meningiomas. This concept is supported by pilot studies of effective meningioma inhibition by blockade of the progesterone receptor[7,8]

Mifepristone (17β-hydroxy-11β-[4-dimethylaminophenyl]-17α-[prop-l-ynyl]estra-4,9-dien-3-one; also called RU 486) is a synthetic

competitive inhibitor of the progesterone receptor and, to a lesser degree, of the glucocorticoid receptor.[9] The mechanism of action of mifepristone leads to irreversible inhibition of the transcriptional activity of the progesterone receptor complex, through an alteration of its conformation causing modifications of DNA signaling through promoter interference, at concentrations much lower than progesterone.[10] Mifepristone was originally developed as an abortifacient and has also been investigated in treatment of Cushing's syndrome,[11-13] endometriosis,[14,15] endometrial cancer,[16] uterine leiomyoma,[15,17] breast cancer,[18,19] and depression.[20] Good tolerability and feasibility of long-term use were reported in a recent phase II study of patients with unresectable meningioma, with eight of 28 patients achieving minor remission.[21]

We report the long-term results of a multicenter, prospective, randomized, placebo-controlled phase III trial conducted by SWOG to determine the role of mifepristone in treating unresectable growing meningioma. The objective of this study was to compare daily oral mifepristone versus placebo with respect to failure-free survival (FFS) in patients with unresectable meningioma. Secondary objectives were to assess overall survival (OS) and tolerance of long-term use of mifepristone.

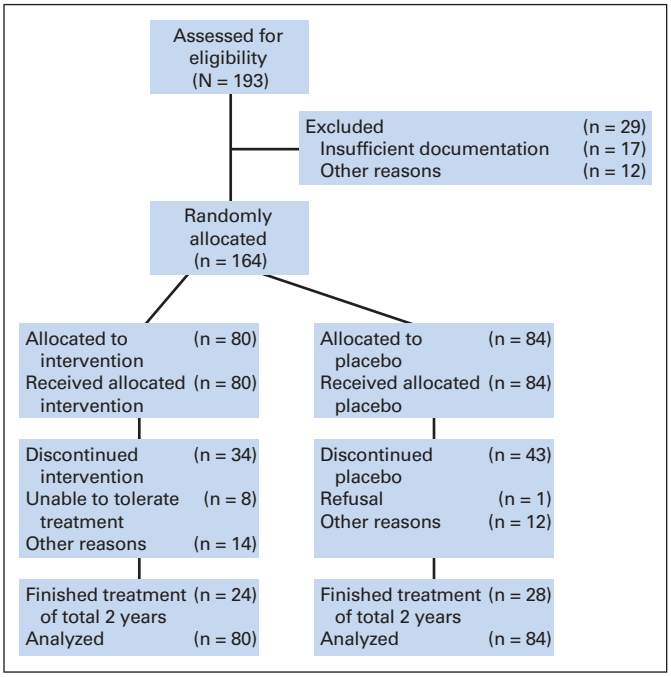

Fig 1. CONSORT diagram of patients participating in this trial.

PATIENTS AND METHODS

Patient Eligibility

Patients age ≥ 18 years with histologically confirmed primary, recurrent, or residual unresectable meningioma were eligible if they had measurable or evaluable disease by computed tomography or magnetic resonance imaging, received radiotherapy for the disease at least 1 year before study enrollment (unless radiotherapy was either inappropriate because of tumor location or declined by patient), documented evidence of disease recurrence or progression within 2 years of random assignment, and performance status of 0 to 2. Adequate hematologic, renal, and hepatic functions were required. Patients were ineligible if they had adrenal insufficiency requiring corticosteroid replacement therapy, known allergy to mifepristone, any additive or ablative modulation of sex hormones or glucocorticoid pathway (excluding stable corticosteroids for cerebral edema), received prior cytotoxic chemotherapy or prior mifepristone for meningioma, other prior or concurrent malignancy within the preceding 5 years (except for surgically treated squamous or basal cell skin cancer or cervical cancer in situ), or meningiomatosis or malignant meningioma. Patients agreed to use a nonhormonal contraceptive method or abstinence during and for 3 months after study therapy. Women who were pregnant or lactating were excluded. Tissue blocks were requested to be submitted if available for assessment of estrogen and progesterone receptors.

The study was approved by the institutional review boards of participating SWOG member sites, and all patients provided informed written consent in accordance with institutional and federal guidelines. The study followed ethical guidelines for placebo-controlled trials, as described in the Declaration of Helsinki. The study was registered with Clinical Trials.gov.

Treatment Plan

Patients were randomly assigned to either oral mifepristone 200 mg daily or placebo for 2 years (Fig 1). The dose of 200 mg was chosen for its antiprogesterone activity and its minimal antiglucocorticoid activity.[22] Patients carried a warning card to alert medical personnel that the investigational treatment could cause subclinical adrenal insufficiency and to recommend administration of exogenous glucocorticoids in case of emergency. After 2 years, patients with stable or responding disease had the option to continue with the same blinded therapy without breaking the randomization code. The randomization code was broken on disease progression. Patients who experienced progression with placebo had the option to cross over and begin daily open-label mifepristone at 200 mg. When disease progressed during mifepristone, patients were taken off study treatment and observed for survival.

Patient Follow-Up and Evaluation

Patients were assessed monthly with complete physical, gynecologic, and neurologic examinations during the first year and every 3 months during the next year. All eligible patients were assessed for toxicities using National Cancer Institute Common Toxicity Criteria (version 2.0). Hematologic, renal, and hepatic functions were tested every 3 months and thyroid and adrenal functions every 6 months. Tumor restaging, using the same technique as at baseline, and automated visual field examination (if vision abnormalities were noted at baseline) were repeated every 6 months. Pill count was performed at each visit. Patients who continued therapy past 2 years were observed on the same schedule, with imaging performed annually.

Criteria for Response

Complete response (CR) was defined as complete disappearance of tumor on computed tomography or magnetic resonance imaging scan. Partial response (PR) was defined as ≥ 50% reduction of the sum of the products of the perpendicular diameters of measurable lesions with no significant neurologic deterioration. For CR or PR, response was confirmed with subsequent examination 4 weeks after first documentation of response. Progressive disease was defined as one of the following: > 25% increase or an increase of 10 cm^2 (whichever was smaller) in the sum of products of perpendicular diameters of measurable lesions over the smallest sum observed, reappearance of any lesion that had disappeared, clear worsening of any evaluable disease, or significant neurologic deterioration. Stable disease was defined as anything else.

Statistical Considerations

At the time of random assignment, patients were stratified by sex and menopausal status (male *v* premenopausal female *v* postmenopausal female), prior radiotherapy or none, and disease status (documented progressive or recurrent disease *v* new diagnosis).

The primary end point of this study was FFS. OS was also recorded with additional follow-up. The study design called for a 4-year accrual period and 2-year follow-up. Assuming 200 eligible patients and median FFS in the placebo group of 12 months, the study had 83% power to detect a 50% improvement (hazard ratio [HR], 1.5) in favor of mifepristone at the 0.045 level. One

formal interim analysis was planned after 75% of accrual was completed, testing superiority of mifepristone at the 0.01 level (overall level for study, 0.05), with consideration for stopping early in the case of positive results.

OS was defined as the date from registration until date of death resulting from any cause. Patients still known to be alive at the time of analysis were censored at the last known date of contact. FFS was defined as the date from registration to the first date of documented progression, significant neurologic deterioration, discontinuation of treatment for any reason, or death resulting from any cause. Patients still known to be alive without treatment failure were considered to be censored at their last follow-up time. OS and FFS estimates and curves were generated using the Kaplan-Meier method. Comparisons between arms for OS and FFS were analyzed using the Cox proportional hazards model, adjusting for the variables used in stratification at time of random assignment.

RESULTS

Patient Characteristics

A total of 193 patients were enrolled between 1992 and 1998. In April 1996, the formal interim analysis was presented to the data and safety monitoring committee, and the trial continued. Of 193 patients, 29 were not eligible (Fig 1) and were excluded from these analyses. Characteristics of eligible patients are listed in Table 1. Treatment and placebo arms were well balanced with regard to baseline characteristics: age, sex, race, menopausal status, prior radiotherapy, histology, and disease status. A majority of patients were female and postmenopausal. Progesterone receptor status was determined for 85 eligible patients based on submitted specimens assessed centrally. Of these, 88% had overexpression of the progesterone receptor and 5% had overexpression of the estrogen receptor by immunohistochemistry.

Table 1. Patient Demographic and Clinical Characteristics (N = 164)

Characteristic	Mifepristone (n = 80)	Placebo (n = 84)	*P*
Age, years			.27
Median	60.6	53.2	
Range	30.7-79.6	20.6-87.1	
Sex			.89
Male	23	25	
Female	57	59	
Menopausal status			.36
Premenopausal	14	19	
Postmenopausal	43	40	
Race			.90
White	68	68	
Black	10	14	
Asian	1	1	
Unknown	1	1	
Prior radiotherapy			.75
Yes	22	25	
No	58	59	
Disease status			.54
Progressive or recurrent	65	65	
Newly diagnosed	15	19	
Baseline disease status			.78
Measurable	55	56	
Nonmeasurable	25	28	
Histology			.88
Atypical meningioma	8	9	
Meningioma NOS	72	75	
Progesterone status	42	43	.48
Positive	36	39	
Negative	6	4	
No/insufficient sample	38	41	

Abbreviation: NOS, not otherwise specified.

Table 2. Treatment Summary

Treatment	Total (N = 164)	Mifepristone (n = 80)	Placebo (n = 84)
Treatment completed as planned at 2 years	52	24	28
Reason for stopping treatment			
Adverse events	8	8	0
Refusal (unrelated to adverse events)	1	0	1
Progression, relapse, or death	77	34	43
Other (not protocol specified)	26	14	12
Total	112	56	56

Clinical Outcome

Eighty eligible patients were assigned to the mifepristone arm and 84 to the placebo arm. Twenty-four patients assigned to mifepristone (30%) received at least 2 years of treatment on study. Thirty-four patients discontinued treatment for disease progression or relapse, eight for intolerable adverse effects, and 14 for various reasons (Table 2). Seventy-one patients receiving mifepristone were assessable for response. One patient (1.4%) had a confirmed PR. One additional patient receiving mifepristone had a shrinkage that was not confirmed with a second assessment. Forty-four patients receiving mifepristone (55%) had stable disease and 25 (31%) had increasing disease as best response. Of the 84 patients assigned to the placebo arm, 28 (33%) received at least 2 years of protocol treatment as planned. Forty-three patients discontinued protocol therapy because of disease progression or death, and 12 were taken off study for various reasons (Table 2). Of

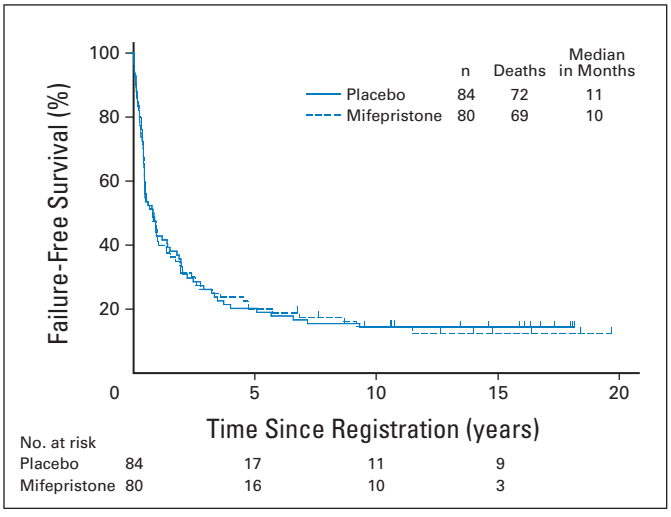

Fig 2. Failure-free survival (FFS) was analyzed using Kaplan-Meier methodology to compare intervention versus placebo. Median FFS: placebo, 11 months (95% CI, 6 to 18 months); mifepristone, 10 months (95% CI, 7 to 13 months).

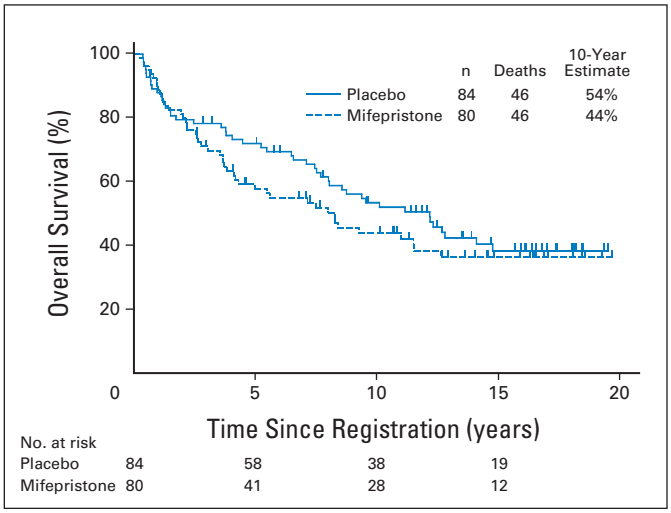

Fig 3. Overall survival (OS) was analyzed using Kaplan-Meier methodology to compare intervention versus placebo. Median OS: placebo, 12 years; mifepristone, 8 years.

73 assessable patients, one patient (1%) had a confirmed PR, 44 (52%) had stable disease, and 28 (33%) had progressive disease.

Median FFS for the placebo arm was 11 months (95% CI, 6 to 18 months); for the mifepristone arm, it was 10 months (95% CI, 7 to 13 months). There was no evidence of superior FFS in the mifepristone arm (two-sided $P = .90$ [adjusted for sex/menopausal status, prior radiotherapy, or disease status]). FFS was nearly the same in the placebo arm, with an estimated mifepristone to placebo HR of 1.02 (95% CI, 0.72 to 1.48; Fig 2). OS was also not significantly better in the mifepristone arm (estimated mifepristone to placebo HR, 1.05; 95% CI, 0.69 to 1.59; two-sided $P = .84$ [adjusted for the same stratification factors]; Fig 3).

Fifty patients who experienced progression with placebo registered for the cross-over phase of the trial. Forty-one patients were eligible and started treatment. Of the 41 patients, six completed the study as planned; 15 patients stopped open-label mifepristone because of disease progression, and no responses were noted.

Table 3. Major Adverse Events

Adverse Event	No. (%) Mifepristone (n = 80)	No. (%) Placebo (n = 84)
Grade 3	31 (39)	24 (29)
Grade 4	6 (8)	1 (6)
Neurologic*		
Headache	36 (45)	35 (42)
Weakness (motor neuropathy)	23 (29)	14 (17)
Dizziness	23 (29)	20 (24)
Ataxia	21 (26)	17 (20)
Mood or consciousness change	19 (24)	16 (19)
Pain	16 (20)	11 (13)
Other*		
Fatigue	60 (75)	46 (55)
Hot flashes	31 (39)	22 (26)
Nausea	25 (31)	21 (25)
Alopecia	22 (28)	9 (11)
Menses change	14 (18)	12 (14)
Gynecomastia	13 (16)	9 (11)

*Grade 1 to 4 in ≥ 15% of patients.

Safety Profile

Most common adverse events are listed in Table 3. There were more adverse effects with mifepristone; most were mild (Table 3; Appendix Table A1, online only). In the placebo arm, 24 patients (29%) reported grade 3 adverse events, and one patient (1%) reported grade 4. With mifepristone, 31 (39%) and six patients (8%) experienced grade 3 or 4 adverse events (χ^2 $P = .03$), respectively. There were no grade 5 events related to treatment. Thirty-six of the 41 patients who crossed over were assessed for toxicities; 11 (31%) and two (6%) experienced grade 3 or 4 adverse events with mifepristone, respectively.

Grade 3 and 4 events likely related to mifepristone (and not seen in patients receiving placebo) included infection (n = 4), cardiac ischemia (n = 3), thrombosis (n = 2), and epistaxis (n = 1). Endocrine-related events were mildly increased with mifepristone and consisted of alopecia, gynecomastia, hot flashes, and vaginal bleeding. Nausea, vomiting, and fatigue were also reported more commonly in patients receiving mifepristone.

DISCUSSION

The diagnosis of meningioma is usually incidental or results from a constellation of neurologic symptoms. Several studies have reported the natural history of meningioma.[23-27] In the largest study of 273 tumors in 244 patients managed conservatively, linear growth was seen in 44% of the tumors and volumetric growth seen in 73% of the patient cases within 4 years.[25] Patient characteristics in our study were comparable to Central Brain Tumor Registry of the United States (CBTRUS) data: higher female to male ratio, advanced age, and majority white. The CBTRUS is the largest database collected from the SEER program and the National Program of Cancer Registries.[28,29]

This randomized study was an attempt to use the biologic evidence of a hormonal environment to treat meningioma. Epidemiologic and observational studies have suggested a role for hormonal modulation in the development and progression of meningioma.[4,30-33] A previous phase II study suggested good tolerability and modest clinical improvement[21] and served as the basis for this prospective, randomized phase III trial. In the phase II study of 28 patients with unresectable meningioma,[21] eight patients achieved minor responses, with maximal reduction in tumor area of 10%. Most responders were men or premenopausal women. The results of our randomized trial failed to confirm the efficacy of progesterone modulation by oral mifepristone in stabilizing unresectable meningioma.

The strenghts of our study are the prospective randomized design and multiple participating institutions. It is also the only phase III trial to our knowledge to have been conducted in this patient population. Progesterone receptor status at study entry did not predict for response, because most meningiomas express the progesterone receptor, and patients treated with the progesterone antagonist mifepristone did not fare better than patients receiving placebo. Progesterone receptors are expressed predominantly in

Table 4. Summary of Current Clinical Trials (targeted therapy) for Meningioma

Drug	Mechanism	Total No. of patients	Meningioma Grade	No. of Patients	PFS		Median OS (months)	ORR (%)
					Median (months)	6 Months (%)		
Imatinib[37]	PDGFR inhibitor	22	I	12	3	45	—	SD, 47; no CR or PR
			II/III	10	2	0	—	
Erlotinib or gefitinib[38]	EGFR inhibitor	25	I	8	2.25	25	13	SD, 32; no objective responses
			II/III	17	4	29	33	
Imatinib plus hydroxyurea[39]	PDGFR-positive cytotoxic	21	I	8	13.9	87.5	66.0	SD, 38
			II/III	13	5.3	46.2	20.9	
Sunitinib[40]	TKI	36	II/III	36	5.2	42	24.6	—
Bevacizumab ± chemotherapy[41,42]	VEGF-A inhibitor	29	I	5	12.2	80	—	SD, 79
			II/III	24	15.8-26	43.8-87.5	—	

Abbreviations: CR, complete response; EGFR, epidermal growth factor receptor; ORR, overall response rate; OS, overall survival; PDGFR, platelet-derived growth factor receptor; PFS, progression-free survival; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor; VEGF-A, vascular endothelial growth factor A.

benign meningiomas with low proliferation indices.[34] Eligibility for our phase III trial required progressive or refractory tumors, which are most likely associated with higher grade. Although the lack of efficacy could have been the result of the loss of progesterone receptor expression in aggressive meningiomas with increased proliferation index and histologic grade,[35] our data do not support the hypothesis, because 88% of patients had progesterone receptor expression in the meningioma. There are at least three isoforms of progesterone receptor in meningioma.[6] Progesterone anticancer activity in hormonally sensitive tumors usually occurs through downregulation of the estrogen receptor, which is present in $< 5\%$ of meningiomas. The progesterone receptor signaling pathway in meningioma does not seem functional, whether related to a lack of estrogen receptor expression, a biologically different progesterone receptor isoform ratio, or an alternative signaling pathway that does not interfere with cell growth. Thus, it is not effectively inhibited by a competitive antagonist,[36] and hormonal modulation may not be the driving force of meningioma progression.

Many small studies of systemic biologic manipulation have recently been performed, rarely on solid mechanistic ground. Most molecules might seem to stabilize disease, but none of them provide survival benefits (Table 4). A few studies have demonstrated that vascular endothelial growth factor A is secreted by meningiomas.[43] Its expression is associated with meningioma vascularity, causing increased tumor size, peritumoral brain parenchyma vascularization, and vascular permeability.[43-46] The use of bevacizumab has been tested in clinical studies for the treatment of meningioma, with disappointing results (Table 4).[41,42,47]

A better understanding of the biologic mechanisms driving meningioma behavior should lead to evidence-based studies. Genomic profiles of meningiomas have recently been published. The tumor suppressor *NF2* is known to be disrupted in approximately half of all meningiomas.[48] Frequent mutations of protein kinase B (*PKB*, also called *AKT1*) and smoothened frizzled family receptor (*SMO*) were seen in patients who did not have *NF2* mutations.[49] Genomic sequencing of a larger set of 50 meningiomas confirmed these results and, in addition to *AKT1* and *SMO* mutations, identified mutations in the tumor necrosis factor receptor associated factor 7 (*TRAF7*), a gene encoding a proapoptotic protein not previously implicated in cancer.[50] Recently, a small-molecule inhibitor of the p21-activated kinase, a validated downstream effector of NF2, showed antitumor activity in NF2-associated schwannoma.[51] One may speculate that this molecule may also have antitumor activity in *NF2*-associated meningioma. In *NF2* wild-type patient cases, targeting the AKT/mammalian target of rapamycin– or SMO-associated hedgehog pathway is a good hypothesis.

In conclusion, the study was the first and only randomized phase III trial to our knowledge to investigate a systemic treatment for meningioma. Despite the presence of progesterone receptors in most meningiomas, mifepristone fails to control the disease. Future studies based on molecular and genetic characteristics will be important to define systemic therapies that have efficacy in treating recurrent, progressive meningioma.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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Manuscript writing: All authors
Final approval of manuscript: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Double-Blind Phase III Randomized Trial of the Antiprogestin Agent Mifepristone in the Treatment of Unresectable Meningioma: SWOG S9005

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Appendix

Accruing institutions for SWOG S9005 study: University of Mississippi Medical Center, University of Southern California School of Medicine, University of California at Los Angeles, Temple University, University of California at Davis, University of Arizona Medical Center, University of Arkansas for Medical Sciences, Loyola University Stritch School of Medicine, Northwest National Cancer Institute (NCI) Community Oncology Research Program (NCORP), Pacific Cancer Research Consortium NCORP, MD Anderson Cancer Center, Atlanta Regional Community Clinical Oncology Program (CCOP), Boston Medical Center, Kansas City NCORP, Oregon Health and Science University, University of Kentucky Medical Center, Columbia University, University of New Mexico, University of Oklahoma Health Science Center, University of Texas Southwestern Medical Center, University of Texas Health Science Center at San Antonio, University of South Alabama Cancer Center Minority-Based CCOP, University of Texas Medical Branch at Galveston, Upstate Carolina CCOP, Brooke Army Medical Center, Cleveland Clinic Foundation, Bay Area Tumor Institute, Cancer Research for the Ozarks NCORP, Kings County CCOP, Louisiana State University Medical Center, NCORP of the Carolinas (Greenville Health System), Santa Rosa Memorial Hospital Regional CCOP, Scott and White Clinic CCOP, St Louis–Cape Girardeau CCOP, Sutter Cancer Research Consortium, University of Colorado Cancer Center, University of Michigan Medical Center, University of Utah Medical Center, University of Vermont, Wayne State University Medical Center, Wichita NCI Community Oncology Research, Henry Ford Hospital, and Eastern Cooperative Oncology Group/American College of Radiology Imaging Network.

Table A1. All Adverse Events

	Mifepristone (n = 80)					Placebo (n = 84)				
	Grade					Grade				
Adverse Event	Unknown	≤ 2	3	4	5	Unknown	≤ 2	3	4	5
Anorexia	2	78	0	0	0	4	80	0	0	0
Endocrine, other	1	78	1	0	0	0	84	0	0	0
Eye, other	1	79	0	0	0	0	83	1	0	0
Seizures	1	78	1	0	0	0	83	1	0	0
Abdominal pain or cramping	0	79	1	0	0	0	84	0	0	0
Alkaline phosphatase increase	0	80	0	0	0	0	84	0	0	0
Alopecia	0	80	0	0	0	0	84	0	0	0
Anemia	0	79	1	0	0	0	84	0	0	0
Anxiety or agitation	0	80	0	0	0	0	84	0	0	0
Arthralgia	0	80	0	0	0	0	84	0	0	0
Ataxia (incoordination)	0	75	5	0	0	0	81	3	0	0
Bilirubin increase	0	80	0	0	0	0	84	0	0	0
Blurred vision	0	80	0	0	0	0	84	0	0	0
Bone pain	0	80	0	0	0	0	84	0	0	0
Cardiac ischemia or infarction	0	78	0	2	0	1	83	0	0	0
Confusion	0	77	3	0	0	0	81	2	1	0
Conjunctivitis	0	80	0	0	0	0	84	0	0	0
Constipation or bowel obstruction	0	80	0	0	0	0	84	0	0	0
Cough	0	80	0	0	0	0	84	0	0	0
Creatinine increase	0	80	0	0	0	0	84	0	0	0
Depression	0	80	0	0	0	0	84	0	0	0
Diarrhea without colostomy	0	80	0	0	0	0	84	0	0	0
Dizziness or light headedness	0	80	0	0	0	0	84	0	0	0
Dizziness or vertigo, NOS	0	78	1	1	0	1	80	3	0	0
Double vision	0	80	0	0	0	0	84	0	0	0
Dry eyes	0	80	0	0	0	0	84	0	0	0
Dry skin	0	80	0	0	0	0	84	0	0	0
Dyspepsia or heartburn	0	80	0	0	0	0	84	0	0	0
Dyspnea	0	80	0	0	0	0	84	0	0	0
Ear, other	0	80	0	0	0	0	83	1	0	0
Edema	0	80	0	0	0	0	84	0	0	0
Epistaxis	0	79	0	1	0	0	84	0	0	0
Erythema, rash, eruption, or desquamation, NOS	0	79	1	0	0	0	82	2	0	0
Erythema multiforme or blistering	0	80	0	0	0	0	84	0	0	0
Fatigue, malaise, or lethargy	0	76	4	0	0	1	77	6	0	0
Flu-like symptoms, other	0	80	0	0	0	0	84	0	0	0

(continued on following page)

Table A1. All Adverse Events (continued)

Adverse Event	Mifepristone (n = 80)					Placebo (n = 84)				
	Grade					Grade				
	Unknown	≤ 2	3	4	5	Unknown	≤ 2	3	4	5
GI, other	0	80	0	0	0	0	84	0	0	0
Gastritis or ulcer, NOS	0	80	0	0	0	0	84	0	0	0
Gynecomastia	0	80	0	0	0	0	84	0	0	0
Headache	0	78	2	0	0	0	77	7	0	0
Hot flashes	0	77	3	0	0	0	82	2	0	0
Hyperglycemia	0	79	1	0	0	0	84	0	0	0
Hyperkalemia	0	80	0	0	0	0	84	0	0	0
Hypertension	0	80	0	0	0	0	84	0	0	0
Hyponatremia	0	80	0	0	0	0	83	1	0	0
Hypothyroidism	0	80	0	0	0	1	83	0	0	0
Incontinence	0	80	0	0	0	0	84	0	0	0
Infection without grade 3 to 4 neutropenia	0	78	2	0	0	0	84	0	0	0
Inner ear, hearing loss	0	77	3	0	0	0	83	1	0	0
Insomnia	0	79	1	0	0	0	84	0	0	0
Leukopenia	0	80	0	0	0	0	84	0	0	0
Libido loss	0	80	0	0	0	0	84	0	0	0
Memory loss	0	79	1	0	0	0	84	0	0	0
Menses changes	0	71	9	0	0	1	78	5	0	0
Metabolic, other	0	80	0	0	0	0	83	1	0	0
Middle ear, hearing loss or otitis	0	80	0	0	0	0	84	0	0	0
Mood or consciousness change, NOS	0	78	1	1	0	0	82	2	0	0
Muscle weakness (not neurologic)	0	79	1	0	0	0	84	0	0	0
Myalgia or arthralgia, NOS	0	80	0	0	0	0	84	0	0	0
Nausea	0	78	2	0	0	0	83	1	0	0
Neurologic, other	0	78	2	0	0	0	84	0	0	0
Neutropenia or granulocytopenia	0	80	0	0	0	0	84	0	0	0
Night blindness	0	80	0	0	0	0	84	0	0	0
Nystagmus	0	80	0	0	0	0	84	0	0	0
Pain, other	0	80	0	0	0	0	83	1	0	0
Personality or behavioral change	0	79	1	0	0	0	84	0	0	0
Pruritus	0	80	0	0	0	0	84	0	0	0
Pyramidal tract dysfunction	0	80	0	0	0	0	84	0	0	0
Rash or desquamation	0	80	0	0	0	0	84	0	0	0
Rectal bleeding or hematochezia	0	80	0	0	0	0	84	0	0	0
Respiratory infect without neutropenia	0	80	0	0	0	0	84	0	0	0
AST increase	0	80	0	0	0	0	84	0	0	0
Sensory neuropathy	0	79	1	0	0	0	82	2	0	0
Skin, other	0	80	0	0	0	0	84	0	0	0
Somnolence or consciousness loss	0	80	0	0	0	0	84	0	0	0
Speech impairment	0	78	2	0	0	0	84	0	0	0
Sweating	0	80	0	0	0	0	84	0	0	0
Taste disturbance	0	80	0	0	0	0	84	0	0	0
Thrombocytopenia	0	80	0	0	0	0	84	0	0	0
Thrombosis or embolism	0	79	0	1	0	0	84	0	0	0
Toxicity of unknown category	0	80	0	0	0	0	84	0	0	0
Tremor	0	80	0	0	0	0	84	0	0	0
Urinary frequency or urgency	0	80	0	0	0	0	84	0	0	0
Urinary retention	0	80	0	0	0	0	84	0	0	0
Urinary tract infection without neutropenia	0	80	0	0	0	0	84	0	0	0
Vaginal bleeding	0	78	2	0	0	1	83	0	0	0
Vision, NOS	0	78	2	0	0	0	83	1	0	0
Vision, flashing or floaters	0	80	0	0	0	0	84	0	0	0
Vomiting	0	79	1	0	0	0	84	0	0	0
Weakness (motor neuropathy)	0	76	4	0	0	0	80	4	0	0
Weight gain	0	80	0	0	0	0	84	0	0	0
Weight loss	0	80	0	0	0	0	84	0	0	0
Maximum-grade any adverse event	0	43	31	6	0	0	59	24	1	0

Abbreviation: NOS, not otherwise specified.