Investigator-Assessed Disease Progression in a Phase 2 Study of Paltusotine in Patients With Neuroendocrine Tumors and Carcinoid Syndrome

C-3

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BACKGROUND

- Paltusotine (PALSONIFY™) is an oral, once-daily, non-peptide, selective somatostatin 2 receptor agonist approved by the US FDA for the treatment of adults with acromegaly who had an inadequate response to surgery and/or for whom surgery is not an option[1,2]
- Paltusotine is currently being investigated for the treatment of carcinoid syndrome (CS); the safety and efficacy for use in this new indication have not been fully evaluated by Regulatory Authorities
- In a phase 2 study, treatment with once-daily, oral paltusotine reduced the frequency and severity of CS symptoms and was well tolerated[3]

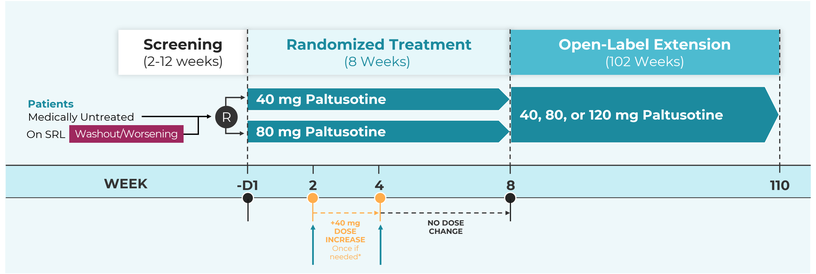
OBJECTIVE

- To explore the anti-tumor effects of paltusotine in patients with neuroendocrine tumors (NETs) and CS

METHODS

- Entry criteria: locally advanced or metastatic, stable, well-differentiated, grade 1 or 2 NETs with CS either:
  - Somatostatin receptor ligand (SRL) treatment naïve or currently untreated and actively symptomatic (average of ≥4 bowel movements per day or >2 flushing episodes per day on ≥2 days over a 2-week period) *or*
  - Symptom control on SRL with demonstrated symptom worsening after SRL washout
- Patients had stable disease in the 6 months prior to study entry

Study Design



*Criteria for uptitration were CS symptoms that required treatment with short-acting injected octreotide at least once within the previous 7 days. SRL = somatostatin receptor ligand.

- Radiographic tumor assessments (computed tomography [CT] or magnetic resonance imaging [MRI]) were conducted pretrial, at Weeks 10, 36, 70, 110, and at end of treatment
  - At each assessment, investigators reported (yes/no) whether imaging represented disease progression, and "investigator-assessed progression-free survival (PFS)" was based on the overall impression of imaging results
- This preliminary analysis assessed tumor progression per investigator assessment
  - The Kaplan-Meier method was used to calculate PFS, which was defined as the time from baseline to the date when the investigator reported "yes" for disease progression

RESULTS

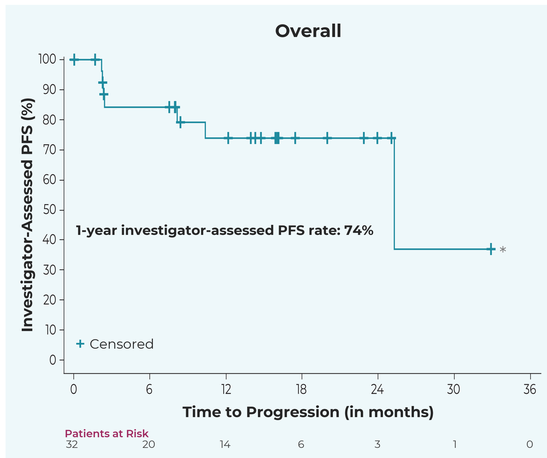
- Thirty-six patients (untreated, n=9; SRL washout, n=27) were randomized (paltusotine 40 mg/day, n=18; paltusotine 80 mg/day, n=18)
- This analysis included 32 patients (untreated, n=8; SRL washout, n=24); 4 patients were excluded due to not having baseline CT/MRI scan or elected not to enroll in the open-label extension

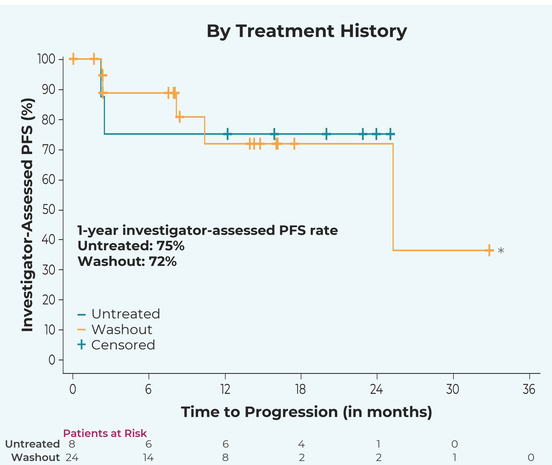
Patient Characteristics

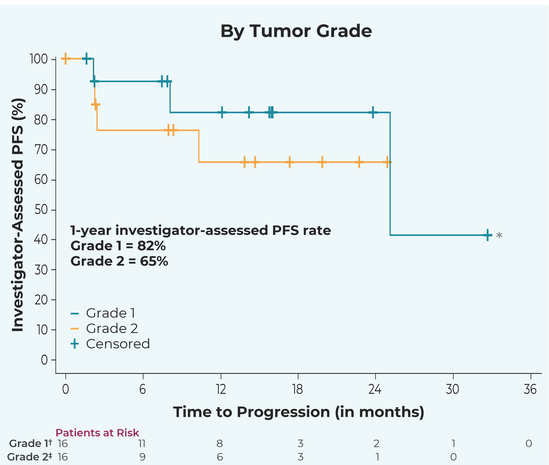
	Patients (n=32)
Age, years, mean (SD)	59.9 (13.5)
Sex, n (%)	
Female	17 (53.1)
Male	15 (46.9)
Duration since CS diagnosis, months, median	66.0
NET grade, n (%)	
Grade 1	16 (50.0)
Grade 2	16 (50.0)
Primary tumor location, n (%)	
Lung	1 (3.1)
Pancreas	2 (6.3)
Small intestine	20 (62.5)
Other	9 (28.1)

CS = carcinoid syndrome; NET = neuroendocrine tumor.

Investigator-Assessed Progression-Free Survival







*The last observation is censored. This patient initially completed the original protocol, which included 50 weeks of OLE. Following a protocol amendment extending the OLE to 110 weeks, the patient was re-enrolled. PFS for this patient includes the entire period, as no disease progression was observed during the time off protocol. The final tumor assessment for this patient occurred at 33 months after randomization in the original protocol. †Ki67 cutoff: <3%. ‡Ki67 cutoff: 3%-20%. OLE = open-label extension; PFS = progression-free survival.

Investigator-Assessed Progression-Free Survival Summary

		Treatment History		Tumor Grade	
	Overall	Untreated	Washout	Grade 1	Grade 2
Total number	32	8	24	16	16
Events	7	2	5	3	4
Censored	25	6	19	13	12
Duration of PFS, months, median	25.3*	NR	25.3*	25.3*	NR
95% CI	(25.3, NR)	(--, --)	(10.4, NR)	(8.2, NR)	(--, --)
PFS probability at Month 12	73.9	75.0	71.6	82.1	65.3
95% CI	(50.3, 87.5)	(31.5, 93.1)	(39.5, 88.6)	(44.4, 95.3)	(30.8, 85.7)

*The last observed timepoint corresponds to a censored observation; therefore, the estimation of median PFS (time to event) should be interpreted cautiously. NR = not reached; PFS = progression-free survival.

CONCLUSION

- In this preliminary analysis of a phase 2 study of paltusotine in patients with CS, the investigator-assessed PFS rate after 1 year of treatment was 74%
- Further investigation in the phase 3 CAREFNDR study (NCT07087054) is underway

LITERATURE REVIEW

- In an observational study of 440 patients with metastatic NETs who received treatment with a single-agent somatostatin analog, median PFS (time to event) was 17 months (95% CI, 14-22 months)[4]
- In a randomized controlled trial of octreotide long-acting release (LAR) in patients with metastatic midgut NETs, median PFS (time to event) was 14.3 months in the subset of octreotide-treated patients with CS[5]
- In a randomized controlled trial of lanreotide in patients with non-functional metastatic gastroenteropancreatic NETs, median PFS (time to event) was not reached at the 22-month analysis in lanreotide-treated patients; the PFS rate at Month 24 was 65%[6]

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AUTHOR DISCLOSURES

A. Mohamed reports serving as a principal investigator and advisor for Crinetics and being a speaker for Ipsen. M. J. Demeure reports serving as a principal investigator for Crinetics and a consultant to Aadi Bioscience, Bayer, Boehringer Ingelheim, Corcept, Crinetics, Lilly, and Pfizer. J. Dillon reports serving as a principal investigator for Crinetics. J. M. O'Connor reports serving as a principal investigator for Crinetics; receiving grant/research funding from Amgen, Bristol Myers Squibb, Merck Serono, MSD, Pfizer, and Sanofi; and receiving honoraria or being an advisor for Bristol Myers Squibb, MSD, Pfizer, and Sanofi. S. Shaheen reports serving as a principal investigator for Crinetics. S. Singh reports serving as a principal investigator for Crinetics and receiving honoraria or serving on advisory boards for Advanz, Camurus, Crinetics, Ipsen, and Novartis. A. Oviedo reports serving as a principal investigator for Crinetics. L. Anthony reports serving as principal investigator for Crinetics. R. Riechelmann reports serving as a principal investigator for Crinetics and speaker for Ipsen. Ł. Hajac reports serving as a principal investigator for Crinetics and receiving research support from Ipsen, Merck Sharp & Dohme, and Novartis/Advanced Accelerator Applications. M. A. Maluccio reports serving as a principal investigator for Crinetics. J. L. Althoff reports serving as a principal investigator for Crinetics. M. Dioca reports serving as a principal investigator for Crinetics. T. R. Halfdanarson reports receiving research support from Camurus, Crinetics, Isotopen Technologien Muenchen, ITM, Novartis/Advanced Accelerator Applications, Perspective Therapeutics, Rezolute, and Thermo Fisher Scientific; and serving as a consultant, advisory board member, and/or steering committee member for Abdera Therapeutics, Biomea Fusion, Boehringer-Ingelheim, Camurus, Crinetics, Curium, Exelixis, Ipsen, ITM Isotopen Technologien Muenchen, Novartis, Perspective Therapeutics, and TerSera Therapeutics. A. E. Hendifar reports serving as a principal investigator for Crinetics. A. R. P. Quidute reports serving as a principal investigator for Crinetics. M. Scandizzo reports serving as an investigator for Crinetics. D. Markova, Z. Xiao, Z. Sharafali, A. Krasner, and B. Zhang are employees of Crinetics Pharmaceuticals. A. Chauhan reports serving as a principal investigator for Crinetics; receiving research support from Bristol Myers Squibb, Clovis Oncology, EMD Serono, Lexicon Pharmaceuticals, Nano-Pharmaceutics, Novartis, Seneca Therapeutics, and TerSera Therapeutics; and being an advisor for Boehringer Ingelheim, Crinetics, Exelixis, Ipsen, Lexicon Pharmaceuticals, Novartis/Advanced Accelerator Applications, Seneca Therapeutics, and TerSera Therapeutics.