A Phase II Trial of a Histone Deacetylase Inhibitor Panobinostat in Patients With Low-Grade Neuroendocrine Tumors

NING JIN,a SAM J. LUBNER,a,b DANIEL L. MULKERIN,a,b SAURABH RAJGURU, a LAKEESHA CARMICHAEL,b,c HERB CHEN,b,d KYLE D. HOLEN,a,b NOELLE K. LOCONTEa,b

aDivision of Hematology/Oncology, Department of Medicine, bCarbone Cancer Center, cDepartment of Biostatistics, and dDepartment of Surgery, University of Wisconsin, Madison, Wisconsin, USA

TRIAL INFORMATION

- ClinicalTrials.gov Identifier: NCT00985946
- Sponsor: Novartis
- Principal Investigator: Noelle K. LoConte
- IRB Approved: Yes

LESSONS LEARNED

- Pancreatic neuroendocrine tumors versus carcinoid tumors should be examined separately in clinical trials.
- Progression-free survival is more clinically relevant as the primary endpoint (rather than response rate) in phase II trials for low-grade neuroendocrine tumors.

ABSTRACT

Background. The most common subtypes of neuroendocrine tumors (NETs) are pancreatic islet cell tumors and carcinoids, which represent only 2% of all gastrointestinal malignancies. Histone deacetylase (HDAC) inhibitors have already been shown to suppress tumor growth and induce apoptosis in various malignancies. In NET cells, HDAC inhibitors have resulted in increased Notch1 expression and subsequent inhibition of growth. We present here a phase II study of the novel HDAC inhibitor panobinostat in patients with low-grade NET.

Methods. Adult patients with histologically confirmed, metastatic, low-grade NETs and an Eastern Cooperative Oncology Group (ECOG) performance status of ≤2 were treated with oral panobinostat 20 mg once daily three times per week. Treatment was continued until patients experienced unacceptable toxicities or disease progression. The study was stopped at planned interim analysis based on a Simon two-stage design.

Results. Fifteen patients were accrued, and 13 were evaluable for response. No responses were seen, but the stable disease rate was 100%. The median progression-free survival (PFS) was 9.9 months, and the median overall survival was 47.3 months. Fatigue (27%), thrombocytopenia (20%), diarrhea (13%), and nausea (13%) were the most common related grade 3 toxicities. There was one grade 4 thrombocytopenia (7%). These results did not meet the prespecified criteria to open the study to full accrual.

Conclusion. The HDAC inhibitor panobinostat has a high stable disease rate and reasonable PFS in low-grade NET, but has a low response rate.

DISCUSSION

Therapeutic options for advanced low-grade NET are limited. First-line therapy involves a somatostatin analog, such as octreotide long-acting repeatable. Biologic therapies targeting mTOR pathway and vascular endothelial growth factor have been approved for the treatment of patients with well-differentiated pancreatic NET: sunitinib and everolimus, respectively. Both agents demonstrated the benefit of prolongation of PFS.

Panobinostat is a potent, orally active, pan-HDAC inhibitor that can affect multiple cancer-related pathways, including cell-cycle regulation, differentiation, and apoptosis. Several preclinical studies indicated that HDAC inhibitors, valproic acid and suberoyl bishydroxamic acid, can activate Notch1 signaling, suppress NET tumor markers, and inhibit NET cell growth. Based on the evidence that Notch1 activation can lead to NET differentiation and suppression of tumor growth, we opened a phase II clinical trial of panobinostat in patients with metastatic low-grade NETs.

The total number of subjects initially planned in this study was 33. An interim analysis was planned when 13 evaluable patients had been accrued. All patients had stable disease as best response (Fig. 1). Because of lack of objective response, the study was closed to accrual. The median progression-free survival was 9.9 months (90% confidence interval [CI], 4.1–16.9), and the median overall survival was 47.27 months (90% CI, 17.87 to not reached), with the total follow-up time of 5 years. Panobinostat was tolerated relatively well in patients in our study.
study. Fatigue, thrombocytopenia, anorexia, diarrhea, and nausea were the most common grade 3 treatment related toxicities (Adverse Events Table). Patients with pancreatic NETs (4 of 5 patients, 80%) underwent more than 10 cycles of panobinostat in this study. This would seem to be a clinically meaningful delay in time to progression of the cancer. It is increasingly clear that pancreatic NETs and carcinoid subtypes have different biology, respond differently to therapeutic agents, and should be evaluated as separate entities in clinical trials.

Our study was terminated early because of the use of objective response rate as the primary outcome measure, which is the shortcoming of this study. We would use progression-free survival (PFS) as the primary endpoint if the study should be repeated. Overall survival is not a practical endpoint for advanced NET studies.

Panobinostat showed favorable clinical activity in different hematologic malignancies, such as in relapsed Hodgkin lymphoma, myelofibrosis, refractory cutaneous T-cell lymphoma, and multiple myeloma, as either single-agent or combination treatment. However, HDAC inhibitors have not demonstrated effectiveness in clinical trials involving solid tumors. Their limitations in solid tumors could be related to drug instability because of short protein kinase half-life, tissue impermeability in tumor microenvironment, drug resistance due to activation of signal transducers and activators of transcription signaling pathway, antiapoptotic effect of nuclear transcription nuclear factor κB, and lack of the specific target in solid tumors. The question regarding the role of Notch1 in well-differentiated NET remains unanswered.

**Additional Details of Endpoints or Study Design**

The primary endpoint was the tumor response rate (complete or partial response) using Response Evaluation Criteria in Solid Tumors (RECIST) criteria. A Simon optimal two-stage design was used to test the null hypothesis that the true response rate was 6% versus the alternative hypothesis that it was 20%. With a significance level of 10% and a power of 85%, at least one response was required among the first 13 evaluable patients to proceed to the second stage, where additional patients would be enrolled for a total of 30 evaluable patients.

**Investigator’s Analysis**

Level of activity did not meet planned clinical trial endpoint.

### Drug Information

| Drug 1 |
|---|
| **Generic/Working name** | Panobinostat |
| **Trade name** | Farydak |
| **Company name** | Novartis |
| **Drug type** | Small molecule |
| **Drug class** | HDAC |
| **Dose** | 20 mg per flat dose |
| **Route** | Oral (po) |
| **Schedule of Administration** | Once daily, three times per week |
| **PATIENT CHARACTERISTICS** |
|----------------------------|
| **Number of patients, male** | 10 |
| **Number of patients, female** | 5 |
| **Stage** | Metastatic low-grade neuroendocrine tumors |
| **Age** | Median (range): 57 (40–80) |
| **Number of prior systemic therapies** | Median (range): Not collected |
| **Performance Status: ECOG** | 0 — 10 |
| | 1 — 5 |
| | 2 — 0 |
| | 3 — 0 |
| | Unknown — |
| **Primary Site:** | Lung and bronchus, 2 |
| | Pancreas, 5 |
| | Rectum, 1 |
| | Small Intestine, 5 |
| | Unknown, 2 |
| **Cancer Types or Histologic Subtypes** | Low,* 6 |
| | Well Differentiated,* 5 |
| | Grade unknown, not stated, or not applicable, 4 |

| **PRIMARY ASSESSMENT METHOD** |
|-------------------------------|
| **Control Arm: Total Patient Population** |
| **Number of patients screened** | 15 |
| **Number of patients enrolled** | 15 |
| **Number of patients evaluable for toxicity** | 15 |
| **Number of patients evaluated for efficacy** | 13 |
| **Response assessment CR** | n = 0 |
| **Response assessment PR** | n = 0 |
| **Response assessment SD** | n = 13 |
| **Response assessment PD** | n = 0 |
| **(Median) duration assessments PFS** | 9.9 months, CI: 90 |
| **(Median) duration assessments OS** | 47.3 months |
| **Kaplan-Meier time units** | Months |

| Time of scheduled assessment and/or time of event | No. progressed (or deaths) | No. censored | Percent at start of evaluation period | Kaplan-Meier % | No. at next evaluation/no. at risk |
|--------------------------------------------------|---------------------------|-------------|-------------------------------------|----------------|-----------------------------------|
| 0                                                | 0                         | 0           | 100.00                              | 100.00         | 13                                |
| 2.27                                             | 0                         | 0           | 100.00                              | 100.00         | 13                                |
| 2.33                                             | 1                         | 0           | 100.00                              | 92.31          | 12                                |
| 3.53                                             | 1                         | 0           | 92.31                               | 84.62          | 11                                |
| 4.1                                              | 1                         | 0           | 84.62                               | 76.92          | 10                                |
| 6.5                                              | 1                         | 0           | 76.92                               | 69.23          | 9                                 |
| 9.1                                              | 1                         | 0           | 69.23                               | 61.54          | 8                                 |
| 9.7                                              | 1                         | 0           | 61.54                               | 53.85          | 7                                 |
| 9.9                                              | 1                         | 0           | 53.85                               | 46.15          | 6                                 |
| 10.73                                            | 1                         | 0           | 46.15                               | 38.46          | 5                                 |
| 12                                               | 1                         | 0           | 38.46                               | 30.77          | 4                                 |
| 16.9                                             | 1                         | 0           | 30.77                               | 23.08          | 3                                 |
| 17.87                                            | 1                         | 0           | 23.08                               | 15.38          | 2                                 |
| 22.4                                             | 1                         | 0           | 15.38                               | 7.69           | 1                                 |
| 28.23                                            | 1                         | 0           | 7.69                                | 0.00           | 0                                 |
| 38.9                                             | 1                         | 0           | 0.00                                | 0.00           | -1                                |

|                                | 0.00 | 0.00 | -1 |

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### Adverse Events

#### Adverse Events At All Dose Levels, Cycle 1

| Name                                                                 | * NC/NA | 1   | 2   | 3   | 4   | 5   | All Grades |
|----------------------------------------------------------------------|---------|-----|-----|-----|-----|-----|------------|
| Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip) | 93%     | 7%  | 0%  | 0%  | 0%  | 0%  | 7%         |
| Hemoglobin                                                           | 47%     | 53% | 0%  | 0%  | 0%  | 0%  | 53%        |
| Leukocytes (total WBC)                                               | 80%     | 13% | 7%  | 0%  | 0%  | 0%  | 20%        |
| Lymphopenia                                                          | 87%     | 13% | 0%  | 0%  | 0%  | 0%  | 13%        |
| Neutrophils/granulocytes (ANC/AGC)                                   | 73%     | 20% | 0%  | 7%  | 0%  | 0%  | 27%        |
| Platelets                                                            | 13%     | 53% | 7%  | 20% | 7%  | 0%  | 87%        |
| Hypotension                                                          | 93%     | 0%  | 7%  | 0%  | 0%  | 0%  | 7%         |
| Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura [TTP] or hemolytic uremic syndrome [HUS]) | 93%     | 7%  | 0%  | 0%  | 0%  | 0%  | 7%         |
| Fatigue (asthenia, lethargy, malaise)                                | —1%     | 27% | 47% | 27% | 0%  | 0%  | 101%       |
| Weight loss                                                          | 47%     | 20% | 33% | 0%  | 0%  | 0%  | 53%        |
| Bruising (in absence of grade 3 or 4 thrombocytopenia)              | 80%     | 13% | 7%  | 0%  | 0%  | 0%  | 20%        |
| Dermatology/Skin - Specify                                          | 93%     | 7%  | 0%  | 0%  | 0%  | 0%  | 7%         |
| Dry skin                                                             | 93%     | 7%  | 0%  | 0%  | 0%  | 0%  | 7%         |
| Hair loss/alopecia (scalp or body)                                   | 93%     | 7%  | 0%  | 0%  | 0%  | 0%  | 7%         |
| Nail changes                                                         | 87%     | 13% | 0%  | 0%  | 0%  | 0%  | 13%        |
| Thyroid function, high (hyperthyroidism, thyrotoxicosis)            | 73%     | 27% | 0%  | 0%  | 0%  | 0%  | 27%        |
| Thyroid function, low (hypothyroidism)                              | 46%     | 47% | 7%  | 0%  | 0%  | 0%  | 54%        |
| Anorexia                                                             | 60%     | 13% | 7%  | 20% | 0%  | 0%  | 40%        |
| Dehydration                                                          | 87%     | 0%  | 13% | 0%  | 0%  | 0%  | 13%        |
| Diarrhea                                                             | 34%     | 33% | 20% | 13% | 0%  | 0%  | 66%        |
| Flatulence                                                           | 93%     | 0%  | 7%  | 0%  | 0%  | 0%  | 7%         |
| Heartburn/dyspepsia                                                  | 93%     | 7%  | 0%  | 0%  | 0%  | 0%  | 7%         |
| Mucositis/stomatitis (clinical exam)                                 | 80%     | 20% | 0%  | 0%  | 0%  | 0%  | 20%        |
| Nausea                                                               | 27%     | 60% | 0%  | 13% | 0%  | 0%  | 73%        |
| Taste alteration (dysgeusia)                                         | 74%     | 13% | 13% | 0%  | 0%  | 0%  | 26%        |
| Vomiting                                                             | 53%     | 13% | 27% | 7%  | 0%  | 0%  | 47%        |
| AST, SGOT (serum glutamic oxaloacetic transaminase)                  | 93%     | 7%  | 0%  | 0%  | 0%  | 0%  | 7%         |
| Albumin, serum-low (hypoalbuminemia)                                 | 80%     | 7%  | 13% | 0%  | 0%  | 0%  | 20%        |
| Alkaline phosphatase                                                 | 67%     | 33% | 0%  | 0%  | 0%  | 0%  | 33%        |
| Cholesterol, serum-high (hypercholesteremia)                        | 73%     | 27% | 0%  | 0%  | 0%  | 0%  | 27%        |
| Creatinine                                                           | 47%     | 53% | 0%  | 0%  | 0%  | 0%  | 53%        |
| GGT (γ-glutamyl transpeptidase)                                      | 80%     | 7%  | 13% | 0%  | 0%  | 0%  | 20%        |
| Glomerular filtration rate                                          | 87%     | 13% | 0%  | 0%  | 0%  | 0%  | 13%        |
| Glucose, serum-high (hyperglycemia)                                  | 40%     | 60% | 0%  | 0%  | 0%  | 0%  | 60%        |
| Magnesium, serum-high (hypermagnesemia)                             | 87%     | 13% | 0%  | 0%  | 0%  | 0%  | 13%        |

Kaplan-Meier curve for median progression-free survival, which is 9.90 months with 90% confidence interval (4.10–16.9 months).
**Assessment, Analysis, and Discussion**

Completion: Study completed
Terminated reason: Did not fully accrue
Pharmacokinetics / Pharmacodynamics: Not Collected
Investigator’s Assessment: Level of activity did not meet planned clinical trial endpoint

NETs are uncommon tumors arising from the neuroendocrine system. The gastrointestinal (GI) tract, pancreas, and lung are the most common primary tumor sites in patients with NETs [1], and gastroenteropancreatic (GEP) NETs represent approximately 2% of all gastrointestinal malignant neoplasms. The clinical evaluation for NETs should incorporate several key factors, such as anatomic site, histology, grade, differentiation, and hormone secretion. In particular, the anatomic site of origin is now recognized as a key determinant of treatment selection [2]. According to the 2010 World Health Organization grading system for GEP NETs, there are three grades (G1, G2, and G3) for differentiation on pathology report, based on Ki-67 and mitotic counts [3]. Well-differentiated NETs include G1 and G2; poorly differentiated NETs are G3.

For patients with well-differentiated and functional tumors, somatostatin analogs such as octreotide long-acting repeatable are the mainstay of treatment for control tumor growth as well as symptomatic control, with improved PFS and quality of life [4, 5]. Recent randomized studies for biologic therapies targeting mTOR pathway and vascular endothelial growth factor demonstrated prolongation of PFS compared with placebo for pancreatic NET; for example, everolimus (11 vs. 4.6 months) [6] or sunitinib (11.4 vs. 5.5 months) [7].

Early studies suggested that activation of the Notch pathway can lead to neuroendocrine differentiation in gastrointestinal carcinoid tumor [8] and inhibit NET cell growth [9]. Of note, it is well recognized that Notch can function as either an oncogene or a tumor suppressor, depending on the cell type [10–12]. Both valproic acid (VPA) and suberoyl bishydroxamic acid, two histone deacetylase (HDAC) inhibitors, can activate Notch1 signaling, suppress neuroendocrine tumor markers, and inhibit NET cell growth both in vitro and in vivo [13, 14]. Furthermore, our group previously conducted a pilot clinical trial of VPA for patients with advanced carcinoid cancer. Five of the six patients (62.5%) assessable for radiographic response were noted to have stable disease by RECIST, and one patient with an unconfirmed partial response was noted to have a 40-fold increase in Notch1 mRNA levels [15].

Panobinostat (LBH589) is a potent, orally active, pan-HDAC inhibitor that can affect multiple cancer-related pathways via nonhistone protein targets, including cell-cycle regulation, differentiation, and apoptosis [16, 17]. Based on the role of Notch1 activation in suppression of NET tumor markers and tumor growth, we opened a phase II clinical trial of HDAC inhibitor panobinostat in patients with metastatic low-grade NETs.

The total number of subjects initially planned for this study was 33. An interim analysis was planned when 13 evaluable patients had been accrued. At least one response was required among the first 13 evaluable patients to proceed to the second stage, where additional patients would be enrolled. Among 15 patients who were accrued, 66.6% were male, age range 40–80...
patients years old, 54% carcinoid, and 33% pancreatic NET (Table 1). Because of the lack of objective response in the interim analysis, the study was closed. Panobinostat was tolerated relatively well in patients in our study. The most common toxicities of all grades were thrombocytopenia, fatigue, diarrhea, nausea, hyperglycemia, hypertriglyceridemia, and thyroid dysfunction. Fatigue (27%), thrombocytopenia (20%), anorexia (20%), diarrhea (13%), and nausea (13%) were the most common treatment-related grade 3 toxicities. There was one case (7%) of grade 4 toxicity of thrombocytopenia (Adverse Events Table). Eight patients needed dose modifications because of adverse events, such as thrombocytopenia, neutropenia, and fatigue, during their treatment courses (data not shown). All patients had stable disease as best response (Fig. 1). Three of 13 patients underwent only 2 cycles of treatment, whereas 7 patients underwent more than 10 cycles of treatment (Table 2). Median progression-free survival was 9.9 months (90% CI, 4.1–16.9) (Fig. 2), and median overall survival was 47.27 months (90% CI, 17.87 to not reached), with the total follow-up time of 5 years (Fig. 3).

Patients with pancreatic NETs (four of five patients; one patient withdrew early) underwent more than 10 cycles of panobinostat in this study, although our sample size is too small to draw any conclusion. It is increasingly clear that pancreatic NETs (PNETs) and carcinoid subtypes have different biology, respond differently to therapeutic agents, and should be evaluated as separate entities in clinical trials [18]. Examination of the PNETs and GI carcinoid demonstrated only a few areas of overlap in the accumulation of genetic aberrations, using comparative genomic hybridization, microsatellite analysis, and sequencing techniques [19]. As to treatment, PNETs are more sensitive to cytotoxic chemotherapy than carcinoid tumors, such as streptozocin, capetabine, and temozolomide, as shown in early clinical trials as well as recent retrospective clinical studies [20–22].

Our study was terminated early because of the use of objective response rate as the primary outcome measure, which is the shortcoming of this study. We would use progression-free survival as the primary endpoint if the study should be repeated. The challenge in phase II studies in NETs is the small patient population available and the often long survival postprogression [23]. Overall survival is not a practical endpoint for advanced NET studies, because of the nature of indolent disease and the availability of multiple sequential therapies [2].

Panobinostat showed favorable clinical activity in different hematologic malignancies, such as in relapsed Hodgkin lymphoma [24], myelofibrosis [25], refractory cutaneous T-cell lymphoma [26], and multiple myeloma [27], as either single-agent or combination treatment. However, the results of recent clinical trials of panobinostat in solid tumors are disappointing, including castration-resistant prostate cancer [28], metastatic renal cell cancer [29], and pancreatic cancer [30]. Generally, HDAC inhibitors have not demonstrated effectiveness in clinical trials involving solid tumors. Their limitations in solid tumors could be related to drug instability due to short protein kinase half-life [31, 32], tissue impermeability in tumor microenvironment, drug resistance due to activation of the signal transducers and activators of transcription signaling pathway [33, 34], antiapoptotic effect of nuclear transcription nuclear factor xB [35], and lack of the specific target in solid tumors [36]. There was no study participant in our trial who underwent pretreatment and posttreatment biopsy for Notch1 activity, which is the limitation of this study.

In conclusion, panobinostat has a high stable disease rate and reasonable PFS in low-grade NET. Oral panobinostat at a dose of 20 mg three times weekly was relatively well tolerated in patients in this study. Four of five patients with PNETs had durable stable disease on panobinostat, which is encouraging. Further studies of panobinostat in combination with other agents are indicated in patients with NETs. The questions regarding off-target effects of panobinostat and the role of Notch1 in well-differentiated NET remain unanswered. In future clinical trials, it is important to develop pharmacodynamics biomarkers to predict treatment response in patients.

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Disclosures

Kyle D. Holen: AbbVie (OI). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (O1) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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**FIGURES AND TABLES**

**Figure 2.** Percentage change in tumor size based on Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Waterfall plot of radiographic changes from baseline to best response of 13 evaluable patients, revealing that every patient (100%) has stable disease. Stable disease is defined as neither sufficient shrinkage to qualify for partial response (less than 30% decrease in the sum of the longest diameters of target lesions) nor sufficient increase to qualify for progressive disease (at least 20% increase in the sum of the longest diameters of target lesions).

**Figure 3.** Kaplan-Meier curve for overall survival, which is 47.27 months with 90% confidence interval, with a follow-up time of 5 years. Abbreviation: CI, confidence interval.
Table 1. Patient characteristics

| Patient characteristic                                      | Patients (n = 15) |
|-------------------------------------------------------------|------------------|
| Age, median (range)                                         | 57 (40–80)       |
| Gender, n (%)                                               |                  |
| Female                                                      | 5 (33)           |
| Male                                                        | 10 (67)          |
| Ethnicity, n (%)                                            |                  |
| Non-Hispanic                                                | 13 (87)          |
| Unknown                                                     | 2 (13)           |
| First metastatic site, n (%)                                |                  |
| Bones, joints, and articular cartilage of limbs             | 1 (7)            |
| Breast                                                      | 1 (7)            |
| Liver and intrahepatic bile ducts                          | 8 (53)           |
| Lymph nodes                                                 | 4 (27)           |
| Bones, joints and articular cartilage of other unspecified sites | 1 (7)           |
| Histology grade, n (%)                                      |                  |
| Low                                                         | 6 (40)           |
| Well-differentiated                                         | 5 (33)           |
| Grade unknown, not stated, or not applicable                | 4 (27)           |
| Performance status, n (%)                                   |                  |
| 0: Fully active                                             | 10 (67)          |
| 1: Restricted                                               | 5 (33)           |
| Primary site, n (%)                                         |                  |
| Lung and bronchus                                           | 2 (13)           |
| Pancreas                                                    | 5 (33)           |
| Rectum                                                     | 1 (7)            |
| Small intestine                                             | 5 (33)           |
| Unknown or missing                                          | 2 (13)           |
| Prior therapy, n (%)                                        |                  |
| Chemotherapy (not otherwise specified)                     | 3 (20)           |
| Chemotherapy multiple agent systemic                        | 1 (7)            |
| Noncytotoxic chemotherapy                                   | 1 (7)            |
| Other                                                       | 6 (40)           |
| Not applicable                                              | 4 (27)           |
| Missing                                                     | 1 (7)            |
| ID  | Primary site       | Grade of histology | No. of cycles | Off-treatment reason                                           |
|-----|--------------------|--------------------|---------------|---------------------------------------------------------------|
| 1   | Lung and bronchus  | Low                | 2             | Disease progression after beginning treatment                |
| 2   | Small intestine    | Grade unknown, not stated, or not applicable | 4             | Disease progression after beginning treatment                |
| 3   | Small intestine    | Low                | 12            | Disease progression after beginning treatment                |
| 4   | Lung and bronchus  | Well differentiated | 1             | Withdrawal or refusal after beginning treatment              |
| 5   | Pancreas           | Well differentiated | 1             | Withdrawal or refusal after beginning treatment              |
| 6   | Unknown or missing | Well differentiated | 2             | Adverse event/Side effects/Complications                      |
| 7   | Pancreas           | Low                | 10            | Disease progression after beginning treatment                |
| 8   | Pancreas           | Well differentiated | 15            | Disease progression after beginning treatment                |
| 9   | Pancreas           | Low                | 15            | Started nonprotocol therapy                                   |
| 10  | Small intestine    | Low                | 8             | Adverse event/side effects/Complications                      |
| 11  | Small intestine    | Grade unknown, not stated, or not applicable | 3             | Adverse event/side effects/Complications                      |
| 12  | Small intestine    | Grade unknown, not stated, or not applicable | 19            | Adverse event/side effects/Complications                      |
| 13  | Rectum             | Well differentiated | 10            | Disease progression after beginning treatment                |
| 14  | Unknown or missing | Low                | 2             | M.D. discretion                                              |
| 15  | Pancreas           | Grade unknown, not stated, or not applicable | 22            | Disease progression after beginning treatment                |

List of NET primary site, grade of histology, total number of cycles completed, and off-treatment reason for all the study participants.

- Patients withdrew from the study owing to fatigue prior to receiving two cycles of therapy and having a disease evaluation CT scan; considered “not evaluable.”
- Patient was hospitalized with extreme fatigue and could not have any more dose modification, then died within 30 days of coming off treatment. The death was considered possibly related to panobinostat treatment and probably related to neuroendocrine cancer.
- Patient was off treatment to undergo surgical resection of the primary.
- Patient underwent embolization owing to progression of hepatic metastasis that did not meet RECIST for progression.