Abstract #39

Multicenter Phase 2 Study of Nintedanib in Patients (pts) with Advanced Progressing Carcinoid Tumors

Renuka Iyer[1], Bhavana Konda[2], Dwight Owen[2], Kristopher Attwood[1], Suman Sarker[1], Sheryl-Ann Suffren[2], John Wilton[1], Robert Bies[1], Danielle Casucci[1],Diane L. Reidy[3], Manisha H. Shah[2]

[1]Roswell Park Comprehensive Cancer Center, Buffalo, NY; [2]Ohio State University Medical Center, Columbus, OH; [3]Memorial Sloan Kettering Cancer Center, New York, NY

renuka.iyer@roswellpark.org Tel 716-845 8195

ROSWELL PARK COMPREHENSIVE CANCER CENTER

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BACKGROUND

Targeting angiogenesis is effective in pancreatic neuroendocrine tumors and thought to drive tumor progression in all neuroendocrine cancers. Serotonin is the cause of carcinoid symptoms and can signal the formation of fibroblasts via fibroblast growth receptors (FGFR). Nintedanib is an oral inhibitor of the FGFR pathway and several angiogenic signaling pathways thought to drive carcinoid tumor progression. We hypothesize that nintedanib may slow tumor progression in patients with progressing carcinoids.

METHODS

This phase 2 study will accrue 30 pts with unresectable/ metastatic carcinoids on a stable dose of somatostatin analogue for ≥ 3 months from two sites over two years. (NCT02399215).

Primary Endpoint: To assess progression free survival (PFS). A true PFS rate at 16 weeks of less than p0 =0.40 is considered unacceptable in carcinoid, and evidence of such will deem the treatment not worthy of further study. The null and alternative hypotheses to be tested are H0: p ≤ p0 versus HA: p > p0. If 16 or more pts are alive and progression free at 16 weeks, the agent would be promising.

Secondary Endpoints: (1.) To assess the objective response (complete response + partial response) using standard RECISTv1.1 criteria

(2.) Overall survival (OS)

(3.) Change in QOL throughout treatment using the EORTC QLQ–GI.NET21 questionnaire for carcinoid pts, in all pts who have filled out at least two QOL questionnaires will be reported by response groups. (4.) Toxicity (graded using the NCI CTCAE version 4.0) will be closely monitored and all toxicities will be tabulated.

Correlative Endpoints:

(1.) Steady state PK of nintedanib will be assessed as exposure in this population given the diarrhea, and concomitant somatostatin use has not been previously studied.

(2.) Baseline Treg, cytokine expression and growth factor levels will be measured and correlated with response

(3.) Gene mutations and copy number alternations in the mtor pathway, protein alterations of akt and other downstream targets will be assessed at baseline and post treatment in a subset.(MSKCC)

TREATMENT PLAN

All patients must be on somatostatin and the dose must be stable for x3 months prior to study enrolment. Nintedanib 250mg PO BID will be given as an outpatient in 28 day cycles. Patients will be required to fill out the QOL questionnaires at baseline and before each cycle.

Patients will have 10 cc of blood drawn pre-study and q 12 weeks for correlative studies and steady state PK. Tumor specimen availability will be confirmed and all specimens banked and sent to RPCI at the end of study accrual for correlative studies. Treatment will continue until progression or toxicity or patient/ physician preference.

ELIGIBILITY

Inclusions:

Patients must have histologically or cytologically confirmed well differentiated or moderately differentiated (low grade or intermediate grade) neuroendocrine tumor that is locally advanced or metastatic and not of pancreatic origin.

Measurable disease determined by triphasic CT or MRI.

2. Age ≥18 years.
3. ECOG performance status 0, 1 or 2.
4. Life expectancy greater than 3 months.
5. Adequate hematologic, hepatic and renal parameters (leukocytes >3,000/µl, ANC>1,500/µl, platelets >100,000/µl, total bilirubin < 2 mg/dl, AST or ALT < 5 times ULN for subjects with documented liver metastases; < 2.5 times ULN for subjects without evidence of liver metastases, creatinine <1.5 mg/dl).
6. Prior treatment will be permitted including surgery (>4 wks), cytotoxic chemotherapy (max 2 prior regimens) radiation, interferon, targeted growth factors >30 days, and prior treatment with octreotide will be allowed.
7. Signed written informed consent.

Key Exclusions:

1. Uncontrolled hypertension, unstable angina, New York Heart Association Grade II or greater congestive heart failure, unstable symptomatic arrhythmia requiring medication, or clinically significant peripheral vascular disease (Grade II or greater).
2. Presence of brain metastases.
3. Significant proteinuria at baseline (≥ 500 mg/ 24 h).

RESULTS

Accrual was completed between June 2015 and May 2017 at 2 sites.

Baseline characteristics: Table 1. Median tumor burden was 8cm (2.5-18.5cm), 27(90%) had liver mets and 23% had progressed on prior everolimus.

Efficacy: The 16wk PFS rate was 86.7% (26 pts, 95%CI: 72-95.3%), which was significantly greater than the historic rate of 40% with everolimus (p<0.001)." Kaplan Meier median PFS and OS estimates were 11 and 27.6 months, respectively, with 6 pts currently on treatment.

Toxicity: No unexpected toxicity signal was seen. Treatment was held in 7 pts (23%) due to AEs. Highest grade AEs: gr2 in 14(47%) and gr3 in 8(27%) pts. The most common gr 2 were GI (9), heme (8) and gr 3 were hypertension (6) and decreased appetite (2). There were 27 patients that had at least one AE and 3 patients had no AEs.

Table 1: PATIENT DEMOGRAPHICS

Characteristic		N(%)
Overall	N	30(100%)
Gender	Male	15(50%)
	Female	15(50%)
Baseline ECOG	0	11(37%)
	1	17(57%)
	2	2(7%)
Center	RPCI	14(47%)
	OSUMC	16(53%)
Age at Consent(yr)	Mean /Std	64.1/8.5
	Median/ Min/Max	64.9/45.1/77.2
Tx Status	On treatment	6(20%)
	Off treatment	24(80%)

Table 2: Primary site for the Tumor

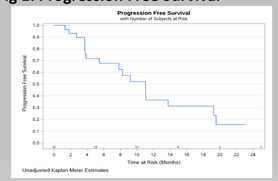
SITE OF ORIGIN	Frequency	Percent	Cumulative Frequency	Cumulative Percent
Colon, NOS	7	23.33	7	23.33
Gastric	1	3.33	8	26.67
Lung, atypical	4	13.33	12	40.00
Small bowel	13	43.33	25	83.33
Unknown primary site	5	16.66	30	100.00

Table 3: Toxicities

Adverse event	Grade 2	Grade 3
Neutropenia	1 (3%)	
Lymphopenia	4 (13%)	
Leukopenia	3 (10%)	
Nausea	2 (7%)	
Diarrhea	3 (10%)	
Vomiting	1 (3%)	
Abdominal pain	4 (13%)	
Fatigue	2 (7%)	1(3%)
Liver function ABN	3 (10%)	
Decreased appetite	2(7%)	2(7%)
Dysgueisia	1 (3%)	
Confusion	1 (3%)	
Renal failure	1 (3%)	
Hypertension	3(10%)	6(20%)
Troponin elevation		1(3%)

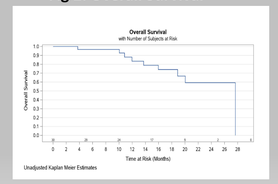
- 5 patients had at most a grade 1 AE;
- 14 patients had at most a grade 2 AE; and
- 8 had at most a grade 3 AE.

Fig 1: Progression Free Survival



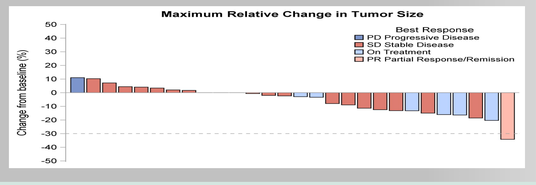
6-mth Surv.Rate (95% CI)	1-yr Surv.Rate (95% CI)	Median Surv. (95% CI)
0.68 (0.47, 0.82)	0.36 (0.17, 0.56)	11.0 (5.5, 19.3)

Fig 2: Overall Survival



6-mth Surv.Rate (95% CI)	1-yr Surv.Rate (95% CI)	Median Surv. (95% CI)
0.97 (0.79, 1.00)	0.83 (0.61, 0.93)	27.6 (18.9, 27.6)

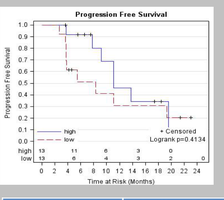
Fig 3: Best Response



RECIST response: PR 1(4%), SD 20(83%), PD 2(8%), NE 1(4%). Reasons for coming off therapy: Progression 14 (58%), toxicity 5(21%), other (17%), death due to disease 1(4%).

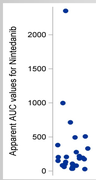
QOL was maintained or improved in at least 50% of subjects while on therapy. 6 patients are currently on treatment.

Fig 4: Pharmacokinetics of Nintedanib



Summary Statistics

AUC	Mean:	314.9
	Median:	179.7
	Std. Dev:	473.5
	IQR:	251.8
	Min:	28.6
	Max:	2349.99



AUC	Median PFS (95% CI)	16-Week PFS (95% CI)	Events/Censored/Total
Low (<= 179.7)	8.3 (3.7, 19.3)	0.85 (0.51, 0.96)	9/4/13
High (>179.7)	11.1 (7.8, 19.5)	0.92 (0.54, 0.99)	7/6/13

PK: There was no statistically significant association between PFS and AUC; whether you examine AUC dichotomized at the median (p=0.41) or treat it as continuous (p=0.41). (Per the IB AUC at 150 Bid is ~ 154 and at 250mg ~ 605 ng.h/ml)

CONCLUSIONS

- Nintedanib has activity in advanced carcinoid patients who have progressed on prior therapies. QOL is preserved.
- Treg and AKT activation status at baseline in immune subsets and correlation with outcomes may allow optimal patient selection.
- Hypertension, and GI and hematological events were the only notable AEs.

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