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Clinical Trial Results

E4206: AMG 706 and Octreotide in Patients with Low-Grade Neuroendocrine Tumors

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Trial Information

- **ClinicalTrials.gov Identifier:** NCT00427349
- **Sponsor(s)**: ECOG
- **Principal Investigator**: Mary Mulcahy
- **IRB Approved**:Yes

Lessons Learned

- Rate of progression-free survival at a particular point in time, i.e., a landmark analysis, is a difficult endpoint for a heterogenous malignancy such as neuroendocrine cancer.
- Landmark analyses can also be complicated by evolution in the standard of care during the conduct of a clinical trial.
- Improvements in biomarker development would be useful in developing future clinical trials in NET to better tailor individualized therapies and assess for possible efficacy endpoints.

Abstract

Background. Neuroendocrine tumors (NETs) are rare malignancies of the gastrointestinal (GI) tract that are highly vascularized and overexpress vascular-endothelial growth factor (VEGF). Sunitinib has demonstrated efficacy in the pancreatic subset of NET. This study explored the activity of another oral VEGF inhibitor, AMG 706 or motesanib, a multikinase inhibitor that targets receptor tyrosine kinases, including VEGFR1, VEGFR2, VEGFR3, KIT, RET, and PDGFR (IC50s = 2, 3, 6, 8, 59, and 84 nM, respectively).

Methods. This was a single-arm, first-line, phase II study run through the Eastern Cooperative Oncology Group. Patients with low-grade NET (as defined by central confirmation of Ki-67 of 0%–2%) were administered a flat dose of 125 mg per day orally combined with octreotide long acting-repeatable (LAR) for patients who had been on a stable dose. The primary objective was to determine the 4-month progression-free survival (PFS).

Results. Forty-four patients were evaluated per protocol. The 4-month PFS was 78.5%. The partial response rate was 13.6% (6/44), stable disease was 54.5% (24/44), 9.1% (4/44) had progressive disease, and 10/44 were not evaluable for response. Common toxicities included fatigue, hypertension, nausea, and headache, and most were grade 1–2. Median PFS was 8.7 months, and overall survival was 27.5 months.

Conclusion. Motesanib (AMG 706) demonstrated a 4-month PFS that met the per-protocol definition of efficacy. Fatigue and hypertension were the most common toxicities, and few grade 3–4 toxicities were encountered. The progression-free survival of 8.7 months in all NETs merits further study. ***The Oncologist*** 2018;23:1006–e104

Discussion

In this study, AMG 706 demonstrated the ability to prolong progression-free survival for patients with advanced NET. The study met its primary endpoint with a 4-month PFS of 78.5% and a median PFS of 8.7 months. The toxicity profile was compatible with earlier-phase data and comparable to data from the studies investigating sunitinib and everolimus for NET. Although the response rate was low, it was greater than the 2% response seen in phase II studies with sunitinib in unselected NET populations. These data, as well as data from sunitinib and bevacizumab trials, provide proof of concept to support targeting the VEGF pathway as a treatment strategy in NET. The idiosyncratic toxicity of

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cholecystitis merits close consideration in future trials to sort out whether the toxicity (a known effect of somatostatin analogues) is attributable to AMG 706 or somatostatin analogue of choice.

When this trial was conceived, the phase III studies of sunitinib and everolimus in pancreatic NET had not yet been completed. The selection of 4-month PFS as the primary endpoint in the study was based on historical controls prior to 2008. In retrospect, the study would have been more impactful if it had been powered to truly assess the PFS rather than PFS at a predefined time point. The PFS of 8.7 months in this study is reasonable in comparison with historical controls but would not be enough for consideration as a first-line agent replacing sunitinib or everolimus. Additionally, the PFS estimate is hindered by the fact that many of the patients were receiving octreotide, which altered the rate of progression. This improvement in PFS was not well described prior to the activation of this trial. As a standard of care, based on RADIANT-2 and RADIANT-4, everolimus would be the preferred first-line agent in this population, and any future trial design with a head-to-head comparison would have to include everolimus as a control arm.

The treatment paradigm for NET is in flux. Many patient-specific (symptom burden) and tumor-specific factors (primary tumor location, overexpression of somatostatin receptors) will play into the selection of somatostatin analogue versus oral targeted agents versus peptide receptor radiotherapy. Novel oral agents like AMG 706 will need to find their therapeutic niche with these factors in mind. By meeting its primary endpoint in this trial, AMG 706 demonstrated potential as a systemic targeted therapy for NET, but where it fits in a treatment algorithm remains unclear. Opportunities for this compound include a second-line treatment against best supportive care alone or combination therapy with mTOR inhibitors. The series of real but modest gains in NET underscores the need for ongoing clinical trials in neuroendocrine tumors of any origin with patient- and tumor-specific factors in mind.

Trial Information	
Disease	Neuroendocrine – other
Stage of Disease/Treatment	Metastatic/advanced
Prior Therapy	None
Type of Study – 1	Phase II
Type of Study – 2	Single arm
Primary Endpoint	Progression-free survival
Secondary Endpoint	Overall response rate
Secondary Endpoint	Overall survival
Secondary Endpoint	Toxicity
Additional Details of Endpoints or Study Design AMG 706 would be considered worthy of further study if its true progression-free survival rate were 40% or better at 4 months. A two-stage design was used. The initial accrual phase consisted of entering 23 patients with low-grade NET (Ki-67 0%–2%), 22 of whom were expected to be eligible (assuming a 5% ineligibility rate). If fewer than 6 of the initial 22 eligible patients were alive and free from progression of disease at 4 months, the study would cease, and the treatment would be abandoned. If 6 or more patients were alive and free from progression of disease at 4 months, 21 additional patients would be accrued, of whom 20 were expected to be eligible, for a total accrual of 44 patients. If at least 12 among the 42 eligible patients were alive and free from progression at 4 months, the regimen would be considered for further study. This two-stage design had at least 90% power to detect a 4-month PFS rate of at least 40% against the null of 20% while maintaining a one-sided type I error rate of less than 10% using an exact binomial test. For cases without documentation of progression, follow-up was censored at the date of last disease assessment without progression.	
Investigator's Analysis	Active but results overtaken by other developments

Drug Information	
Drug 1	
Generic/Working Name	Motesanib, AMG 706
Company Name	Amgen
Drug Type	Small molecule
Drug Class	Angiogenesis – VEGF
Dose	125 milligrams (mg) per flat dose
Route	Oral (po)
Schedule of Administration	Daily

Patient Characteristics	
Number of Patients, Male	24
Number of Patients, Female	20
Stage	Metastatic

Age	Median (range): 65 (38–81) years
Number of Prior Systemic Therapies	Median (range): 0
Performance Status: ECOG	0 — 29 1 — 14 2 — 1 3 — Unknown —
Cancer Types or Histologic Subtypes	GI neuroendocrine tumors Pancreatic neuroendocrine tumors

Primary Assessment Method

Title	Total Patient Population
Number of Patients Screened	46
Number of Patients Enrolled	46
Number of Patients Evaluable for Toxicity	45
Number of Patients Evaluated for Efficacy	44
Evaluation Method	RECIST 1.0
Response Assessment CR	$n = 0$ (0%)
Response Assessment PR	$n = 6$ (14%)
Response Assessment SD	$n = 24$ (55%)
Response Assessment PD	$n = 4$ (9%)
Response Assessment OTHER	$n = 10$ (22%)
(Median) Duration Assessments PFS	9 months, CI: 6–13
(Median) Duration Assessments OS	28 months, CI: 14–45
Outcome Notes	4-month PFS (defined as the primary endpoint) was 78.3% (95% CI: 65.8%–90.9%)

Adverse Events

		Grade					
Adverse event	NC/NA	1	2	3	4	5	All
Hypertension	30%	43%	27%	0%	0%	0%	70%
Fatigue	34%	52%	14%	0%	0%	0%	66%
Diarrhea	43%	48%	9%	0%	0%	0%	57%
Weight loss	53%	45%	2%	0%	0%	0%	47%
Headache	63%	32%	5%	0%	0%	0%	37%
Anorexia	63%	32%	5%	0%	0%	0%	37%
Platelet count decreased	68%	25%	5%	2%	0%	0%	32%
Nausea	68%	25%	7%	0%	0%	0%	32%
Anemia	70%	25%	5%	0%	0%	0%	30%

Adverse events observed at least once in 20% or more patients across all cycles of therapy.
Abbreviation: NC/NA, no change from baseline/no adverse event.

Assessment, Analysis, and Discussion

Completion	Study completed
Investigator's Assessment	Active but results overtaken by other developments

Low-grade neuroendocrine tumors (NETs) are increasingly common, and the treatment paradigm has evolved over the last few years. Imaging and pathologic data suggest that NETs are highly vascular and overexpress vascular-endothelial growth factor (VEGF) [1]. Phase II data suggested that bevacizumab and octreotide have an antitumor effect, but an

improvement in survival was not seen in the phase III study [2, 3]. Somatostatin analogues have demonstrated improvements in progression-free survival (PFS), but more potent antitumor agents were needed [4]. Sunitinib showed a response rate and survival benefit in pancreatic NET, leading to its approval, but a similar response was not seen in nonpancreatic NET [5, 6]. Everolimus has demonstrated improvements in overall survival in all gastrointestinal (GI) NET and has been approved for use in both settings [7–9]. We designed this trial to assay for a preliminary efficacy signal in GI NET using motesanib (AMG 706).

Our study met its primary endpoint of improving 4-month progression-free survival (78.5%), with a partial response rate of 13.6%. The treatment was well tolerated, with manageable side effects. However, it has not been moved into phase III studies, as it has been surpassed by other treatments. This study reflects some of the challenges of performing research in NET.

Our study was designed in 2007, before the differential tumor biology in pancreatic NET and nonpancreatic NET relative to its response to targeted agents was well described. Thus, the population was heterogeneous enough to confound the survival results. This study was designed with a short, predefined 4-month PFS interval and a two-stage design in the hopes of discarding an inefficacious treatment quickly but assaying for a potential signal in the combined population. That 4-month time interval was based on rates of progression from the pre-somatostatin analogue era, but perhaps did not provide a robust enough signal of efficacy. Additionally, some of the enrolled patients were lost to follow-up for a lack of a confirmed response on imaging or coming off treatment too soon. If we were to redesign the trial, we would reassess our response evaluation to include these patients in an intention-to-treat analysis.

The hope is that with the advent of peptide-receptor radiotherapy, the use of targeted agents can fit in the treatment algorithm to improve survival. Future trial design will look into the optimal sequencing of treatment for patients with NET between long acting somatostatin analogues, peptide receptor radiotherapy, and other chemotherapeutic agents. Additionally, for patients with tumors that do not overexpress somatostatin receptors, targeted agents like motesanib may have a role.

Acknowledgments

This study was coordinated by the Eastern Cooperative Oncology Group-American College of Radiology Imaging Network Cancer Research Group (Robert L. Comis, M.D., and Mitchell D. Schnall, M.D., Ph.D., Group Co-Chairs) and supported in part by Public Health Service Grants CA180794, CA180820, CA23318, CA66636, CA21115, CA180799, CA21076, CA17145, CA15488, CA14548, CA180853, CA27525, CA63848, CA180853, and CA14548 and grants from from the National Cancer Institute, National Institutes of Health, and the Department of Health and Human Services. The contents of this study are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute.

Disclosures

Mary Mulcahy: BTG (RF); **Neal Meropol:** Flatiron Health; **Al Benson:** Bristol-Myers Squibb, Guardant Health, Eli & Lilly Co., Exelixis, Purdue Pharma, Harborside, Xcenda, NCCN, Emron, inVentive Health, Genentech, Bayer, Merck (C/A), Acerta, Celegene, Advanced Accelerator Applications, Novartis, Infinity Pharmaceuticals–DMC, Merck Sharp and Dohnme, Taiho Pharmaceutical, Bristol-Myers Squibb, Medimmune/AstraZeneca, Xencor, Bristol-Myers Squibb DMC. The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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