Synergistic Multi-Pathway Targeting: Widening Cancer Treatment Horizons

2025.01

Bispecific Small Molecules

with Oral Bioavailability by De Novo Design

LIT0814: FIC of a Novel Modality

LittDD

Advantages of Bispecific small molecules (dual-targeting) over traditional small molecules:

♦ Synergistic effects ♦ Reduced toxicity ♦ Overcoming drug resistance

MOA: LIT0814 was de novo rationally designed based on that inhibition of both ATR and PI3K-mTOR pathways generates synergistic effect leading to better efficacy and larger therapeutic windows

Modality: oral small molecule

Targets: ATR & mTOR (Novel MOA) (AACR 2025)

Specialties: BBB penetrable (brain metastasis)

Patent status: China issued, PCT entered

Combination potential: TOP1 inhibitors or TOP1-ADCs

Development stage: Phase Ia/Ib

Indication: 1. gastroesophageal junction cancer (GEJC) (most patients only qualified for chemotherapies, great unmet medical need)
2. melanoma (BRAF/NRAS wild-type, current standard therapies as combination of chemotherapies)

CDP: single arm accelerated conditional approval due to the great unmet medical needs

Biomarkers: cytoplasmic pAkt1-S473

LIT0814 Potential Therapy for GEJC and Melanoma

LittDD

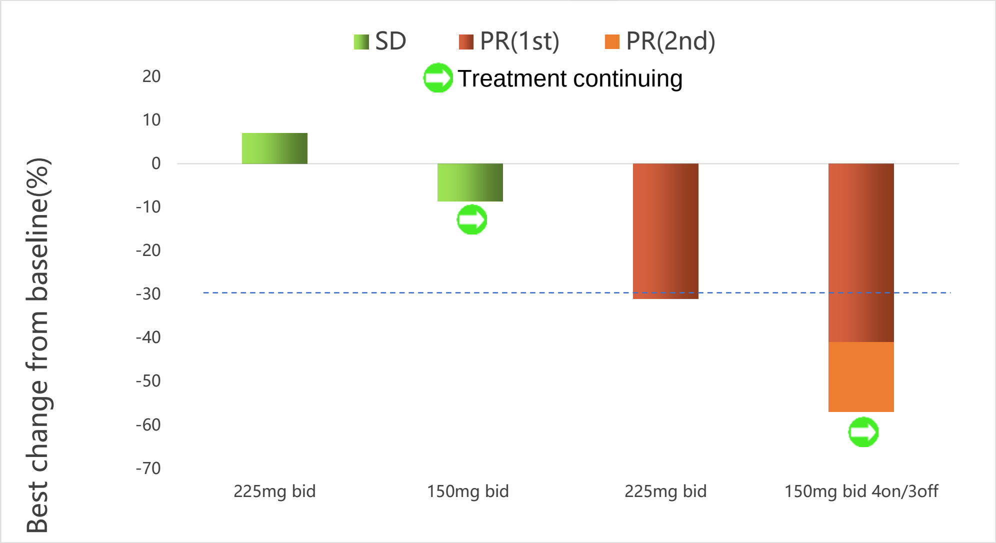
LIT0814

- Ph1a escalation 250mg BID completed, 275mg cohort recruiting
- Tumor shrinks observed, 3 PRs with 1 confirmed PRs

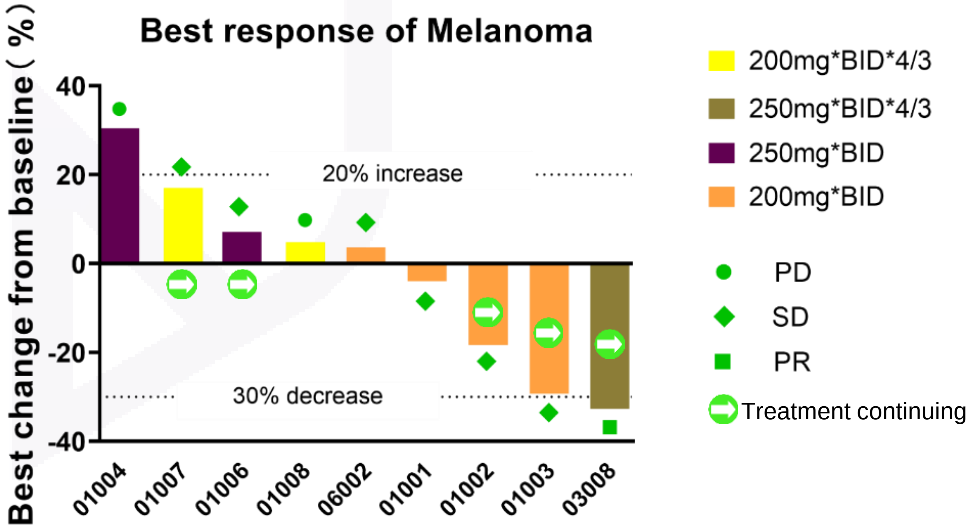
(Kp,uu: 0.26)

- Ph 1b expansion at 150mg BID enrolled
- Biomarker pAkt1-S473 screening applied, preliminary data demonstrates that DCR improved from 66.7% to 87.5% over patient group without screening

Total 4 GEJC Patients at Various Dosages



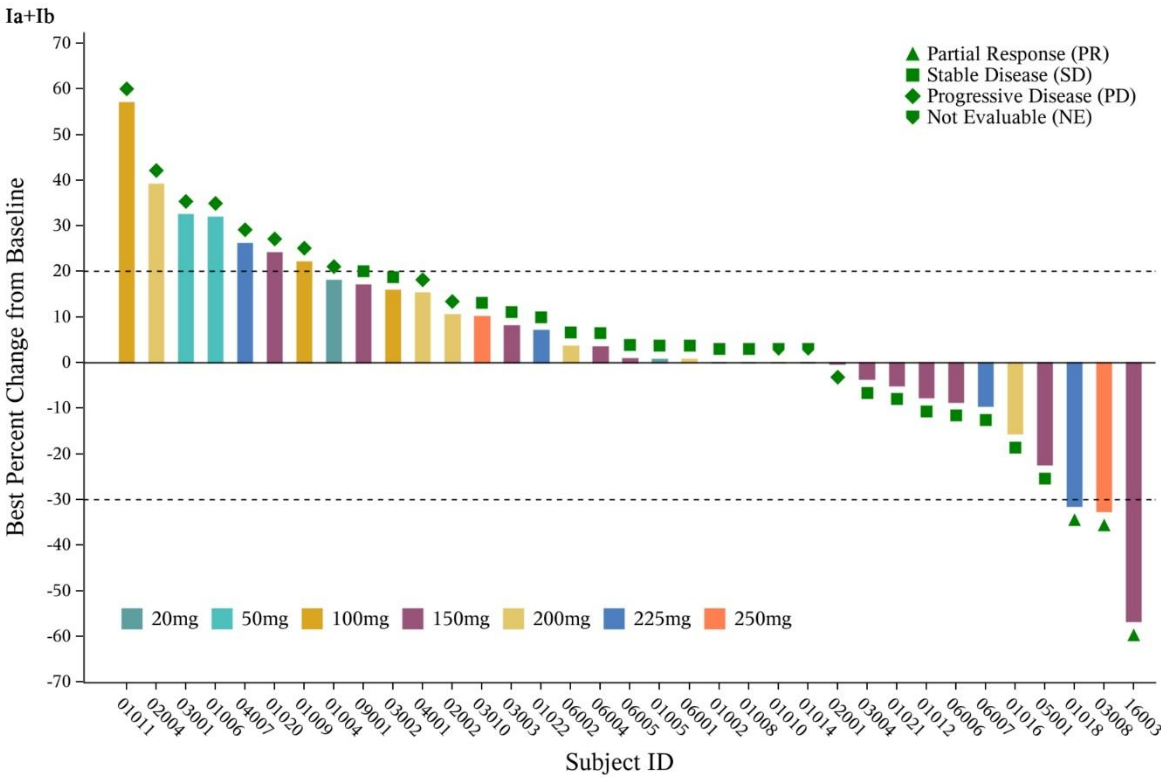
Total 9 Melanoma Patients at Various Dosages

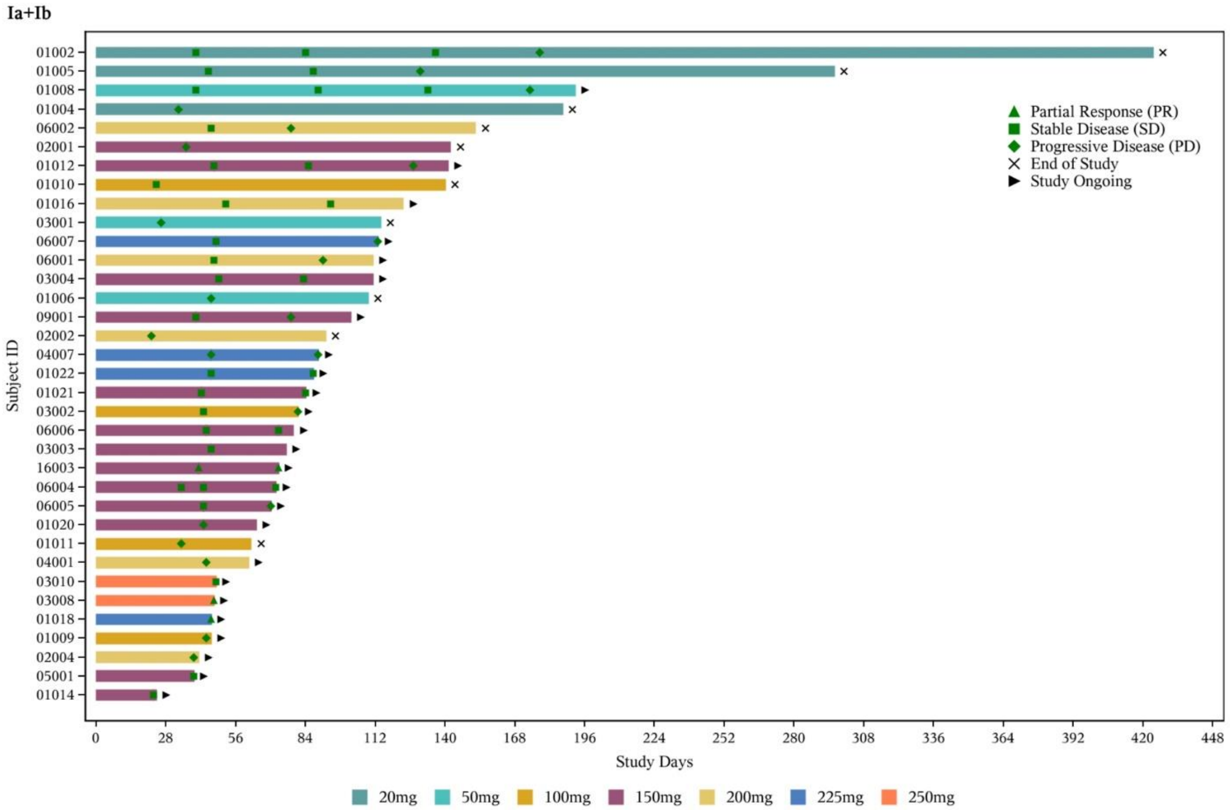


Summary of Efficacy in LIT0814 Phase Ia Trial

- Preliminary efficacy and safety data available upon request. Among all evaluation eligible patients, DCR was 62.2%, tumor shrink observed in multiple patients including three partial responses (PR)
- Dose escalation at 275mg (BID, 4on/3off) enrolling, expansion at various dosages recruiting

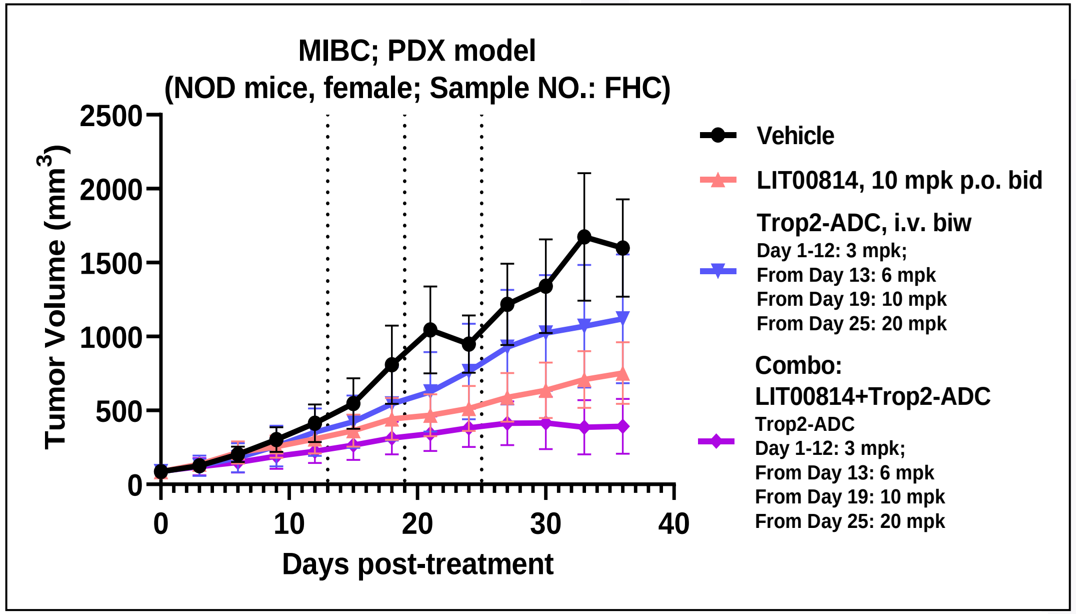
Phase Ia+Ib: total 33 evaluated Patients: 3 PR, 19 SD, 66.7% DCR

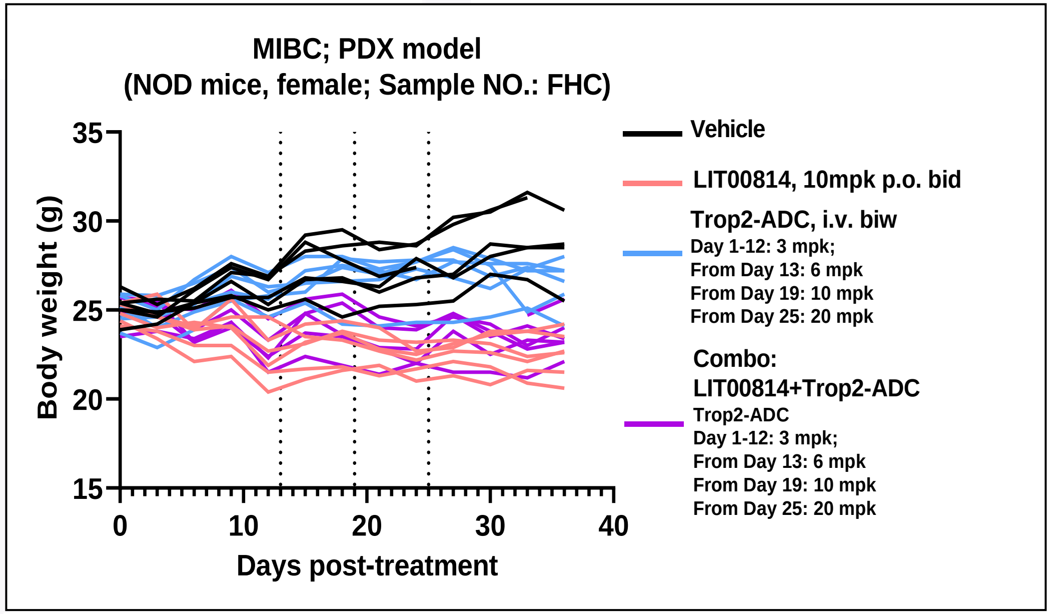




Great Potential to Combine with ADCs

- The MOA of LIT0814 leads to hypothesize that LIT0814 can synergize with topoisomerase inhibitors to block tumor growth
- LIT0814 can enhance efficacy of ADCs with TOP1 inhibitors as toxin to improve therapeutic window to achieve synergistic efficacy *in vivo* models
- Great potential in clinical to improve ADCs efficacy and therapeutic window





LIT0922: First mTORC2 Selective Inhibitor

LittDD

MOA: mTORC2 as the key effector of PI3K and RAS pathways plays essential role in tumor prognostic growth, LIT0922 was the first selective inhibitor of mTORC2 over mTORC1 to reduce clinical toxicities due to inhibition of mTORC1, de novo rationally designed against both mTORC2 and a target from DNA damage response (DDR) pathway to increase efficacy and therapeutic windows

Modality: oral small molecule

Targets: mTORC2 & DDR (Novel MOA)

Specialties: BBB penetrable (Brain metastasis)

Patent status: filed

Novelty: anti-angiogenesis
highly selectivity over mTORC1 *in vivo*

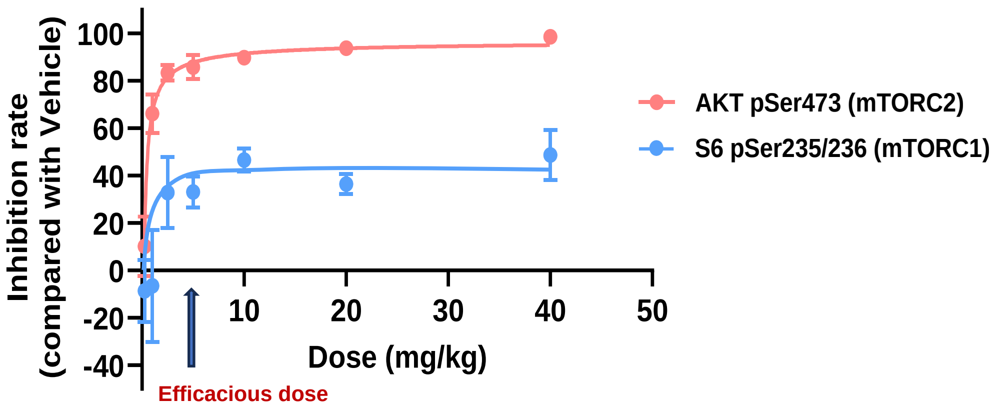
Development stage: IND filed, Phase I FIH in March 2025

Indication: Brain metastatic NSCLC, BrCa (HR+) neuroendocrine tumor/carcinoma

Biomarkers: pNRF2 positive

CDP: single arm accelerated approval

Tumor, LoVo xenograft model
(Balb/c nude mice, male; LIT0922, p.o., qd for 7 days)



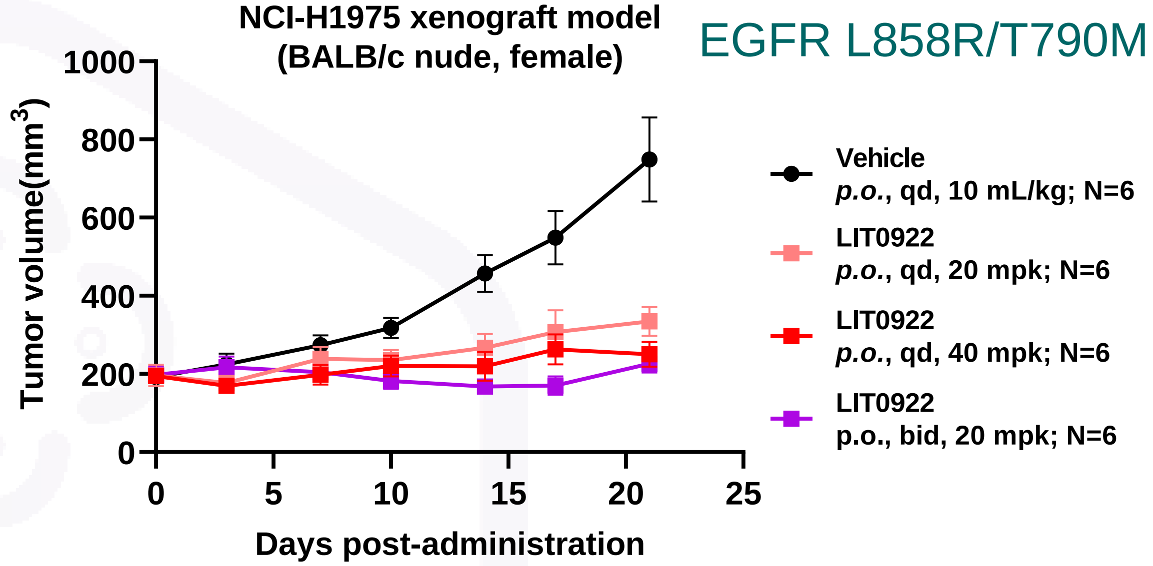
LIT0922 Advantages

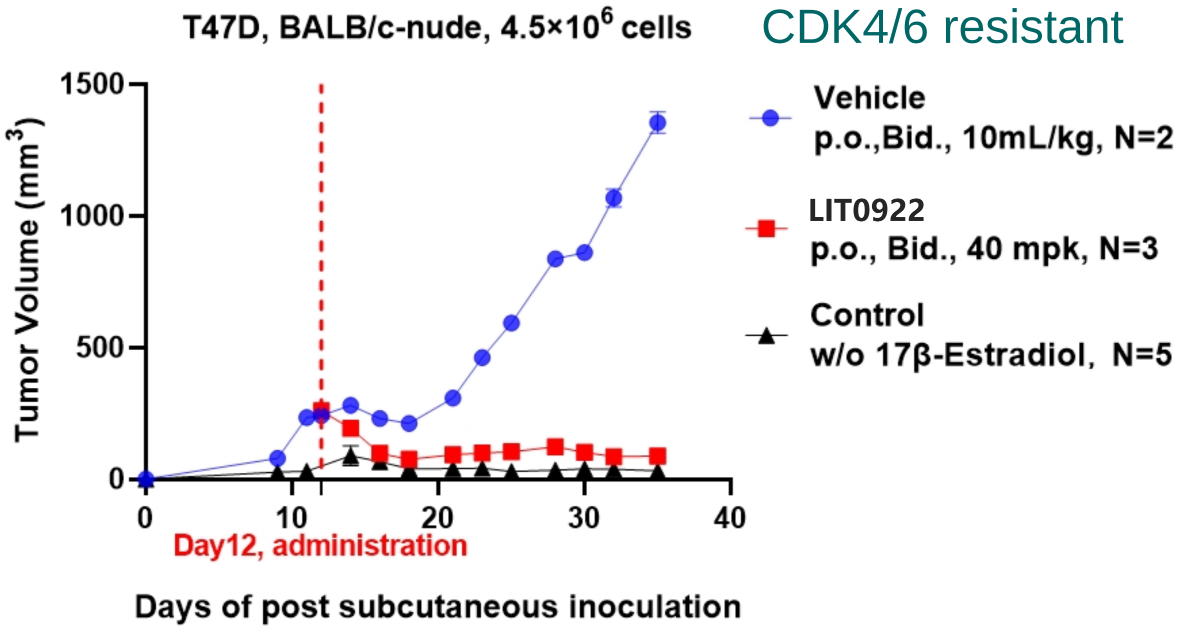
Larger therapeutical window

With larger exposure at the same dose and similar cellular activity compared to pan-mTOR inhibitor TAK-228 or mTORC1 selective allosteric inhibitor everolimus, LIT0922 demonstrated greater than **40** folds of MTD in wild-type mice

Broader Indications in pre-Clinical Studies

- ❑ Efficacious in Small cell lung cancer models
- ❑ Efficacious in EGFR mutated and Exon19del NSCLC models
- ❑ Potential efficacious in all EGFR treatments resistant patients
- ❑ Efficacious in Her2 positive breast cancer models
- ❑ Efficacious in CDK4/6 resistant breast cancer models





LIT0406: Novel c-Myc Regulation MOA Inhibitor

MOA: based on the novel biology discovered in house of c-Myc regulation specifical in tumors, de novo rationally designed small molecules targeting two pathways of c-Myc regulation leading to synergistic effect to increase efficacy and therapeutic windows

Modality: oral small molecule

Targets: dual targets (undisclosed, novel biology)

Patent status: filed

Development stage: PCC, Phase I in 2025 Q4

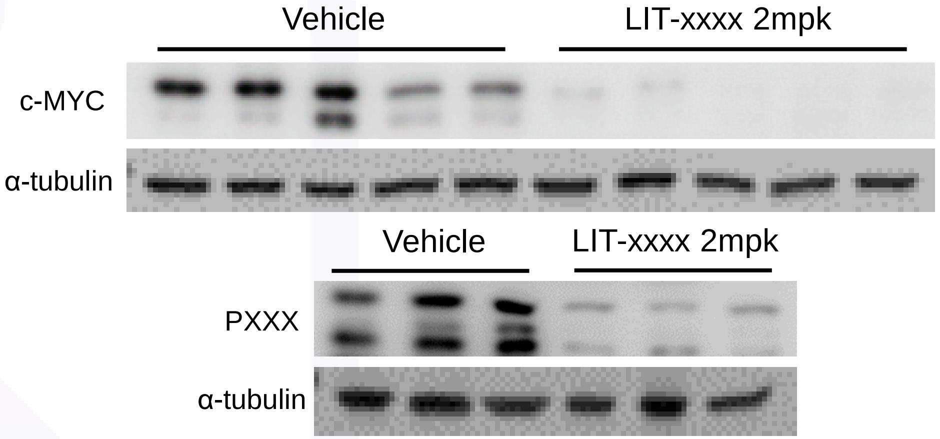
Indication: gynecological cancers (primary ovarian cancer), TNBC

Biomarkers: c-Myc

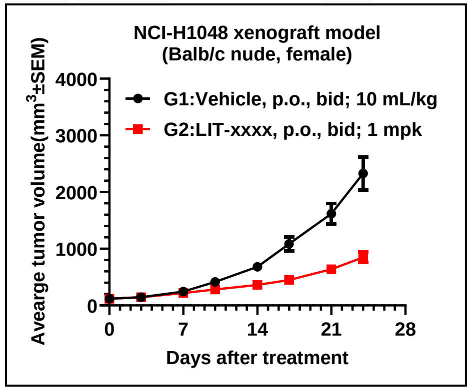
CDP: single arm accelerated approval

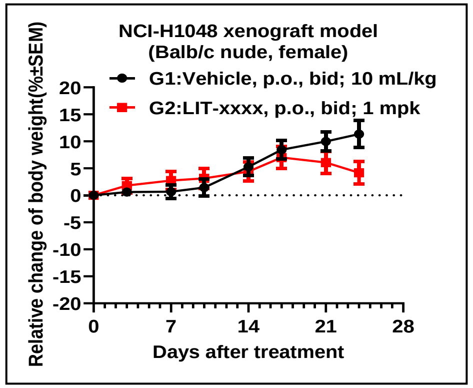
Novelty: tumor specific c-Myc regulation biology discovered (organ development transcription factor (PXXX) abnormally activated in tumors related to c-Myc dysregulation)

MDA-MB-231 xerographic model (2mpk BID)



PXXX: a critical transcription factor for female organ development





Pipeline Execution Plan

Program	Primary Target	Second Target	Indications	2023	2024	2025	2026	2027
LIT0814	PI3K-Akt-mTOR Pathway	ATR	Melanoma, GEJC/EC, BC	IND filing	Phase I		Pivotal Trial (AA)	PNDA
LIT0922	mTORC2	DDR Pathway	NEN, NSCLC, BrCa	Discovery	IND enabling studies	IND filing	Phase I	Phase II
LIT0406	c-Myc Pathway	DDR Pathway	Gynecologic Cancers, TNBC		Discovery	IND enabling studies, IND filing		Phase I
LIT-P008	Undisclosed	Undisclosed	CRC/HCC			Discovery	IND enabling studies	IND filing, Phase I
LIT-P009	Undisclosed	Undisclosed	KRAS Mutated			Discovery	IND enabling studies	IND filing
LIT-P010	Undisclosed	Undisclosed	NSCLC/BrCa			Discovery	IND enabling studies	IND filing

- ❑ Indications in Red are primary indication for each program
- ❑ Indication expansion and combo trials for each program are not listed here

Thank you!

LittDD Medicines Ltd

Address: 88 Jiangling Rd, Building 4 Floor 4

Hangzhou, Binjiang District

Tel: +86-0571-86050850

Email: partnering@littdd.com