LX-101, a novel, clinical stage, payload-bearing IGF-1R targeted therapy, demonstrates activity in patients with high IGF-1R tumor expression

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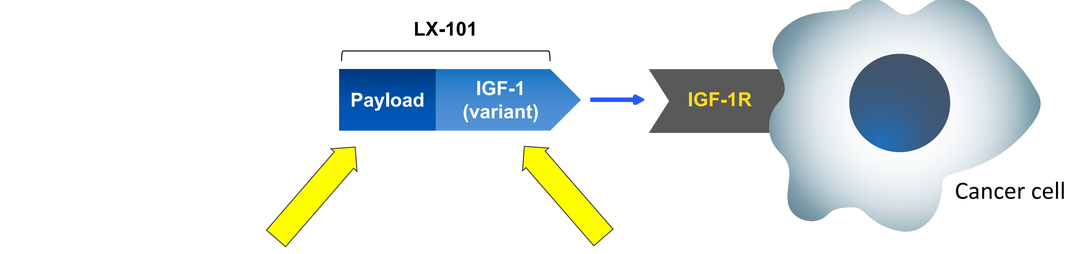
A. DUDEK[1], M. HOBERMAN[2]
[1]Mayo Clinic, Rochester, MN, USA, [2]Lirum Therapeutics, New York, USA

BACKGROUND

- The insulin-like growth factor-1 receptor (IGF-1R) pathway is well-established in a wide range of cancers, and is associated with cancer proliferation, migration, invasion, metastasis, treatment resistance, poor prognosis, and shortened survival.
- Prior attempts at targeting IGF-1R consisted of non-payload bearing naked monoclonal antibodies or small molecule tyrosine kinase inhibitors. These agents produced a range of clinical outcomes, including some partial and complete responses, but none were ultimately approved in an oncology setting.
- These previous approaches may not have been potent enough thereby allowing cancer cells to evade receptor blockade via redundant signaling pathways and other escape mechanisms.
- In contrast to these past approaches, LX-101 is a novel, next-generation, payload-bearing targeted therapy directed to IGF-1R. LX-101 consists of a proprietary IGF-1 variant coupled to a cytotoxic methotrexate (MTX) payload.
- LX-101 was previously evaluated (as 765IGF-MTX) in a Phase 1a trial of adult patients with advanced, pretreated cancers, where it was well-tolerated and demonstrated single agent activity. Neither a dose limiting toxicity (DLT), nor a maximum tolerated dose (MTD) were reached, leaving potential room for additional dose escalation and schedule optimization. Moreover, notably, while patients had some level of IGF-1R expression, the trials were not specifically designed to enrich for tumors with high IGF-1R expression and/or well-established ties to the IGF-1R pathway.
- **Herein, we conducted a post hoc analysis to determine the quantity and clinical outcomes of those patients with high levels of IGF-1R expression.**

LX-101, A NOVEL APPROACH TO TARGETING IGF-1R

- Next generation IGF-1R-directed agent that delivers a potent payload with high precision to target cells
- Consists of an optimized variant of the IGF-1 ligand, covalently conjugated to MTX, a cytotoxic inhibitor of DNA synthesis, repair, and cellular replication that has been used to treat patients with a variety of cancers and autoimmune disease
- Designed with additional binding sites, via a proprietary N-terminal leader sequence, to allow for the conjugation of increased number of MTX molecules in an effort to enhance potency
- Targeted delivery of MTX directly to the cells of interest designed for increased precision versus systemically administered high dose MTX
- The IGF-1 variant used in LX-101 designed to have reduced binding affinity to circulating serum IGF binding proteins (IGFBPs) to optimize bioavailability



Payload
- Multiple (6-10) molecules of the cytotoxic anti-metabolite, methotrexate, covalently linked to IGF-1 variant

IGF-1 Variant
- Increased payload binding sites
- Decreased affinity for circulating IGF binding proteins (IGFBPs)

PREVIOUS PHASE 1a

- Patients with pretreated, advanced cancers with detectable IGF-1R expression
  - Cancers treated include: colon, endometrial, pancreatic, Hodgkin's lymphoma, breast, basal cell, and others
- LX-101 (formerly, 765IGF-MTX) administered by IV on days 1, 8, and 15, of a 28-day cycle
- Dose levels tested included 0.05 uEq/kg, 0.1 uEq/kg, 0.2 uEq/kg, 0.4 uEq/kg, 0.8 uEq/kg
  - Additional dose levels of 1.6 uEq/kg, and 2.5 uEq/kg were planned, but not tested due to financial constraints by previous sponsor
- Primary endpoint was to determine MTD
- Secondary endpoints included safety and efficacy
- 2 additional patients, both with myelodysplastic syndrome (MDS), were treated in a separate Phase 1 trial at 0.2 uEq/kg

METHODS

- Immunohistochemical (IHC) staining for IGF-1R expression was performed on formalin-fixed-paraffin-embedded (FFPE) tumor specimens (Ventana G11, DAKO PharmDx). IGF-1R expression was analyzed both qualitatively and quantitatively by 2 board-certified pathologists, and scored as intensity score (IS, 0 = no stain, 1 = weak stain, 2 = intermediate stain, 3 = strong stain) and proportion score based on % of cells with IGF-1R positivity (PS, 0% - 9% = 0, 10% - 24% = 1, 25% - 49% = 2, 50% - 74% = 3, 75% - 100% = 4) combined to create a Q score (range 0-7)
- Our retrospective, post hoc analysis considered Q scores ≥ 6 with IGF-1R expression ≥ 90% to constitute high IGF-1R expression.

RESULTS

Patients Screened	IGF-1R$^+$ Patients	High Expressers
• 72 patients' tumor samples were screened for IGF-1R expression	• 42 patients of the 72 screened were determined to be IGF-1R$^+$, defined as >10% of cancer cells expressing IGF-1R • 17 of these patients went on to be treated in the Phase 1a trial • 2 MDS patients treated in separate Phase 1 study	• Of the 19 patients treated, we determined that 4 patients were high IGF-1R expressers, defined as Q score ≥ 6, and IGF-1R expression ≥ 90%

RESULTS: HIGH IGF-1R EXPRESSERS ARE SENSITIVE TO LX-101

Table 1. Phase 1a High Expressers are Sensitive to LX-101 Therapy

Dose (uEq/kg)	n[1] (eval)	Best Response	High IGF-1R Expressers
0.80	7 (4)	•PR	+
0.40	3 (3)	•PD	+
0.20	9 (7)	•SD (with pathologic CR) •N/E •SD[2] •BMCR[2]	+ + NT[2] NT[2]
0.10	1 (1)		
0.05	1 (1)		

100% (1/1)
Disease Control Rate at highest dose tested

67% (2/3)
Disease Control Rate at all evaluable doses tested

PR = Partial Response, PD = Progressive Disease, SD = Stable Disease, CR = Complete Response, N/E = Not Evaluable, BMCR = Bone Marrow Complete Response, NT = Not Tested
[1] 2 patients were treated at two different dose levels
[2] MDS patients treated in separate Phase 1 trial. Although patient was not tested for IGF-1R expression, IGF-1R has been shown to be significantly overexpressed in malignant bone marrow nucleated cells in MDS

CANCERS WITH TIES TO THE IGF-1 / IGF-1R PATHWAY

Table 2. Select Cancers with IGF-1 / IGF-1R Pathway Involvement

Cancer Type	Epigenetic and Genetic Alterations	
Ewing's sarcoma	IGF-1R overexpression	EWSR1-FLI1
Rhabdomyosarcoma	IGF-1R and short survival	PAX3/7-FKHR/FOXO1
GIST	High IGF-1R in peds (WT)	NBF1-IGF1R
Synovial Sarcoma	IGF-1R and more aggressive	SYT-SSX1/2
Neuroblastoma	IGF-1R and poor outcomes	
Osteosarcoma	IGF-1R and poor prognosis	
Wilms Tumor	IGF-1R and poor outcomes	IGF-1R gene amplification
DSRCT	IGF-1R and upregulation	EWSR1-WT1
Adrenocortical carcinoma	IGF-2 overexpression	
Adenoid cystic carcinoma	IGF-2 overexpression	MYB-NF1B
H&N cancer, HPV(-) Bladder cancer, invasive Breast cancer, triple negative	IGF-1R associated with poor outcomes, mortality and shortened survival	
Many cancer type subsets, including lung, breast, colorectal, prostate, ovarian, gastric, esophageal, etc.	IGF-1R over-expression and poor outcome features	

SUMMARY AND CONCLUSIONS

- **LX-101, a clinical stage next-generation, targeted therapy directed to IGF-1R, was previously evaluated (as 765IGF-MTX) in Phase 1a trials of adult patients with advanced, pretreated cancers, where it was well-tolerated and demonstrated single agent activity.**
  - **Neither a DLT nor an MTD were reached, leaving room for possible further dose escalation and schedule optimization**
  - **Also, an enrichment strategy was not employed which presents the opportunity for a more focused tumor-type-specific approach**
- **Prior IGF-1R-targeting drug candidates were non-payload-bearing naked monoclonal antibodies or small molecule tyrosine kinase inhibitors, and thus may not have addressed redundant pathways and other escape mechanisms that enable cancer cells to evade therapy**
- **In contrast, LX-101, with its novel payload-bearing construction, could provide a more potent therapeutic approach to targeting IGF-1R$^+$-prominent cancers than has been employed in the past**
- **LX-101 (as 765IGF-MTX) demonstrated tolerability and single agent activity and disease control in Phase 1a trials of patients with advanced pre-treated cancers. Moreover, and notably, the majority of evaluable patients with high expression levels of IGF-1R experienced disease control, including the one patient at the highest dose tested who experienced an objective response**
- **Given these encouraging data, new clinical trials with LX-101 are being planned in indications with strong ties to the IGF-1R pathway, focusing on cancers mentioned in Table 2 (above)**

REFERENCES

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A. Dudek acts as a consultant for Lirum Therapeutics and has no other relevant disclosures

CONTACT INFORMATION: MHOBERMAN@LIRUMTX.COM