Phase 1 Study of Oral Rigosertib in Patients with Advanced Solid Tumors

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ABSTRACT #3017

Background: Rigosertib (ON 01910.Na) is a novel multi-targeted inhibitor of several kinases, including polo-like kinase 1 and PI-3 kinase, and is in advanced trials for myelodysplastic syndrome and pancreatic cancer as an IV agent. An oral formulation with good oral bioavailability has entered phase 1 in patients (pts) with advanced solid tumors to determine the dose limiting toxicities (DLT), recommended phase 2 dose, pharmacokinetic (PK) profiles, and to document any antitumor activity of this compound.

Methods: Pts with histologically confirmed solid tumors refractory to standard therapy were given escalating doses of rigosertib (70, 140, 280, 560, 700 mg) twice daily continuously. Doses were escalated until intolerable grade 2 or grade 3/4 toxicities, at which point the previous dose level was expanded to define the MTD. All pts were assessed for safety, PK, PD and response. Urinary PK assessments were also performed at the MTD.

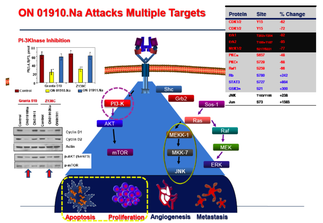
Results: 25 pts (median age= 59; median ECOG PS= 1) received a median of 6 weeks of therapy at 5 dose levels: (70 mg n=3; 140 mg n=2 ; 280 mg n=3; 560 mg n=10; 700 mg n=7). The DLT was dysuria at 700 mg and led to expansion at 560 mg bid. There were no DLTs in the expansion cohort. Grade 2/3 toxicities related to rigosertib included dysuria (5/1), cystitis (4/0), urinary frequency (3/0), hematuria (2/1), abdominal pain (2/0), pelvic pain (1/1), nausea (1/0), distention/bloating (1/0) and hyponatremia (0/1). Improvements in dysuria were seen with oral hydration and sodium bicarbonate. A confirmed PR occurred in 1 pt (HN squamous cell ca, 42+ weeks), and SD was observed in 2 pts with ovarian cancer (56 weeks, 28 weeks), and 1 pt each with pancreatic neuroendocrine (40 weeks), carcinoid (32 weeks), nasopharyngeal (24 weeks) and renal cell (32+ weeks) tumors. Preliminary PK data reveal plasma rigosertib levels above the predicted pharmacodynamically active levels.

Conclusions: The MTD of oral rigosertib administered twice daily continuously is 560mg. Dysuria is the dose limiting and most common toxicity and can be managed with oral hydration and sodium bicarbonate. Antitumor activity has been observed. Final safety and efficacy results, plasma and urinary PK relationships, and mutational analyses from archival tissue will be presented.

Rigosertib Background

Rigosertib: PLK-1 & PI3K Pathway Inhibitor

- Mechanism of action
  - PI3K inhibition
  - Inhibits PLK-1 pathway: causes spindle formation abnormalities and multiple centrioles
- Cytotoxic to tumor but not to normal cells
  - IC50 ranges from 50 nM (gastric) to 250 nM (colorectal)
  - IC50 >10,000 nM for fibroblasts and endothelial cells
- Efficacious as single agent and in combination with other chemotherapeutic agents in animal models
- IV formulation currently in pivotal clinical trials
  - Refractory MDS to hypomethylating agents
  - Combination with gemcitabine in first line metastatic pancreatic cancer



Study Design and Methods

- Objectives
  - Determine the MTD of orally administered rigosertib
  - Evaluate the pharmacokinetics of oral rigosertib
  - Evaluate antitumor activity
  - Explore potential biomarkers of response
- Key Inclusion Criteria
  - Histologically confirmed solid tumor
  - Incurable or untreatable by established standard therapies
  - ECOG PS 0 or 1
  - Measurable disease by RECIST 1.1
- Key Exclusion Criteria
  - Significant comorbidity
  - Inadequate bone marrow, renal, or hepatic function

- Methods
  - 2 patient dose escalation cohorts in the absence of drug-related ≥ grade 2 toxicity
  - 100% dose increase between cohorts until final escalation with an expansion at MTD
  - Tumor restaging q2 cycles (every 6 weeks)
  - Archived tumor biopsies for mutations in PIK3CA, EGFR, KRAS, p53, BRAF
- Treatment
  - Twice daily rigosertib for 21 day cycles
  - DLT defined as ≥ grade 3 toxicity in cycle 1

Patient Demographics

Age	**59.5 (39-81)**
Sex	**Male 19 Female 17**
Tumor type	
Squamous cell carcinoma of the head and neck	5
Colorectal	5
Ovarian	3
Renal cell	3
Esophageal	3
Squamous cell carcinoma of the cervix/vulva	2
Breast	2
Uterine/endometrial	2
Adrenal gland	1
Adenocystic carcinoma of the nasopharynx	1
Carcinoid	1
Craniopharyngioma	1
GIST	1
Hepatocellular	1
Pancreatic neuroendocrine	1
Urothelial	1
Vulvovaginal melanoma	1

Dose Escalation & Treatment Duration

Dose Level (mg)	Number Patients	Range of Duration of Treatment (weeks)
70	3	2-42
140	2	12-30
280	3	1-51
560	21	2-27
700	7	1-27
Total	36	1-51

Patient Disposition

- Median/average number of weeks on study was 6/11 ± 2 (SE) (range <1-51)
- 64% patients came off study for progression of disease

Status	Number of patients	Time on study (median/average weeks ± SE)
Off study		
Progression	23	6/10 ± 2
Investigator decision	5	6/7 ± 2
Adverse Event	1	4
Withdrawal of consent	1	18
Active	6	12/17 ± 7
TOTAL	36	6/11 ± 2

Tolerability: Grade ≥ 2 Drug Related AEs

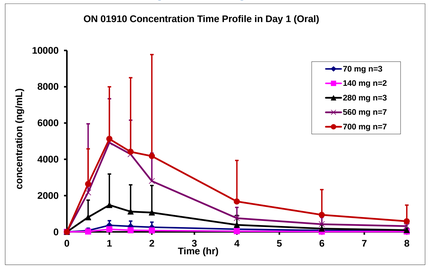
Rigosertib BID Dosing (mg)	70	140	280	560	700
Total Patients	3	2	3	22	7
Dysuria	0	0	0	5*	4
Hematuria	1	0	0	1*	2**
Cystitis	0	1	0	2	0
Micturition urgency	0	1	0	0	2
Hypertonic bladder	0	0	0	1	0
Abdominal discomfort	0	0	0	0	1
Abdominal pain upper	0	0	0	0	1
Pelvic discomfort	1	0	0	0	0
Nausea	0	0	0	0	1
Hyponatremia	0	0	0	0	1

*1 DLT (grade 3 hematuria and dysuria at week 3)

**1 DLT (grade 3 hematuria at week 2)

Plasma Pharmacokinetics

Cycle 1 Day 1



At 560 mg dosing AUC (ng-hr/ml) ± CV = 11875 ± 60

Cmax (ng/ml) ± CV = 5707 ± 50

Urinary Toxicity is Unrelated to PKs

- Urinary toxicity is dose limiting
- Peak plasma concentration (Cmax) and drug exposure (AUC) is unrelated to urinary toxicity
- 24 hour urine drug exposure is also unrelated to urinary symptoms

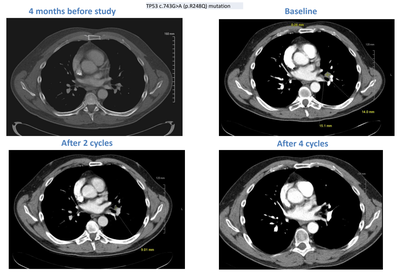
Rigosertib PK Parameter Mean ± SE (N)	C max (ng/mL)	AUC (ng-hr/mL)	24h Urine (mg)
Urinary Symptoms	8732 ± 1931 (15)	4164 ± 862 (15)	21 ± 4 (11)
No Urinary Symptoms	13137 ± 7909 (7)	4260 ± 2161 (7)	33 ± 13 (9)

Best Responses in All Patients

- Best PR + SD rate of 50% at ≥ 6 weeks
- PR+SD of 39% for ≥ 12 weeks

Dose (mg)	Tumor type	Response	Duration (weeks)
70	Ovarian carcinoma	SD	44
70	Ovarian carcinoma	SD	18
140	Neuroendocrine pancreatic tumor	SD	18
140	Vulvovaginal melanoma	SD	12
280	Carcinoid tumor of liver	SD	23
280	Squamous cell H&N carcinoma	PR	46+
560	Adenoid cystic carcinoma of the nasopharynx	SD	27
560	Craniopharyngioma	SD	12
560	Colon adenocarcinoma	SD	13
560	Metastatic poorly-differentiated squamous cell carcinoma	SD	12
560	Squamous cell carcinoma of the vulva	SD	22
700	Renal cell carcinonoma	SD	30
700	Base of tongue squamous cell carcinoma	SD	12
700	Basoloid squamous cell carcinoma	SD	12

PR Squamous Carcinoma Head and Neck 46 weeks+



Mutational Testing

- Mutational status acquired in 26/36 pts
  - 17 completed
    - 2 PIK3CA point mutations (both with PD)
    - 1 p53 mutation (pt with prolonged PR)
    - 1 Kras mutation (pt on study for 42 weeks)
  - 6 in process
  - 1 rejected due to inadequate tissue

CONCLUSIONS

- Oral Rigosertib is active and well tolerated
- MTD declared to 560 mg twice daily
  - Further confirmation of the MTD is ongoing
  - Urinary toxicity is dose limiting and independent of urinary and plasma PK
- A significant number of patients experienced stable disease or a partial response