A Phase I/Ib Study of Crenolanib with Ramucirumab/Paclitaxel as Second-line Therapy (2L tx) for Advanced Esophagogastric Adenocarcinoma (EGA)

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Abstract

Background

Paclitaxel (PTX)/ramucirumab (RAM) as 2L tx for patients (pts) with EGA is a standard-of-care based on the RAINBOW trial (Lancet Oncol 2014;15:1224). However, benefits remain modest. Upregulation of the platelet-derived growth factor (PDGF)/PDGF receptor-β (PDGFR-β) pathway causes resistance to VEGF inhibition. Crenolanib is a selective inhibitor of PDGFR-β. We report initial results of the dose escalation phase of a study of crenolanib plus RAM/PTX in pts with previously treated advanced EGA.

Methods

This phase I/Ib study is enrolling ECOG PS 0-1 EGA pts with progression on first-line chemo. PTX 80 mg/m^2/day on day 1, 8, 15 and RAM 8 mg/kg q 14 days were administered with escalating doses of crenolanib (60, 80, 100 mg BID, 100 mg TID) after a 7 day "run-in" of crenolanib to assess crenolanib-related toxicities. The primary objective was to determine the maximum tolerated dose (MTD) of crenolanib plus RAM/PTX. Safety of the combination was examined.

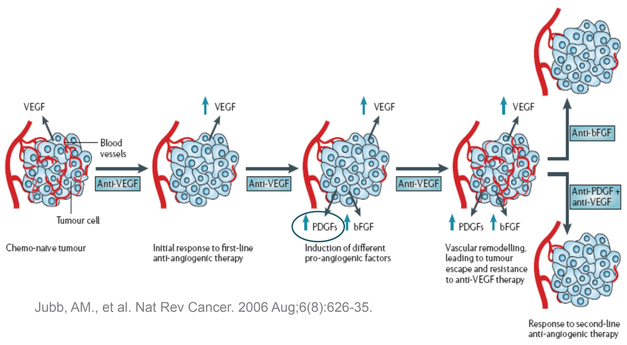
Results

16 pts were treated; 13 male, median age 58 (32-73), 69% were ECOG PS 1. Primary site was gastric in 10 pts, GEJ in 4 pts and esophageal in 2 pts. 3 pts each received crenolanib 60 mg BID and 80 mg BID, 6 pts received 100 mg BID and 4 pts received 100 mg TID. At data cutoff, 5 pts continued study treatment. 12 pts completed the DLT evaluation period across 3 dose levels (60 to 100 mg BID). A fourth dose level (100 mg TID) was added after no DLTs were observed in the first 3 cohorts. 5 patients are continuing treatment at dose levels 3 and 4; and 5 pts remained on treatment more than 5 months. The combination was well tolerated, with no serious adverse events (SAEs) attributed to study drug. The most common treatment emergent adverse events were fatigue (62.5%), abdominal pain (50%), and nausea (50%). Disease progression was the most common reason for treatment discontinuation; no pt discontinued due to study drug related AEs. 16 pts were evaluable for response. 3 pts had objective response; 9 patients had stable disease.

Conclusion

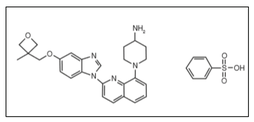
Crenolanib plus RAM/PTX appears well tolerated at a dose level up to 100 mg BID. Crenolanib plus RAM/PTX appears not to yield unexpected toxicities or side effects. Further evaluation is needed to determine efficacy. Accrual is ongoing at 100 mg TID dose level. Once the MTD is defined, the dose expansion phase will enroll 25 pts. *Updated from submitted abstract.*

PDGF Pathway Activation is a Mechanism of Resistance to VEGF Inhibition

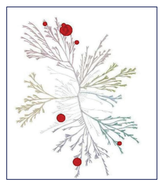


Jubb, AM., et al. Nat Rev Cancer. 2006 Aug;6(8):626-35.

Crenolanib: A Highly Selective, Potent and Specific Inhibitor of PDGFRβ



Crenolanib besylate molecular structure



Kinome scan of crenolanib

Panetta et al., American Society of Hematology. 2015.

Crenolanib is a selective and potent inhibitor of PDGFRβ

RTK	Crenolanib K_d (nM)
PDGFRβ	2.1

Heinrich et al., Clin Cancer Res 2012

Dose Escalation and Expansion Study Design

Key Eligibility:

- Adenocarcinoma of the esophagus, GEJ or stomach
- Stage IV disease or locally advanced/unresectable tumors
- Prior progression on only 1 line of chemotherapy
- No prior treatment with any drugs that target VEGF/PDGF

Patients will be enrolled in two phases: dose escalation phase and dose expansion phase

DOSE ESCALATION PHASE
Primary Endpoint: MTD

DOSE EXPANSION PHASE
Primary Endpoint: Response Rate (RR)

Crenolanib Dose Escalation

ROLLING-6 DESIGN
- Cohort 4, 100 mg TID N=3 to 6
- Cohort 3, 100 mg BID N=3 to 6
- Cohort 2, 80 mg BID N=3 to 6
- Cohort 1, 60 mg BID N=3 to 6

MTD → Patient enrollment at MTD (N=25)

Patients Receive a Combination of Paclitaxel, Ramucirumab and Crenolanib

Treatment Schedule

Treatment	Dose	Day
Paclitaxel	IV 80 mg/m^2	Days 1, 8 and 15 q28 days
Ramucirumab	IV 8 mg/kg	Days 1 and 15 q28 days
Crenolanib	1 of 4 doses: 60 mg BID 80 mg BID 100 mg BID 100 mg TID	Continuously on days 1-28 q28 days

16 Patients Enrolled with Gastric, Esophageal, or GEJ Primary Tumors

Patient Characteristics

Characteristics, n (%)	Total (n=16)
Age (years), median [range]	57 [32-73]
Sex, Male (%)	13 (81%)
Baseline ECOG Performance Status	
0	5 (31%)
1	11 (69%)
Prior systemic anticancer agents	
FOLFOX	14 (88%)
Capecitabine	3 (19%)
Trastuzumab	2 (13%)
Other	5 (31%)
Pembrolizumab, oxaliplatin, mDCF, nivolumab, ipilimumab, cisplatin	
Site of Primary Tumor	
Gastric	10 (62%)
GE Junction	4 (25%)
Esophageal	2 (13%)
Metastatic Sites	
Peritoneum	8 (50%)
Lymph nodes	9 (56%)
Liver	3 (19%)
Lungs	2 (13%)
Other	5 (31%)
Previous gastrectomy	5 (31%)

5 Patients Still Ongoing at Dose Cohorts 3 and 4

Dose Cohort	Age/Sex	Dose	Prior Therapy	Tumor Primary Site (Metastases)	Days on Study*	Best Response	Current Status
1	50/F	60 mg BID	FOLFOX	GEJ (lesions in hepatic capsule, lymph nodes, peritoneum, lung, adnexal masses)	118	SD	Deceased
	61/M	60 mg BID	FOLFOX	Gastric (peritoneum)	60	PD	Deceased
	32/M	60 mg BID	FOLFOX, cisplatin	Esophageal (periceliac and left para-aortic lymph nodes, hepatic lesions)	184	PD	Off study, Alive
2	43/M	80 mg BID	FOLFOX	Gastric (peritoneum)	126	SD	Deceased
	68/F	80 mg BID	FOLFOX	Gastric (gastrohepatic ligament, thoracic and retroperitoneal lymph nodes, lung nodules)	155	PR	Off study, Alive
	59/M	80 mg BID	FOLFOX	Esophageal (mediastinal and retroperitoneal lymph nodes)	42	PD	Deceased
3	58/F	100 mg BID	FOLFOX	Gastric (peritoneum and lymph node)	76	SD	Off study, Alive
	52/M	100 mg BID	FOLFOX	Gastric (ileum and peritoneum)	230+	PR	On study
	53/M	100 mg BID	FOLFOX, capecitabine	GEJ (liver and abdominopelvic nodes)	188+	PR	On study
	68/M	100 mg BID	FOLFOX	Gastric (liver, pericardia lymphadenopathy, peritoneum, paraesophageal adenopathy)	105	SD	Off study, Alive
	73/M	100 mg BID	FOLFOX	Gastric (peritoneum)	162+	SD	On study
	47/M	100 mg BID	FOLFOX, ipilimumab, nivolumab	Gastric (peritoneum)	99	SD	Off study, Alive
4	56/M	100 mg TID	Pembrolizumab, trastuzumab, oxaliplatin, capecitabine	GEJ (mediastinal and thoracic lymph nodes)	127+	SD	On study
	60/M	100 mg TID	FOLFOX	Lower esophagus/GEJ (widespread osseous mets)	126+	SD	On study
	71/M	100 mg TID	FOLFOX	Gastric (periesophageal lymph node)	99	SD	Off study, Alive
	56/M	100 mg TID	mDCF, trastuzumab, capecitabine	Gastric (omentum)	65	PD	Off study, Alive

*Data as of January 10, 2019
+Patients remain on study

Summary of TEAEs Occurring in ≥ 20% of Patients, Regardless of Causality

			Maximum TEAE Grade by Patient			
Preferred Term	Total AEs	Percent	Grade 1	Grade 2	Grade 3	Grade 4/5
Fatigue	10	(62.5%)	6	4	0	0
Abdominal pain	8	(50.0%)	5	3	0	0
Nausea	8	(50.0%)	5	3	0	0
Hypertension	7	(43.8%)	7	0	0	0
Constipation	6	(37.5%)	5	1	0	0
Hyperglycaemia	6	(37.5%)	6	0	0	0
Anaemia	5	(31.3%)	4	0	1	0
Decreased appetite	5	(31.3%)	3	2	0	0
Vomiting	4	(25.0%)	4	0	0	0
Blood alkaline phosphatase increased	4	(25.0%)	1	1	2	0
White blood cell count decreased	4	(25.0%)	2	2	0	0
Hypoalbuminaemia	4	(25.0%)	4	0	0	0
Back pain	4	(25.0%)	2	2	0	0
Peripheral sensory neuropathy	4	(25.0%)	4	0	0	0

No DLTs Observed in Dose Finding Cohorts 1-3: Current Enrollment at Dose Cohort 4

Age/Sex	Dosing Cohort	Dose Modification	DLTs
Cohort 1: 3 Pts treated at 60 mg BID, no DLTs seen			
50/F	60 mg BID	No	No
61/M	60 mg BID	No	No
32/M	60 mg BID	No	No
Cohort 2: 3 Pts treated at 80 mg BID, no DLTs seen			
43/M	80 mg BID	No	No
68/F	80 mg BID	No	No
59/M	80 mg BID	No	No
Cohort 3: 6 Pts treated at 100 mg BID, no DLTs seen			
58/F	100 mg BID	No	No
52/M	100 mg BID	No	No
53/M	100 mg BID	No	No
68/M	100 mg BID	No	No
73/M	100 mg BID	No	No
47/M	100 mg BID	No	No
Cohort 4 (Currently Enrolling): 4 Pts treated at 100 mg TID*			
56/M	100 mg TID	No	No
60/M	100 mg TID	No	No
71/M	100 mg TID	Yes**	Yes**
56/M	100 mg TID	No	No

*Enrollment began September 2018. A total of 6 pts will be enrolled at 100 mg TID

**Dose reduced to 100 mg BID due to Gr 3 AST/ALT

References

- Jubb, AM., et al. Nat Rev Cancer. 2006 Aug;6(8):626-35
- Panetta et al., American Society of Hematology. 2015
- Heinrich et al., Clin Cancer Res. 2012 Aug 15;18(16):4375-84

Conclusions

- Crenolanib plus RAM/PTX appears well tolerated at a dose level up to 100 mg BID. Further evaluation is needed to determine efficacy.
- Crenolanib plus RAM/PTX appears not to yield unexpected toxicities or side effects.
- PK/PD and correlative analysis are ongoing.
- Accrual is ongoing at the 100 mg TID dose level. Once the MTD is defined, the dose expansion phase will enroll 25 patients.