A Pilot Study of the Cyclin Dependent Kinases 4, 6 Inhibitor Ribociclib in Patients with Foregut Neuroendocrine Tumors

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ABSTRACT

Background: Increased cyclin dependent kinases 4, 6 (cdk 4/6) activity is noted in the majority of well differentiated foregut neuroendocrine tumors (fNETs) due to mutations in *MENIN* and other aberrations. These tumors also have preserved Rb function making cdk 4/6 inhibitors attractive agents for therapy.

Methods: In this single institution study (NCT02420691), 20 patients (pts) with advanced, progressive fNETs were treated with ribociclib 600 mg by mouth daily for 3 weeks (w) and off for 1 week in 4w cycles (c). All patients were required to have progressive disease in the past 12 months; patients with pancreatic NETs (pNETs) were required to have progression on prior therapy in addition. Paired biopsies were obtained at baseline and c2d1. Re-staging scans were obtained every 3 c.

Results: 10 pNET; 7 lung NET and 3 other fNET with median age 56 (range 29 – 76; 65% male) and median prior therapies 2 (range 0-3) were enrolled. Although there were no radiographic responses, an encouraging improvement in progression free survival was noted (median: 10.4 months, m; 95% CI 7.4 m – 13.5 m). 7 patients had PFS > 12 m. No related grade (g) ≥ 4 adverse events (AE) were noted and the most common related g 3 AEs were neutropenia (6 pts), febrile neutropenia, anemia, thrombocytopenia and fatigue (1 pt each). Paired biopsies were obtained in 18 pts and in contrast to clinical benefit, did not show significant reduction in Ki-67 or phospho-Rb levels.

Conclusions: Ribociclib was well tolerated in this cohort of fNETs without any unanticipated AEs. Although pharmacodynamics studies did not show robust target inhibition perhaps related to intermittent dosing, clinical benefit was noted with prolonged stable disease in patients with prior progression.

INTRODUCTION

- Evidence suggests aberrant cell cycle regulation due to aberrations in MENIN (MEN1), p27 (CDKN1B), p16 (CDKN2A), and Cyclin D1 (CCND1) is critical in the carcinogenesis and malignant progression of NETs.

INTRODUCTION

- The most common genetic cancer syndrome leading to the development of NETs is MEN1 leading to the development of lung, thymic, and pancreatic NETs.
- Mutations in MEN1 appear to mediate carcinogenesis of NETs through dysregulation of p27, and p18.
- Somatic mutation in MENIN is also the most common genetic abnormality in sporadic foregut NETs and have been identified in approximately 40% of pancreatic and lung NETs.
- Other aberrations may also lead to increased MEN1 activity: homozygous deletion of CDKN2A, CDKN2B (p15), copy number amplification of CCND1 and methylation of p16.

METHODS

Key Eligibility Criteria:

- Advanced, unresectable, progressive histologically confirmed foregut NETs irrespective of functional status with radiographically measurable disease.
- Progressive disease over last 12 months
- Adequate organ function and ECoG PS of 0-1

Primary Objective: To estimate the RECIST (ver 1.1) objective response rate of ribociclib among patients with advanced fNETs.

Key Secondary Objectives: To evaluate PFS; To evaluate safety and tolerability

Key Exploratory Objective: To determine pharmacodynamics changes including Ki-67 and pRb by immunohistochemistry from paired biopsies (baseline & c2d1) upon treatment with ribociclib

Treatment: Ribociclib 600 mg by mouth daily for 3 w and off for 1 w in 4w cycles (c). Re-staging scans were obtained every 3 c.

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RESULTS

Table 1: Patient Characteristics

	n (%)
Age, Median (Range)	56 (29-76)
Male	13 (65%)
Prior systemic therapies, Median (Range)	2 (0-3)
Lung NET	7 (35%)
pNET	10 (50%)
Others	3 (15)
Functional	2 (10%)
Ki-67 > 20%	3 (15%)

	All Grades		Grade 3*	
Adverse Event	No.	%	No.	%
Neutropenia	16	80	6	30
Anemia	10	50	1	5
Fatigue	10	50	1	5
Thrombocytopenia	9	45	1	5
Gastroparesis	1	10	1	5
Febrile Neutropenia	1	5	1	5
Nausea	10	50		
Elevated creatinine	7	35		
Elevated LFTs	6	30		
Anorexia / Wt. loss	6	30		
Diarrhea	4	20		
Hypomagnesemia	4	20		
Dyspnea	3	15		
Edema	3	15		
Rash	3	15		
Infection	3	15		

Table 2: Treatment Related Adverse Events with Incidence > 10% and / or Grade 3. *No ≥ grade 4 events were noted LFTs = Liver function tests

RESULTS

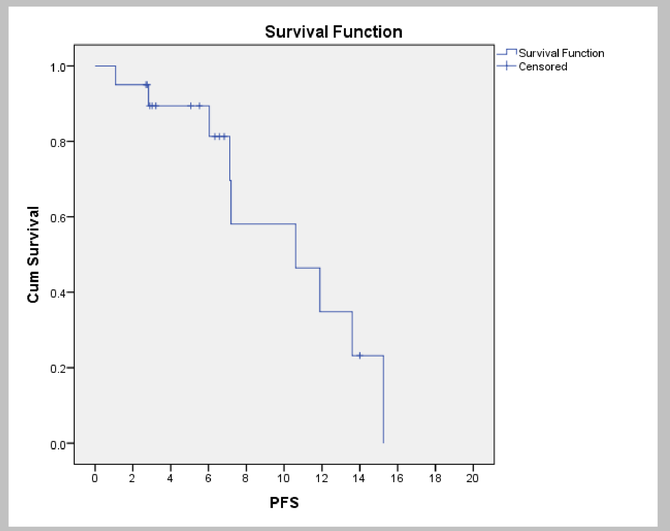

Figure 2: Progression Free Survival
Median 10.44 months
95% CI 7.37 – 13.49 months

	n (%)
Progression	17 (85%)
Patient Preference	2 (10%)
Toxicities	1 (5%)

Table 3: Reasons for Discontinuation

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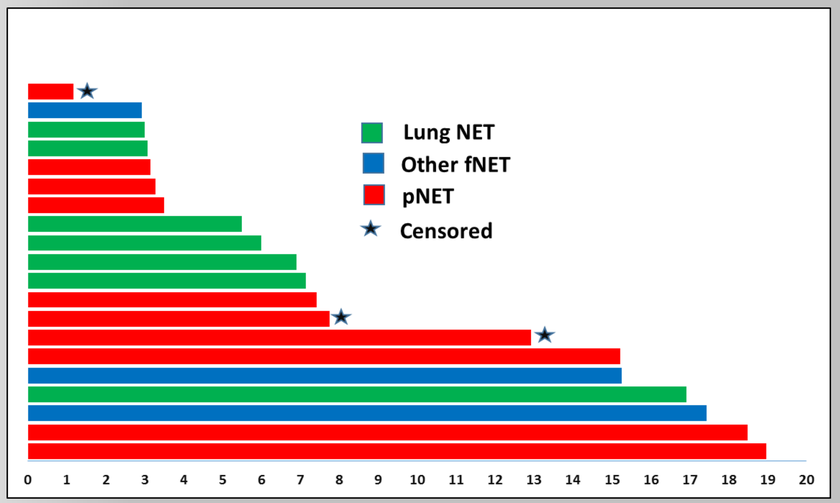

Figure 3: Progression Free Survival (mos) According to Primary Site

Descriptive Statistics

	N	Mean	Std. Deviation	Minimum	Maximum	Percentiles 25th	50th (Median)	75th
HscorePre	19	236.47	67.259	0	291	209.00	246.00	280.00
HscorePost	19	238.32	39.564	172	297	198.00	245.00	279.00

Ranks

		N	Mean Rank	Sum of Ranks
HscorePost - HscorePre	Negative Ranks	9[a]	6.94	62.50
	Positive Ranks	5[b]	8.50	42.50
	Ties	4[c]		
	Total	18		

a. HscorePost < HscorePre
b. HscorePost > HscorePre
c. HscorePost = HscorePre

Test Statistics[a]

	HscorePost - HscorePre
Z	-.628[b]
Asymp. Sig. (2-tailed)	.530
Exact Sig. (2-tailed)	.552
Exact Sig. (1-tailed)	.276
Point Probability	.010

a. Wilcoxon Signed Ranks Test
b. Based on positive ranks.

Descriptive Statistics

	N	Mean	Std. Deviation	Minimum	Maximum	Percentiles 25th	50th (Median)	75th
Ki67Pre	18	13.61	10.182	4	46	7.50	11.00	16.00
ki67Post	18	19.11	17.835	0	76	7.75	16.00	22.25

Ranks

		N	Mean Rank	Sum of Ranks
ki67Post - Ki67Pre	Negative Ranks	4[a]	9.63	38.50
	Positive Ranks	13[b]	8.81	114.50
	Ties	0[c]		
	Total	17		

a. ki67Post < Ki67Pre
b. ki67Post > Ki67Pre
c. ki67Post = Ki67Pre

Test Statistics[a]

	ki67Post - Ki67Pre
Z	-1.803[b]
Asymp. Sig. (2-tailed)	.071
Exact Sig. (2-tailed)	.072
Exact Sig. (1-tailed)	.036
Point Probability	.002

a. Wilcoxon Signed Ranks Test
b. Based on negative ranks.

Table 4: Changes in pRb Ser 780 (left) and Ki-67 (right) with Treatment by IHC H-Score and Compared with Wilcoxon Sign Rank Test (*3 pts with Ki-67 > 20%)

CONCLUSIONS

- Ribociclib 600 mg by mouth 3 weeks on 1 week off in 4 week cycles was well tolerated in this cohort of foregut NETs without any unanticipated adverse effects.
- No radiographic responses were noted as expected with this class of drugs.
- Clinical benefit was noted with prolonged stable disease in patients with prior progression. The median PFS was 10.44 months with 7 patients having PFS > 12 months.
- Paired biopsies were obtained at baseline and on cycle 2, day 1 for evaluation of changes in Ki-67 and pRb Ser 780 by immunohistochemistry.
- Pharmacodynamic studies from paired biopsies did not show robust target inhibition perhaps related to intermittent dosing.
- The protocol is being amended to evaluate the combination of everolimus and ribociclib in patients with foregut NETs with paired biopsies.