ESMO2017 #406P

Ongoing Phase 1 Trial of SL-801, a Novel XPO-1 Inhibitor, in Patients with Advanced Solid Tumors; Interim Results

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Background and Highlights

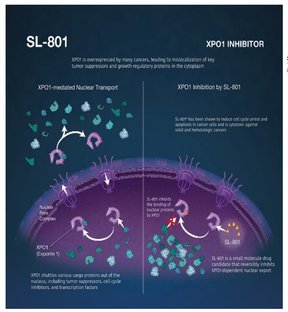
SL-801 Background

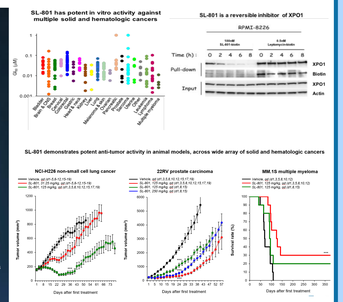
- SL-801 is an orally administered, novel small molecule XPO1 (Exportin 1) inhibitor
- XPO1 is a key nuclear transport oncogene overexpressed in a variety of cancers
- Inhibition of XPO1 has been clinically validated in multiple cancer types
- SL-801 demonstrated potent in vitro and in vivo activity 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 ongoing dose escalation are reported here

XPO-1 Background

- XPO1 is the key mediator of nuclear-cytoplasmic transport and is involved with the export of more than 200 nuclear proteins, including:
  - 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)[1,2]
- 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 shortened progression-free survival (PFS) and overall survival (OS)[1]

SL-801 Mechanism of Action and Preclinical Rationale





Study Design

Stage 1 (Dose- escalation) - Enrollment Ongoing

• Advanced solid tumors
• SL-801 orally administered
  – Dose escalation (mg/day)
  o 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:
  o Safety and tolerability
  o DLT and MTD
• Secondary endpoints:
  o Pharmacokinetics
  o 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:
  o ORR
  o Safety profile
• Secondary endpoints:
  o CR, DoR, PFS, OS

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

Patient Demographics

Age, years	
Median [range]	64 [39-76]
Gender [n, (%)]	
Male	13 (54)
Lines of therapy prior to the study [n, (%)]	
1st Line	1 (4)
2nd Line	5 (22)
≥ 3rd Line	18 (74)
KRAS mutation [n, (%)]	
Yes	4 (16.6)
No	7 (29)
Unknown	13 (54)
ECOG performance status [n, (%)]	
0	6 (25)
1	17 (71)
2	1 (4)
Follow-up time on study, months	
Median [range]	1.4 [0.2 – 4.9]

Cancer Diagnosis	n
Colorectal cancer (CRC)	5
Breast cancer	3
Non-small cell lung cancer (NSCLC)	2
GI adenocarcinoma (GI Adeno)	2
Pancreatic cancer	2
Neuroendocrine (Neuro-endo)	2
Biliary	1
Renal	1
Bladder	1
Ovarian carcinoma	1
Basal cell carcinoma (BCC)	1
Small bowel	1
Mesothelioma (Mesoth)	1
Anal squamous cell carcinoma (Anal SCC)	1

Inclusion / Exclusion

Select inclusion criteria

- Advanced (metastatic or locally advanced and unresectable) relapsed or refractory solid tumors
- ECOG 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

Safety and Tolerability

Treatment Related Adverse events (AEs) (N= 24 patients)

Most Common Treatment Related Adverse Events (≥ 15%)						
Preferred Term	All Grades n (%)		TRAEs n (%)			
	TRAEs	All AEs	G1 & 2	G3	G4	G5
Nausea	10 (41.7)	14 (58.3)	9 (37.5)	1 (4.2)	--	--
Fatigue	7 (29.2)	10 (41.7)	7 (29.2)	--	--	--
Diarrhea	5 (20.9)	8 (33.3)	4 (16.7)	1 (4.2)	--	--
Vomiting	4 (16.7)	10 (41.7)	4 (16.7)	--	--	--
Decreased appetite	4 (16.7)	7 (29.2)	4 (16.7)	--	--	--

As of 31-Jul-2017. Investigator-assessed data; unaudited
There was also one grade 3 TRAE of acute kidney injury reported at 30 mg/day dose level

Cohort	Dose (mg/day)	n
1	5	3
2	10	4
3	20	3
4	30	6
5	35	3
6	40	5
7	45	enrolling

As of 31-Jul-2017. Investigator-assessed data; unaudited.

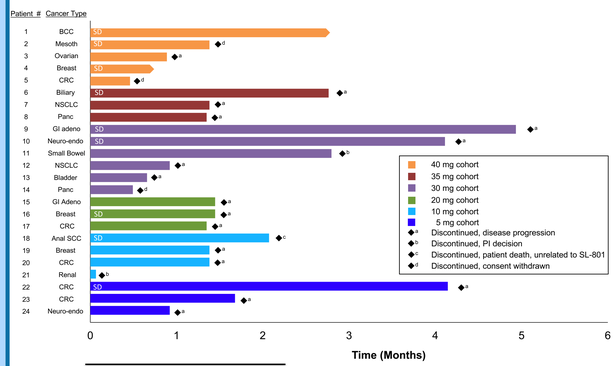
- No DLT's reported
- No MTD
- Dose escalation ongoing
- Currently enrolling 7th cohort (45 mg/day)

Clinical Activity

Dose	Tumor Histology	No. of lesions	Sum of target lesions (measurable)		% Δ of target lesions	Overall response assessment	Time to Best Response	Last dose received	Remains on Therapy
			Screening (mm)	Best Response (mm)					
30 mg	Neuro-endo	2	44	35	-20.5%	SD	C2	C6D1	No
30 mg	GI Adeno	2	40	34	-15.0%	SD	C4	C7D1	No
40 mg	BCC	1	47.5	41	-13.7%	SD	C2	C3D11	Yes
40 mg	Breast	5	193	184	-4.7%	SD	C2	C2D1	Yes
5 mg	CRC[1]	3	76	74	-2.6%	SD	C2	C6D1	No
10 mg	Anal SCC	2	38	38	0	SD	C2	C4D1	No
40 mg	Mesoth	3	70	71	+1.4%	SD	C2	C2D1	No
20 mg	Breast	3	195	206	+5.6%	SD	C2	C2D1	No

As of 31-Jul-2017. Investigator-assessed data; unaudited
(-) = reduction; (+) = increase; SD = Stable Disease
1. Patient with KRAS mutation present at screening
An additional patient (cholangiocarcoma) sustained SD on SL-801 (35mg cohort); data on tumor size pending

Best Response and Treatment Duration[1] (n = 24)

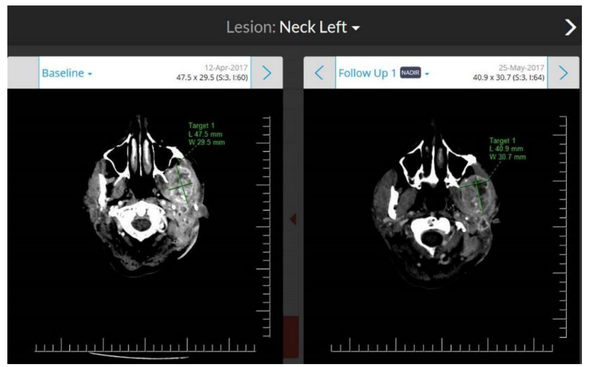


[1]Time from C1D1(first dose) to end of treatment or ongoing
As of 31-Jul-2017. Investigator-assessed data; unaudited.

Representative Patient CT Scans

Representative target lesion response

- 74 year old female with a metastatic stage IV basal cell carcinoma (BCC) located in the head and neck. 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 13.7% (47.5 → 41 mm)
- Patient remains on SL-801 with durable SD (7 cycles, ongoing)



Baseline **Cycle 2 Day 21**

SL-801 Pharmacokinetics

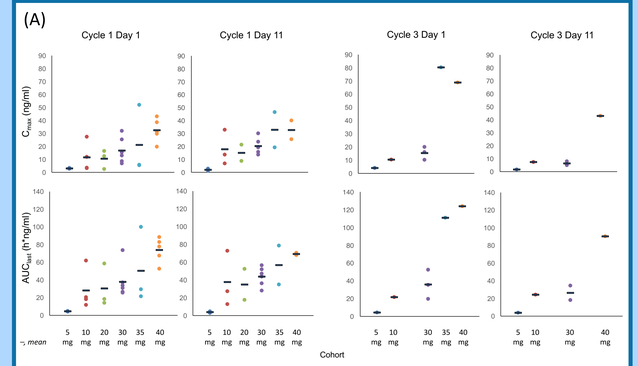


Figure A: SL-801 pharmacokinetics. (A) SL-801 C_{max} and AUC_{last} of each cycle and day by dose cohort.

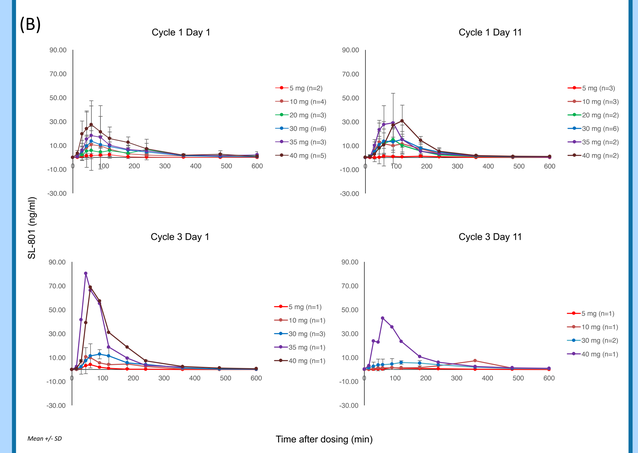


Figure B: Mean +/- SD plasma SL-801 concentration vs. time plot by cycle and day

Conclusions

Safety
- Manageable safety and tolerability profile during dose escalation, with no modification of dosing schedule required thus far
- No DLT or MTD has been reached up to 40 mg/day
- Most common TRAEs were grade 1-2, with no grade 4 or 5 toxicity reported
- Dose escalation continues

Efficacy
- Ideal therapeutic dose not yet determined as dose escalation continues
- Stable disease achieved in 37.5% (9/24) of patients
- 20% disease shrinkage noted in one patient with heavily pre-treated neuroendocrine tumor

Pharmacokinetics
- Dose-dependent increases in exposure observed

Study Status and Next Steps
- Dose escalation continues, seventh cohort (45 mg/day) currently enrolling
- Manageable safety and tolerability profile demonstrated thus far
- Achievement of multiple cases of stable disease, including with tumor reductions in some patients with relapsed/refractory tumors
- Further safety, pharmacokinetic (PK), pharmacodynamic (PD), and efficacy updates expected next year
- Additional trials planned (including single agent, combination, hematologic cancers)

References

1. Turner et al. Biochemical pharmacology 2012; 83(3): 1021-32
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4. Hung et al. Journal of cell science 2011; 124(Pt 20): 3381-92
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Disclosures: *Brooks*: Stemline - employment, equity ownership; *Chen*: Stemline - employment, equity ownership; *Shemesh*: Stemline - employment, equity ownership; *Bullington*: Stemline - employment, equity ownership; *Olguin*: Stemline – employment, equity ownership;