A Novel Endoscopic Ultrasound-Guided Extended-Release siRNA Implant Targeting *KRAS* G12D/V in Localized Pancreatic Cancer

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Background: Locally advanced pancreatic cancer (LAPC) accounts for 30% of pancreatic cancer (PC). LAPC incurs high mortality. We evaluated a novel extended-release siRNA targeting *KRAS* G12D/V (G12D/V) mutations (Loder™) in combination with standard chemotherapy.
Methods A two-cohort, Phase 2 multicenter, open-label trial was conducted. Cohort 1: Patients (pts) with LAPC randomized to: Loder™ +gemcitabine/nab-paclitaxel (GnP); or GnP. Cohort 2: pts with Borderline Resectable (BR) PC or LAPC single arm, Loder™ +(modified)FOLFIRINOX ((m)FFX) or GnP. The Loder™ was inserted into primary tumor via endoscopic ultrasound (EUS 19G needle) q3 mo. for 2-3doses. mITT, all patients > 1 treatment. Key study endpoints: overall survival (OS), safety.
Results N= 49 pts in mITT (6 BRPC, 43 LAPC, Loder™ n=38, control n=11). *KRAS* G12x status known for n=31: G12V, n=16; G12D, n=7; G12R, n=8. For mITT: no difference in OS for Loder™ + chemo vs. chemo (OS=22.1 vs. 22.1 mo.). However, in pts with G12D/V a non-statistically significant numerical advantage was seen in Loder™ + (m)FFX or GnP arm (n=18, Cohorts 1,2) median OS = 21.1 mo. vs. 13.8 mo. Loder™ treatment was well tolerated. Safety events were primarily related to procedure; mainly reversible abdominal pain. Four Grade 5 events(visceral arterial ischemia, sepsis; 2 progression of disease), assessed as unrelated.
Conclusions Loder with chemotherapy is feasible, safe, and shows a promising signal in *KRAS* G12D/V BR, LAPC. Further evaluation is warranted.
Clinical trial identification NCT01676259

BACKGROUND

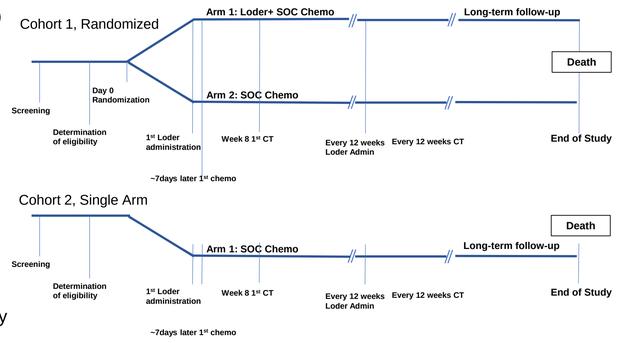
- The majority of PCs (~90%) harbor *KRAS* mutations; with ~75% *KRAS* G12D and G12V (*KRAS* G12D/V)
- Small interfering RNA (siRNA) can target *KRAS* G12D mutations (~40% PC) to prevent the production of this oncogenic protein, using an extended release depot formulation administered intra-tumorally (Loder™)[1]
- Phase 1 trial in combination of Loder™ and standard of care chemotherapy (SOC) in localized non-resectable-PC demonstrated the Loder™ to be safe[2]
- In the current study we tested Loder™ with SOC chemotherapy, in a Phase 2 trial with overall survival (OS) being a key study endpoint.

STUDY DESIGN

2 part, open-label, multinational study which included:

- Cohort 1: Pts LAPC randomized to Loder™ + gemcitabine/nab-paclitaxel (GnP) (treatment arm); or to GnP (control arm)
- Cohort 2: Pts with Borderline Resectable (BR) PC or LAPC in a single treatment arm, Loder™ + (modified) FOLFIRINOX ((m)FFX) or GnP. After completion of Cohort 1, Cohort 2 was enrolled
- For both cohorts, pts enrolled to the study without identifying if their tumor had a *KRAS* mutation. The ECOG (Eastern Cooperative Oncology Performance Status) ≤ 1
- The Loder™ was administered by insertion into the primary tumor via endoscopic ultrasound (EUS 19G needle) for 2-3 doses, once every 3 months

STUDY SCHEMA



PATIENT DEMOGRAPHICS

	Demographics	Total	Cohort 1	
			Treatment	Control
1	Sex (M/F)	Male: 25 Female: 24	Male: 7 Female: 11	Male: 7 Female: 4
2	Race			
	American Indian or Alaska Native	1	1	0
	Asian	2	1	0
	Black or African American	1	0	0
	Other	1	1	0
	White	41	14	9
	Unknown	3	1	2
3	Median Diagnosis Age (Range)	70 (50-85)	71.5 (54-82)	75 (61-85)

KRAS MUTATION FREQUENCY

KRAS was determined for n=31 pts, 21 treated with Loder™

KRAS G12x Mutation	Cohort 1 Arm 2 (Control)	Cohort 1 Arm 1 (Treatment)	Cohort 1 % Arm 1 Tx	Cohort 2 (Treatment)	All Treated %
R	5/10	1/12	8	2/9	26 (8/31)
D	2/10	3/12	25	2/9	23 (7/31)
V	3/10	8/12	67	5/9	52 (16/31)

STUDY ENDPOINTS

- mITT : all pts receiving ≥ 1 treatments
- Key study endpoints: OS, response rate (RR, RECIST v1.1), safety
- Exploratory sub-analyses:
  - All pts in randomized Cohort 1 with *KRAS* G12D/V mutation, comparing treatment to control
  - Treatment arm Cohort 1+Cohort 2, compared to control arm of Cohort 1

EFFICACY RESULTS

Cohort/Arm	Median OS (mo.)	Hazard Ratio (95% CI) p value	RR (partial) (%)
All Pts, mITT n=49			
Arm 1, Cohort 1+Cohort 2: Loder™+GnP/(m)FFX, n=38	22.1	1.6 (0.7-3.5) NS	9/38 (24)
Arm 2, Cohort1: GnP, n=11	22.1		2/11 (18)
All *KRAS* G12D/V mutations, (Treatment from Cohorts (1+2) vs. Control from Cohort 1) (Exploratory sub-analysis) LAPC (n=21), BRPC (n=2)			
Arm 1,Cohort 1+Cohort 2: Loder™+GnP/(m)FFX, n=18	21.1	**0.62** (0.2,1.9) NS	4/18 (22)
Arm 2: GnP, n=5	13.8		0/5 (0)
Randomized Cohort 1, LAPC pts bearing only G12D/V mutations (Exploratory sub-analysis)			
Arm 1: Loder™+GnP, n=11	22.8	**0.59** (0.18,2) NS	2/11 (18)
Arm 2: GnP, n=5	13.8		0/5 (0)

p value NS = Not significant

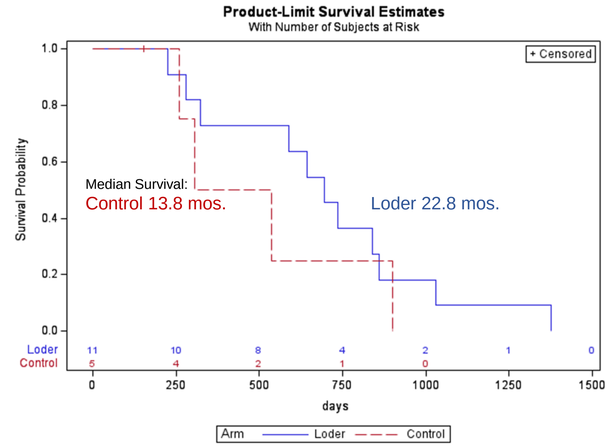
Number of subjects with Loder™ cycles:

#Cycles	Cohort 1 # subjects	Cohort 2 # of subjects
1	5	6
2	4	6
3	3	8
4	1	0
5	5	0
Total	18	20
Mean	2.83	2.1

SAFETY and ADVERSE EVENTS

- Loder treatment was well tolerated.
- Safety events were primarily related to procedure
  - mainly reversible abdominal pain
- Two unrelated Grade 5 events
  - visceral arterial ischemia
  - sepsis

Fig. Randomized Cohort 1 which bears a *KRAS* G12D/V mutation, comparing treatment to control (Exploratory sub-analysis)



CONCLUSIONS

- **siRNA is a novel targeted approach against mutant *KRAS***
- **Intratumor administration of extended-release siRNA via EUS is feasible and safe**
- **For allcomers independent of KRAS allele type, no difference in median OS between Loder™ + chemotherapy vs. chemotherapy was observed**
- **Among patients with *KRAS* G12D/V, chemotherapy and siRNA-LODER showed promise**
- **Further investigation of siRNA and chemotherapy in localized PDAC is warranted**

REFERENCES

[1] Golan et al, *Oncotarget* 6: 24560. 2015
[2] Zorde Khvalevsky et al, *PNAS* 110: 20723. 2013

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