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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

- Felezonexor (SL-801) is a reversible XPO1 inhibitor that offers the potential for an improved safety profile / therapeutic window
- Regimen modified (Schedule A to B) to improve tolerability while maintaining dose intensity; 1 patient in Schedule B (n=7) experienced grade 3 weakness, cohort expanded, dose escalation continues
- One partial response (PR) in patient with heavily pretreated colorectal cancer with microsatellite stability and KRAS mutation
- Multiple cases of stable disease (SD) observed in heavily pretreated patients
- Pharmacokinetic (PK) analyses suggest dose-dependent increases in exposure; studies ongoing
- Ideal therapeutic dose not yet determined as dose escalation continues
- Further updates expected as Phase 1 trial continues to enroll

Background

Felezonexor (SL-801) Background

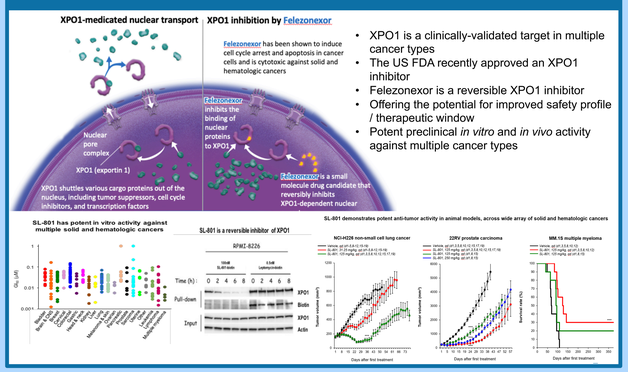
- Felezonexor is an orally administered, novel small molecule XPO1 (Exportin 1) inhibitor
- XPO1 is a key nuclear transport oncogene overexpressed in a variety of cancers
- Inhibition of XPO1 has been clinically validated in multiple cancer types
- The US FDA recently approved an XPO1 inhibitor in patients with multiply relapsed or refractory MM†
- Felezonexor demonstrated potent in vitro and in vivo activity against a wide array of solid and hematologic cancer models
- Felezonexor reversibly inhibits XPO1 offering the potential for a favorable therapeutic window
- Results from the ongoing Phase 1 trial of felezonexor monotherapy in patients with advanced solid tumors (NCT#02667873) 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]

†Selinexor US FDA approved for treatment of adult patients with relapsed or refractory multiple myeloma who have received at least 4 prior therapies

Mechanism of Action and Rationale



- XPO1 is a clinically-validated target in multiple cancer types
- The US FDA recently approved an XPO1 inhibitor
- Felezonexor is a reversible XPO1 inhibitor
- Offering the potential for improved safety profile / therapeutic window
- Potent preclinical *in vitro* and *in vivo* activity against multiple cancer types

Study Design

Stage 1 (Dose- escalation) - Enrollment Ongoing

- Advanced solid tumors
- Felezonexor orally administered; Once daily dosing
  - Dose escalation (mg/day)
    - 5, 10, 20, 30, and by 5 mg increments thereafter
  - Standard 3x3 design
- Regimen:
  - Schedule A (original): D1-4 and D8-11 of a 21-day cycle
  - Schedule B (revised): D1-2, 8-9, 15-16 and 22-23 of a 28-day cycle
- 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
- Felezonexor 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 felezonexor 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

- **Heavily pre-treated patients: ~90% 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	26 (50)
Lines of therapy prior to the study [n, (%)]*	
1	5 (10)
2	7 (14)
3	9 (18)
≥ 4	30 (59)
RAS mutation [n, (%)]**	
KRAS mutation:	
Yes	7 (17)
No	10 (24)
Unknown	22 (52)
Other mutation:	3 (7)
ECOG performance status [n, (%)]	
0	16 (31)
1	34 (65)
2	2 (4)
Follow-up time on study, weeks	
Median [range]	6.1 [0.4 – 46.9]

Cancer Diagnosis	n
Colorectal cancer (CRC)	10
Breast cancer	4
Non-small cell lung cancer (NSCLC)	4
GI adenocarcinoma (GI Adeno)	4
Squamous cell carcinoma (SCC)	4
Neuroendocrine (Neuro-endo)	3
Pancreatic cancer	3
Adenoid Cystic Carcinoma (ACC)	3
Ovarian carcinoma	2
Renal	2
Basal cell carcinoma (BCC)	2
Leiomyosarcoma (LMS)	2
Biliary	1
Bladder	1
Gallbladder	1
Small bowel	1
Mesothelioma	1
Appendix carcinoma	1
Paraganglioma	1
Thyroid	1
Prostate	1

* One patient did not have their prior systemic therapy history available
** RAS mutation data not yet available for recently enrolled patients

Dosing, Safety and Tolerability

Dosing

Cohort	Dose (mg/day)	Schedule	n
1	5	A	3
2	10	A	4
3	20	A	3
4	30	A	6
5	35	A	3
6	40	A	5

Cohort	Dose (mg/day)	Schedule	n
7	45	A	4
8	50	A	3
9	55	A	4
10	60	A	7
11	65	A	3
12	70	B[1]	4
13	75	B	3[2]

Safety and Tolerability
Treatment Related Adverse Events (n=45 patients)
(Schedule A only)

Most Common Treatment Related Adverse Events (TRAEs, ≥ 15%)						
Preferred Term	**All Grades n (%)**		**TRAEs n (%)**			
	TRAEs	**All AEs**	**G1 & 2**	**G3**	**G4**	**G5**
Nausea	31 (69)	32 (71)	27 (60)	4 (9)	--	--
Vomiting	24 (53)	31 (69)	23 (51)	1 (2)	--	--
Fatigue	20 (44)	24 (53)	18 (40)	2 (4)	--	--
Decreased appetite	11 (24)	15 (33)	11 (25)	--	--	--
Diarrhea	10 (22)	14 (31)	8 (17)	2 (4)	--	--

[1]Schedule A was revised to Schedule B due to non-dose limiting GI effects
[2]In Schedule B, one grade 3 weakness was reported; cohort expanded and currently enrolling

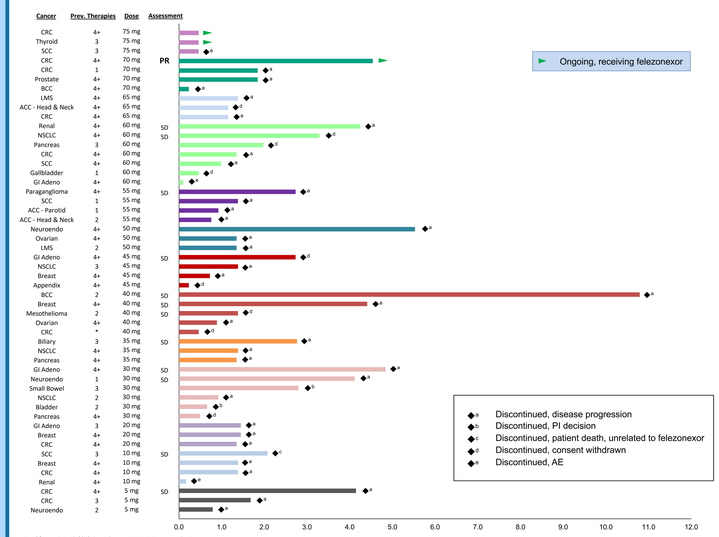
Schedule A data as of 06-May-19. Investigator-assessed data; unaudited
Additionally, there was a one grade 3 TRAE of hypophosphatemia reported at 60 mg/day dose level and one grade 3 TRAE of neutropenia reported at 10 mg/day dose level

Overview of Disease Control

Dose	Tumor Histology	Best Response	No. of lesions	Sum of target lesions (measurable)		% Δ of target lesions	Time on treatment (wks)	Last dose received
				Screening (mm)	Best Response (mm)			
70 mg	CRC[1]	PR	2	39.4	18.6	-53%	18.3	C6
30 mg	Neuro-endo	SD	2	44	35	-20%	17.8	C6
60 mg	Renal	SD	3	96	82	-15%	18.3	C6
30 mg	GI adenocarcinoma	SD	2	40	34	-15%	20.9	C7
40 mg	BCC	SD	1	47.5	40.9	-14%	46.9	C14
40 mg	Breast	SD	5	192.9	174.6	-9%	19.1	C6
55 mg	Paraganglioma	SD	5	155.4	149.6	-4%	11.7	C3
5 mg	CRC[1]	SD	3	76	75	-1%	17.8	C6
35 mg	Biliary	SD	2	182.4	n/a	n/a	12.1	C4
60 mg	NSCLC[1]	SD	1	90.4	n/a	n/a	14.3	C4
10 mg	SCC	SD	2	38	38	0	9.1	C4
45 mg	GI Adeno	SD	3	184	187	+1%	11.7	C4

As of 01-Sep-2019. Investigator-assessed data; unaudited
PR = Partial Response; SD = stable disease; (-) = reduction; (+) = increase
[1]Patient with KRAS mutation present at screening

Treatment Duration[1]



As of September 1st, 2019. Investigator-assessed data; unaudited.
[1]Time from C1D1 to end of treatment or ongoing
* One patient did not have their systemic therapy history available

Partial Response (PR) in Heavily-Pretreated CRC with MSS and KRAS Mutation

- 74 year old male with metastatic, microsatellite stable (MSS), KRAS-mutant colorectal cancer that has spread to the lung and peritoneum
- Treatment history includes surgery, radiation, and multiple rounds of chemotherapy including fluorouracil, leucovorin, oxaliplatin, bevacizumab, capecitabine, and irinotecan
- Received felezonexor at 70 mg, adjusted to 65 mg due to elevated creatinine
- Achieved partial response (PR) while receiving felezonexor by RECIST criteria; CT scans demonstrated serial reductions in the two target lesions
- 53% tumor size reduction (39.4 → 18.6 mm) during most recent follow-up scan
- Response evolved into PR after 2 cycles; currently receiving 6th cycle (18.3+ weeks)
- Treatment with 65mg felezonexor ongoing (cycle 6); Next staging pending

	Baseline	Follow up 1	Follow up 2	Follow up 3
Days on Treatment:	--	55	111	139
Liver Lesion Measurement:	22.6 x 11.6 mm	17.7 x 7.4 mm	15.7 x 5.6 mm	13.2 x 5.8 mm
Spleen Lesion Measurement:	16.8 x 9.8 mm	10.5 x 9.4 mm	5 x 5.0 mm	5.4 x 5.0 mm
% Change from Baseline:		-28.43%	**-47% PR**	**-53% PR (confirmed)**

Pharmacokinetics

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

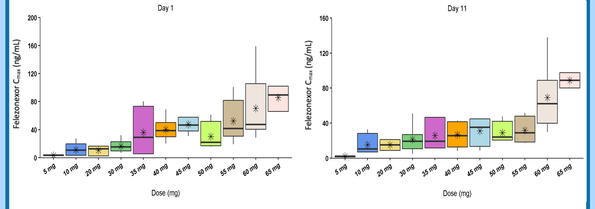


Figure A: Box Plot of Felezonexor C_{max} by Day (Combined Cycles)

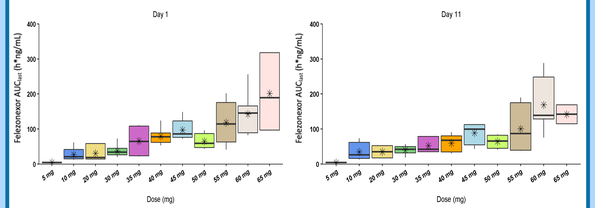


Figure B: Box Plot of Felezonexor AUC_{last} by Day (Combined Cycles)

Solid line = Median; Box = 25% and 75% quartiles (IQR); Whiskers = Lowest/highest values within 1.5*IQR of the lower/upper quartiles; * = Mean

Summary

Efficacy

- Ideal therapeutic dose and regimen not yet determined; dose escalation and regimen optimization continues
- One partial response (PR) achieved in patient with KRAS, MSS with 4th line colorectal cancer (18+ weeks, ongoing)
- Stable disease (SD) achieved in 12 patients, with 11/12 3rd line or greater
- Five patients had SD for 4-11 months, including 1 BCC patient with SD for ~11 months duration
  - 20% disease shrinkage noted in one patient with heavily pre-treated neuroendocrine tumor

Safety

- Dose escalation and regimen optimization continues with Schedule B

Pharmacokinetics

- Dose-dependent increases in exposure observed

Study Status

- Manageable safety and tolerability profile demonstrated thus far
- Achievement of a PR in heavily pretreated CRC patient, and multiple cases of stable disease, including with tumor reductions, in patients with heavily pre-treated solid tumors
- Dose escalation continues using Schedule B, now expanded, with 75 mg/day cohort currently enrolling

Takeaways and Next Steps

- Phase 1 trial of felezonexor, a novel XPO1 inhibitor, in heavily pre-treated patients with solid tumors
- Dose escalation ongoing utilizing new dosing regimen (Schedule B); 75 mg/day cohort, now expanded, currently enrolling
- PR (ongoing) achieved in KRAS+, MSS colorectal cancer patient
- Multiple cases of stable disease (SD) seen in a heavily pretreated solid tumor patient population
- Pharmacokinetic (PK) analyses suggest dose-dependent increases in exposure; studies ongoing
- Ideal therapeutic dose and regimen not yet determined as dose escalation continues
- Further updates expected as Phase 1 trial continues to enroll

References

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