Phase II study of monthly pasireotide LAR (SOM230C) for recurrent or progressive meningioma

Andrew D. Norden, MD, MPH
Keith L. Ligon, MD, PhD
Samantha N. Hammond, BA
Alona Muzikansky, MA
David A. Reardon, MD
Thomas J. Kaley, MD
Tracy T. Batchelor, MD, MPH
Scott R. Plotkin, MD, PhD
Jeffrey J. Raizer, MD
Eric T. Wong, MD
Jan Drappatz, MD
Glenn J. Lesser, MD
Sam Haidar, BS
Rameen Beroukhi, MD, PhD
Eudocia Q. Lee, MD, MPH
Lisa Doherty, MSN
Debra LaFrankie, RN, OCN
Sarah C. Gaffey, BA, BS
Mary Gerard, BA
Katrina H. Smith, BS
Christine McCluskey, BA
Surasak Phuphanich, MD
Patrick Y. Wen, MD

Correspondence to
Dr. Wen:
pwen@partners.org

Supplemental data
at Neurology.org

ABSTRACT

Objective: A subset of meningiomas recur after surgery and radiation therapy, but no medical therapy for recurrent meningioma has proven effective.

Methods: Pasireotide LAR is a long-acting somatostatin analog that may inhibit meningioma growth. This was a phase II trial in patients with histologically confirmed recurrent or progressive meningioma designed to evaluate whether pasireotide LAR prolongs progression-free survival at 6 months (PFS6). Patients were stratified by histology (atypical [World Health Organization grade 2] and malignant [grade 3] meningiomas in cohort A and benign [grade 3] in cohort B).

Results: Eighteen patients were accrued in cohort A and 16 in cohort B. Cohort A had median age 59 years, median Karnofsky performance status 80, 17 (94%) had previous radiation therapy, and 11 (61%) showed high octreotide uptake. Cohort B had median age 52 years, median Karnofsky performance status 90, 11 (69%) had previous radiation therapy, and 12 (75%) showed high octreotide uptake. There were no radiographic responses to pasireotide LAR therapy in either cohort. Twelve patients (67%) in cohort A and 13 (81%) in cohort B achieved stable disease. In cohort A, PFS6 was 17% and median PFS 15 weeks (95% confidence interval: 8–20). In cohort B, PFS6 was 50% and median PFS 26 weeks (12–43). Treatment was well tolerated. Octreotide uptake and insulin-like growth factor-1 levels did not predict outcome. Expression of somatostatin receptor 3 predicted favorable PFS and overall survival.

Conclusions: Pasireotide LAR has limited activity in recurrent meningiomas. The finding that somatostatin receptor 3 is associated with favorable outcomes warrants further investigation.

Classification of evidence: This study provides Class IV evidence that in patients with recurrent or progressive meningioma, pasireotide LAR does not significantly increase the proportion of patients with PFS at 6 months. *Neurology*® 2015;84:280–286

GLOSSARY

CI = confidence interval; **IGF-1** = insulin-like growth factor-1; **OS** = overall survival; **PFS** = progression-free survival; **PFS6** = progression-free survival at 6 months; **RANO** = Response Assessment in Neuro-Oncology; **SSTR** = somatostatin receptor; **WHO** = World Health Organization.

Meningiomas are the most common type of benign primary brain tumors in adults.¹ Surgical resection is the treatment of choice, and gross total resection is predictive of long-term disease-free survival. Atypical (World Health Organization [WHO] grade 2) and malignant meningiomas (WHO grade 3) confer low rates of long-term survival, especially when gross total resection is not achieved. The typical treatment approach for recurrent disease includes reoperation, frequently accompanied by radiation therapy or stereotactic radiosurgery. These interventions delay a subsequent recurrence but rarely prevent it entirely. When surgery and radiation therapy are no longer

From the Division of Cancer Neurology, Department of Neurology (A.D.N., E.Q.L., P.Y.W.), and Departments of Pathology (K.L.L.) and Medicine (R.B.), Brigham and Women's Hospital, Boston, MA; Center for Neuro-Oncology (A.D.N., S.N.H., D.A.R., R.B., E.Q.L., L.D., D.L., M.G., K.H.S., C.M., P.Y.W.), Dana-Farber/Brigham and Women's Cancer Center; Department of Medicine (R.B.), Harvard Medical School (A.D.N., K.L.L., D.A.R., T.T.B., S.R.P., E.T.W., R.B., E.Q.L., P.Y.W.), Boston; Department of Medical Oncology, Center for Molecular Oncologic Pathology (K.L.L., S.H.), and Departments of Medical Oncology and Cancer Biology (R.B.), Dana-Farber Cancer Institute, Boston; Massachusetts General Hospital Biostatistics Center (A.M.); Brain Tumor Center (T.J.K.), Memorial Sloan-Kettering Cancer Center, New York, NY; Pappas Center for Neuro-Oncology (T.T.B., S.R.P.), Massachusetts General Hospital, Boston; Department of Neurology (J.J.R.), Northwestern University Feinberg School of Medicine, Chicago, IL; Brain Tumor Center (E.T.W.), Beth-Israel Deaconess Medical Center, Boston; Adult Neuro-Oncology Program (J.D.), University of Pittsburgh Medical Center, Pittsburgh, PA; Comprehensive Cancer Center (G.J.L.), Wake Forest University Baptist Medical Center, Winston-Salem, NC; and Departments of Neurosurgery and Neurology (S.P.), Cedars-Sinai Medical Center, Los Angeles, CA.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

available, patients with meningiomas have very few treatment options. A variety of cytotoxic chemotherapy agents and targeted molecular therapies have been tried without evidence of efficacy.²⁻⁴ The failure to find effective targeted agents is disappointing in light of major recent advances in understanding the biology and molecular pathogenesis of meningiomas.^{5,6} In a recent study of the platelet-derived growth factor receptor inhibitor imatinib for recurrent meningiomas, overall median progression-free survival (PFS) was only 2 months, and 6-month PFS (PFS6) was 29%.⁷ There were no radiographic responses. For benign meningiomas, median PFS was 3 months, and PFS6 was approximately 40%. For atypical and malignant meningiomas, median PFS was 2 months, and PFS6 was 0%. The Response Assessment in Neuro-Oncology (RANO) Working Group recently analyzed all of the published clinical trials of medical therapy in recurrent meningioma and calculated weighted PFS6 averages to be used as benchmarks for future studies. The suggested benchmarks are 29% for benign (WHO grade 1) meningiomas and 26% for atypical and malignant tumors.⁸

Nearly 90% of meningiomas express somatostatin receptors, especially the sst2A subtype. This accounts for the antiproliferation effects of somatostatin on meningioma cells *in vitro*.^{9,10} A recent pilot study examined the impact of a sustained-release somatostatin preparation (Sandostatin LAR; Novartis, East Hanover, NJ) on 16 patients with recurrent meningiomas.¹¹ To confirm that all of the tumors expressed somatostatin receptors, indium 111-octreotide gamma scanning was performed. After 3 months of therapy, nearly one-third of patients had achieved partial response and similar proportions had stable disease and progressive disease. The drug was very well tolerated, and the cohort had a PFS6 of 44%, which is superior to previously published results.

Similar to octreotide, pasireotide LAR (Signifor LAR, Novartis) has a favorable adverse-effect profile. Pasireotide LAR exhibits a binding affinity for human somatostatin receptors 1, 3, and 5 that is substantially higher than octreotide. This suggests that pasireotide may be more effective against meningioma, as has been observed in some cases of metastatic carcinoid tumors.¹²

Therefore, we designed an open-label, single-arm, phase II study of monthly pasireotide LAR for patients with recurrent or progressive meningioma. The primary endpoint was PFS6, and patients were stratified into 2 cohorts (cohort A: atypical/malignant meningiomas; cohort B: benign meningiomas).

METHODS Primary research question. Does treatment with pasireotide LAR 60 mg IM every month prolong PFS6 in patients with recurrent or progressive meningioma? This study provides Class IV evidence that it does not. In 18 patients with atypical/malignant meningiomas (cohort A), PFS6 was only 17%. In 22 patients with benign meningiomas (cohort B), PFS6 was 50%.

Study objectives. The coprimary objectives were PFS6 in each cohort; secondary objectives were overall survival (OS), radiographic response rate, and safety; and the exploratory objective was to correlate outcome with tumor tissue somatostatin receptor (SSTR) immunohistochemistry, octreotide scanning, and serum insulin-like growth factor-1 (IGF-1) levels.

Eligibility criteria. Subjects were at least 18 years old, had a life expectancy of at least 3 months, and had Karnofsky performance status of at least 60. Eligible subjects had histologically confirmed recurrent or progressive meningioma of any grade. Central pathology review was completed for all subjects (by K.L.). Patients with neurofibromatosis type 2 or a classic radiographic appearance of meningioma were permitted to enroll without histologic confirmation. Subjects were required to have radiographically measurable disease. There was no limit on the number of previous therapies, but previous somatostatin or other hormonal therapies for meningioma were not permitted. At least 4 weeks had to have elapsed from previous antitumor therapy. Subjects were excluded if they had poorly controlled diabetes mellitus, symptomatic cholelithiasis, or QT interval prolongation. Adequate bone marrow and organ function were required.

Treatment plan. Pasireotide LAR (SOM230C) was administered IM every 4 weeks, at a starting dose of 60 mg. Treatment continued until subjects developed progressive disease or unacceptable toxicity. During treatment, physical and neurologic examinations were completed every 3 months after an initial period of bimonthly examinations. Brain imaging with MRI was performed at baseline, after 2 months, and then every 3 months. Serum IGF-1 levels were checked at the same time points. Octreotide scans were performed before the start of therapy, using a 111-indium pentetreotide tracer.

Dose interruption was required for any CTCAE (Common Terminology Criteria for Adverse Events) version 3.0 grade 3 or 4 toxicity judged as at least possibly study drug-related. A dose reduction to 45 mg was required after a treatment delay up to 14 days. A dose reduction to 30 mg was required after a treatment delay of 15 to 28 days. If the toxicity failed to return to grade 1 or less after a 28-day delay, study drug discontinuation was required. Discontinuation was also required for recurrence of the same event after a delay and dose reduction. For subjects who developed hyperglycemia, dose delay and modification were not required unless glucose control could not be achieved despite optimal medical management.

Response assessment and statistical analysis. Responses were assessed using modified Macdonald criteria, in which partial response is defined as at least a 50% reduction in maximum cross-sectional area of enhancing tumor, complete response as

Table 1 Patient characteristics at baseline

	Overall	Cohort A	Cohort B
Participants	34	18	16
Median age, y	54	59	52
Age range, y	36–81	39–74	36–81
Male/female ratio	17:17	8:10	9:7
Median KPS score	85	80	90
KPS range	60–100	60–100	70–100
Median duration of disease, y	5.8	5.4	5.9
Duration of disease, range	0–30	2–30	0–24
Previous systemic therapy	13 (38)	10 (56)	3 (19)
Previous radiation therapy	28 (82)	17 (94)	11 (69)
Previous therapeutic surgery (resection, not biopsy only)	33 (97)	17 (94)	16 (100)

Abbreviation: KPS = Karnofsky performance status.

Data are n (%) unless otherwise indicated. Cohort A (World Health Organization grade 2/3); cohort B (World Health Organization grade 1).

elimination of enhancing tumor, progressive disease as at least a 25% increase in maximum cross-sectional area of enhancing tumor, and stable disease as all other conditions.¹³ Patients were stratified into 2 cohorts with a planned sample size of 40 patients (cohort A: 18 atypical/malignant meningiomas; cohort B: 22 benign meningiomas). Subjects who received at least one dose of pasireotide LAR were evaluable for toxicity and response. In cohort A, the sample size was calculated to have 83% power to detect a difference between the null hypothesis (PFS6 = 5%) and the alternative hypothesis (PFS6 = 30%) using a one-sided, binomial hypothesis test with a target significance level of 0.05. In cohort B, the sample size was calculated to have 81% power to detect a

difference between the null hypothesis (PFS6 = 40%) and the alternative hypothesis (PFS6 = 70%) using a one-sided, binomial hypothesis test with a significance level of 0.05. Descriptive statistics were used to summarize results. The Kaplan-Meier technique was used to estimate PFS and OS. The 95% confidence intervals (CIs) were calculated for all point estimates.

Immunohistochemistry. Immunohistochemistry of tumor samples was performed according to a previously published protocol.^{14,15} Rabbit monoclonal primary antibodies included anti-SSTR1 (Abcam ab137083, 1:30), anti-SSTR2a (Abcam ab134152, 1:100), anti-SSTR3 (Abcam ab137026, 1:500), and anti-SSTR5 (Abcam ab109495, 1:600). Antibody binding was detected using a diaminobenzidine-peroxidase visualization system (EnVision+; Dako, Carpinteria, CA). Mayer's hematoxylin was used for counterstaining.

Immunoreactivity was scored manually and semiquantitatively and took into account the percentage of tumor cells stained and the intensity of the stain. Staining percentage scoring was as follows: 0 = no tumor cells demonstrating membranous/cytoplasmic positivity; 1+ = <10% tumor cells positive; 2+ = 10%–70% tumor cells positive; and 3+ = >70% tumor cells positive. The staining intensity of immunoreactive cells was scored using a 3-level scale: 1+ = weak intensity; 2+ = intermediate intensity; and 3+ = strong intensity. All intensities were relative to control staining in human pancreas islet cells. Univariate Cox regression models were constructed to assess the statistical relationships between SSTR levels and PFS or OS.

Standard protocol approvals, registrations, and patient consents. The study was approved by institutional review boards at all of the participating sites. Written informed consent was obtained from all participants. The study is registered in ClinicalTrials.gov (NCT00859040).

RESULTS Patient characteristics. Eighteen patients were accrued to cohort A (12 atypical meningiomas and 6 malignant meningiomas) and 16 to cohort B between March 2009 and June 2011 at 8 brain tumor centers in the United States. Cohort B was halted prematurely because of slow accrual and lack of efficacy observed in cohort A. Patient characteristics are summarized in table 1. Overall, the population was heavily pretreated with previous radiation therapy (n = 17, 94%) and previous systemic therapy (n = 10, 56%) in the majority of cohort A subjects. Cohort B was also pretreated but had lower rates of radiation therapy (n = 11, 69%) and systemic therapy (n = 3, 19%). In cohort A, 5 patients (28%) had 3 or more previous radiation therapies and more than one previous systemic therapy. Patients had many prior surgical resections, with a range of 0–12 operations (median 2), and 6 patients study-wide (18%) had 4 or more operations.

Response and survival. The majority of patients came off treatment because of progressive disease (n = 28, 82%). Other reasons for completion of study therapy included withdrawal of consent to pursue alternative therapy (n = 1), unacceptable toxicity (n = 2), and physician decision (n = 1). Two patients remain on treatment at the time of analysis.

Figure 1 Progression-free survival

Kaplan-Meier curve showing progression-free survival stratified by cohort.

Table 2 Adverse events judged at least possibly related to pasireotide LAR

Adverse event	No. of events (no. of patients affected)			
	Grade 1	Grade 2	Grade 3	Grade 4
Abdominal distention/bloating	1 (1)	0	0	0
Abdominal pain	5 (3)	1 (1)	0	0
Alkaline phosphatase	1 (1)	0	0	0
Allergic reaction	1 (1)	0	0	0
ALT, SGPT	3 (3)	0	0	0
Amylase	1 (1)	0	1 (1)	0
Anorexia	2 (2)	0	0	0
Arthritis	8 (1)	0	0	0
AST, SGOT	2 (2)	0	0	0
CPK	1 (1)	0	0	0
Diarrhea	37 (11)	0	0	0
Dizziness	1 (1)	0	0	0
Dry skin	1 (1)	0	0	0
Dyspepsia	1 (1)	0	0	0
Fatigue	7 (6)	1 (1)	2 (2)	0
Flatulence	5 (5)	0	0	0
GGT	2 (2)	2 (2)	0	0
GI, other	6 (1)	0	0	0
Headache	3 (3)	0	0	0
Hemoglobin	2 (2)	0	0	0
Hypercalcemia	1 (1)	0	0	0
Hypercholesterolemia	4 (4)	0	0	0
Hyperglycemia	17 (12)	11 (6)	7 (5)	1 (1)
Hyperthyroidism	1 (1)	0	0	0
Hypertriglyceridemia	1 (1)	0	0	0
Hypoglycemia	1 (1)	1 (1)	0	1 (1)
Hypokalemia	0	0	1 (1)	0
Incontinence, anal	2 (1)	0	0	0
Injection site reaction	2 (1)	0	0	0
Leukocytes	1 (1)	0	0	0
Lipase	2 (2)	2 (1)	3 (2)	0
Muscle pain	1 (1)	0	0	0
Muscle weakness	1 (1)	1 (1)	0	0
Nausea	10 (7)	0	0	0
Pain, other	2 (2)	0	0	0
Platelets	1 (1)	0	0	0
Sinus bradycardia	1 (1)	1 (1)	0	0
Vomiting	2 (2)	0	0	0

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; GGT = gamma glutamyl transpeptidase; GI = gastrointestinal; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase.

There were no radiographic responses. Of 32 evaluable patients, 24 (75%) had stable disease as their best response. Twelve patients in cohort A (67%) achieved stable disease for a median of 4 cycles (range 2–12), and 13 patients in cohort B (81%) achieved stable disease for a median of 7 cycles (range 2–35).

At the time of analysis, 15 patients (44%) had died, 10 in cohort A and 5 in cohort B. Overall, median OS was not reached, median PFS was 18 weeks (95% CI: 10–20), and PFS6 was 32%. In cohort A, median OS was 104 weeks (77–158), median PFS was 15 weeks (8–20), and PFS6 17%. In cohort B, median OS was not yet reached, median PFS was 26 weeks (12–43), and PFS6 was 50%. PFS data are summarized in figure 1.

Toxicity. The treatment was generally well tolerated. Adverse events that were at least possibly related to pasireotide LAR are summarized in table 2. Serious events occurred in small numbers and included hyperglycemia, hypoglycemia, elevated amylase, elevated lipase, fatigue, and hypokalemia. Two patients discontinued study treatment because of toxicity (one with persistent grade 3 amylase and one with persistent grade 3 lipase). Had a third patient not progressed, he would have come off of treatment as well because of persistent grade 3 lipase. There were no treatment-related deaths. Common, mild toxicities included fatigue, nausea, diarrhea, flatulence, abdominal pain, headache, transaminase elevation, and hyperglycemia.

Exploratory studies. Serum IGF-1 levels were checked at baseline and every 3 months. In 25 cases, 2 or more measurements were obtained. The IGF-1 level decreased in all but 5 (20%) of these cases (figure 2). There was no relationship observed between the direction or magnitude of IGF-1 level change and PFS.

Baseline octreotide scans revealed at least intermediate octreotide uptake in 30 of 32 (94%) tumors (table e-1 on the *Neurology*® Web site at Neurology.org). Octreotide uptake did not correlate with PFS.

Immunohistochemistry stains were scored as described above and then scores were analyzed as continuous variables (figure 3, table e-2). Percentage of staining for SSTR3 was predictive of favorable OS (hazard ratio 0.44, $p = 0.02$) and PFS (hazard ratio 0.64, $p = 0.04$). SSTR1, SSTR2, SSTR4, and SSTR5 staining were not predictive. For subjects whose tumors showed no SSTR3 staining, PFS6 was 10%; for subjects whose tumors showed any SSTR3 staining, PFS6 was 37% ($p = 0.07$). Other comparisons and multivariate analysis could not be performed because of inadequate sample size.

DISCUSSION In this phase 2 study of pasireotide LAR for recurrent meningioma, there was no definite evidence of antitumor activity. None of the subjects

Figure 2 Percent change in IGF-1 levels

Plot showing percent change in IGF-1 level for each subject in whom serial IGF-1 measurements were obtained. IGF-1 = insulin-like growth factor-1.

had radiographic responses. In cohort A, PFS6 was 17%, and in cohort B, PFS6 was 50%. Interpreting PFS results in meningioma trials has been challenging because there are no large, historical datasets for comparison. The benchmarks suggested by the RANO Working Group will be helpful in this regard.⁸ It is important to note that the heterogeneity inherent in

published studies results in wide CIs around the RANO benchmarks (benign meningiomas: 29% [95% CI: 20%–38%]; atypical/malignant meningiomas: 26% [95% CI: 19%–33%]). This degree of variability makes it possible to miss a weak efficacy signal, particularly in the context of a relatively small sample size. The RANO report suggests that a PFS6 <30% should be considered “not of interest” in studies of atypical/malignant meningiomas. For benign meningiomas, a rate <40% would not be of interest but >50% would “probably be of interest.” The current PFS6 result of 17% in cohort A is far from the 30% threshold for potential efficacy established by RANO. In cohort B, the PFS6 result is 50%, which might be considered borderline in comparison to the RANO benchmark for benign meningiomas. Considering both cohorts together and the relatively small sample size, we do not recommend further investigation of pasireotide in unselected patients with recurrent meningioma.

It is also important to note that there are no accepted and widely available response criteria for use in meningioma clinical trials,¹⁶ although the RANO Working Group is in the process of developing them. While volumetric measurements might be more accurate than the 2-dimensional Macdonald criteria measurements developed for use in glioma trials, practical concerns mandated that we use the more traditional 2-dimensional approach. Given the short PFS times reported here, it seems doubtful that

Figure 3 SSTR immunohistochemical stains

Examples of spectrum of immunohistochemical staining for SSTRs in meningioma. (A) Hematoxylin & eosin showing typical grade 2 meningioma histology. (B) SSTR1 with no immunoreactivity (score 0). (C) Strong and homogeneous membranous expression of SSTR2, which was seen in a high percentage of cases (intensity and percentage score = 3). (D) Typical diffuse and moderate SSTR3 expression (intensity and percentage score = 3). (E) High power of (D) showing punctate and dot-like SSTR3 signal. (F) SSTR5 with moderate but diffuse signal (intensity and percentage score = 1). SSTR = somatostatin receptor.

the measurement approach we selected accounts for the lack of observed efficacy. In addition, because meningiomas often have inconsistent and unpredictable growth kinetics, future clinical trials may be improved by examining pretreatment growth rates and comparing them with posttreatment growth rates.

In an effort to identify a subgroup of subjects who may benefit from pasireotide LAR therapy, we assessed a number of putative biomarkers including serum IGF-1 levels, octreotide scans, and SSTR immunohistochemistry. Of note, in this dataset, tumors with increased SSTR3 expression showed a possible trend toward more favorable outcomes. Because this was a single-arm study, one cannot necessarily attribute the benefit to pasireotide therapy, because the SSTR3 subgroup might also represent a subgroup with improved prognosis. There are no published data that would help to distinguish between these possibilities. In addition, small sample numbers precluded testing for the proportional hazards assumption or performing multivariate analysis, which would have been required to exclude the possibility that the findings reflect

confounding by known prognostic factors. It is worth noting that earlier reports suggest that SSTR3 may trigger apoptosis via a p53-dependent mechanism.^{9,17} In pituitary tumors, SSTR3 may mediate the antineoplastic effects of somatostatin analogs.^{18,19} This intriguing possibility warrants further investigation.

An unresolved question is how one can reconcile these generally disappointing results with the promising ones reported in a pilot study of sustained-release octreotide.¹¹ That pasireotide has higher sst2A binding affinity than octreotide (1.0 vs 0.4 nmol/L)²⁰ has been used as a rationale for pasireotide therapy. However, recent data suggest that despite both binding with high affinity, octreotide and pasireotide may have different effects on the SSTR.^{21,22} Specifically, after undergoing endocytosis provoked by ligand binding, sst2A receptors appear to return to the plasma membrane much more rapidly when exposed to pasireotide than octreotide.²² In theory, this might increase the availability of functional receptors to bind endogenous ligands. This would not explain why our results are consistent with 2 more recent studies of octreotide for recurrent meningioma in which no compelling evidence of activity was observed.^{23,24}

Despite the limitations noted above, the results of this phase 2 study of pasireotide LAR in patients with recurrent meningioma suggest that the agent has limited activity. It is unclear whether there is a role for other somatostatin analogs in the treatment of meningiomas.

AUTHOR CONTRIBUTIONS

All authors participated in revising the manuscript for content, study concept or design, and analysis or interpretation of data.

ACKNOWLEDGMENT

The authors are grateful to Herbert Schmid for sharing immunohistochemistry data in advance of publication.

STUDY FUNDING

This study was supported by Novartis.

DISCLOSURE

A. Norden is a consultant for Parexel. K. Ligon, S. Hammond, and A. Muzikansky report no disclosures relevant to the manuscript. D. Reardon has served on an advisory board for Novartis. T. Kaley, T. Batchelor, S. Plotkin, J. Raizer, E. Wong, J. Drappatz, G. Lesser, and S. Haider report no disclosures relevant to the manuscript. R. Beroukhi consults for and receives grant funding from Novartis. E. Lee, L. Doherty, D. Lafrankie, S. Gaffey, M. Gerard, K. Smith, C. McCluskey, and S. Phuphanich report no disclosures relevant to the manuscript. P. Wen has research support from Novartis and served on its advisory board. Go to Neurology.org for full disclosures.

Received April 17, 2014. Accepted in final form September 10, 2014.

REFERENCES

1. CBTRUS. Statistical Report: Primary Brain Tumors in the United States, 2004–2008. Hinsdale, IL: Central Brain Tumor Registry of the United States; 2012.

Comment: Medical therapy for recurrent or progressive meningiomas remains elusive

Patients with recurrent or progressive meningiomas who are no longer candidates for further surgical resection, radiation therapy, or radiosurgery have limited treatment options, with no approved medical therapies or standards of care. This well-conducted multicenter single-arm phase II study evaluated whether the long-acting somatostatin analog pasireotide LAR had any efficacy in this patient population.¹ Somatostatin receptors are widely expressed in meningiomas and somatostatin analogs have antimeningioma activity in vitro and in small clinical series.

Eighteen patients with atypical (grade 2) or malignant (grade 3) meningiomas and 16 with benign (grade 1) tumors received pasireotide LAR monthly at the standard doses used in trials for Cushing disease. Although pasireotide LAR was well-tolerated, there were no radiographic responses and the progression-free survival at 6 months (PFS6) rates were too low (17% of grade 2 or 3 meningiomas and 50% of grade I meningiomas) to suggest efficacy.

There are several unanswered questions on how phase 2 trials can best screen drugs that could be active in meningiomas. A limitation of single-arm phase 2 trials is the lack of good historical control data. The Response Assessment in Neuro-Oncology (RANO) working group has reported PFS6 benchmarks based on available literature.² However, meningiomas have heterogeneous growth kinetics and rare tumor responses with standard therapies; there is no established correlation between PFS6 and survival endpoints; enrollment of patients has been difficult and slow; and existing studies have had variable designs, inclusion criteria, and endpoints. PFS6 may not, therefore, be the best surrogate marker. Better reporting on tumor growth rates at baseline could be useful in evaluating decisions to proceed to larger confirmatory efficacy trials. More well-conducted trials such as the one reported by Norden and colleagues¹ are needed and patients with meningiomas who are not candidates for standard treatments should be encouraged to enroll.

1. Norden AD, Ligon KL, Hammond SN, et al. Phase II study of monthly pasireotide LAR (SOM230C) for recurrent or progressive meningioma. *Neurology* 2015;84:280–286.
2. Kaley T, Barani I, Chamberlain M, et al. Historical benchmarks for medical therapy trials in surgery- and radiation-refractory meningioma: a RANO review. *Neuro Oncol* 2014;16:829–840.

Fabio M. Iwamoto, MD

From the Division of Neuro-oncology, College of Physicians and Surgeons, Columbia University, New York, NY.

Study funding: No targeted funding reported.

Disclosure: The author reports no disclosures. Go to Neurology.org for full disclosures.

2. Norden AD, Drappatz J, Wen PY. Advances in meningioma therapy. *Curr Neurol Neurosci Rep* 2009;9:231–240.
3. Wen PY, Quant E, Drappatz J, Beroukhi R, Norden AD. Medical therapies for meningiomas. *J Neurooncol* 2010;99:365–378.
4. Vogelbaum MA, Leland Rogers C, Linskey MA, Mehta MP. Opportunities for clinical research in meningioma. *J Neurooncol* 2010;99:417–422.
5. Brastianos PK, Horowitz PM, Santagata S, et al. Genomic sequencing of meningiomas identifies oncogenic SMO and AKT1 mutations. *Nat Genet* 2013;45:285–289.
6. Clark VE, Erson-Omay EZ, Serin A, et al. Genomic analysis of non-NF2 meningiomas reveals mutations in TRAF7, KLF4, AKT1, and SMO. *Science* 2013;339:1077–1080.
7. Wen PY, Yung WK, Lamborn KR, et al. Phase II study of imatinib mesylate for recurrent meningiomas (North American Brain Tumor Consortium Study 01–08). *Neuro Oncol* 2009;11:853–860.
8. Kaley T, Barani I, Chamberlain M, et al. Historical benchmarks for medical therapy trials in surgery- and radiation-refractory meningioma: a RANO review. *Neuro Oncol* 2014;16:829–840.
9. Arena S, Barbieri F, Thellung S, et al. Expression of somatostatin receptor mRNA in human meningiomas and their implication in in vitro antiproliferative activity. *J Neurooncol* 2004;66:155–166.
10. Schulz S, Pauli SU, Handel M, Dietzmann K, Firsching R, Holtt V. Immunohistochemical determination of five somatostatin receptors in meningioma reveals frequent overexpression of somatostatin receptor subtype sst2A. *Clin Cancer Res* 2000;6:1865–1874.
11. Chamberlain MC, Glantz MJ, Fadul CE. Recurrent meningioma: salvage therapy with long-acting somatostatin analogue. *Neurology* 2007;69:969–973.
12. Schmid HA. Pasireotide (SOM230): development, mechanism of action and potential applications. *Mol Cell Endocrinol* 2008;286:69–74.
13. Macdonald DR, Cascino TL, Schold SC Jr, Cairncross JG. Response criteria for phase II studies of supratentorial malignant glioma. *J Clin Oncol* 1990;8:1277–1280.
14. Ligon KL, Alberta JA, Kho AT, et al. The oligodendroglial lineage marker OLIG2 is universally expressed in diffuse gliomas. *J Neuropathol Exp Neurol* 2004;63:499–509.
15. Schmid HA, Lambertini C, van Vugt HH, et al. Monoclonal antibodies against the human somatostatin receptor subtypes 1–5: development and immunohistochemical application in neuroendocrine tumors. *Neuroendocrinology* 2012;95:232–247.
16. Quant EC, Wen PY. Response assessment in neuro-oncology. *Curr Oncol Rep* 2011;13:50–56.
17. Patel YC. Somatostatin and its receptor family. *Front Neuroendocrinol* 1999;20:157–198.
18. Casarini AP, Jallad RS, Pinto EM, et al. Acromegaly: correlation between expression of somatostatin receptor subtypes and response to octreotide-lar treatment. *Pituitary* 2009;12:297–303.
19. Ruan W, Fahlbusch F, Clemmons DR, et al. SOM230 inhibits insulin-like growth factor-I action in mammary gland development by pituitary independent mechanism: mediated through somatostatin subtype receptor 3? *Mol Endocrinol* 2006;20:426–436.
20. Bruns C, Lewis I, Briner U, Meno-Tetang G, Weckbecker G. SOM230: a novel somatostatin peptidomimetic with broad somatotropin release inhibiting factor (SRIF) receptor binding and a unique antiseecretory profile. *Eur J Endocrinol* 2002;146:707–716.
21. Poll F, Lehmann D, Illing S, et al. Pasireotide and octreotide stimulate distinct patterns of sst2A somatostatin receptor phosphorylation. *Mol Endocrinol* 2010;24:436–446.
22. Lesche S, Lehmann D, Nagel F, Schmid HA, Schulz S. Differential effects of octreotide and pasireotide on somatostatin receptor internalization and trafficking in vitro. *J Clin Endocrinol Metab* 2009;94:654–661.
23. Johnson DR, Kimmel DW, Burch PA, et al. Phase II study of subcutaneous octreotide in adults with recurrent or progressive meningioma and meningeal hemangiopericytoma. *Neuro Oncol* 2011;13:530–535.
24. Simo M, Argyriou AA, Macia M, et al. Recurrent high-grade meningioma: a phase II trial with somatostatin analogue therapy. *Cancer Chemother Pharmacol* 2014;73:919–923.

WriteClick® rapid online correspondence

Have a comment on a recent *Neurology*® article you would like to share? Now it is easier and more convenient. *Neurology.org* has launched WriteClick on the home page and sidebars of each article to encourage remarks and debate among users.

WriteClick is restricted to comments about studies published in *Neurology* within the last eight weeks.

Learn more at Neurology.org/letters