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Interim Results from a Phase 1 Trial of SL-801, a Novel XPO1 Inhibitor, in Patients with Advanced Solid Tumors

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Introduction and Highlights

- SL-801 is a reversible XPO1 inhibitor that offers the potential for improved safety profile / therapeutic window
- Interim results from this ongoing Phase 1 dose escalation trial indicates that SL-801 demonstrates a manageable safety and tolerability profile, with largely grade 1-2 adverse events (AEs), seen to date
- No maximum tolerated dose (MTD) reached; Dose escalation ongoing; 11th cohort (65 mg/day) currently enrolling
- Multiple cases of stable disease (SD) in a heavily pretreated solid tumor patient population
- Pharmacokinetic (PK) analyses suggest dose-dependent increases in exposure; studies ongoing
- Ideal therapeutic dose not yet determined as dose escalation continues
- Given favorable data profile thus far with SL-801, coupled with clinical validation of the XPO1 target, additional SL-801 trials, including in hematologic cancers and combination studies, planned

Background

SL-801 Background

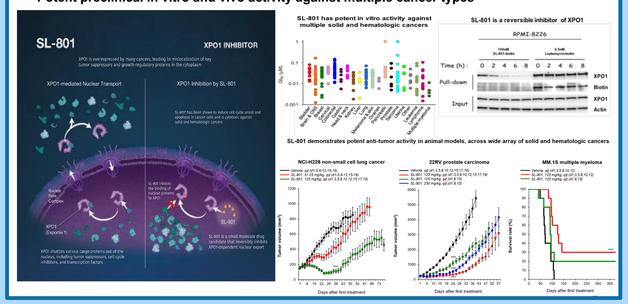
- SL-801 is an orally administered, novel small molecule XPO1 (Exportin 1) inhibitor
- XPO1 is a key nuclear transport oncogene overexpressed in a variety of cancers
- Inhibition of XPO1 has been clinically validated in multiple cancer types
- SL-801 demonstrated potent in vitro and in vivo activity against a wide array of solid and hematologic cancer models
- SL-801 reversibly inhibits XPO1 offering the potential for a favorable therapeutic window
- A Phase 1 trial of SL-801 monotherapy in patients with advanced solid tumors is underway (NCT#02667873)
  - Results from the ongoing dose escalation trial are reported here

XPO1 Background

- XPO1 is the key mediator of nuclear-cytoplasmic transport and is involved with the export of more than 200 nuclear proteins, including[1,2]:
  - tumor suppressor proteins (p53, APC, Rb, BRCA1, FOXO family proteins)
  - cell cycle inhibitors (p21/CIP1, p27/KIP1)
  - transcription factors (ATF2)
  - oncogenic proteins (CIP2A, Erk)
  - immune response regulators (IkBa)
  - molecular chaperone proteins (hsp90)
- XPO1 also exports specific subsets of messenger ribonucleic acid (mRNA) via export adaptor proteins[3]
- Mislocalization of a nuclear protein into the cytoplasm can render it ineffective as a tumor suppressor[4]
- XPO1 is overexpressed in various solid tumors, including breast, cervical, ovarian, and pancreatic cancers, glioma, and osteosarcoma, as well as hematologic malignancies, including acute myeloid leukemia, chronic lymphocytic leukemia, multiple myeloma, and lymphoma[1,5]
- XPO1 overexpression has been associated with poor prognosis, including being correlated with tumor grade, size, metastases, resistance to chemotherapy, as well as shorter progression-free survival (PFS) and overall survival (OS)[1]

Mechanism of Action and Rationale

- **XPO1 is a clinically-validated target in multiple cancer types**
- **SL-801 is a reversible XPO1 inhibitor; Potential for improved safety profile / therapeutic window**
- **Potent preclinical in vitro and vivo activity against multiple cancer types**



Study Design

Stage 1 (Dose-escalation) - Enrollment Ongoing

- Advanced solid tumors
- SL-801 orally administered
  - Dose escalation (mg/day)
    - 5, 10, 20, 30, and by 5 mg increments thereafter
  - D1-4 and D8-11 of a 21-day cycle
  - Standard 3x3 design
- Primary endpoints:
  - Safety and tolerability
  - DLT and MTD
- Secondary endpoints:
  - Pharmacokinetics
  - Efficacy (ORR, DCR, DoR, PFS and OS)

Stage 2 (Expansion) - Not started yet

- Disease-specific cohorts (up to 4 cohorts)
  - ~20 patients per cohort
- SL-801 orally administered
  - Dose and regimen selected from Stage 1
- Primary endpoints:
  - ORR
  - Safety profile
- Secondary endpoints:
  - CR, DoR, PFS, OS

Abbreviations: DLT = dose-limiting toxicity; MTD = maximum tolerated dose; ORR = overall response rate; DCR = disease control rate; DoR = duration of response; PFS = progression-free survival; OS = overall survival; CR = complete response

Inclusion / Exclusion Criteria

Select inclusion criteria

- Advanced (metastatic or locally advanced and unresectable) relapsed or refractory solid tumors with histologic evidence
- Measurable disease and evaluable by RECIST 1.1
- ECOG PS of 0-2
- Adequate organ function, including:
  - Creatinine ≤1.5x ULN, albumin ≥ 2.5 g/dL, bilirubin ≤1.5x ULN, AST/ALT ≤2.5x ULN (≤5x for hepatic metastases), prothrombin time ≤1.5x ULN (and partial thromboplastin time ≤1.5xULN)
- Adequate hematologic function, including:
  - ANC ≥1.5x10^9/L, Hgb ≥8 g/dL (w/o RBC transfusions within prior 14 days), platelet count ≥ 100x10^9/L (w/o platelet transfusions within prior 14 days)

Select exclusion criteria

- Persistent clinically significant (≥G2) toxicities from prior anticancer therapies (excluding G2 chemotherapy-related neuropathy, and G2-3 lab abnormalities if not associated with symptoms and not considered clinically significant by PI)
- Chemotherapy, external-beam radiation or other systemic anticancer therapy within prior 28 days to first dose
- Prior treatment with SL-801 or another drug that inhibits XPO1/CRM1 pathway
- Active secondary malignancy that may confound assessment of study endpoints
- Clinically significant cardiovascular disease, uncontrolled clinically significant pulmonary disease, suspected brain or leptomeningeal metastases
- Immunosuppressive therapy for a prior organ transplant
- Uncontrolled intercurrent illness
- Infection with HIV or chronic Hep B or Hep C

Demographics

- **42 heavily pre-treated patients: 72% patients were 3rd line or greater**
- **Wide spectrum of solid tumors, including GI, breast, lung, neuroendocrine, ovarian, et al**

Age, years	
Median [range]	64 [39-83]
Gender [n, (%)]	
Female	22 (52)
Lines of therapy prior to the study [n, (%)]*	
1st Line	4 (9)
2nd Line	7 (17)
3rd Line	7 (17)
≥ 4th Line	23 (55)
RAS mutation [n, (%)]	
KRAS mutation:	
Yes	7 (17)
No	10 (24)
Unknown	22 (52)
Other mutation:	3 (7)
ECOG performance status [n, (%)]	
0	13 (31)
1	27 (64)
2	2 (5)
Follow-up time on study, weeks	
Median [range]	6.1 [0.4 – 46.9]

Cancer Diagnosis	n
Colorectal cancer (CRC)	6
Breast cancer	4
Non-small cell lung cancer (NSCLC)	4
GI adenocarcinoma (GI Adeno)	4
Neuroendocrine (Neuro-endo)	3
Pancreatic cancer	3
Squamous cell carcinoma (SCC)	3
Adenoid Cystic Carcinoma (ACC)	2
Ovarian carcinoma	2
Renal	2
Biliary	1
Bladder	1
Gallbladder	1
Basal cell carcinoma (BCC)	1
Small bowel	1
Mesothelioma	1
Leiomyosarcoma (LMS)	1
Appendix carcinoma	1
Paraganglioma	1

*** One patient did not have their prior systemic therapy history available**

Safety and Tolerability

Treatment Related Adverse Events (AEs) (n=42 patients)

Preferred Term	All Grades n (%)		TRAEs n (%)			
	TRAEs	All AEs	G1 & 2	G3	G4	G5
Nausea	27 (64)	28 (67)	24 (57)	3 (7)	--	--
Vomiting	20 (48)	27 (64)	19 (45)	1 (2)	--	--
Fatigue	16 (38)	21 (50)	14 (33)	2 (5)	--	--
Diarrhea	10 (24)	14 (33)	8 (19)	2 (5)	--	--
Decreased appetite	10 (24)	14 (33)	10 (24)	--	--	--

TRAEs by dose level (n=42 patients)

		Nausea					Vomiting					Fatigue					Diarrhea					Decreased appetite				
N	Dose level	G 1-2	G3	G4	G5	Tot	G 1-2	G3	G4	G5	Tot	G 1-2	G3	G4	G5	Tot	G 1-2	G3	G4	G5	Tot	G 1-2	G3	G4	G5	Tot
3	5 mg	1	-	-	-	1	-	-	-	-	0	1	-	-	-	1	-	-	-	-	0	-	-	-	-	0
4	10 mg	1	-	-	-	1	-	-	-	-	0	1	-	-	-	1	1	1	-	-	2	-	-	-	-	0
3	20 mg	1	-	-	-	1	1	-	-	-	1	-	-	-	-	0	1	-	-	-	1	-	-	-	-	0
6	30 mg	3	-	-	-	3	1	-	-	-	1	3	-	-	-	3	1	-	-	-	1	2	-	-	-	2
3	35 mg	2	-	-	-	2	2	-	-	-	2	-	-	-	-	0	-	-	-	-	0	-	-	-	-	0
5	40 mg	3	1	-	-	4	2	-	-	-	2	2	-	-	-	2	1	-	-	-	1	2	-	-	-	2
4	45 mg	3	1	-	-	4	3	1	-	-	4	1	-	-	-	1	1	-	-	-	1	2	-	-	-	2
3	50 mg	1	1	-	-	2	1	-	-	-	1	1	-	-	-	1	1	1	-	-	2	-	-	-	-	0
4	55 mg	3	-	-	-	3	4	-	-	-	4	3	-	-	-	3	1	-	-	-	1	1	-	-	-	1
7	60 mg	6	-	-	-	6	5	-	-	-	5	2	2	-	-	4	1	-	-	-	1	3	-	-	-	3

Cohort	Dose (mg/day)	n
1	5	3
2	10	4
3	20	3
4	30	6
5	35	3

Cohort	Dose (mg/day)	n
6	40	5
7	45	4
8	50	3
9	55	4
10	60	7
11	65	Enrolling

- No MTD reached
- Dose escalation continues
- Currently enrolling 11th cohort (65 mg/day)

As of 28-Sep-18. Investigator-assessed data; unaudited
Additionally, there was a one grade 3 TRAE of hypophosphatemia reported at 60 mg/day dose level and one grade 3 TRAE of neutropenia reported at 10 mg/day dose level

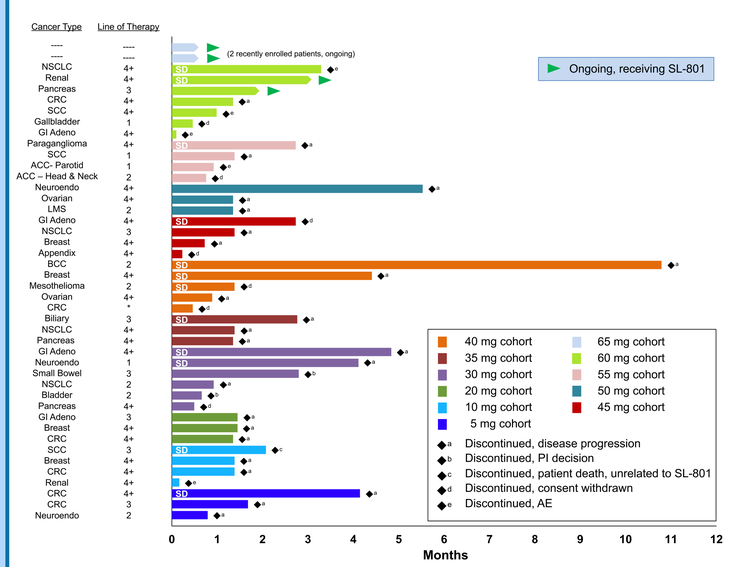
Overview of Disease Control

Dose	Line	Tumor Histology	Disease Control	No. of lesions	Sum of target lesions (measurable)		% Δ of target lesions	Time on treatment (wks)	Last dose received
					Screening (mm)	Best Response (mm)			
30 mg	1	Neuro-endo	SD	2	44	35	-20%	17.8	C6
30 mg	4+	GI adenocarcinoma	SD	2	40	34	-15%	20.9	C7
40 mg	2	BCC	SD	1	47.5	40.9	-14%	46.9	C14
40 mg	4+	Breast	SD	5	192.9	174.6	-9%	19.1	C6
60 mg	4+	Renal	SD	3	96	88	-8%	13*	C5
55 mg	4+	Paraganglioma	SD	5	155.4	149.6	-4%	11.7	C3
5 mg	4+	CRC[1]	SD	3	76	75	-1%	17.8	C6
35 mg	3	Biliary	SD	2	182.4	n/a	n/a	12.1	C4
60 mg	4+	NSCLC[1]	SD	1	90.4	n/a	n/a	14.3	C4
10 mg	3	SCC	SD	2	38	38	0	9.1	C4
45 mg	4+	GI Adeno	SD	3	184	187	+1%	11.7	C4
40 mg	2	Mesothelioma	SD	3	70	71	+1%	6.1	C2

As of 28-Sep-2018. Investigator-assessed data; unaudited
SD = stable disease; (-) = reduction, (+) = increase in tumor size
[1]Patient with KRAS mutation present at screening

Patient ongoing, still receiving SL-801
Tumor shrinkage > 10%

Treatment Duration[1]

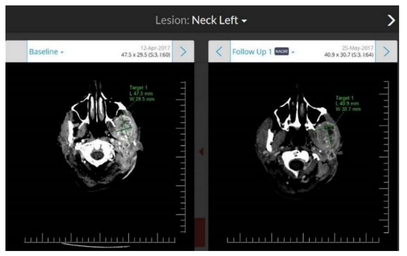


As of September 28th, 2018. Investigator-assessed data; unaudited.
[1]Time from C1D1 to end of treatment or ongoing
* One patient did not have their systemic therapy history available

Patient CT Scans

Target lesion response

- 74 year old female with metastatic stage IV basal cell carcinoma (BCC) in the head and neck region
- Prior therapies included vismodegib and an experimental anti-CD40 therapy
- Achieved stable disease (SD) while receiving SL-801; CT scans (day 21 of cycle 2 vs baseline) indicated a **reduction in target lesions of 14%** (47.5 → 41 mm)
- Durable SD for 14 cycles (46.9 wks)



Baseline CT – 12-Apr-17 **Post-baseline CT – 25-May-17**

Pharmacokinetics

- **Pharmacokinetic (PK) analyses suggest dose-dependent increases in SL-801 exposure**

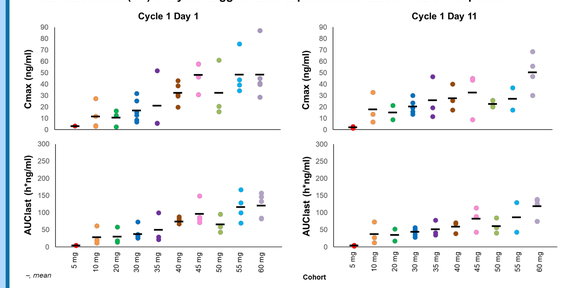


Figure A : SL-801 Cmax and AUClast of C1D1 and C1D11 by dose cohort

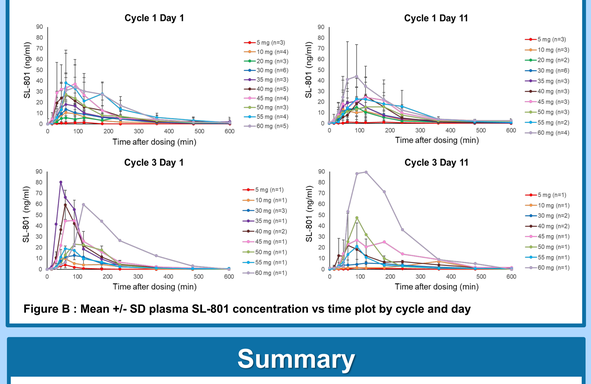


Figure B : Mean +/- SD plasma SL-801 concentration vs time plot by cycle and day

Summary

Efficacy

- Ideal therapeutic dose not yet determined as dose escalation continues
- Stable disease (SD) achieved in 29% (12/42) of patients in a heavily pretreated (72% 3rd line or greater) patient population
- Five patients had SD over 4+ months, including 1 BCC patient with SD for ~11 months duration
  - 20% disease shrinkage noted in one patient with heavily pre-treated neuroendocrine tumor
- Four patients at the two highest doses (60 and 65 mg) are receiving SL-801, ongoing

Safety

- Manageable safety and tolerability profile observed during dose escalation
- No modification of dosing schedule required thus far
- No MTD has been reached up to 60 mg/day
- Most common TRAEs were grade 1-2

Pharmacokinetics

- Dose-dependent increases in exposure observed

Study Status

- Manageable safety and tolerability profile demonstrated thus far
- Achievement of multiple cases of stable disease, including with tumor reductions, in some patients with heavily pre-treated solid tumors
- Dose escalation continues, eleventh cohort (65 mg/day) currently enrolling

Takeaways and Next Steps

- Phase 1 trial of SL-801, a novel XPO1 inhibitor, in heavily pre-treated patients with solid tumors
- Manageable safety and tolerability profile, largely grade 1-2 adverse events (AEs), to date
- No maximum tolerated dose (MTD) reached; Dose escalation ongoing; 11th cohort (65 mg/day) currently enrolling
- Multiple cases of stable disease (SD) in a heavily pretreated solid tumor patient population
- Pharmacokinetic (PK) analyses suggest dose-dependent increases in exposure; studies ongoing
- Ideal therapeutic dose not yet determined as dose escalation continues
- Further updates expected next year
- Given favorable data profile thus far with SL-801, coupled with clinical validation of the XPO1 target, additional SL-801 trials, including in hematologic cancers and combination studies, planned

References

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Disclosures: *Qi:* Stemline - employment, equity ownership; *Olguin:* Stemline - employment, equity ownership; *Bullington*: Stemline - employment, equity ownership; *Sardone*: Stemline - employment, equity ownership; *Shemesh*: Stemline - employment, equity ownership; *Chen*: Stemline - employment, equity ownership; *Brooks*: Stemline - employment, equity ownership