New Directions in Cancer Therapy

HELIXBIOPHARMA

Partnering Presentation

September 2023

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Executive Summary

- Helix BioPharma is developing a novel **first and best-in-class** anti-cancer therapy stemming from its proprietary technology platform
- Our lead Tumor Defence Breaker™ L-DOS47 is a unique **tumor microenvironment** modifying drug. It breaks the tumor defence against the innate (cellular) immune system by normalizing tumor acidification using a bioconjugate of a tumor-specific antibody and urease - potentially allowing for better efficacy in **combination** with chemotherapy, checkpoint inhibitors and CAR-T
- L-DOS47 has demonstrated good tolerability and safety in its use in over 100 patients, in monotherapy and combination treatments in NSCLC and PDAC
- We have seen **promising data in a NSCLC trial** in combination with Pemetrexed/Carboplatin chemotherapy; a trial in pancreatic patients is underway
- We are interested in partnering and/or out licensing opportunities to combine L-DOS47 with chemo- or IO agents to bring enhanced therapies to patients

ONCOLOGY REMAINS A SIGNIFICANT UNMET MEDICAL NEED

Lung Cancer in US

Estimated New Cases in 2022	236,740
% of All New Cancer Cases	12.3%
Estimated Deaths in 2022	**130,180**
% of All Cancer Deaths	**21.4%**

5-Year Relative Survival
22.9%
2012–2018

Colorectal Cancer in US

Estimated New Cases in 2022	151,030
% of All New Cancer Cases	7.9%
Estimated Deaths in 2022	**52,580**
% of All Cancer Deaths	**8.6%**

5-Year Relative Survival
65.1%
2012–2018

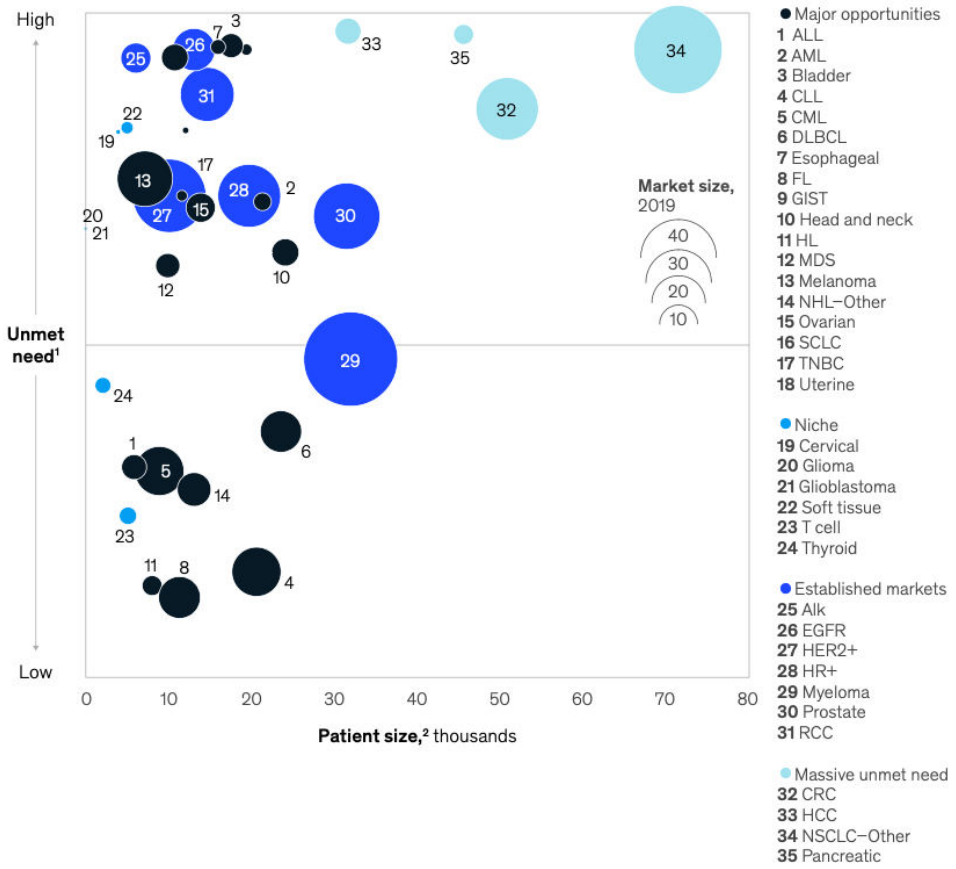
Head and Neck Cancer in US

Estimated New Cases in 2022	54,000
% of All New Cancer Cases	2.8%
Estimated Deaths in 2022	**11,230**
% of All Cancer Deaths	**1.8%**

5-Year Relative Survival
68.0%
2012–2018

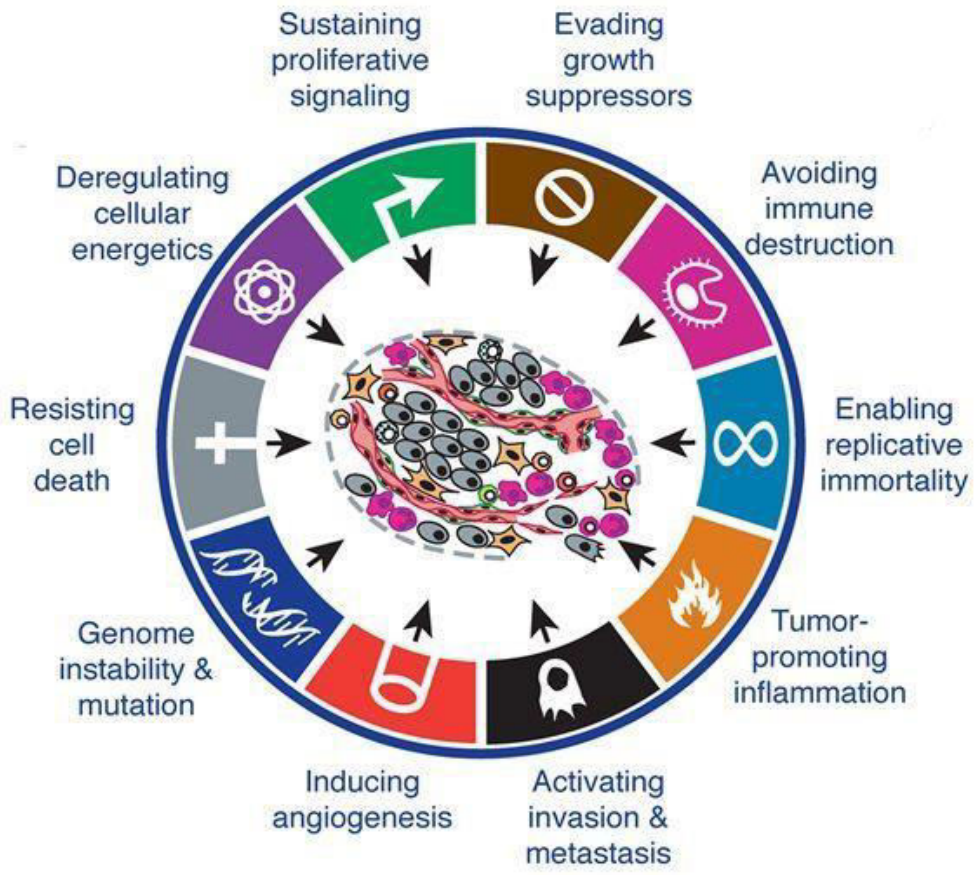
From NCI SEER Program – Accessed 1/30/2023

Several tumor types impacting large populations have persistently high unmet need



[1]Unmet need defined as one- minus five-year survival rate (overall for heme, metastatic for solid).
[2]Patient size calculated as annual incidence for heme, and larger of mortality and metastatic incidence for solid.

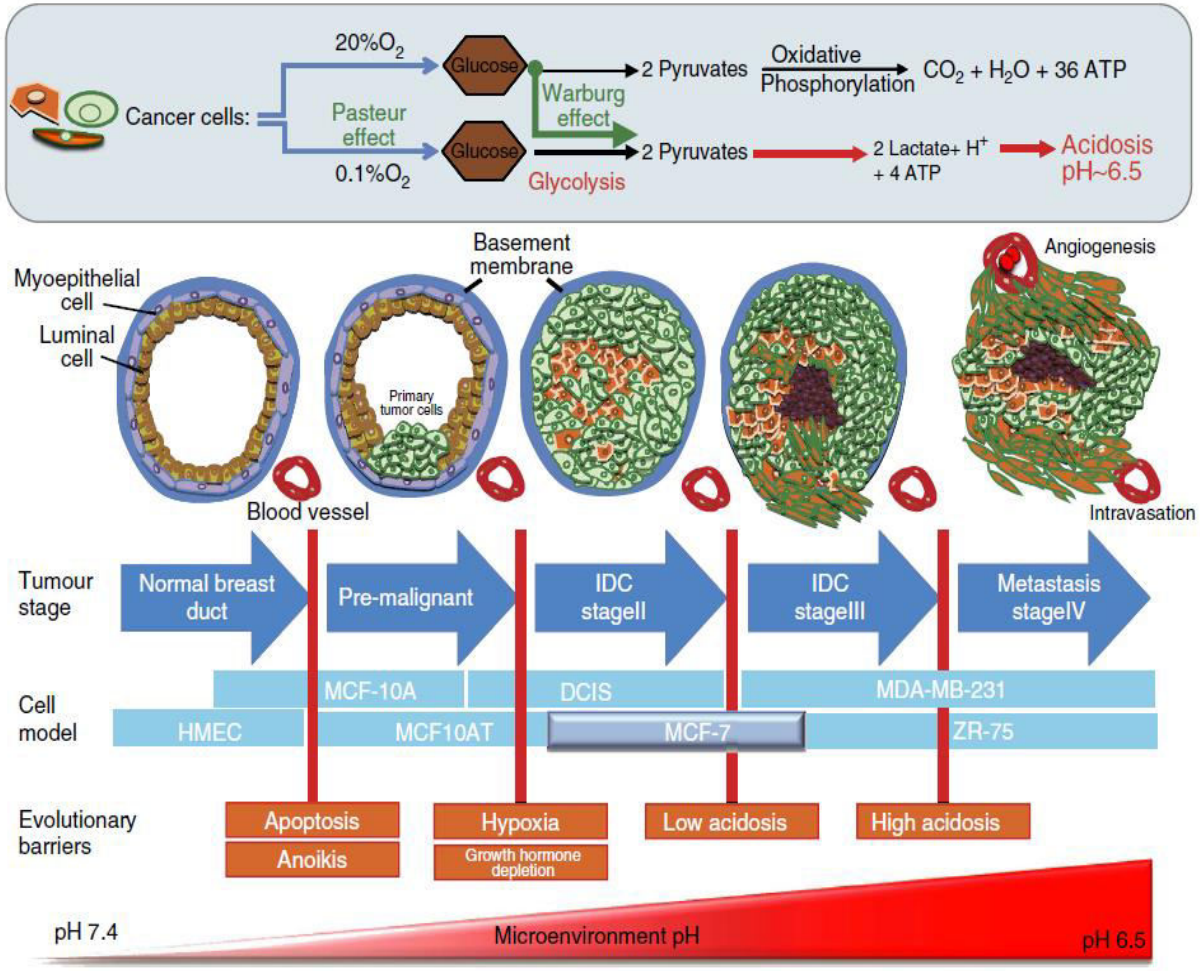
THE HALLMARKS OF CANCER



- The characteristics of cancer can be organized into multiple hallmarks or traits
- These hallmarks provide a framework to study cancer and to develop drugs
- **Targeted drugs** are developed against specific traits, but cancers often acquire resistance and escape
- Missing are therapeutics against an emerging cancer hallmark focused on **tumor acidity,** which serves a general **defense** for the tumor

Source: Cell 2011 144, 646-674

EFFECT OF ACIDOSIS ON TUMOR PROGRESSION



- Hypoxia, poor vasculature and increased flux of carbons through fermentative glycolysis leads to extracellular acidosis in solid tumors (Pasteur effect).
- Cancer cells can maintain the glycolytic phenotype even in the presence of oxygen (Warburg effect) causing further and constant acidification of the tumor microenvironment.
- Adaptation and development of resistance to acidosis is one of the key issues in cancer development and evolution that leads to a more aggressive phenotype.

Source: Damaghi, M. et al. (2015). Nature Communications | 6:8752 | DOI: 10.1038/ncomms9752 |www.nature.com/naturecommunications

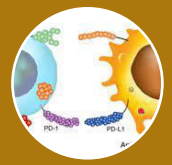
EFFECT OF ACIDOSIS ON TUMOR PHENOTYPE

1. Increases Radiotherapy Resistance

Under hypoxic conditions, there may be insufficient O_2 for radiosensitisation[1]

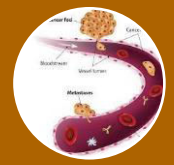
2. Increases Chemotherapy Resistance

Doxorubicin becomes highly ionized, inhibiting uptake across cell membranes in low pH[2]



3. Increases Immuno-Oncology Therapy Resistance

Acidic pH can lead to increased expression of immune checkpoint proteins including PD1/PDL1, CTLA4, TIGIT, TIM3, LAG3 CD226[3]



4. Promotes Metastasis

Varied mechanisms, e.g., increased proteinase expression and matrix metalloprotease activity thereby degrading extracellular matrix aiding cancer cell invasion and migration[4-10]

5. Hinders Immune Cell Function

Inhibits effector T and NK cells, while enhancing protumor macrophage polarization immunosuppression *via* MDSCs[11-13]

6. Higher Mutation Rate

Reversed gradient of acidic extracellular pH and alkaline pH inside cells inhibits apoptosis as caspase activation requires acidic pH. Basic intracellular pH also promotes DNA synthesis and cell proliferation, leading to tumor growth and higher rates of mutation in cancer cells, favoring cellular survival resulting in rapid disease progression[1,14-16]

7. Promotes Cancer Stem Cell Phenotype / Angiogenesis

Acidic pH enhances glioma cell malignancy, promoting expression of stem cell markers and promoting angiogenesis by increasing VEGF *via* an acidic pH-driven increase in HIF-2α. Increases expression of IL-6, IL-8 and VEGF, supporting tumor progression and angiogenesis[17-20]

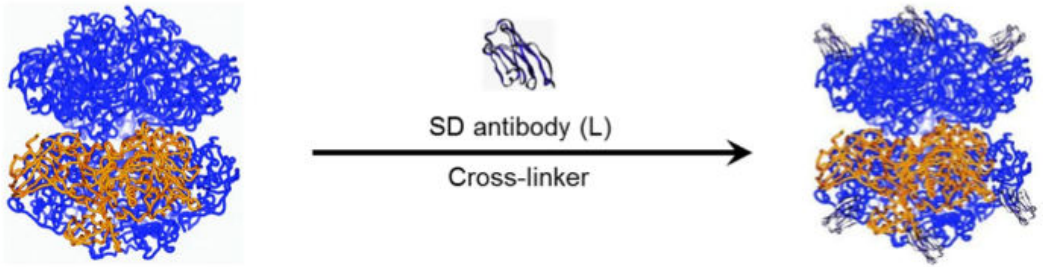
Acidic Tumor Microenvironment

Sources: [1]Webb BA *et al. Nat Rev Cancer* 2011; [2]Gerweck LE *et al. Mol Cancer Ther* 2006; [3]Hyung-seung J *et al. Journal of Controlled Release* 2019; [4]Parks SK *et al. Nat Rev Cancer* 2013; [5]Gatenby RA et al. *Br J Cancer* 2007; [6]Rofstad EK *et al. Cancer Res* 2006; [7]Walenta S et al. *Cancer Res* 2000; [8]Gatenby RA et al. *Cancer Res* 2006; [9]Bourguignon LY *et al. J Biol Chem* 2004; [10]Estrella V *et al. Cancer Res.* 2013; [11]Nakagawa Y *et al. Immunol Lett* 2015; [12]Chanmee T *et al. Cancers* 2014; [13]Nasi A *et al. J Immunol* 2013; [14]Matsuyama S *et al. Nat Cell Biol* 2000; [15]Schreiber R *et al. J Membr Biol* 2005; [16]Ward C *et al. Cancer Treat Rev* 2013; [17]Pillai SR *et al. Cancer Metastasis Rev.* 2019; [18]Kareva I *et al. Cancer Res.* 2013; [19]Xu L *et al. J Biol Chem* 2002; [20]Rafiee P *et al. Am J Physiol Gastrointest Liver Physiol* 2009.

L-DOS47: A PLATFORM TECHNOLOGY TARGETING TUMOR MICROENVIRONMENT

1. Tumor acidity is an escape mechanism that cancer cells utilize to evade the anti-tumor immune response.
2. Tumor acidity has been shown to correlate with resistance to anti-cancer treatment and poor prognosis for cancer patients.
3. L-DOS47 is designed to reduce tumor acidity with a novel mechanism of action that is synergistic with other therapies
   i. It is an immune bioconjugate that binds to CEACAM6-expressing cancer cells
   ii. It converts urea into ammonia and raises pH: Acidity reversal may augment and repair immune function
   iii. L-DOS47 may improve uptake of weak-base chemotherapeutics
   iv. Preliminary data suggest that L-DOS47 can enhance efficacy of Anti-PD1 therapy
4. Favorable drug safety profile

L-DOS47: ANTI-CEACAM6 -UREASE BIOCONJUGATE



CEACAM6

- Glycosylated 90 kDa (286 aa) GPI-linked membrane protein
- Intercellular adhesion molecule forming homotypic and heterotypic bonds with CEACAM-1, -5 and -8
- Tumor antigen highly expressed on lung, colon, pancreatic and other cancer cells

Anti-CEACAM6 antibody: AFAIKL2

- Proprietary camelid single chain antibody
- As urease is a large protein, the small size of the camelid antibody (15 kDa) is beneficial – multiple antibodies conjugated to urease do not considerably increase total protein size

Conjugation of urease to a tumor-specific antibody allows targeted urease delivery by iv injection

Preclinical Studies

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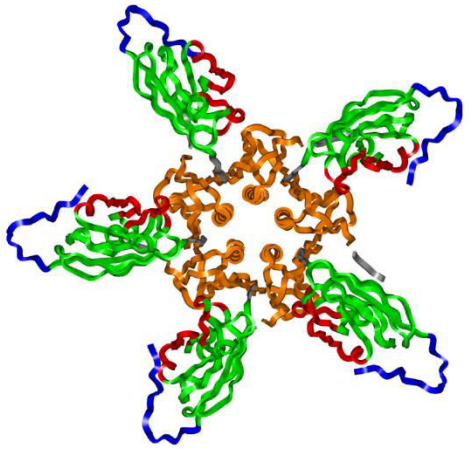
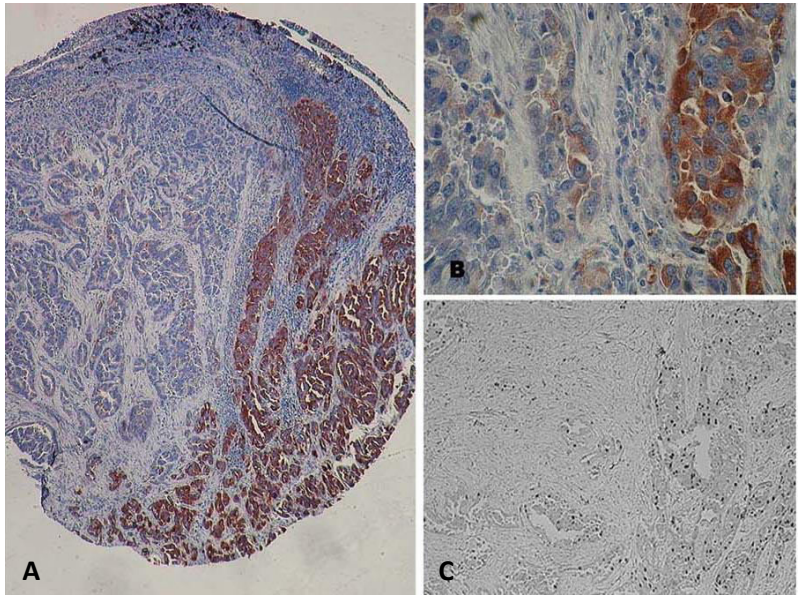
CEACAM6 IS OVEREXPRESSED ON MANY DIFFERENT TUMORS

ES1, a pentameric version of AFAIKL2, detects CEACAM6 on a range of tumors





Immunohistostaining of moderately differentiated lung adenocarcinoma. **A**: Staining with ES1. **B**: High magnification (X400) of an area in A. **C**: Staining with MIB1 (anti-Ki67) to indicate proliferation.

Table 2. A comparison of the immunoreactivity of ES1 with non-squamous large cell lung carcinomas and non-lung carcinomas

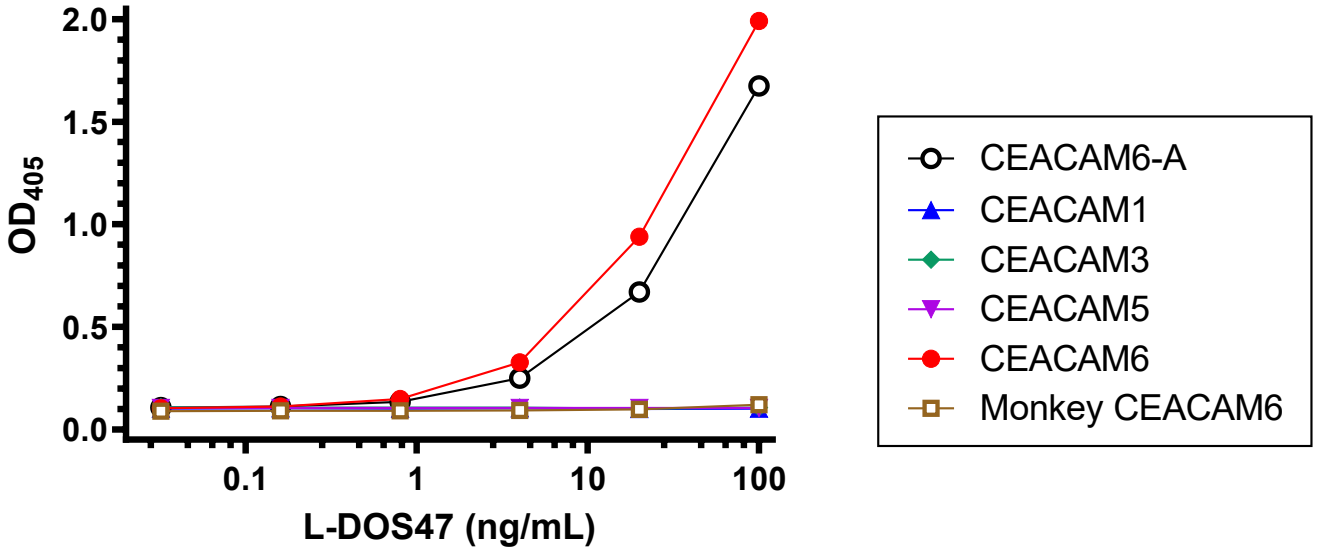
		Immunoreactivity	
Tissue	Total	Positive	Weak or negative
Non-squamous large cell carcinomas of the lung	35	34	1
Colonic adenocarcinoma	15	11	4
Breast carcinoma, urothelial carcinomas and non-colonic mucus-secreting adenocarcinomas*	38	18	20

*Pancreas, stomach, gallbladder, ovary (non-serous), urinary bladder and oesophagus.
The sensitivity of ES1 immunoreactivity for lung non-squamous and non-small cell carcinomas was 97% (34/35). The specificity was 45% (24/53). The positive predictive value was 54% (34/63).

Source: Modified from Mai, KT *et al. Histopathology*, 2006

L-DOS47 BINDS TO HUMAN CEACAM6 WITH HIGH SPECIFICITY

L-DOS47 (multiple AFAIKL2 conjugated to urease) binds human CEACAM6, <u>not</u> other human CEACAMs (1, 3, and 5) or cynomolgus monkey CEACAM6

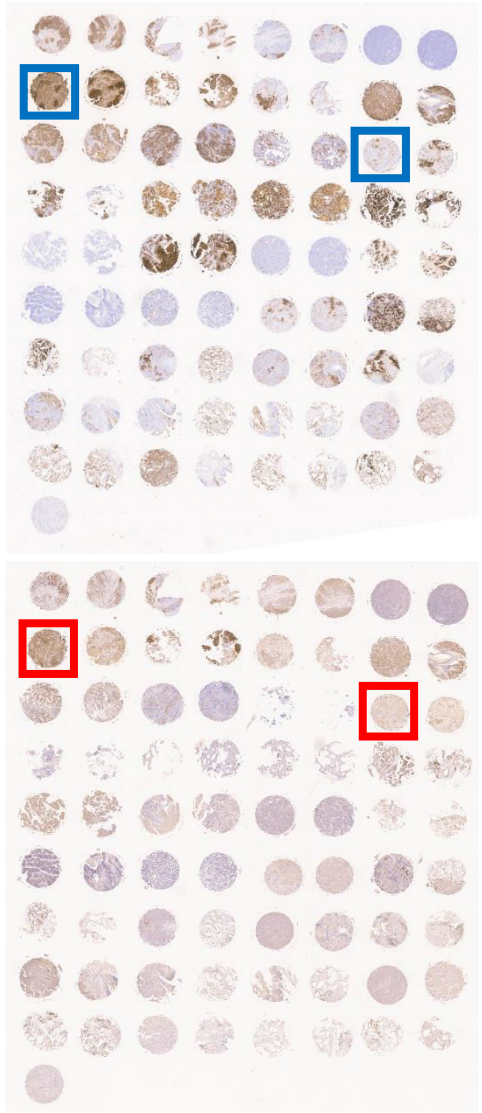


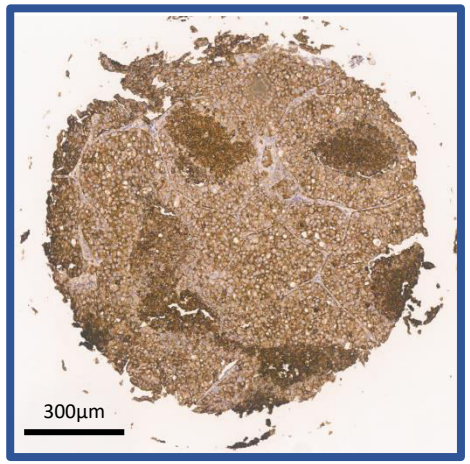
ELISA; CEACAM6 = full length, CEACAM6A = peptide

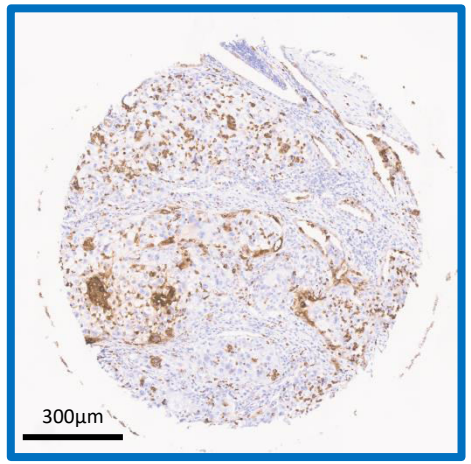
L-DOS47 BINDS WELL TO A HIGH PERCENTAGE OF NON-SMALL-CELL LUNG ADENOCARCINOMA EXPRESSING HIGH LEVELS OF CEACAM6

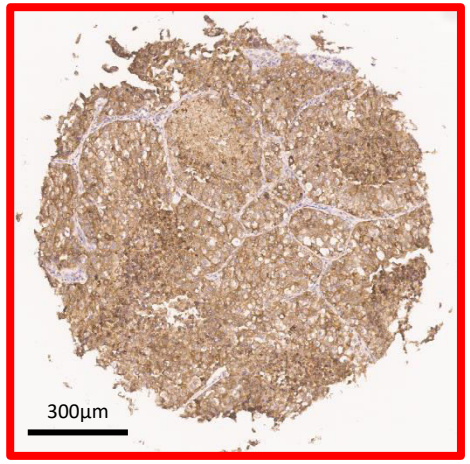
anti-CEACAM6

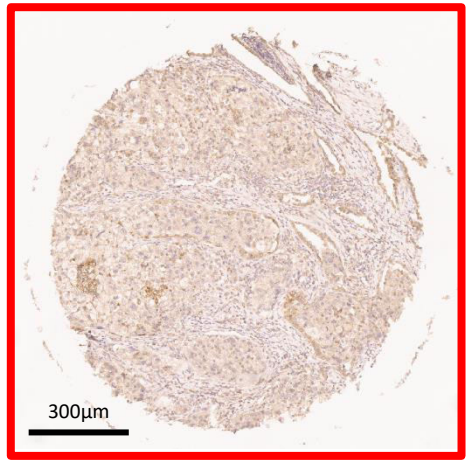
L-DOS47









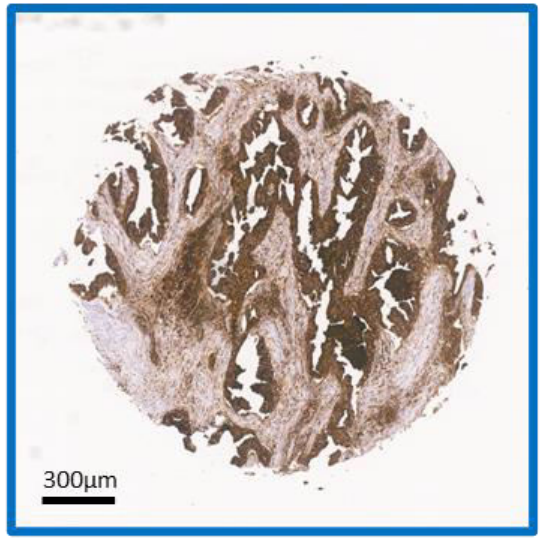


Representative examples of high and low CEACAM6-expressing NSCLC tumors. Additional analysis is ongoing.

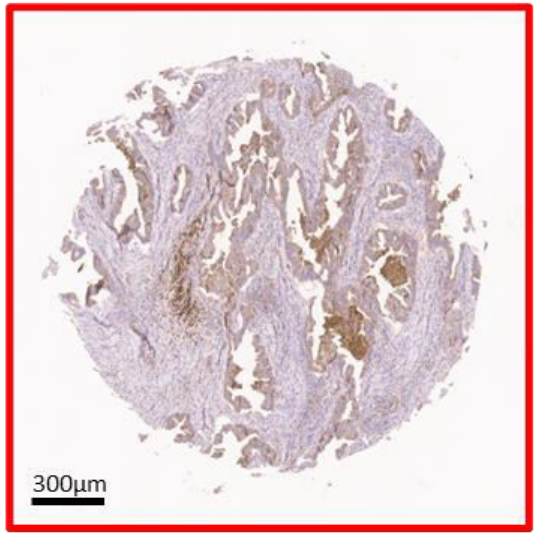
Lung

TMA from US BioLabs
stained by Young Ou, scored by Martin Koebel, University of Calgary

L-DOS47 BINDS WELL TO A HIGH PERCENTAGE OF PANCREATIC ADENOCARCINOMA EXPRESSING HIGH LEVELS OF CEACAM6



306145 anti-CEACAM6



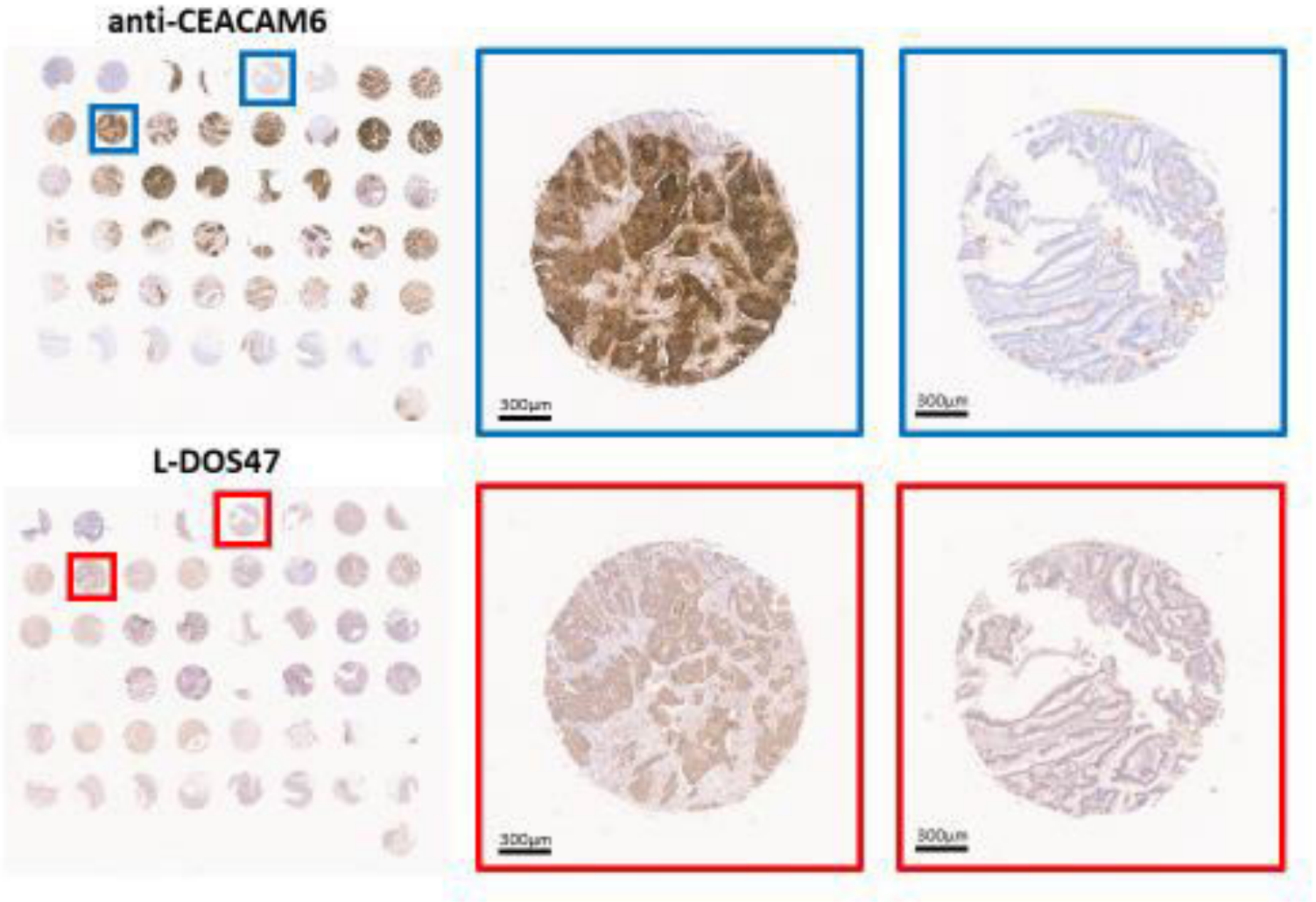
306146 L-DOS47

Representative example: 80% (8/10) cases were CEACAM6 positive

PDAC

TMA from TissueArray.com
stained by Young Ou, scored by Martin Koebel, University of Calgary

L-DOS47 BINDS WELL TO A HIGH PERCENTAGE OF COLORECTAL CANCER CASES EXPRESSING HIGH LEVELS OF CEACAM6

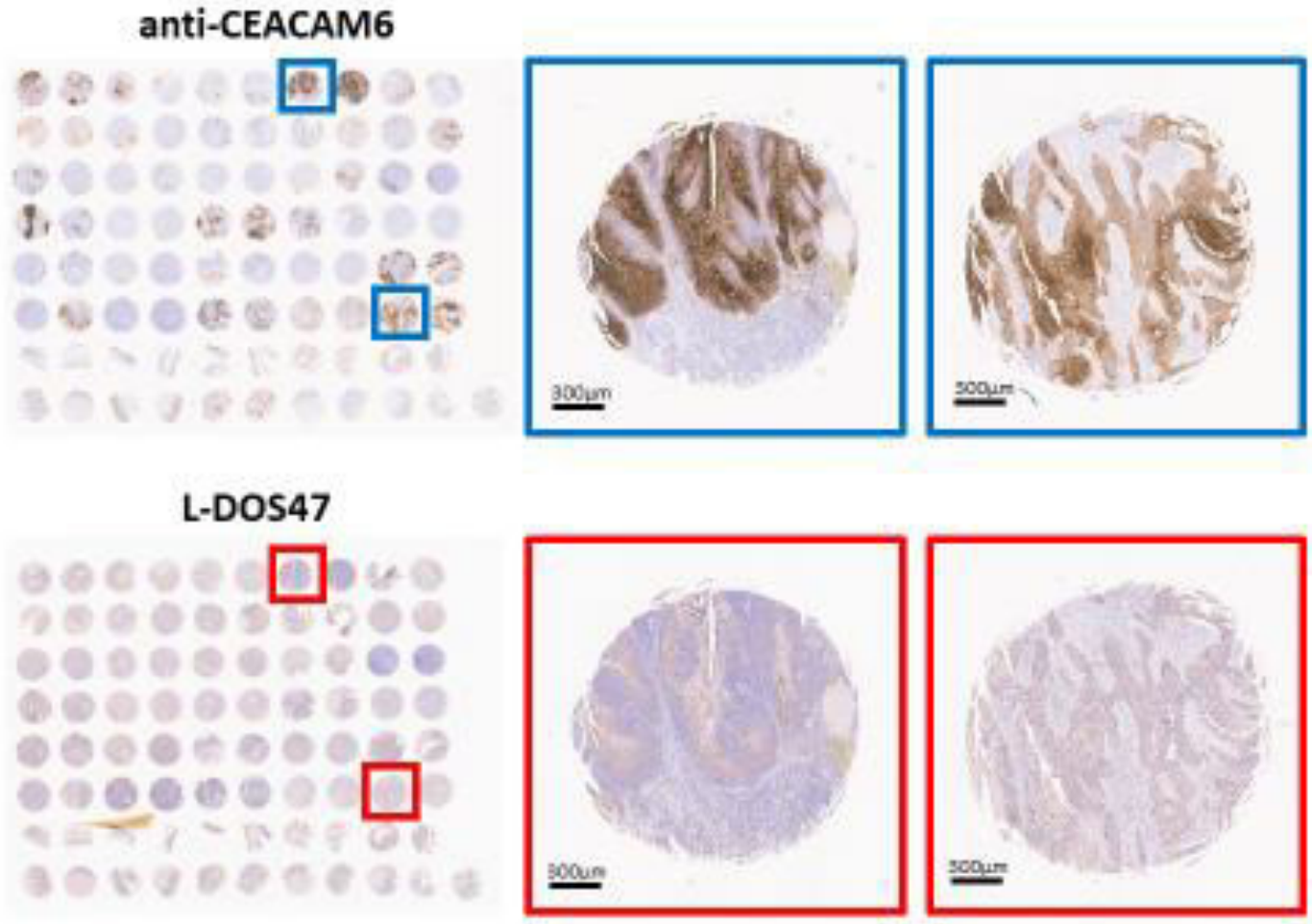


Representative examples of high and low CEACAM6-expressing CRC tumors. 75% of cases (15/20) expressed high levels, 15% were low expressors and 10% did not express CEACAM6*

*based on H-score = intensity x distribution

TMA from TissueArray.com
stained by Young Ou, scored by Martin Koebel, University of Calgary

HEAD AND NECK CANCERS EXPRESS VARIABLE LEVELS OF CEACAM6

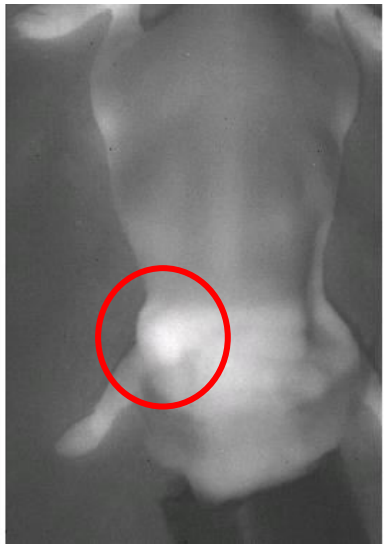


Representative examples of high and low CEACAM6-expressing H&N Cancers. Additional analysis is ongoing.

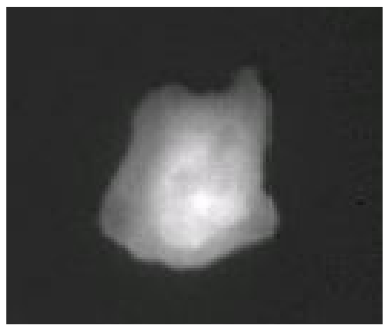
TMA from TissueArray.com
stained by Young Ou, scored by Martin Koebel, University of Calgary

L-DOS47 LOCALIZES TO CEACAM6-EXPRESSING TUMORS

8% of iv – injected L-DOS47 accumulated by 48 hours post-injection

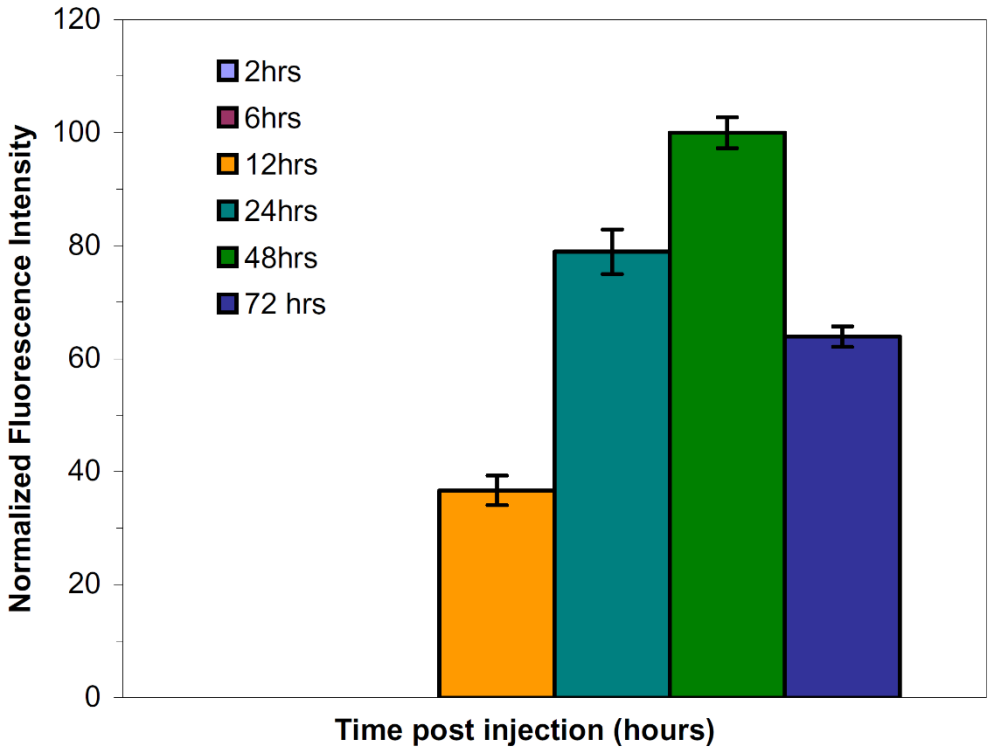


Fluorescence image of subcutaneous A549 lung tumor in nude mouse 72 hours after injection with Cy5.5-labelled L-DOS47



Fluorescence of extracted tumor (magnified)

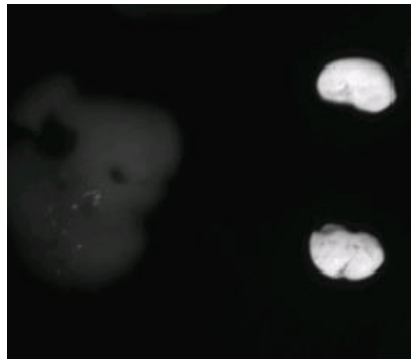
n = 4 mice sacrificed after imaging at each time point



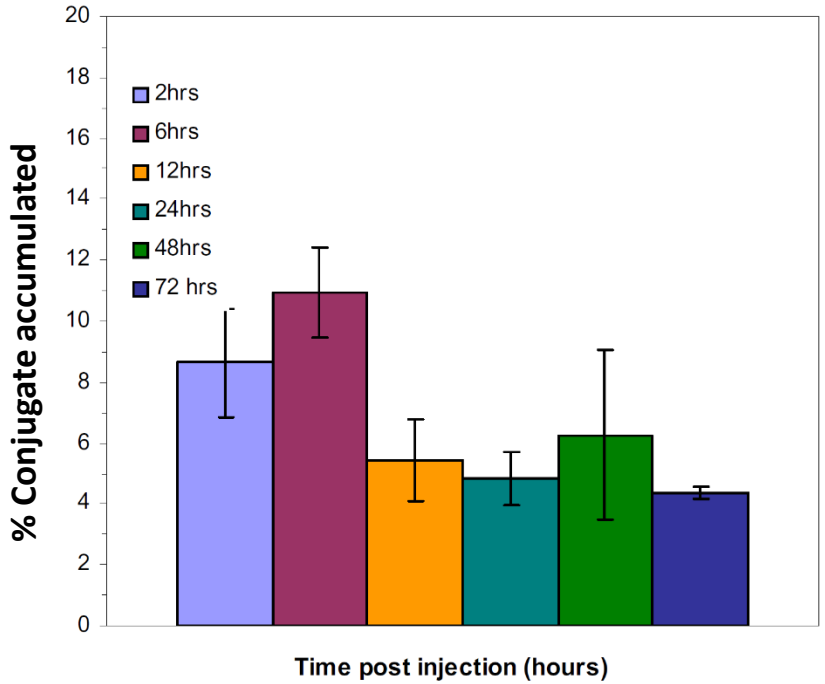
Mean normalized peak fluorescence intensity of tumors measured *in vivo* as a function of time; ~8% of iv-injected conjugate accumulated in tumors by 48hrs.

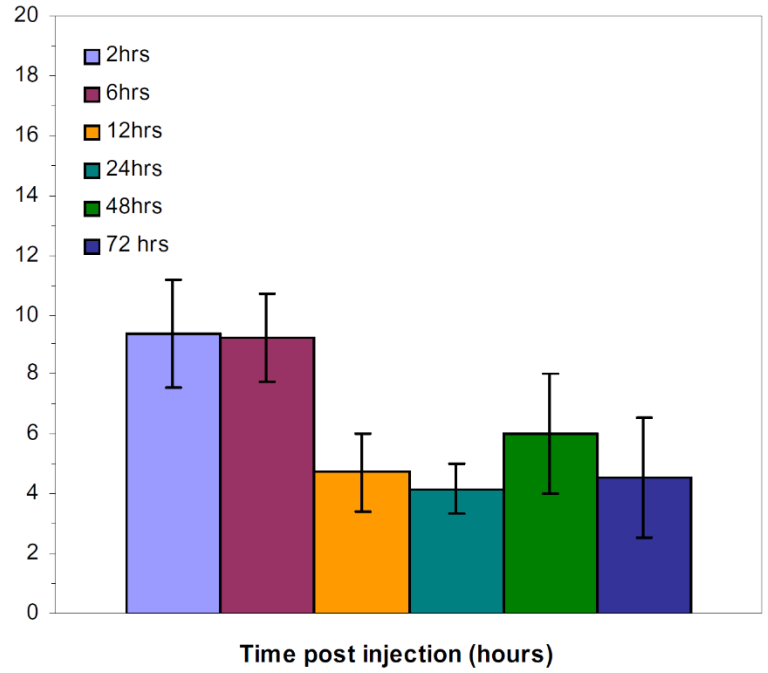
L-DOS47 RAPIDLY CLEARS LIVER AND KIDNEYS

Kidney accumulation of injected L-DOS47 Cy5.5 peaked at 18% at 2-6 hours and decreased thereafter



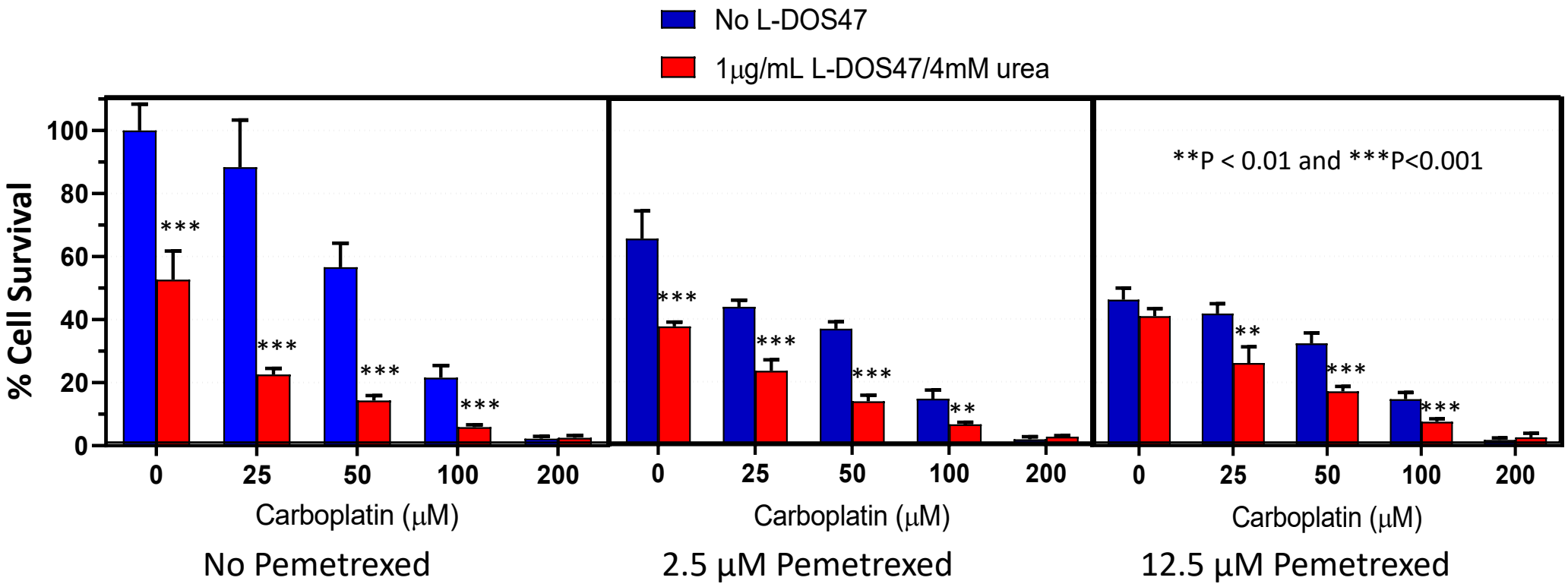
Ex vivo images of isolated liver (left) and kidneys (right) 72 hours post-injection





The percentage of total possible fluorescence was calculated for pooled data from the left (left) and right (right) kidneys harvested and imaged (from n = 4 mice per time point). No fluorescence was detected in blood, spleen, heart or lungs. Weak signals were detected in liver. No fluorescence was observed in any organ or tumor in mice injected with free dye.

L-DOS47 ENHANCES CYTOTOXICITY OF CARBOPLATIN



- A549 lung adenocarcinoma cells treated for 72 hours – too short for Pemetrexed efficacy
- L-DOS47 + urea alone cytotoxic (red bars, 0 μM Carboplatin)

L-DOS47 DOES NOT ACTIVATE PRIMARY HUMAN OR MONKEY PBMCs *IN VITRO*

In the absence of its substrate, urea, L-DOS47 does not impact viability or induce proliferation in unstimulated PBMCs

Human and monkey PBMCs were treated *in vitro* with a range of L-DOS47 concentrations (1 – 50 µg/mL, corresponding to 1 – 50 mg/kg in human dosing) and proliferation was assessed by tritiated thymidine incorporation:

- human PBMCs did not proliferate in response to any L-DOS47 concentration tested
- viability was not impacted
- overall, the same was true for monkey PBMC except in one case (of six tested)

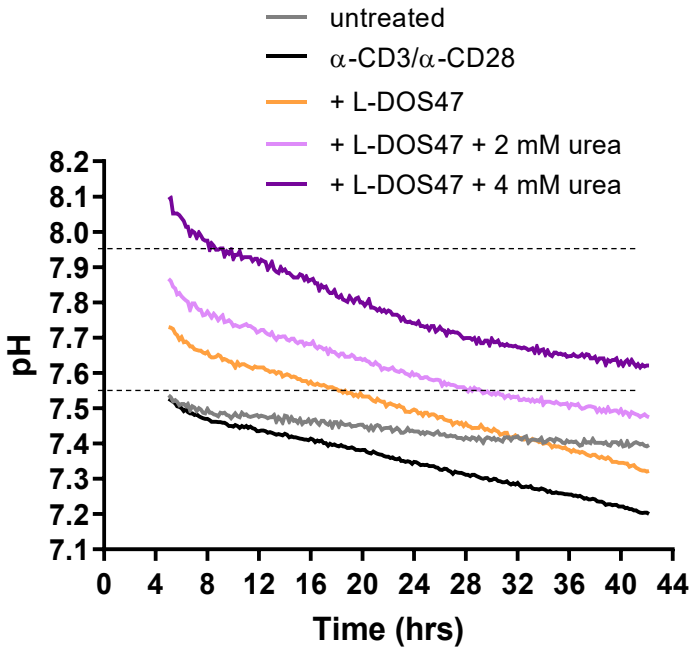
Similarly, L-DOS47 does not directly induce cytokine production by PBMCs *in vitro*

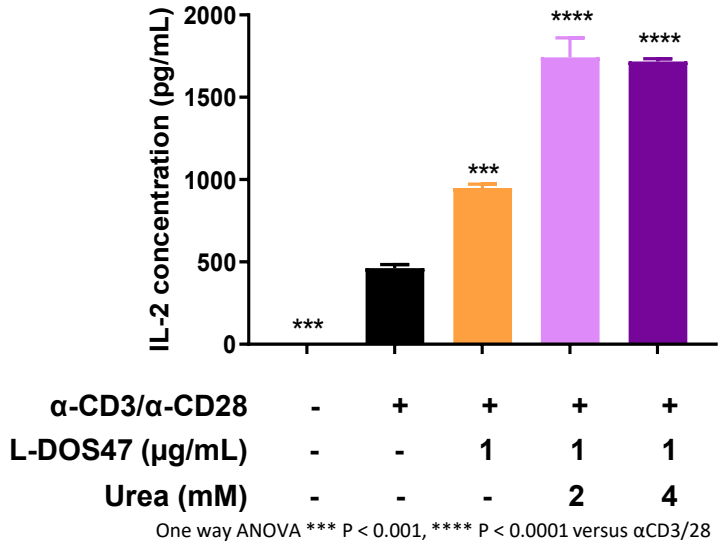
Human and monkey PBMCs were treated with 0.5 – 20 µg/well L-DOS47 and cytokine release into supernatants was quantified by Luminex assay:

- Compared to negative controls, there was no significant induction of cytokines

L-DOS47 REDUCES ACIDITY THEREBY INCREASING IMMUNE CELL RESPONSES *IN VITRO*

A 0.4 unit increase in pH significantly enhances IL-2 secretion by CD8+ T cells

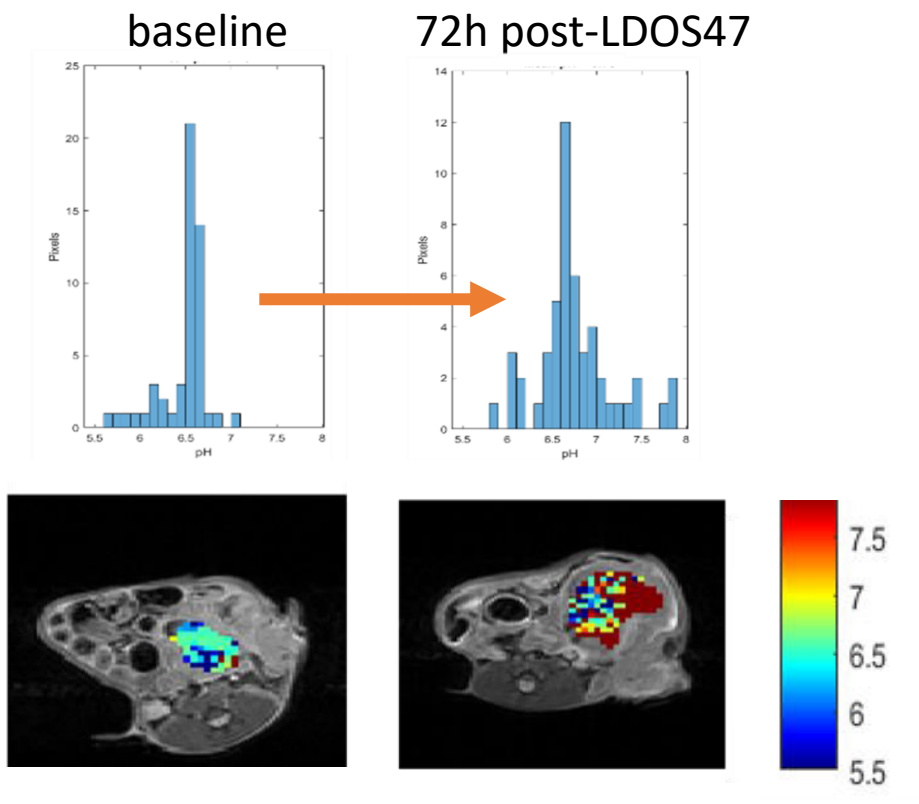




Purified CD8+ T cells activated with anti-CD3/anti-CD28 (to mimic antigen stimulation) for 3 days were continuously monitored *via* PreSens pH sensors for 44h

L-DOS47 INCREASES TUMOR pH *IN VIVO*

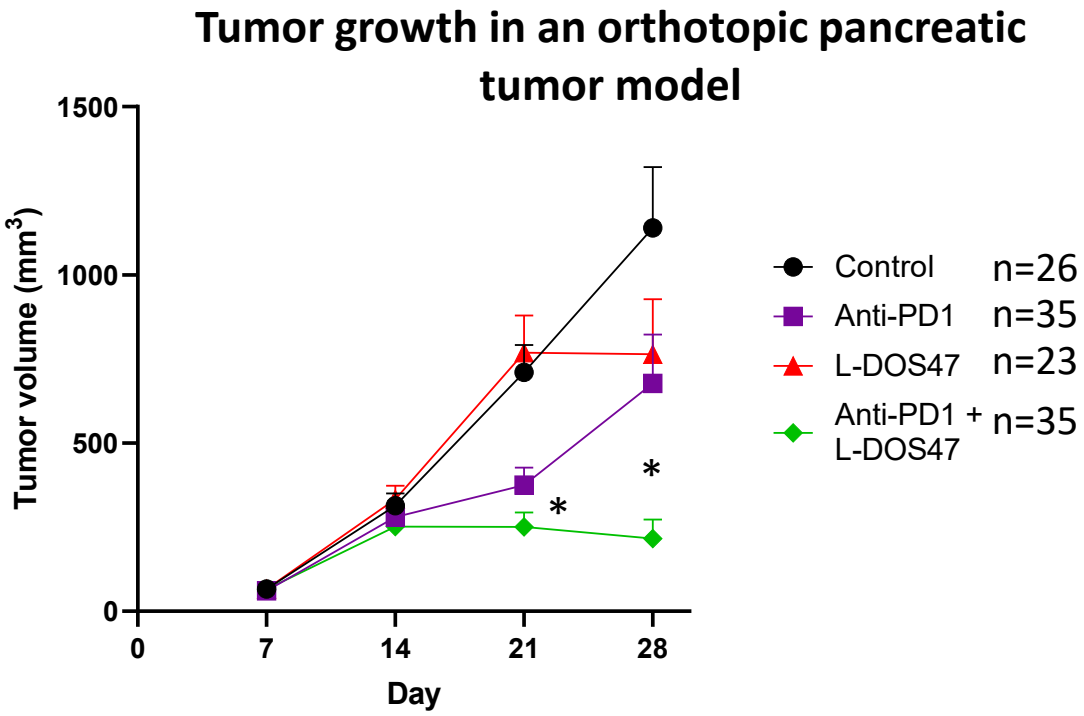
CEST MRI reveals pH increases between 4-72 hours post-L-DOS47 administration.



- Murine KPC961 pancreatic cancer cells expressing human CEACAM6 were orthotopically established in B6.129 mice
- CEST MRI images were taken prior to and at various time points after a single bolus injection of L-DOS47 (90 µg/kg) was administered
- Representative matched heatmaps and corresponding histograms show extracellular pH pixel distributions in tumors before (baseline) and at 72h post-L-DOS47 administration

Jardim-Perassi, BV *et al* submitted to *Cancer Discovery*

L-DOS47 INHIBITS TUMOR GROWTH IN COMBINATION WITH ANTI-PD1



Adjusted P values (Tukey) indicated significant differences:
* $P < 0.05$ combination versus anti-PD-1 and $P < 0.0001$ for anti-PD-1 or the combination versus control, as well as combination versus L-DOS47 alone at days 21 and 28.

- Anti-PD1 + L-DOS47 significantly reduced KPC961-1B6 tumor growth compared to anti-PD1 alone
- Tumor volumes were measured by ultrasound
- A linear mixed effects model was employed in which the endpoint tumor volume was fixed at 750 mm^3; Kenward-roger degrees of freedom were applied

Jardim-Perassi, BV *et al* submitted to *Cancer Discovery*

ADDITIONAL ONGOING STUDIES

- *In vitro* and *in vivo* assessment of impacts of L-DOS47, pH changes and ammonium on primary human immune cells as well as on CEACAM6 and checkpoint marker expression on tumor cells
- Advanced imaging to confirm biodistribution of L-DOS47
- Assessment of tumor metabolism and acidity in refractory versus responsive settings
- Confirmatory studies to measure extracellular tumor pH changes in response to L-DOS47 in various preclinical cancer models
- Confirmatory *in vivo* efficacy of L-DOS47 + anti-PD1, testing both dosing orders in KPC961 orthotopic pancreatic cancer model
- Therapeutic efficacy of combination therapies in additional orthotopic cancer models

Clinical Studies

HELIXBIOPHARMA

TUMOR DEFENCE BREAKER TECHNOLOGY PLATFORM

CLINICAL TRIALS		
L-DOS47 monotherapy NSCLC (clinical trial # NCT02340208)		
PRECLINICAL	PHASE 1	PHASE 2
L-DOS47 combo PEM/CARBO NSCLC (clinical trial # NCT02309892)		
PRECLINICAL	PHASE 1	PHASE 2
L-DOS47 combo DOXO Pancreas (clinical trial # NCT04203641)		
PRECLINICAL	PHASE 1	PHASE 2
RESEARCH		
L-DOS47 combo Immune Checkpoints		
PRECLINICAL	PHASE 1	PHASE 2

LDOS002 STUDY DESIGN: MONOTHERAPY PHASE 1 & 2 IN NSCLC

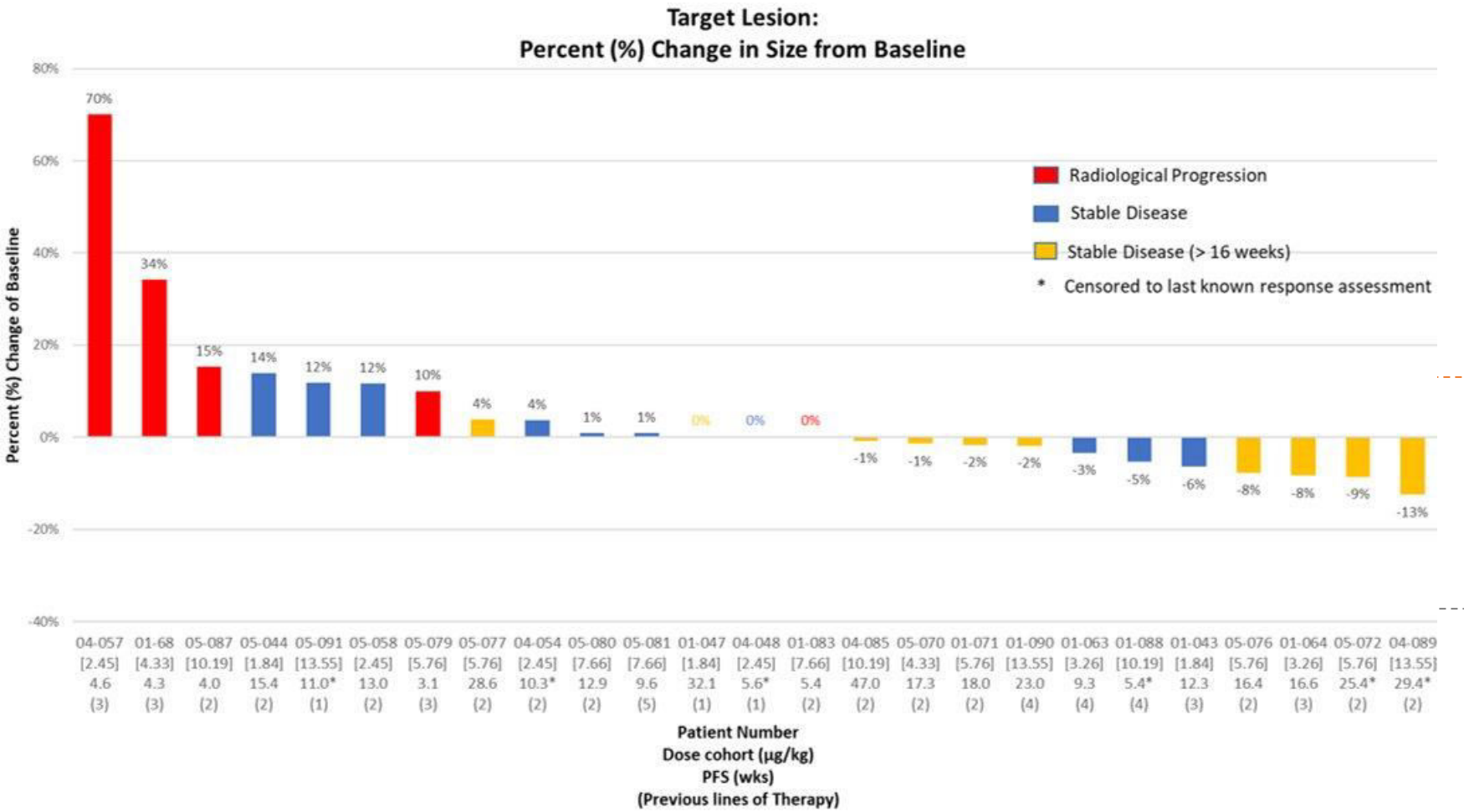
Phase I:

- Dose escalation with modified Fibonacci, 3 + 3 design
- L-DOS47 was administered once weekly over 14 days (Days 1 and 8) followed by 7 days rest cycle q 21 days

Phase 2:

- Cohort 16 dose (13.55 µg/kg) selected for Phase II
- Dosing schedule intensified in Phase II to twice weekly in 2 weeks (Days 1, 4, 8, 11) q 21
- Phase II two-stage study design where ≥ 1 responder out of 17 evaluable patients required to advance to stage 2

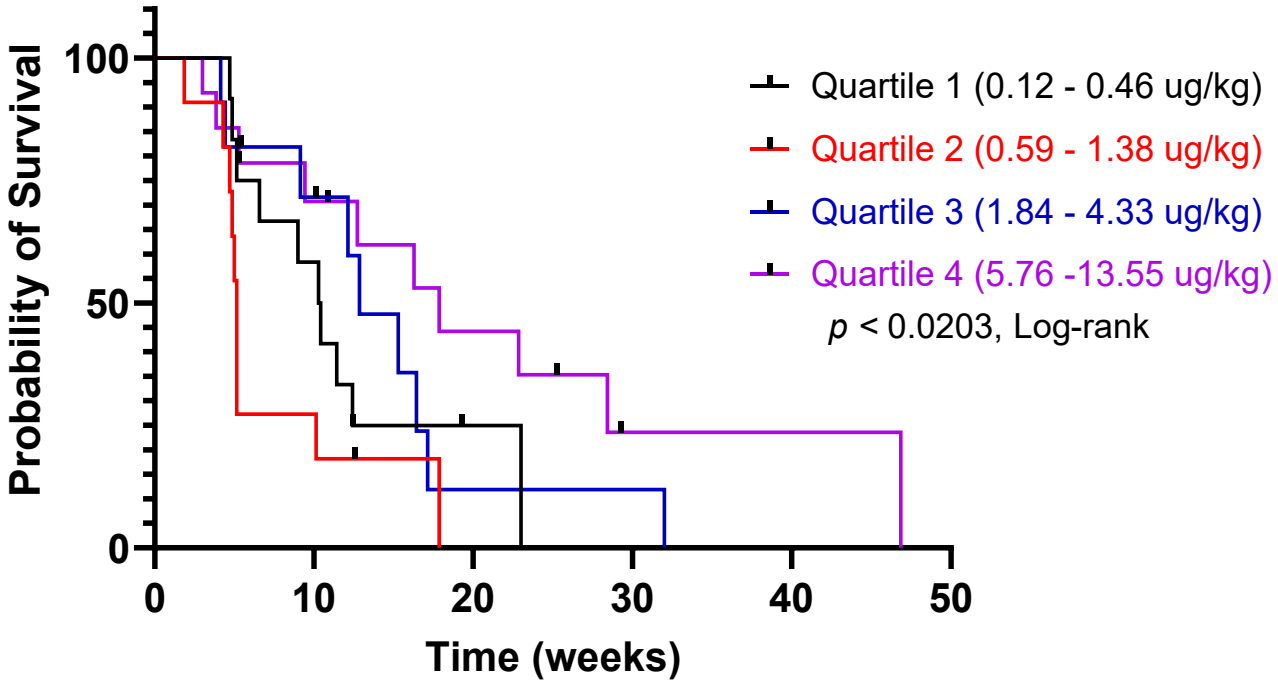
LDOS002 RESULTS: L-DOS47 MONOTHERAPY SHOWED NOTEWORTHY TUMOR REDUCTION AND STABLE DISEASE IN SECOND PLUS LINE OF THERAPY



L-DOS47 MONOTHERAPY IN NSCLC

1. L-DOS47 as a monotherapy is safe and well tolerated up to a dose of 13.55 µg/kg
2. 22 out of 26 patients showed stable disease with L-DOS47 monotherapy
3. 10 patients showed SD for protocol defined > 16 weeks in range of dosing cohorts (1.84 – 13.55 µg/kg)
4. Meaningful benefits were observed in patients who have had ≥2 lines of therapy

LDOS002: DOSE DEPENDANT BENEFIT IN PROBABILITY OF SURVIVAL WAS OBSERVED WITH L-DOS47 MONOTHERAPY DESPITE HEAVILY PRE-TREATED PATIENT POPULATION



Treatment	% Prior lines of Therapy (0/1/≥2)	Median PFS (months)
L-DOS47 (0.12 - 0.46 µg/kg)	33.3/8.3/58.3	2.4
L-DOS47 (0.59 - 1.38 µg/kg)	30.8/7.7/61.5	1.2
L-DOS47 (1.84 - 4.33 µg/kg)	0/20.0/80.0	3.0
L-DOS47 (5.76 - 13.55 µg/kg)	0/6.7/93.3	4.1
Pemetrexed[1] (500 mg/m2)	0/100/0	3.1
Pembrolizumab[2] (2 or 10 mg/kg)	0/69.1/28.7	5.3 (PD-L1 TPS ≥ 50%)
		4.0 (PD-L1 TPS ≥ 1%)

[1]Russo, F., Bearz, A., Pampaloni, G., & Investigators of Italian Pemetrexed Monotherapy of NSCLC Group (2008). Pemetrexed single agent chemotherapy in previously treated patients with locally advanced or metastatic non-small cell lung cancer. *BMC cancer*, *8*, 216.
[2]Herbst, R. S., Garon, E. B., Kim, D. W., Cho, B. C., Gervais, R., Perez-Gracia, J. L., . . . Baas, P. (2021). Five Year Survival Update From KEYNOTE-010: Pembrolizumab Versus Docetaxel for Previously Treated, Programmed Death-Ligand 1-Positive Advanced NSCLC. *J Thorac Oncol, 16*(10), 1718-1732.

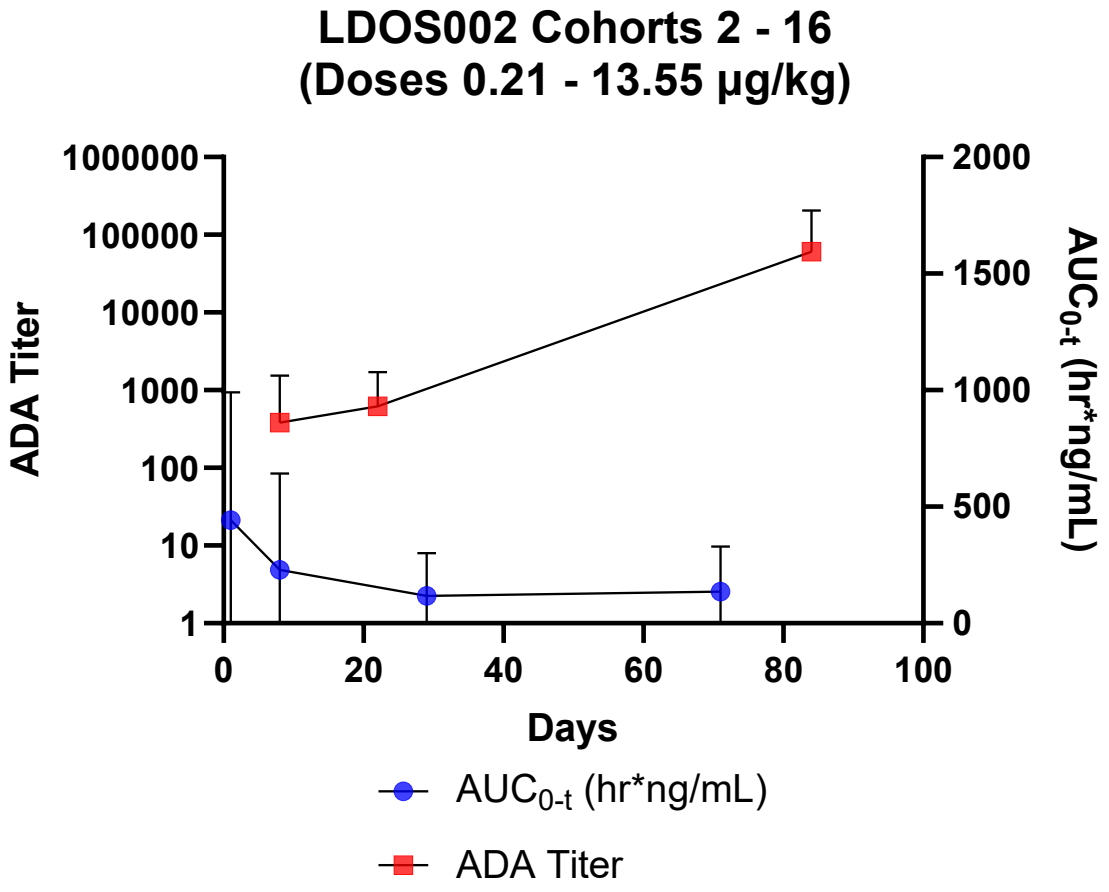
L-DOS47 monotherapy patients in second plus line of therapy portrayed a favorable median PFS of 4.1 months vs. patients treated with chemotherapy or IO therapy that were in earlier lines of therapeutic treatments

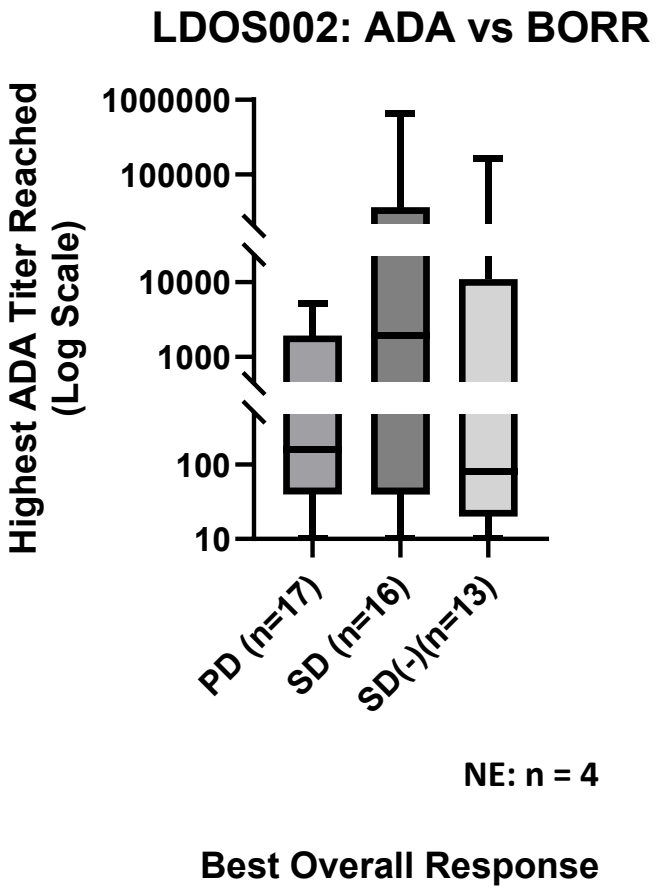
LDOS002 Phase I: TEAES WITH ≥ 5% INCIDENCE

System Organ Class Preferred Term	Toxicity Grade (Number of patients)					Cohorts															Number of Patients (N=55)	Percentage of Patients (%)
	1	2	3	4	5	1–0.12 µg/kg	2–0.21 µg/kg	3 –0.33 µg/kg	4–0.46 µg/kg	5–0.59 µg/kg	6–0.78 µg/kg	7–1.04 µg/kg	8– 1.38 µg/kg	9–1.84 µg/kg	10–2.45 µg/kg	11–3.26 µg/kg	12–4.33 µg/kg	13–5.76 µg/kg	14–7.66 µg/kg	15–10.19 kg/kg	16–13.55 µg/kg		
Blood and Lymphatic System Disorders						1									1	1	1			1		5	9%
Anemia		1	4			1									1	1	1			1		5	9%
Gastrointestinal Disorder						1	1	1	1		1				1	1	1		1	2		11	20%
Abdominal pain	2	1				1	1									1						3	5%
Nausea	3	5					1	1			1				1	1			1	2		8	15%
Vomiting	4		1								1				1	1				2		5	9%
General Disorder and Admin Site Conditions						2	3	1		1	2	2	1	1	1	1		3		2	1	21	38%
Asthenia	2	2	1							1		1			1	1					1	5	9%
Edema Peripheral	1	2				1		1								1						3	5%
Fatigue	4	4				1	1				2							2		2		8	15%
General physical health deterioration		2		1	1	1	1						1			1						4	7%
Non-cardiac chest pain	2	1				1						2										3	5%
Infections and Infestations						1	2	1				1		1					1	1		8	15%
Pneumonia		2	2			1	1					1							1			4	7%
Metabolism and Nutritional Disorder						2					1	1			1	1				1		7	13%
Decreased Appetite	1	4									1	1			1	1				1		5	9%
Musculoskeletal and Connective Tissue Disorders								1	1		1	1			1			2		1		8	15%
Bone pain		2		1											1			1		1		3	5%
Neoplasms Benign, Malignant and Unspecified[1]						1							2	1	1	1	1					7	13%
Non-small cell lung cancer				1	4								2	1	1	1						5	9%
Psychiatric Disorders						1	2			1					1	1	1			1		8	15%
Insomnia	3	3				1	2									1	1			1		6	11%
Respiratory, Thoracic and Mediastinal Disorders						2	1		3	2		2	1		1	1	1	3	1	2	1	21	38%
Cough	4	2				1			2									1		1	1	6	11%
Dyspnea	5	7		2	1	2	1		1	2		2	1		1		1	2	1	1		15	27%

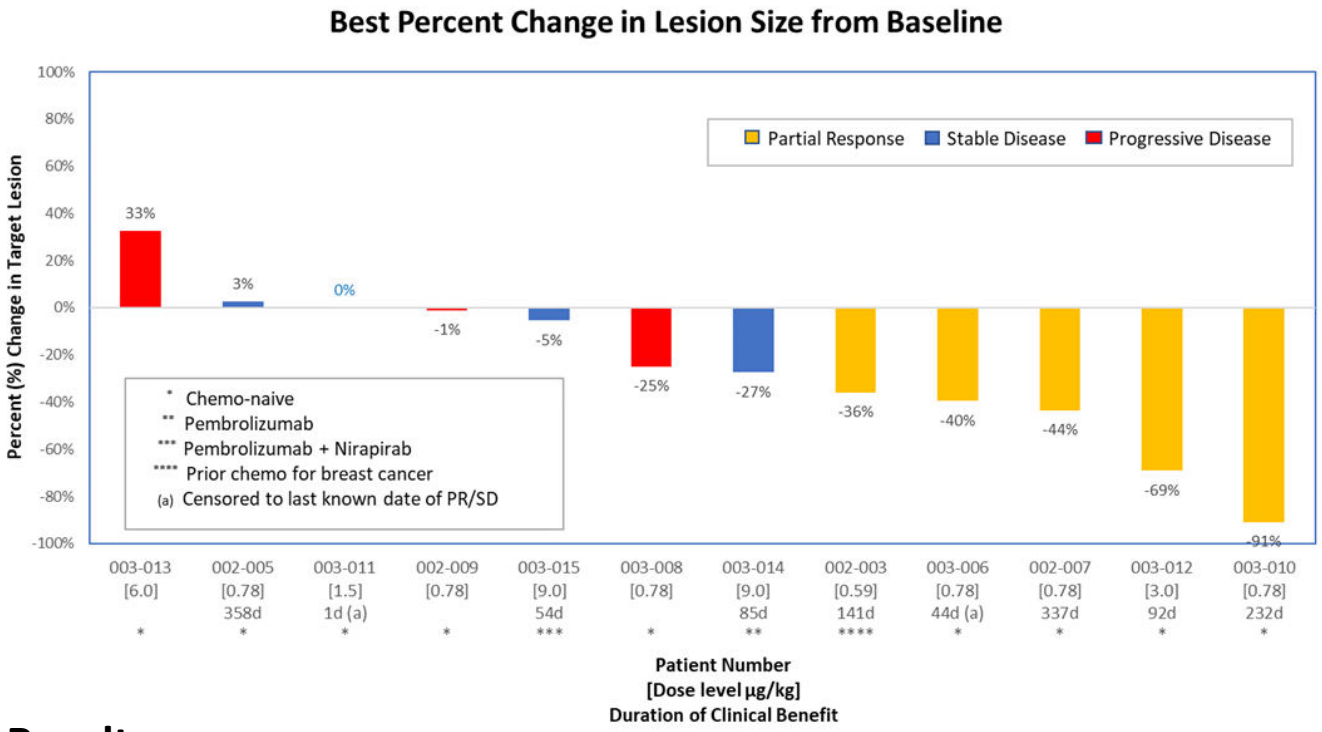
= Dose limiting toxicity

LDOS002 - SYSTEMIC EXPOSURE TYPICALLY DECREASES OVER TIME AS ADA TITER INCREASES, BUT EFFICACY IS STILL OBSERVED IN MONOTHERAPY





LDOS001: L-DOS47 COMBINED WITH PEMETREXED/CARBOPLATIN DOSE ESCALATION IN NSCLC



LDOS001 Phase I Trial Design

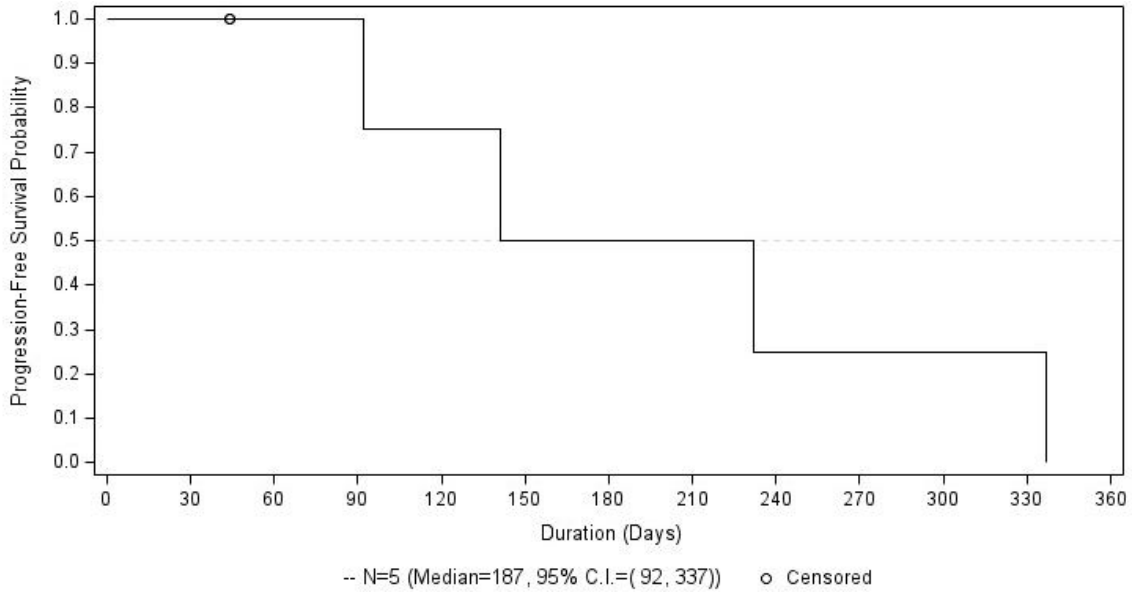
- Dose escalation with 7 dosing cohorts
- Standard “3+3” design, accelerated design; 3 cohorts (1.5, 3.0 and 6.0 µg/kg)
- Protocol defined up to four treatment cycles of combination treatment with L-DOS47 + pemetrexed/carboplatin then weekly LDOS 47 alone as an option
- Each cycle 21 days: L-DOS47 dosed once weekly with pemetrexed/carboplatin dosed on Day 1 of each treatment cycle

Results

- Study therapy was safe and well tolerated in patients with recurrent or metastatic NSCLC at doses up to 9.0 µg/kg with no DLTs reported.
- Of six patients who continued once-weekly dosing of L-DOS47, duration of exposure ranged from 162 to 398 days.
- 5/12 patients evaluable **(42%), all partial RECIST response** , additional **4 patients (33%) for SD,** and 3 patients (25%) PD. **Overall clinical benefit rate was 75%.**

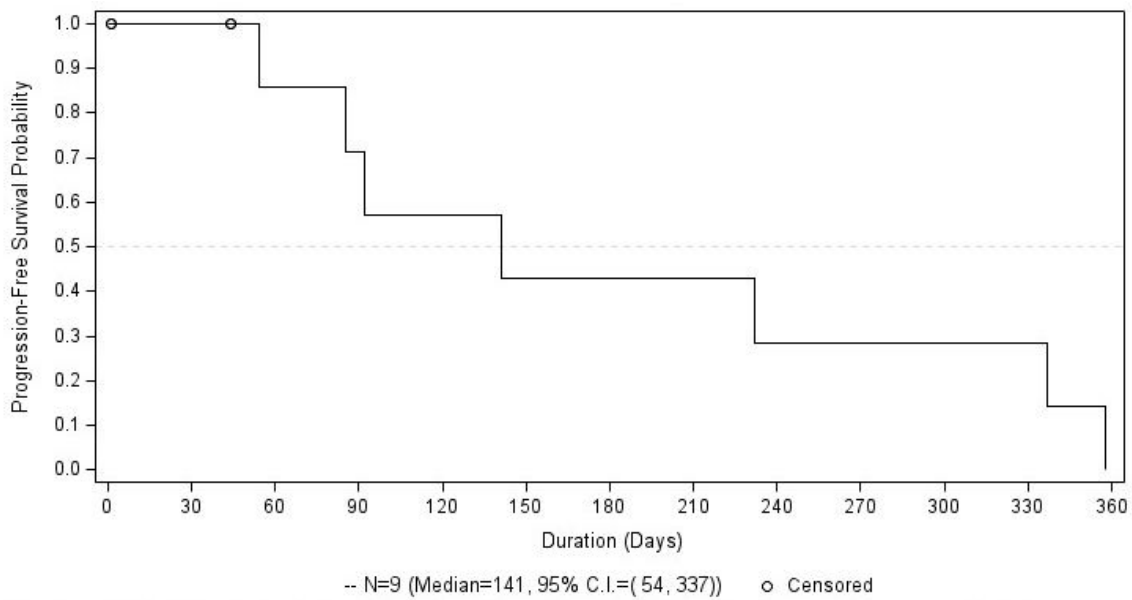
LDOS001: PATIENTS CONTINUING ON ONCE WEEKLY L-DOS47 MAINTENANCE DOSING SHOWED EXTENDED DURATION OF RESPONSE AND CLINICAL BENEFIT

Duration of Response: Efficacy Evaluable (N=5)



Duration of Response is calculated from date of first response (first occurrence of CR or PR) to first date of recurrence or objectively documented PD (not including symptomatic deterioration) or death due to any cause. For a patients without evidence of objective disease progression or death, duration of response will be censored at the date of the last evaluable tumor assessment. Only patients with a confirmed PR or CR are included in the analysis.

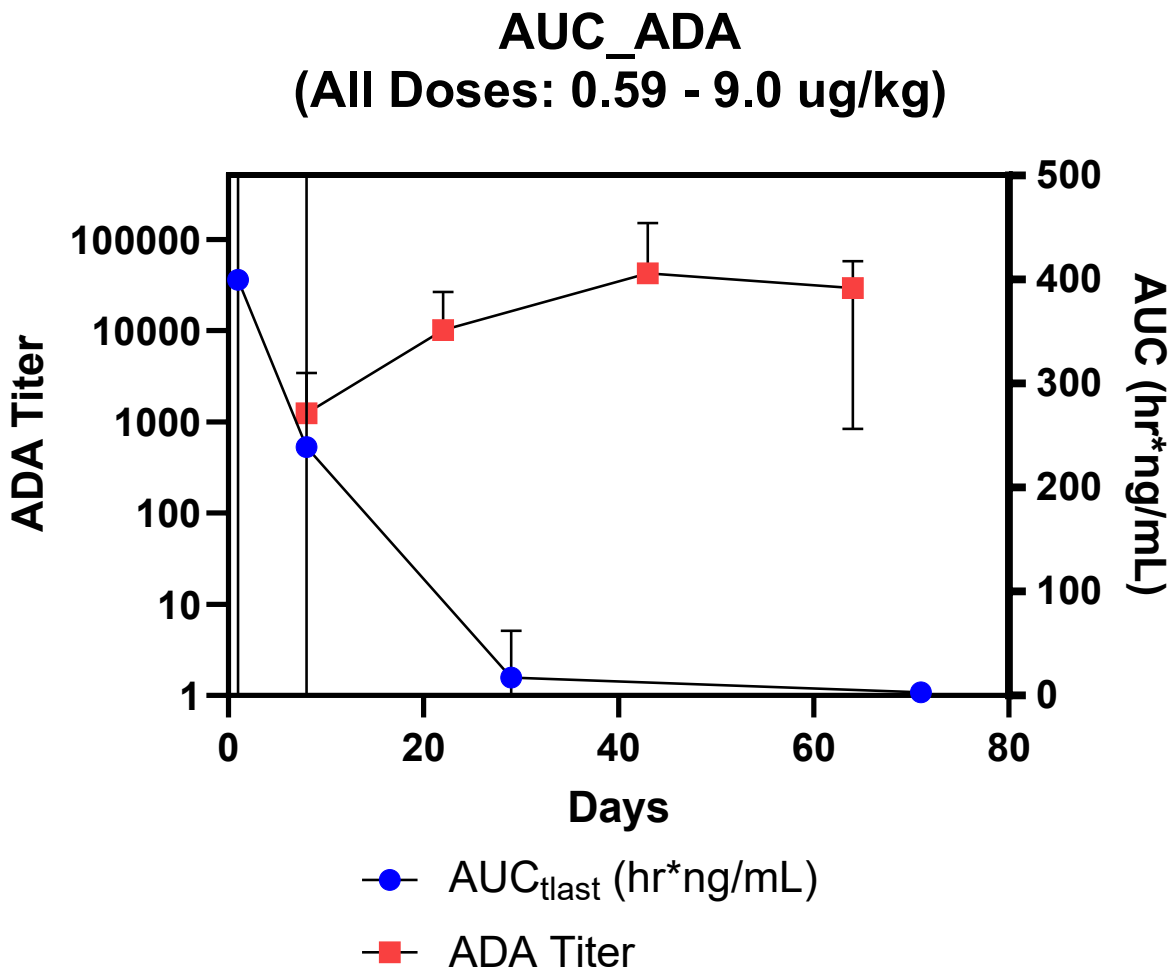
Duration of Clinical Benefit: Efficacy Evaluable (N=9)

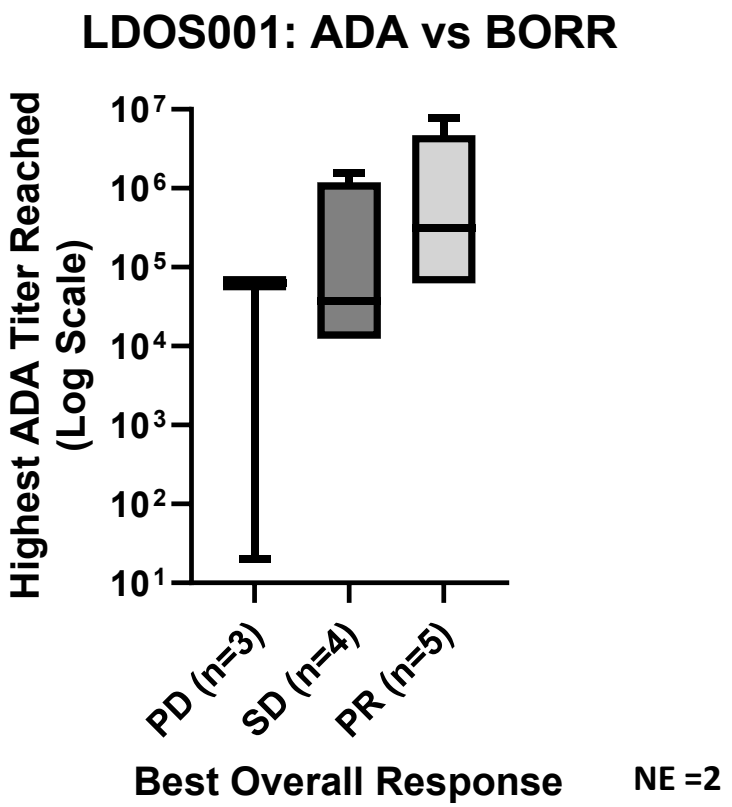


Duration of Clinical Benefit is calculated from date of first response (CR, PR or SD) to first date of recurrence or objectively documented PD (not including symptomatic deterioration) or death due to any cause. For a patients without evidence of objective disease progression or death, duration of clinical benefit will be censored at the date of the last evaluable tumor assessment. Only patients with a confirmed SD, PR or CR are included in the analysis.

Patients displayed long durations of response and clinical benefit suggesting possible beneficial changes to the tumor microenvironment that allowed increase in the probability of PFS

LDOS001 - SYSTEMIC EXPOSURE TYPICALLY DECREASES OVER TIME AS ADA TITER INCREASES, BUT EFFICACY IS STILL OBSERVED





Best responses were observed in patients with highest ADA titers

TREATMENT EMERGENT ADVERSE EVENTS (TEAES) SUMMARY: LDOS001, LDOS002 AND LDOS003 (IN NSCLC)

System Organ Class	All TEAEs (N=99)	L-DOS47 Related Any Grade (N=119)	Any Relationship Grade ≥3 (N=119)	L-DOS47 Related Grade ≥3 (N=119)
Blood and lymphatic system disorders	22 (22.2%)	6 (5.0%)	11 (9.2%)	2 (1.7%)
Cardiac disorders	11 (11.1%)	3 (2.5%)	0 (0.0%)	0 (0.0%)
Eye disorders	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Gastrointestinal disorders	45 (45.5%)	17 (14.3%)	5 (4.2%)	2 (1.7%)
General disorders	40 (40.4%)	11 (9.2%)	7 (5.9%)	0 (0.0%)
Hepatobiliary disorders	2 (2.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Immune system disorders	1 (1.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
Infection	14 (14.1%)	0 (0.0%)	3 (2.5%)	0 (0.0%)
Injury, poisoning and procedural complications	2 (2.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Investigations	17 (17.2%)	1 (0.8%)	8 (6.7%)	0 (0.0%)
Metabolism and nutritional disorders	21 (21.2%)	2 (1.7%)	5 (4.2%)	0 (0.0%)
Musculoskeletal and connective tissue disorders	18 (18.2%)	3 (2.5%)	2 (1.7%)	2 (1.7%)
Neoplasms benign, malignant and unspecified	15 (15.2%)	0 (0.0%)	7 (5.9%)	0 (0.0%)
Nervous system disorders	12 (12.1%)	1 (0.8%)	2 (1.7%)	0 (0.0%)
Psychiatric disorders	15 (15.2%)	0 (0.0%)	2 (1.7%)	0 (0.0%)
Renal and urinary disorders	9 (9.1%)	1 (0.8%)	1 (0.8%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders	36 (36.4%)	2 (1.7%)	12 (10.1%)	2 (1.7%)
Skin and subcutaneous tissue disorders	13 (13.1%)	5 (4.2%)	0 (0.0%)	0 (0.0%)
Vascular disorders	2 (2.0%)	2 (1.7%)	1 (0.8%)	1 (0.8%)

TEAES RELATED TO L-DOS47 BY STUDY

System Organ Class	All TEAEs (N=99)	ALL TEAEs LDOS002 (N=76)	L-DOS47 Related LDOS002	ALL TEAEs LDOS001 (N=14)	L-DOS47 Related LDOS001	ALL TEAEs LDOS003 (N=9)	L-DOS47 Related LDOS003
Blood and lymphatic system disorders	22 (22.2%)	6 (7.9%)	1 (1.3%)	7 (50.0%)	2 (14.3%)	9 (100.0%)	3 (33.3%)
Cardiac disorders	11 (11.1%)	8 (10.5%)	2 (2.6%)	1 (7.1%)	0 (0.0%)	4 (44.4%)	1 (11.1%)
Eye disorders	1 (1.0%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Gastrointestinal disorders	45 (45.5%)	23 (30.3%)	12 (15.8%)	13 (92.9%)	2 (14.3%)	7 (77.8%)	3 (33.3%)
General disorders	40 (40.4%)	29 (38.2%)	6 (7.9%)	10 (71.4%)	4 (28.6%)	1 (11.1%)	1 (11.1%)
Hepatobiliary disorders	2 (2.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (22.2%)	0 (0.0%)
Immune system disorders	1 (1.0%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Infection	14 (14.1%)	10 (13.2%)	0 (0.0%)	4 (28.6%)	0 (0.0%)	1 (11.1%)	0 (0.0%)
Injury, poisoning and procedural complications	2 (2.0%)	2 (2.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Investigations	17 (17.2%)	8 (10.5%)	0 (0.0%)	6 (42.9%)	1 (7.1%)	3 (33.3%)	0 (0.0%)
Metabolism and nutritional disorders	21 (21.2%)	8 (10.5%)	1 (1.3%)	10 (71.4%)	1 (7.1%)	2 (22.2%)	0 (0.0%)
Musculoskeletal and connective tissue disorders	18 (18.2%)	18 (23.7%)	3 (3.9%)	5 (35.7%)	0 (0.0%)	2 (22.2%)	0 (0.0%)
Neoplasms benign, malignant and unspecified	15 (15.2%)	11 (14.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Nervous system disorders	12 (12.1%)	5 (6.6%)	0 (0.0%)	5 (35.7%)	1 (7.1%)	2 (22.2%)	0 (0.0%)
Psychiatric disorders	15 (15.2%)	10 (13.2%)	0 (0.0%)	4 (28.6%)	0 (0.0%)	1 (11.1%)	0 (0.0%)
Renal and urinary disorders	9 (9.1%)	2 (2.6%)	0 (0.0%)	4 (28.6%)	0 (0.0%)	3 (33.3%)	1 (11.1%)
Respiratory, thoracic and mediastinal disorders	36 (36.4%)	27 (35.5%)	4 (5.3%)	8 (57.1%)	1 (7.1%)	0 (0.0%)	0 (0.0%)
Skin and subcutaneous tissue disorders	13 (13.1%)	5 (6.6%)	2 (2.6%)	7 (50.0%)	3 (21.4%)	1 (11.1%)	0 (0.0%)
Vascular disorders	2 (2.0%)	4 (5.3%)	1 (1.3%)	6 (42.9%)	2 (14.3%)	2 (22.2%)	0 (0.0%)

LDOS006: PHASE IB/II L-DOS47 DOXORUBICIN COMBINATION IN ADVANCED PANCREATIC CANCER

Phase Ib:

- Initial dose escalation phase applying a standard 3 + 3 algorithm, combining doxorubicin with L-DOS47 in a 4-week cycle
- Patients in each cohort receive weekly L-DOS47 (Days 1, 8, 15, 22) in combination dose of 15 mg/m^2 doxorubicin (Days 2, 9, 16, 23)
- A DLT defined as any occurrence within 28 days of commencing study regimen of following NCI CTCAE v5.0 events: Grade 4 neutropenia >5 days or Grade 3/4 neutropenia with fever/infection; Grade 4 thrombocytopenia (or Grade 3 with bleeding)
- Patients who have not progressed may continue for up to 8 treatment cycles

Phase II:

- Additional 11 patients to be enrolled based on dose confirmed in Phase Ib portion of the study

Primary objective:

- To determine overall safety and tolerability of the treatment regimen
- To determine recommended Phase II
- To assess preliminary anti-tumour activity

Secondary objectives:

- To assess the effect of L-DOS47 in combination with doxorubicin on tumour pH (as measured by SUV on FDG-PET)
- To determine the effect of combination treatment on pancreatic cancer biomarkers (change in CA19-9/CA-125)
- To assess the immunogenicity of L-DOS47 (presence of anti-L-DOS47 antibody)

LDOS006: PHASE IB/II L-DOS47 DOXORUBICIN COMBINATION IN ADVANCED PANCREATIC CANCER

Cohort 1
L-DOS47 3 µg/kg + Doxorubicin 20 mg/m^2
Dec 2019

→

Cohort 1 (Amended)*
L-DOS47 3 µg/kg + Doxorubicin 15 mg/m^2
Feb 2021

→

Cohort 2
L-DOS47 6 µg/kg + Doxorubicin 15 mg/m^2
May 2022

→

Cohort 3
L-DOS47 9 µg/kg + Doxorubicin 15 mg/m^2
Dec 2022

→

Cohort 4
L-DOS47 13.55 µg/kg + Doxorubicin 15 mg/m^2
Aug 2023

→

Phase II
Dose TBD
Fall 2023

Phase Ib

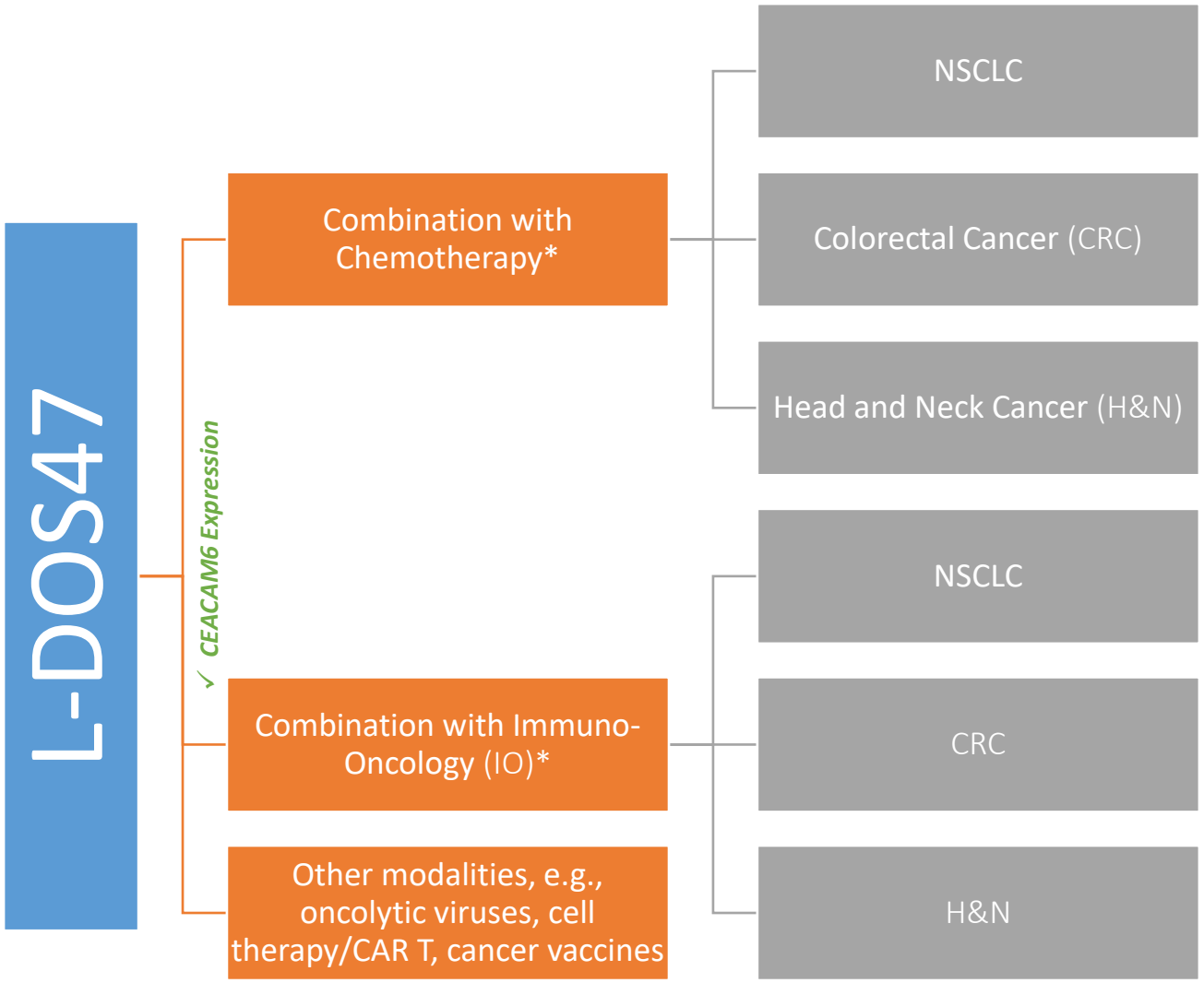
Cohort	1	1 (Amended)*	2	3	4
Dose (µg/kg)	3	3	6	9	13.55
Minimum Cohort Size	3	3	3	3	3
Patients Dosed	6	8	4	4	-
Patients DLT Evaluable	3	6	3	3	-

* Doxorubicin fixed dose was amended from 20 → 15 mg/m^2

Phase II

Dose (µg/kg)	TBC
Target Enrolment	11
Patients Dosed	-

L-DOS47 PLATFORM: PORTFOLIO-IN-A-PRODUCT STRATEGY



L-DOS47 Platform

Combination with Chemotherapy

- ✓NSCLC – proof of concept with clinical data
- ➢*CRC*
- ➢*H&N*

Combination with IO Therapies

- ➢*NSCLC*
- ➢*CRC*
- ➢*H&N*

Ongoing preclinical testing

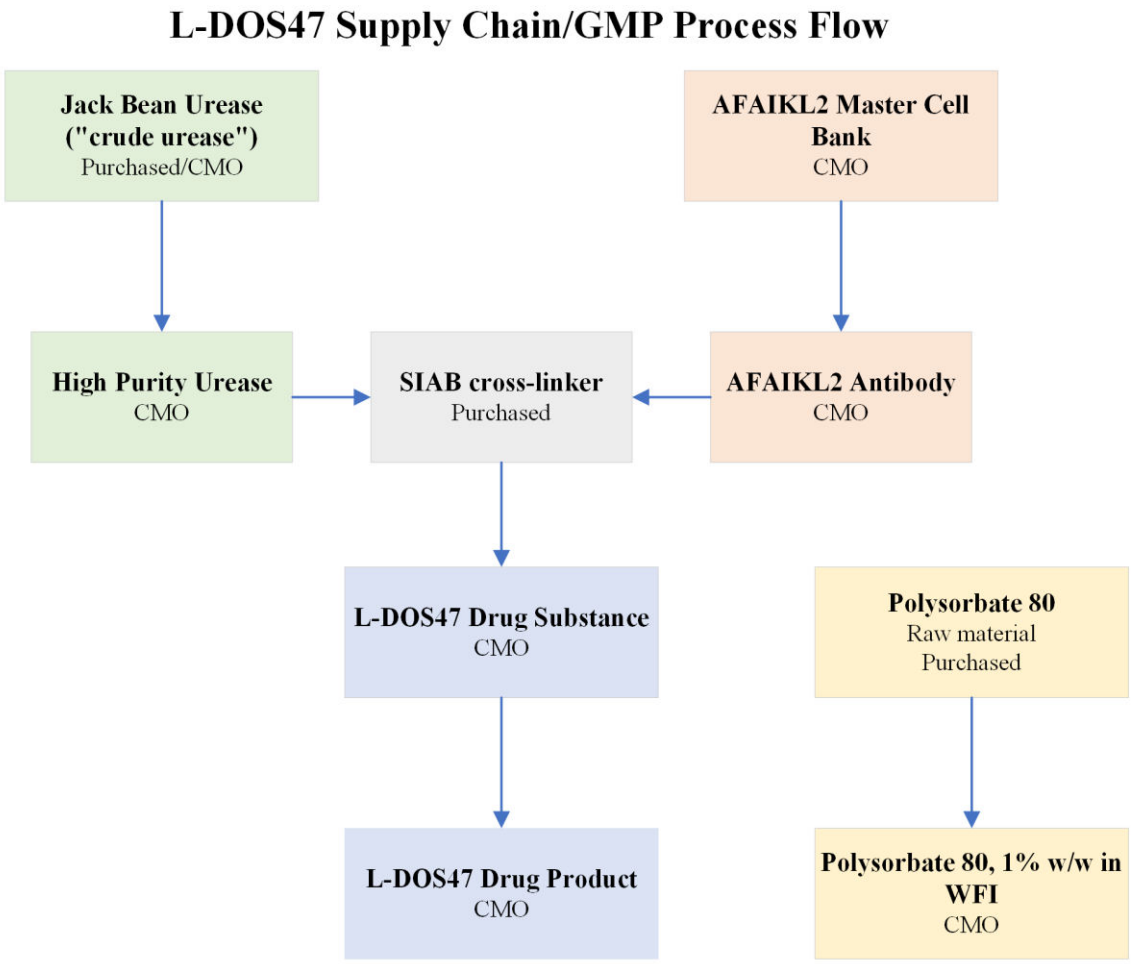
*Other potential indications being currently explored

Manufacturing

HELIXBIOPHARMA

A WELL-ESTABLISHED SCALED-UP CMC PROCESS WILL ALLOW RAPID SUPPLY FOR CLINICAL TRIALS AND LAUNCH

L-DOS47 CMC Program



Current Status

- Three lots of L-DOS47 and 5 lots of Poly 80, 1% diluent have been used in clinical trials, all with **excellent stability**
  - Up to 8 years shelf life for L-DOS47
  - Up to 5 years shelf life for Poly 80, 1%
  - Established cGMP manufacturing process
- **Extensive QC** program for L-DOS47 and its components
  - Well-established specifications and reference standards
  - Qualified methods for identity, purity, potency, concentration, impurity profile and stability

Intellectual Property

HELIXBIOPHARMA

STRONG BARRIER TO ENTRY WITH IP

RESTORING FUNCTION TUMOR ACIDIFIED T CELLS	METHOD AND COMPOSITION FOR INHIBITING CANCER CELL GROWTH USING UREASE AND WEAKLY BASIC ANTI-CANCER COMPOUNDS	ANTIBODY-UREASE CONJUGATES FOR THERAPEUTIC PURPOSES		USE OF ANTIBODY-UREASE CONJUGATES FOR DIAGNOSTIC AND THERAPEUTIC PURPOSES	USE OF UREASE FOR INHIBITING CANCER CELL GROWTH (foundation technology)	
pH/urease direct effects on T cell function (Con't: Method to decrease expression of PD-L1 on cancer cell using urease) PCT/CA2017/051116	Use of composition to reduce amount of weakly basic anti-cancer compound to reduce tumor growth, unit dose of 10-50 units/mL urease & an anti-tumor antigen antibody to enhance the delivery of the urease to tumor. unit dose reduces the amount of said weakly basic anti-cancer compound 2-5-fold lower than without urease.	sdAb:AFAIKL2 urease conjugate (CEACAM6) optimized with novel conjugation ratios (3-12) PCT/IB2016/050342		2.5 120kDa Abs conjugated to urease enzyme, multiple points of conjugation on the antibody PCT/CA2014/050334	Pharmaceutical composition for inhibiting growth of cancer cells, comprising urease enzyme, and chemical entity effective to enhance the delivery of the enzyme to cancer cells. PCT/CA2003/001061	
U.S. 10,640,806 *U.S. 16/847,490 *CA 3,045,327 *EP 3515473 *CN 110011891	CA 2,493,282	U.S. 15/545,549 CA 2,973,538 AU 2016210551 EP 3261678 (validated in CH, DE, FR, GB, IT, NL, SE, and ES)	IN 367556 IL 253549 JP 6876618 SK 10-2318994 PL 238187	U.S. 10,316,311 AU 2014252666 CA 2,908,475 *EP 2984170	U.S. 7,211,250 U.S. 7,264,800 CA 2,492,472 EP 1530482+ (validated 30 countries) EP 2324846 (DE, FR,UK)	IN 245306 & 293956 JP 5850561 SK 10-1352826 NZ 538284 PL 217626 IL 166249 NO 336811
** Patent term expires Sept 22, 2037 (if all required annuities paid)	** Patent term expires Jan 31, 2025 (if all required annuities paid)	** Patent term expires January 22, 2036 (if all required annuities paid)		** Patent term expires April 3, 2034 (if all required annuities paid)	** Patent term expires July 16, 2023 (if all required annuities paid)	

Corporate

HELIXBIOPHARMA

CORPORATE BRIEF

- Est. 1996, clinical-stage biopharmaceutical company
- Listed/trades on the Toronto Stock Exchange (TSX): Helix BioPharma Corp. (“Helix”) / Ticker symbol – HBP
- Shares outstanding: around 200 M
- Share price: CAD 0.205 (08/31/2023)
- Market Capitalization: CAD 44.42 M
- Backed by high-net-worth investors
- Experienced Management Team

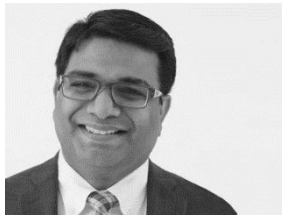
MANAGEMENT TEAM

Jacek Antas, CEO
- Supervisory Board Chairman
- Over 25 years of experience in financial services/Board member for various companies

Gary Renshaw, MD, CMO
- Former CMO Zhejiang DTRM Biopharma
- Former Oncology Director at Eisai

Hatem Kawar, CFO
- Experienced CFO with proven track record in managing financial business in a listed company

Advisors to the Board



Atul Deshpande, PhD MBA
- Experienced biotech entrepreneur, Commercial launch, fundraising and IPO experience for an IO company
- Former CEO, Immediate Therapeutics, Chief Strategist Harbour BioMed

Christof Boehler, PhD
- Biomedical scientist and experienced biotech entrepreneur
- Working with Big Pharma (Takeda) with a focus on drug delivery and Oncology

BOARD OF DIRECTORS

Jacek Antas
CEO, Chair Board of Directors

Jerzy Leszczynski
Board Member

Janusz Grabski
Board Member

Malgorzata Laube
Board Member

SUMMARY

- Current standards of care, including checkpoint inhibitors, have limited efficacy in addressing cancers
- Helix is developing novel anti-cancer therapies stemming from its proprietary technology platforms that could help address these efficacy challenges
- L-DOS47
  - Unique immuno-bioconjugate drug targeting the tumor microenvironment
  - Monotherapy proven safe in lung cancer study
  - Showed additional clinical benefit when combined with chemo in lung cancer
  - In clinical development for both lung and pancreatic cancer
- Expect to reach additional clinical and pre-clinical milestones in 2023

Thank You!

Contact:
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