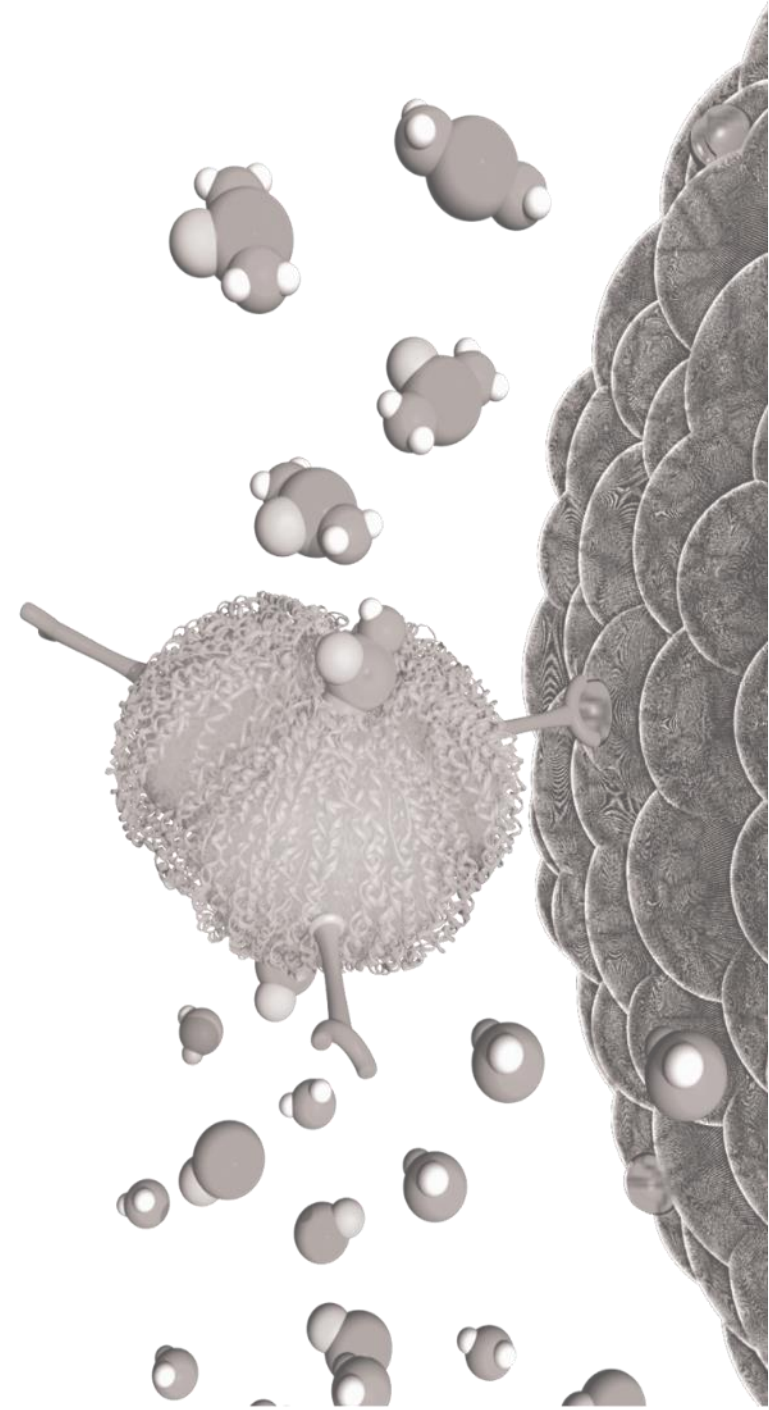


# Helix BioPharma Corp



# Forward-looking Statements

This presentation document contains certain forward-looking statements and information (collectively, “forward-looking statements”) within the meaning of applicable securities laws. Forward-looking statements are statements and information that are not historical facts but instead include financial projections and estimates; statements regarding plans, goals, objectives, intentions and expectations with respect to Helix’s future business, operations, research and development, including the focus of Helix on its DOS drug candidate generally and L-DOS47 in particular, the anticipated timelines for the commencement or completion of certain activities, including enrolment of patients in Helix’s Phase I/II clinical trial for L-DOS47 in Poland, the expansion of the DOS47 platform into other compounds and indications and other information in future periods. Forward-looking statements, which may be identified by words including, without limitation, “expects”, “plans”, “will”, “intends”, “may”, “pending”, “objective”, “exploring”, “potential”, “projected”, “possible” and other similar expressions, are intended to provide information about management’s current plans and expectations regarding future operations.

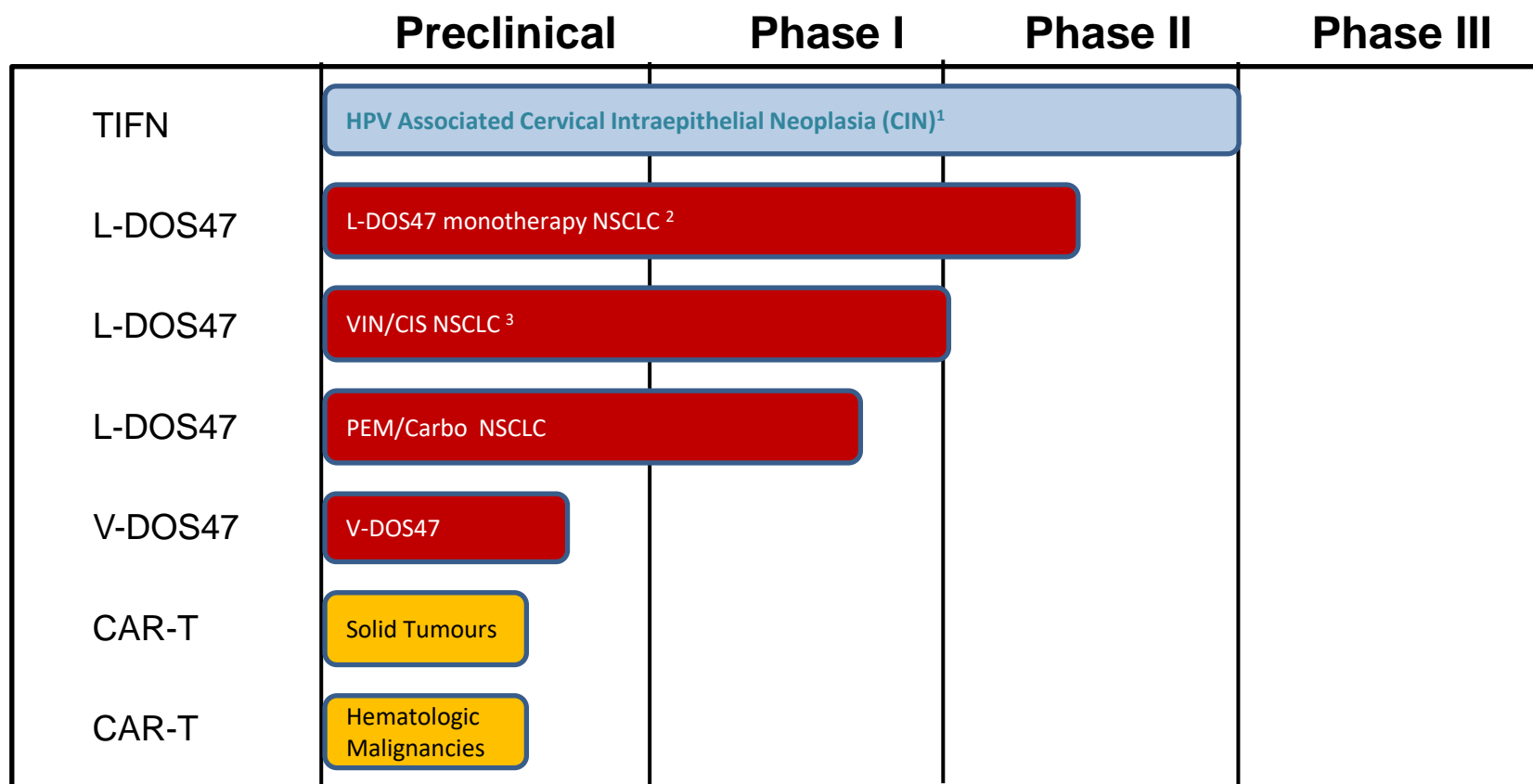
Although Helix believes that the expectations reflected in such forward-looking statements are reasonable, such statements involve risks and uncertainties that may cause actual results or events to differ materially from those anticipated and no assurance can be given that these expectations will be realized, and undue reliance should not be placed on such statements. Risk factors that could cause actual results or events to differ materially from the forward-looking statements include, without limitation: (i) the inherent uncertainty involved in scientific research and drug development, including with respect to costs and difficulties in predicting accurate timelines for the commencement or completion of certain activities; (ii) the risks associated with delay or inability to complete clinical trials successfully and the long lead-times and high costs associated with obtaining regulatory approval to market any product which may result from successful completion of such trials; (iii) need to secure additional financing on terms satisfactory to Helix or at all, including that the additional funding required in order to complete the proposed U.S. Phase I clinical trial will be obtained on terms satisfactory to Helix or at all; (iv) clinical trials that yield negative results, or results that do not justify future clinical development, including that Helix’s ongoing Polish Phase I/II clinical trial for L-DOS47 and/or that Helix’s proposed U.S. Phase I clinical trial will yield negative results; (v) Helix’s clinical development plan for the proposed US Phase I clinical trial does not proceed in the manner or on the timelines anticipated by Helix or at all; and (vi) those risks and uncertainties affecting Helix as more fully described in Helix’s most recent Annual Information Form, including under the headings “Forward-Looking Statements” and “Risk Factors”, filed under Helix’s profile on SEDAR at [www.sedar.com](http://www.sedar.com) (together, the “Helix Risk Factors”). Certain material factors and assumptions are applied in making the forward-looking statements, including, without limitation, that the Helix Risk Factors will not cause Helix’s actual results or events to differ materially from the forward-looking statements. Helix.

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# Company Brief

- Helix BioPharma Corp. (“Helix”) / Ticker symbol: HBP
- Est. 1996, clinical-stage, Immuno-oncology company
- Listed/trades on the Toronto Stock Exchange (TSX) and Frankfurt Stock Exchange (FSE)
- Shares outstanding = 100.06M
- Market cap = CAD 84.5 million
- Share price = CAD 0.84
- 52wk hi-low= CAD1.5 – CAD0.70
- Backed by high net worth investors; No debt

# Product Development Pipeline

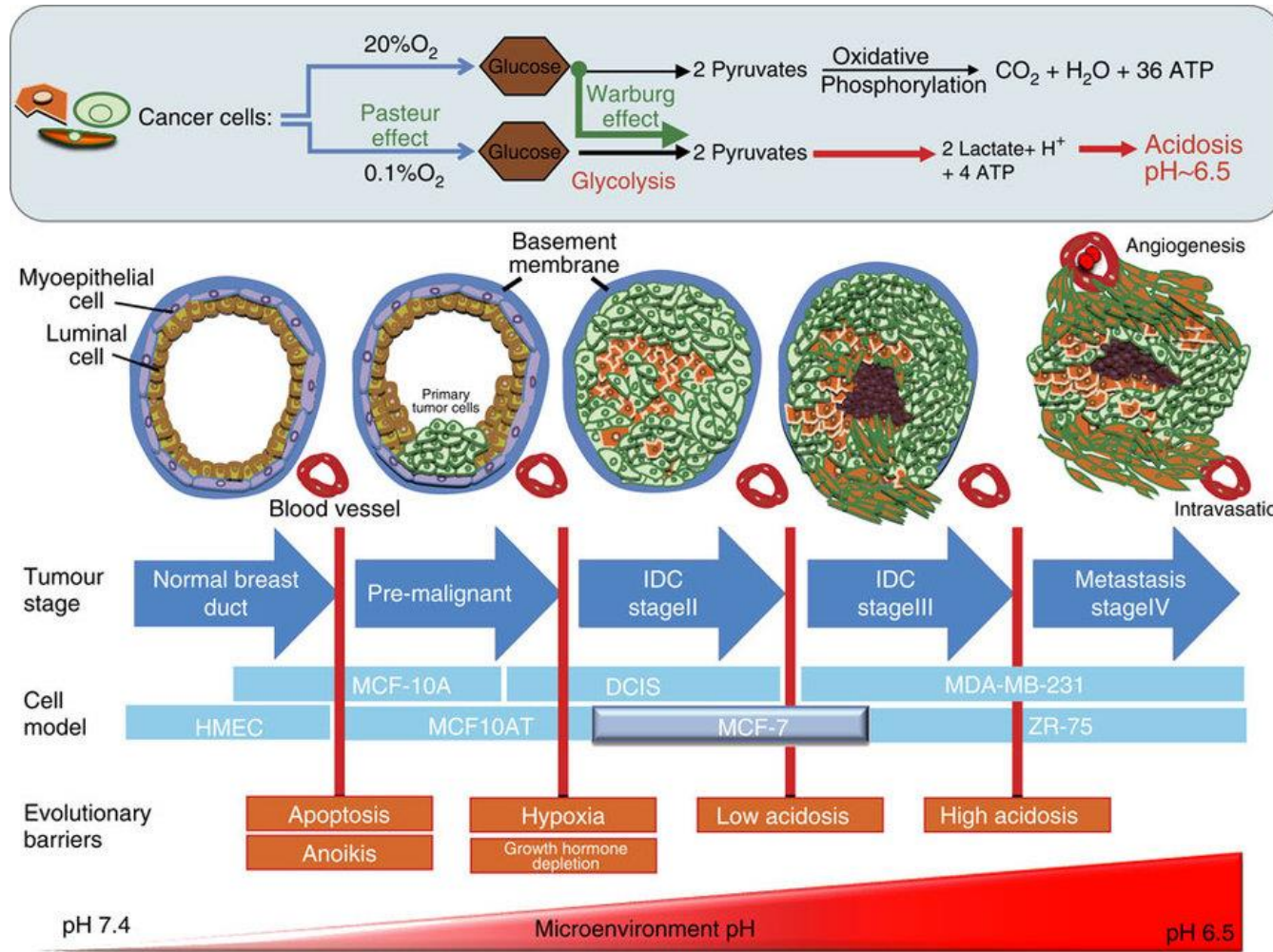


<sup>1</sup> Partnered

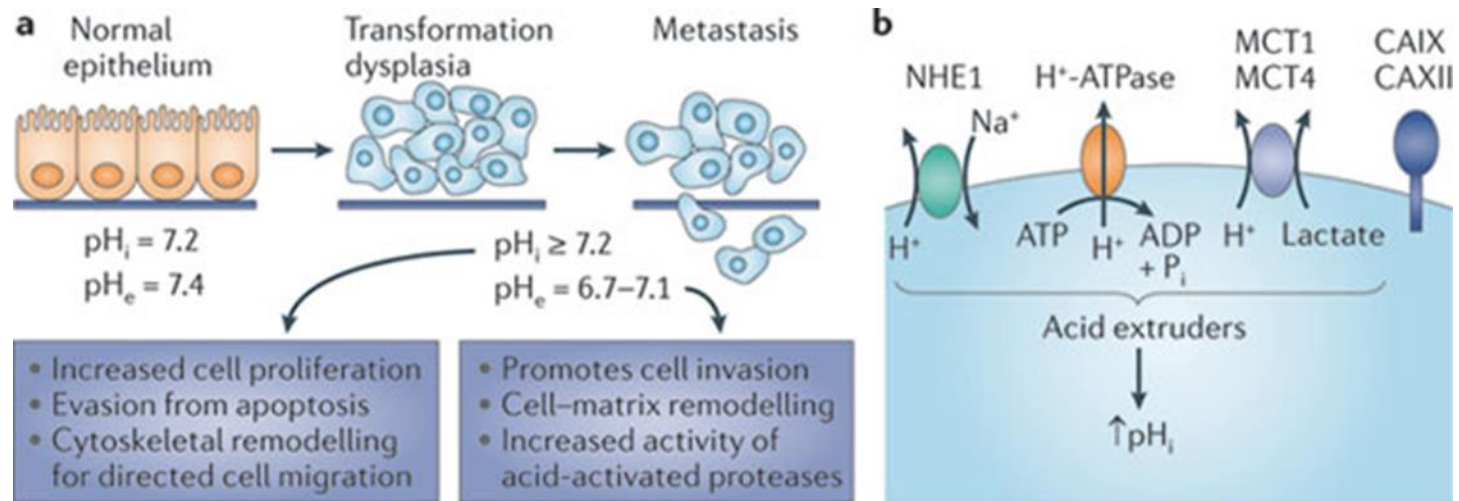
<sup>2</sup> Phase II stage 1 completed, not advancing

<sup>3</sup> not yet enrolling

# Acidosis and Tumor Progression

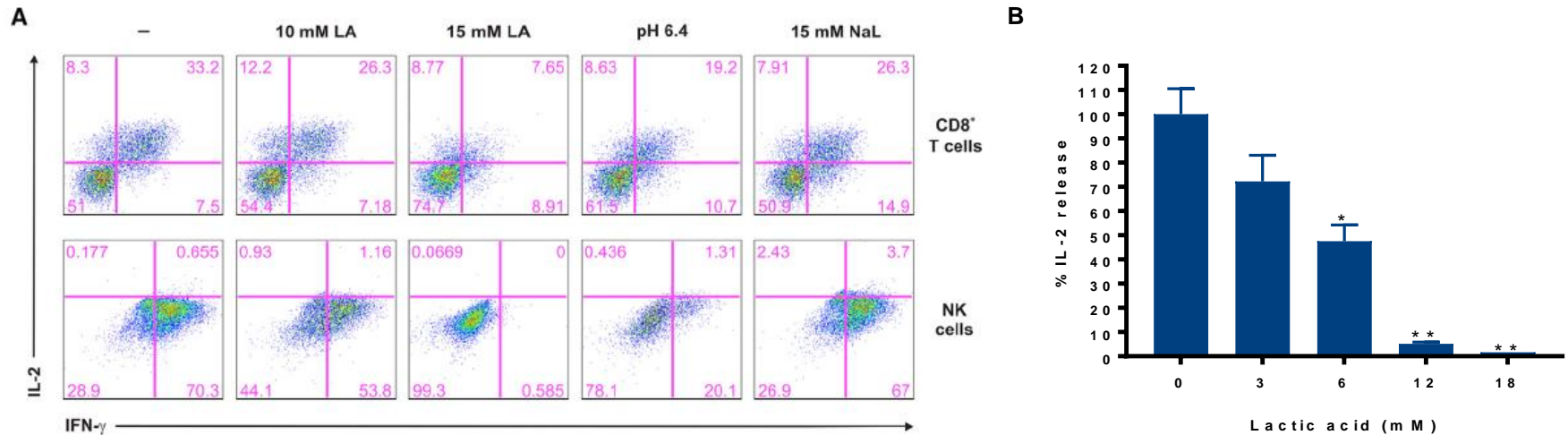


# Dysregulated pH is Emerging as a Hallmark of Cancer



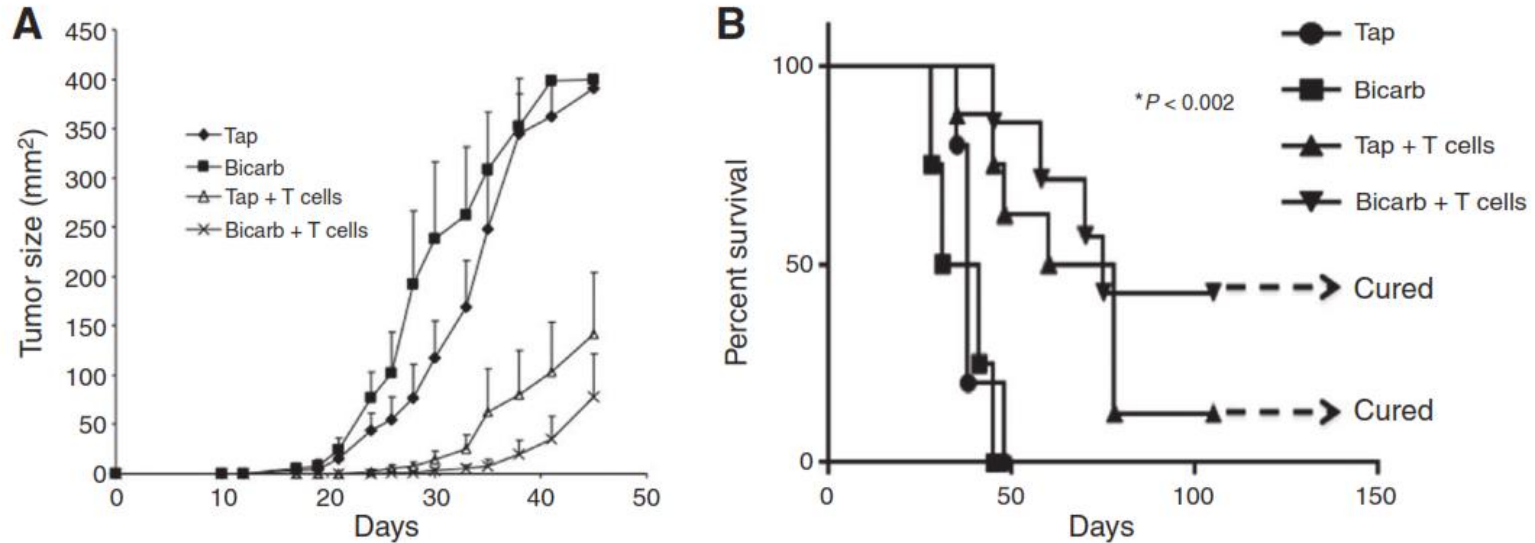
Nature Reviews | **Cancer**

# Suppression of Cytokine Production at Low pH



- **A.** Lactic acid (10, 15mM LA) or low pH but not sodium lactate (15mM NaL) suppress the production of IL-2 and IFN- $\gamma$  in activated mouse T and NK cells
- **B.** Similar results are observed with human Jurkat T cells (\*  $p < 0.05$  and \*\*  $p < 0.01$  as compared to the control)

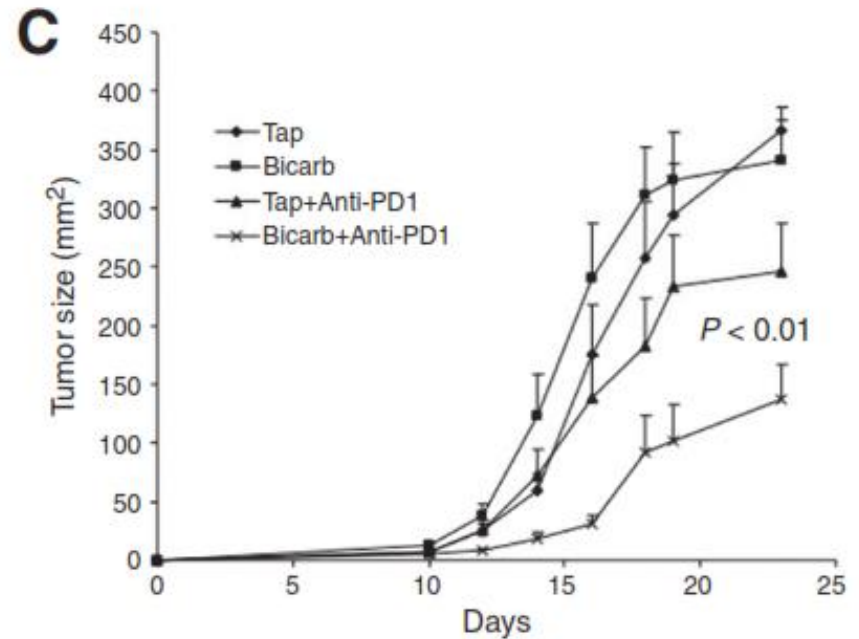
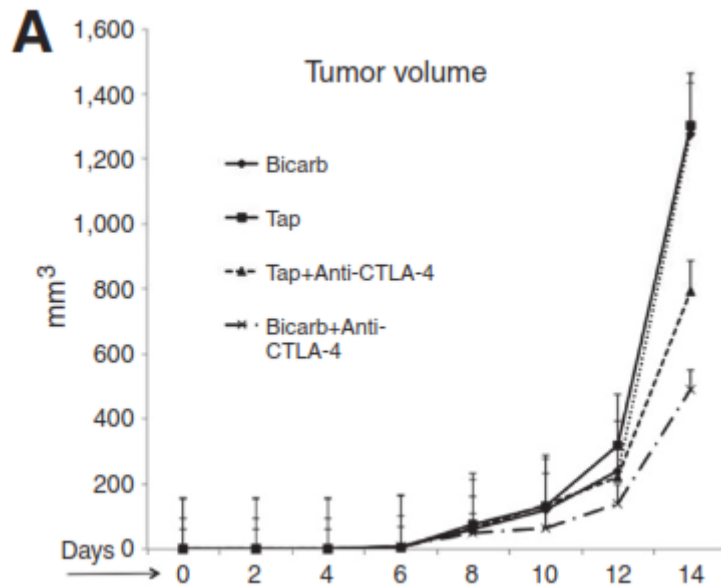
# Acidity Affects Adoptive T cell Therapy



Effect of bicarbonate on adoptive T-cell transfer. A, Tumor growth after adoptive transfer of T cells or controls in combination with or without buffer therapy. Group mean differences between T cells vs. T cells vs bicarbonate were not significant. However, there was a survival advantage, as shown in the survival curve in B

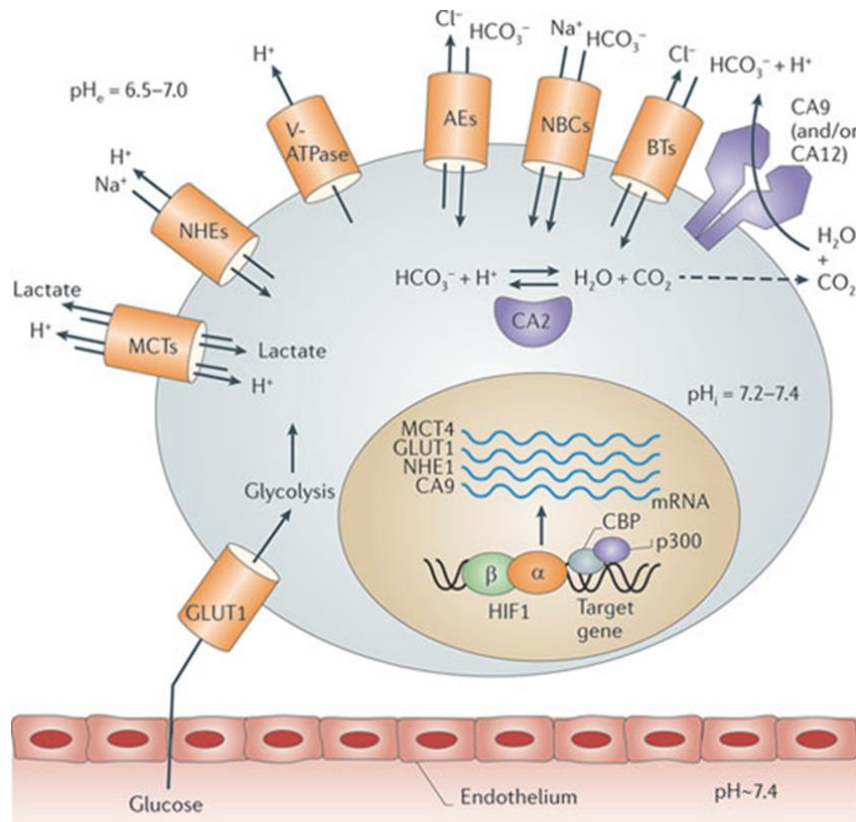


# Tumor pH and Check-Point Inhibitors



Buffer therapy enhances efficacy of anti-immunotherapy in B16 melanoma. C57BL/6

# Therapeutic Strategy Against Acidosis

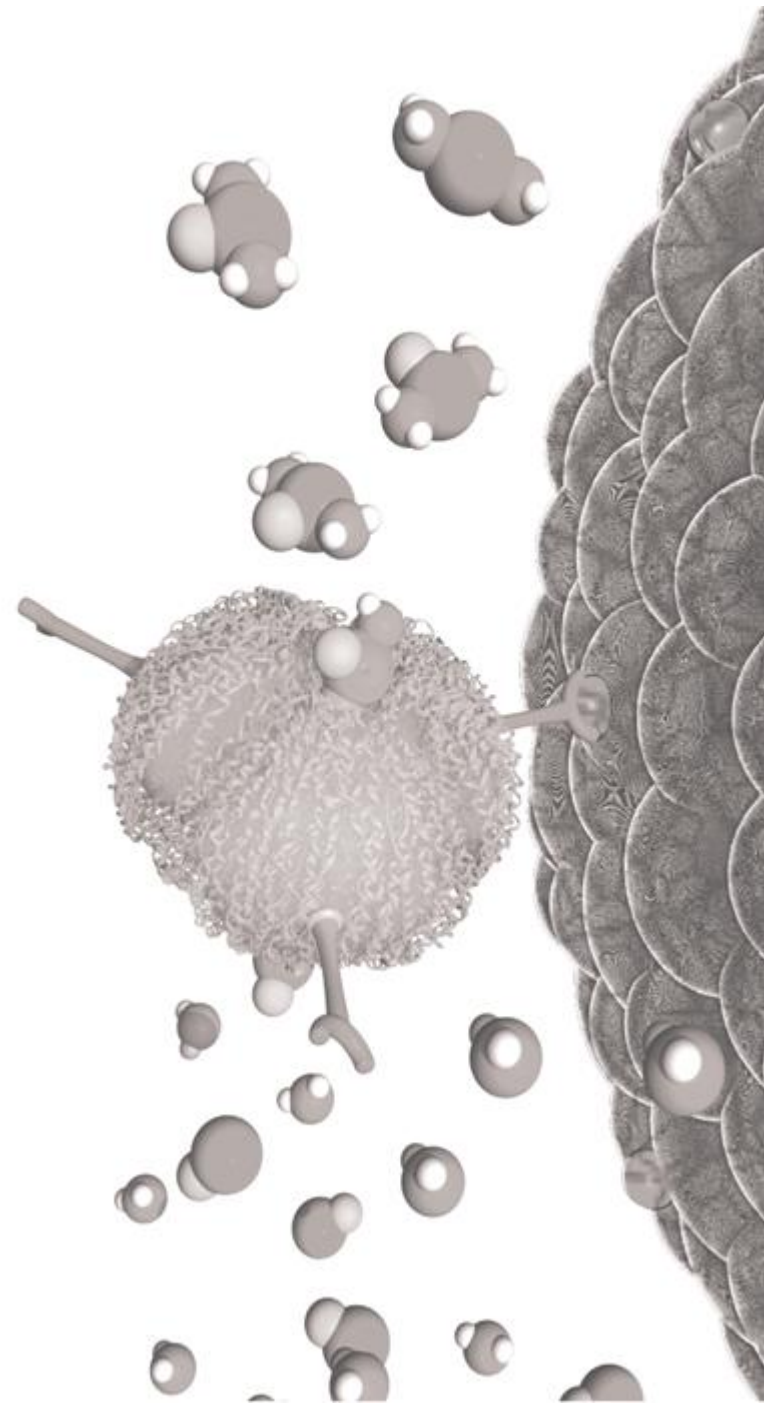


Nature Reviews | Drug Discovery

- Inhibitors (small molecules or antibodies) to target:
  - Carbonic anhydrase isoforms
  - V-ATPase inhibitors and proton pump inhibitors
  - Na<sup>+</sup>/HCO<sub>3</sub><sup>-</sup> co-transporters, anion exchangers and Na<sup>+</sup>/H<sup>+</sup> exchanger 1
  - Monocarboxylate transporter inhibitors
- Targeting a specific protein to combat Tumor acidity is not easily achieved; many of these regulators have multiple isoforms and some have critical function in cellular homeostasis
- Other strategy attempted includes systemic alkalization using sodium bicarbonate solution
- Helix's approach: targeted delivery of alkalizing enzyme

Targeting the Tumor Acidic Barrier

**DOS47**

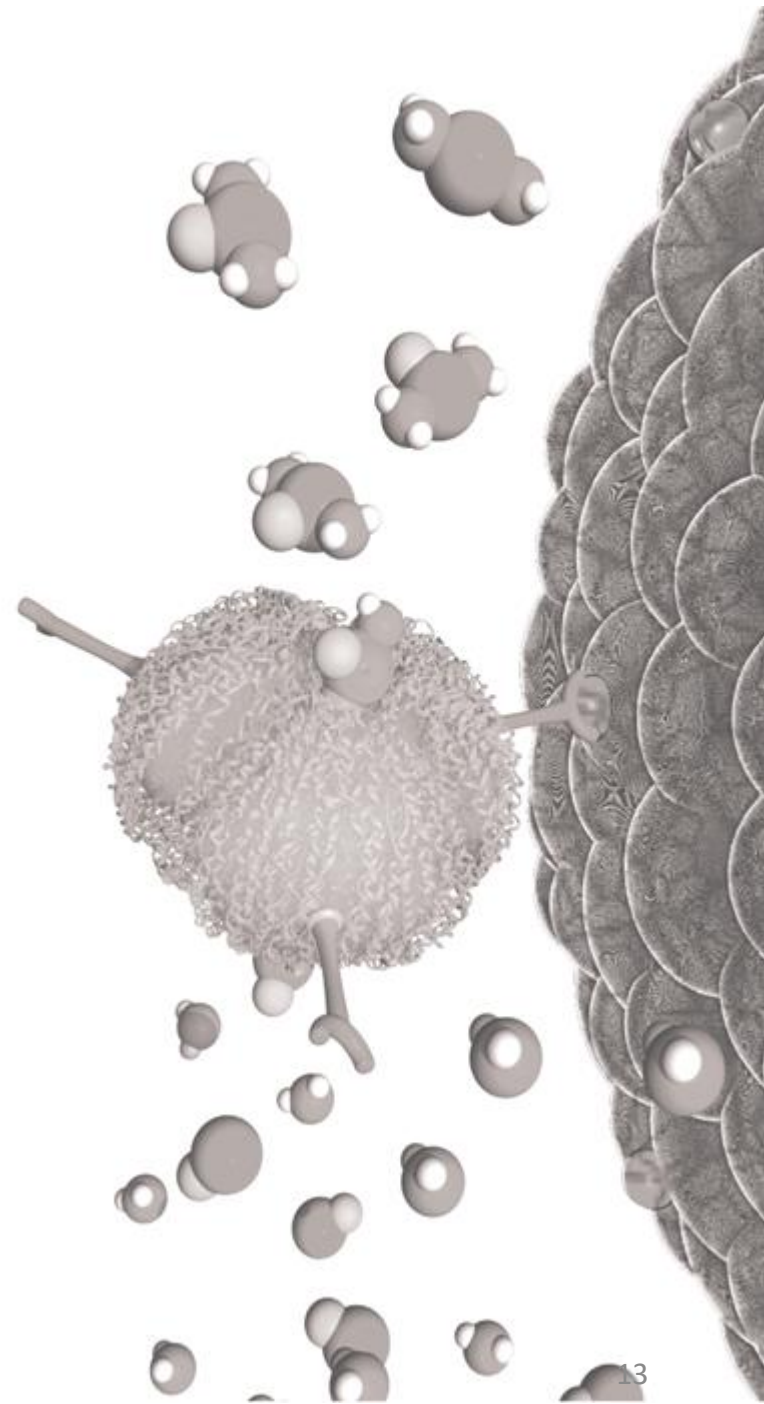


# DOS47

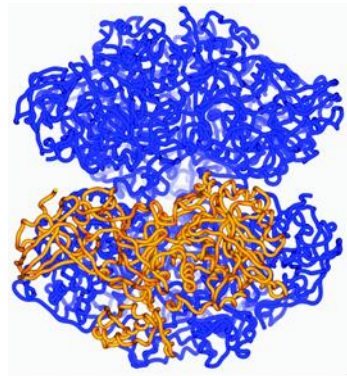
- DOS47 is a technology that changes the Tumor microenvironment from acidic to alkaline using the enzyme 'urease'
- Alkalinizing the Tumor has the potential to
  - To exert direct cytotoxic effect on Tumors
  - to increase the action of certain chemo-therapies
  - to correct an impaired immune microenvironment

Helix First Clinical Drug Candidate

# L-DOS47



# L-DOS47

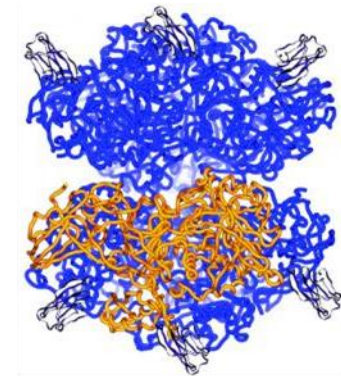


DOS47



SD antibody (L)

Cross-linker



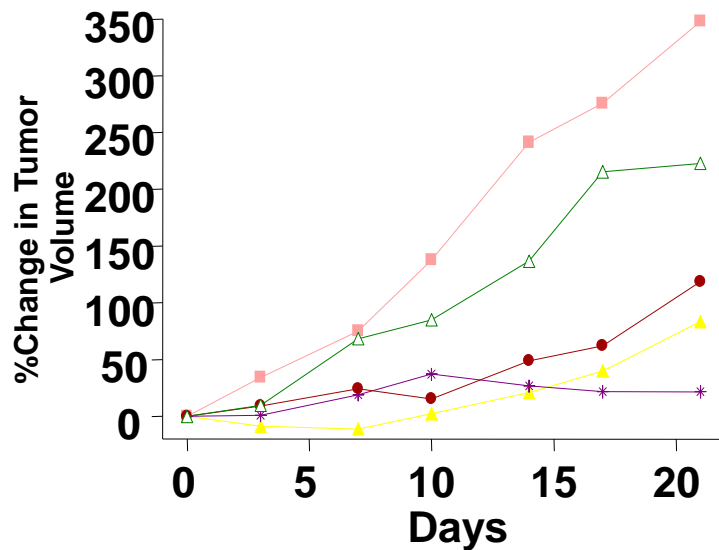
L-DOS47

- L-DOS47 is a conjugate of urease with a proprietary camelid single domain antibody specific for CEACAM6
- CEACAM6 is a cell surface Tumor antigen highly expressed on lung, colon, pancreatic and other cancer cells
- L-DOS47 is in clinical studies for the treatment of non-squamous, non-small cell lung cancer (NSCLC)

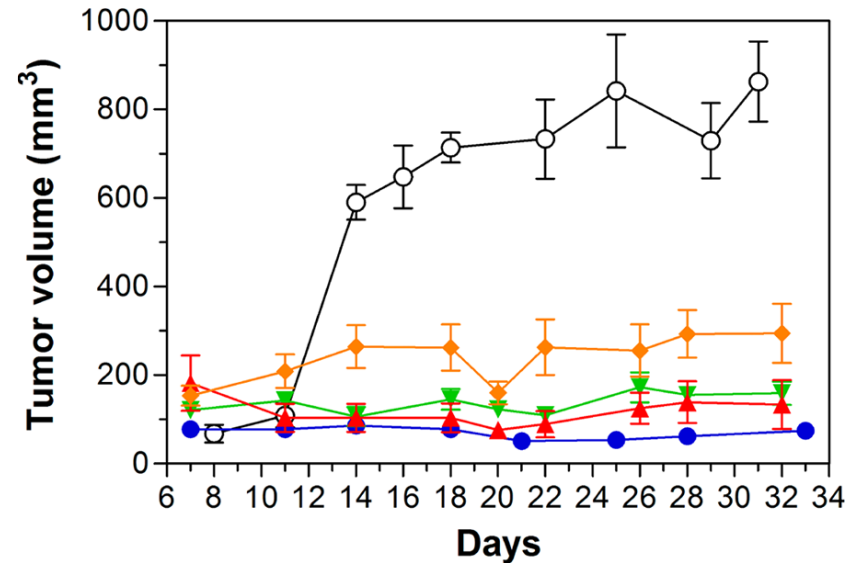
# L-DOS47 Binds to CEACAM6 Positive Cancer Patient Tissues

Samples	Tumor Tissue		Age-matched Normal Tissue
	Positive	Negative	Negative
Kidney carcinoma		12/12	12/12
Parathyroid adenoma		1/1	n/a
Placenta, umbilical cord, allantois		n/a	1/1
Myofibroblastic Tumor		1/1	n/a
Prostate carcinoma		4/4	4/4
Thyroid carcinoma		2/2	2/2
Pancreas adenocarcinoma	7/57 weak 8/57 v. weak	42/57	25/25
Neuroendocrine Tumors		9/9	n/a
Brain, heart muscle, testis, spleen		n/a	30/30
Testis - teratoma and seminoma		3/3	3/3
Parotis Tumor		1/1	1/1
Cervix squamous carcinoma		2/2	n/a
Thymoma		2/2	n/a
Colon adenocarcinoma	14/24 weak	10/24	24/24
- lymph node metastasis		3/3	
Breast adenocarcinoma		13/13	13/13
- lymph node metastasis		2/2	
Leiomyoma - lung metastasis		1/1	n/a
Ovary carcinoma		4/4	n/a
Bladder carcinoma		42/42	36/36
- lymph node metastasis	1/1 strong		
- squamous carcinoma metastasis		2/2	
Lung - small cell carcinoma		1/1	5/5
- adenocarcinoma	5/5 strong		
Stomach adenocarcinoma		3/3	3/3
Liver carcinoma		4/4	4/4
Soft tissue Tumors		3/3	n/a
Melanoma		48/48	18/18
- metastasis		18/18	

# L-DOS47 Inhibits Tumor Growth in Lung and Pancreatic Models



A549 (lung)  
L-DOS47 (10,20,35U/kg)  
Cisplatin control

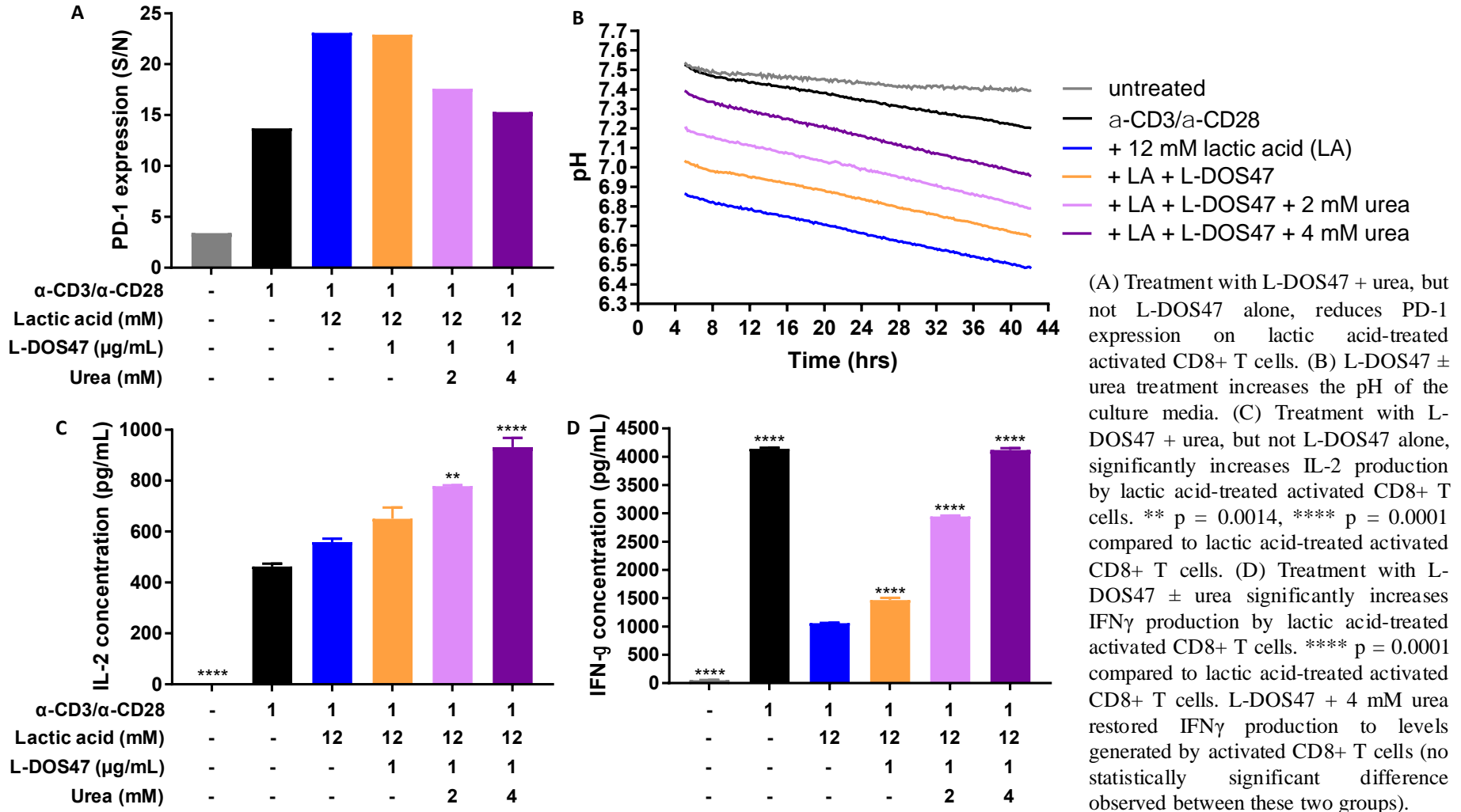


BxPC3 (Pancreatic)  
L-DOS47 (7,35,175ug/kg)  
Paclitaxel control

Tian et. al. Bioconjug Chem. 2015 Jun  
17;26(6):1144-55



# L-DOS47 Restores Acid Induced Cytokine Suppression



# L-DOS47 Clinical Update

- L-DOS47 Phase I / II Trial (LDOS002)
  - Monotherapy in advanced NSCLC patients
  - Phase I and stage 1 of Phase II completed
- L-DOS47 Phase I with Expansion Trial (LDOS001)
  - Combination with pemetrexed and carboplatin in NSCLC patients (1st line)
  - Currently enrolling
- L-DOS47 Phase II (LDOS003) randomized trial
  - Combination with vinorelbine and cisplatin NSCLC patients (1<sup>st</sup> line)
  - Expect to enroll Q1 2018

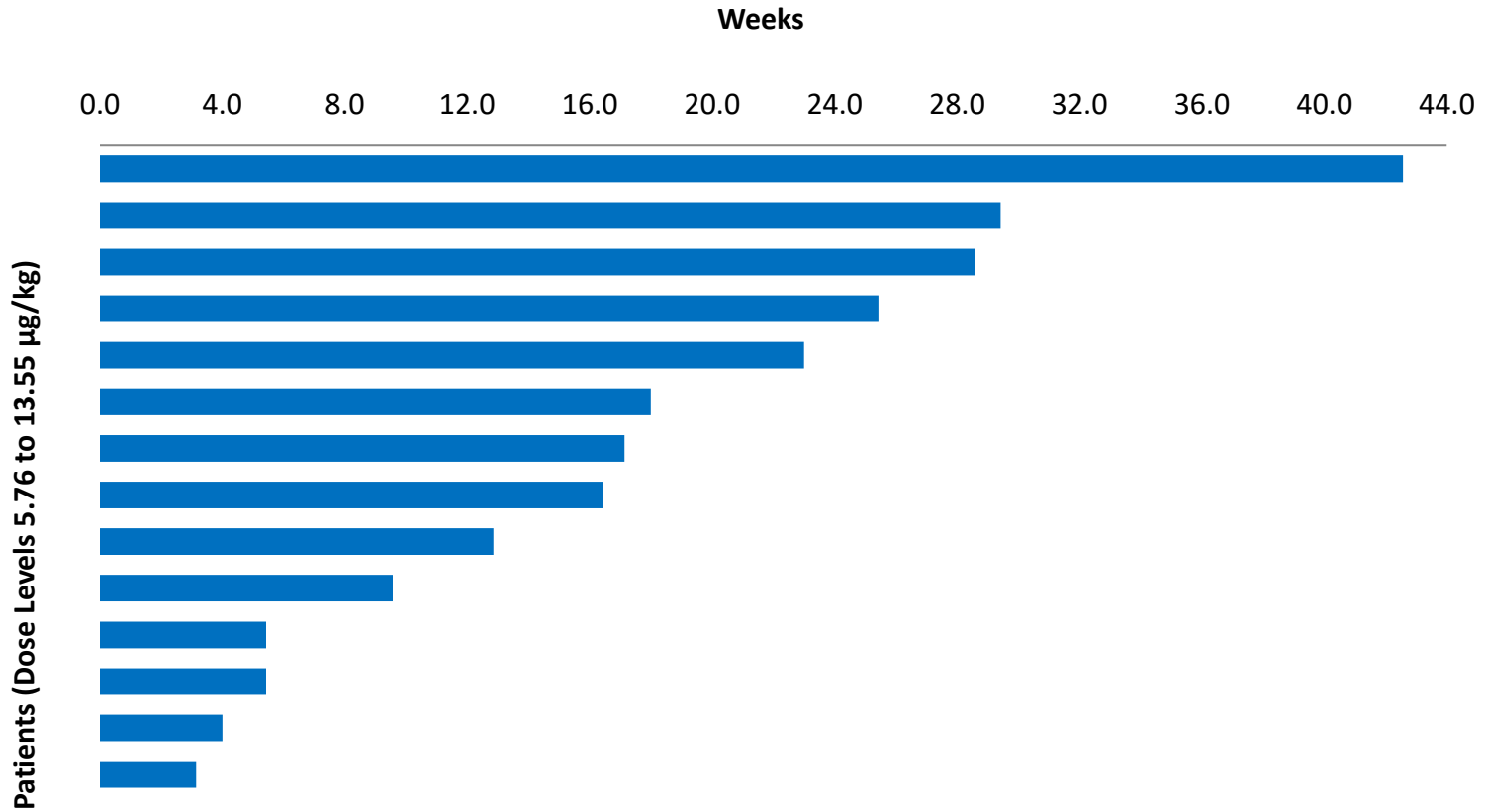
## L-DOS47 Monotherapy Phase I / II Trial (LDOS002)

- Monotherapy treatment protocol in NSCLC patients that have not responded to other treatments;
- Stage IIIb / IV, metastatic, and progression after several lines of chemo, rad, surgery or chemo-naïve patients that have refused other lines of therapy;
- Dosed once a week for 2 weeks, 1 week rest (3-week cycle);
- Conducted in 5 Centers in Poland :The Maria Sklodowska-Curie Institute of Oncology, Military Institute of Health Institute, Mazovian Centre of Pulmonary Diseases and Tuberculosis in Otwock, Department of Oncology, Poznan University of Medical Sciences, National Tuberculosis and Lung Diseases Research Institute
- Phase II dosing schedule is twice a week for 2 weeks follow by 1 week rest (3-week cycle);

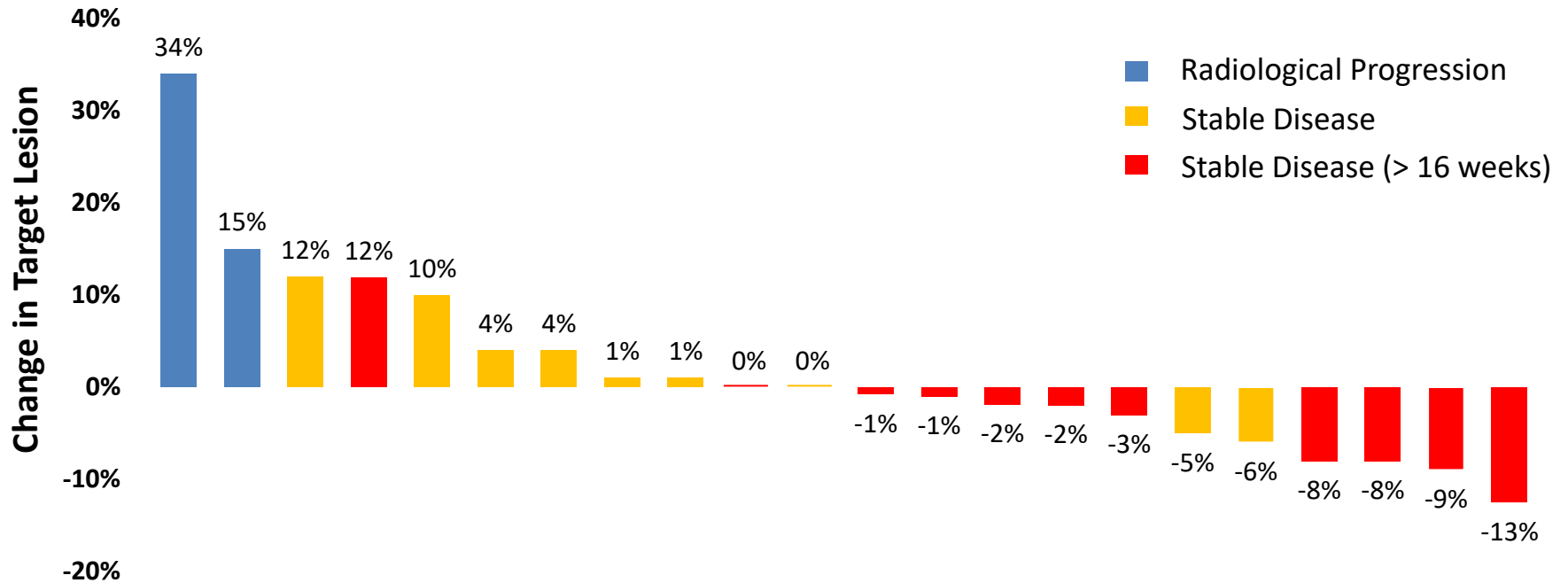
# L-DOS47 Monotherapy (Cohorts 13 to 16) LDOS002

## Swimmer Plot

### Response Evaluable Population



# Waterfall Plot: Target Lesion Response (Cohorts 9 - 16)



# LDOS002 Monotherapy Phase I Summary

- Currently has completed 16 cohorts
- MTD at 13.55  $\mu\text{g}/\text{kg}$
- One Dose Limiting Toxicity (DLT);
- No safety issues beyond those observed in pre-clinical toxicology studies or expected in the population of patients being studied;
- Immunogenicity consistent with what was observed pre-clinically;

## LDOS002 Monotherapy Phase II (Stage 1) Summary

- Non-randomised study using Simon's optimal two-stage design
- Patients were dosed twice a week for 2 weeks follow by 1 week rest (3-week cycle) at 13.55 µg/kg
- 21 patients were successfully dosed with 19 considered evaluable at stage 1
- L-DOS47 was well tolerated despite the intensified schedule
- Since no objective response was observed under this new schedule, company decided not to continue enrollment to focus resources on other combination trials

# L-DOS47 PEM/CARBO Phase I (LDOS001)

- Combination therapy in first-line treatment of NSCLC:
  - Stage IIIb / IV, metastatic, and chemo-naïve;
- Patients receive 4 cycles of combination treatment with L-DOS47 + pemetrexed/carboplatin
- Patients who have not progressed following 4 cycles of combination treatment and who have not experienced unacceptable toxicity can have the option to receive weekly L-DOS47
- Seven (7) dose escalation cohorts (0.59, 0.78, 1.5, 3.0, 6.0, 9.0, and 12.0 µg/kg) were planned
- Two cohorts are now completed
- Based on LDOS002 monotherapy safety data, FDA accepted an accelerated dose design of “1+2” up to 6µg/kg followed by a standard “3+3” design for the final two dosing cohorts, 9 and 12 µg/kg, respectively
- Nine (9) additional patients to be enrolled to complete dose escalation if there are no dose limiting toxicity (DLT) or other safety concerns



## LDOS001 PEM/CARBO Phase I Cohort 1 and 2 Summary

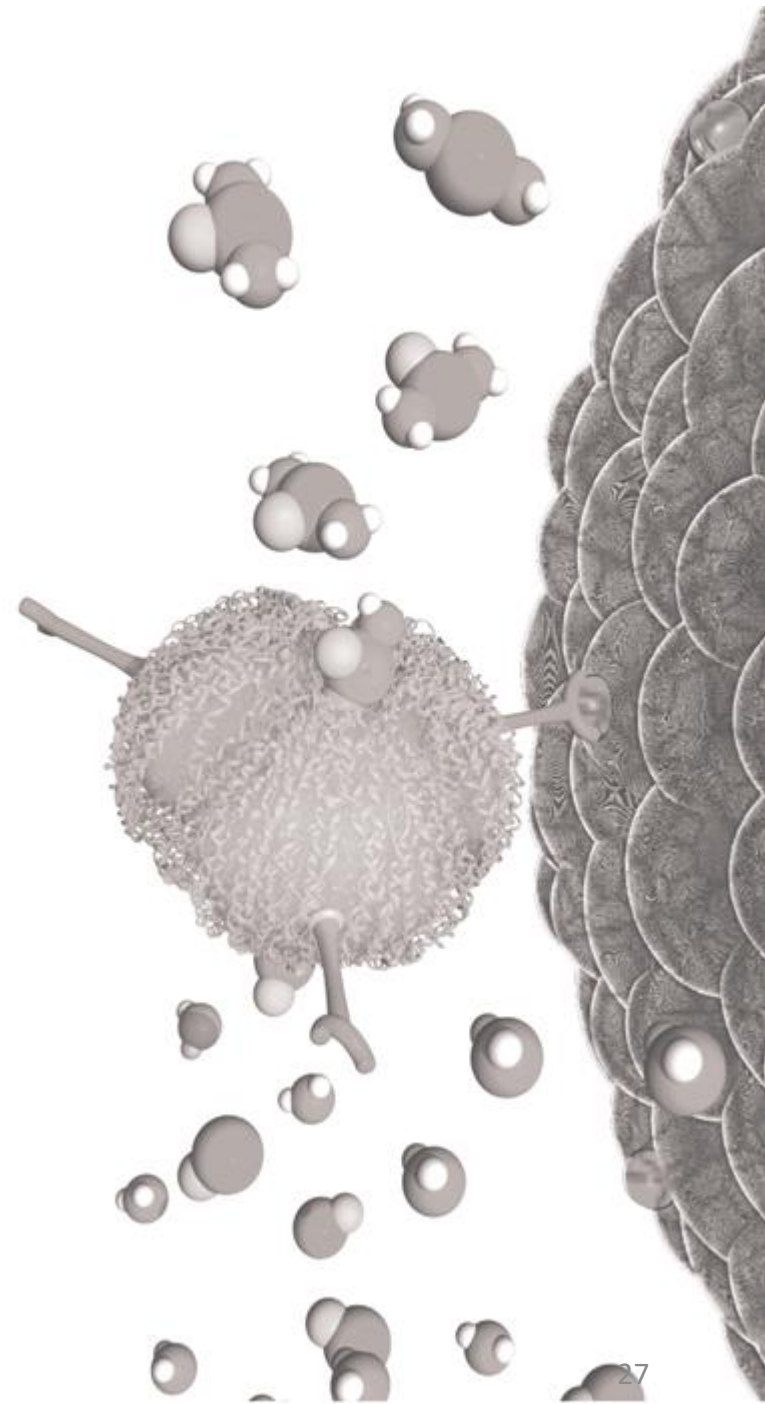
- Three patients dosed at 0.59 µg/kg (cohort 1); six patients dosed at 0.78 µg/kg (cohort 2)
- One patient in cohort 1 with PR (36%) and 5.9 months PFS with L-DOS47 alone in the maintenance phase
- One patient in cohort 2 with stable disease and 13.3 months PFS with L-DOS47 alone in the maintenance phase
- Three patients in cohort 2 with PR (40%, 44% and 86%) and up to 12.4 months PFS with L-DOS47 alone in the maintenance phase

# LDOS003 VIN/CIS Randomized Phase II Study

- Phase IIb, open-label, randomized study in patients with metastatic lung adenocarcinoma.
- In Part 1 of the study (dose escalation), patients will receive eight (8) doses of L-DOS47 over four (4) cycles.
- On Day 1 and Day 8 of each cycle, L-DOS47 will be administered 24 hours before vinorelbine/cisplatin.
- Once the maximum tolerated dose of L-DOS47 as an adjunct to vinorelbine/cisplatin is determined, patients in Part 2 of the study (Randomized Treatment) will be randomly assigned to receive L-DOS47 in combination with vinorelbine/cisplatin or vinorelbine/cisplatin alone.
- A number sites have been identified in Poland and the Ukraine. Competent Authority and Ethics Committee approvals are pending with patient enrollment anticipated in the first quarter of 2018

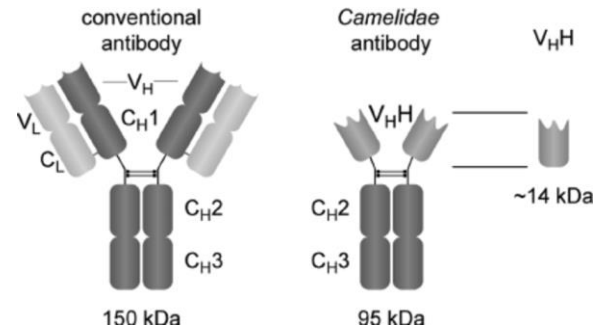
SINGLE DOMAIN ANTIBODY

**CAR-T**

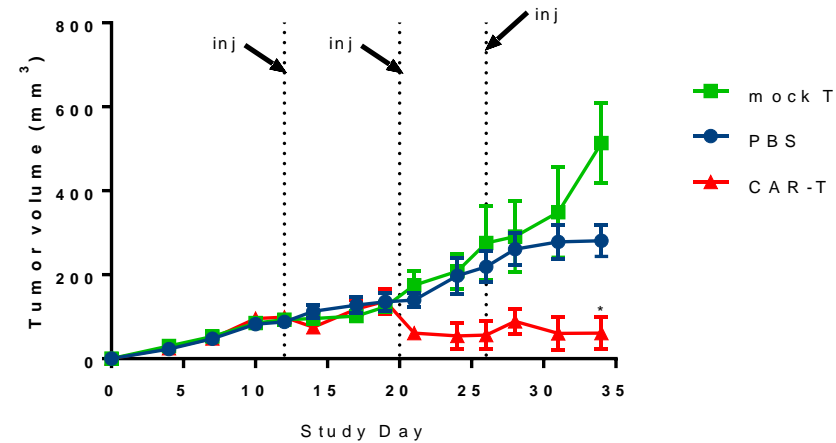
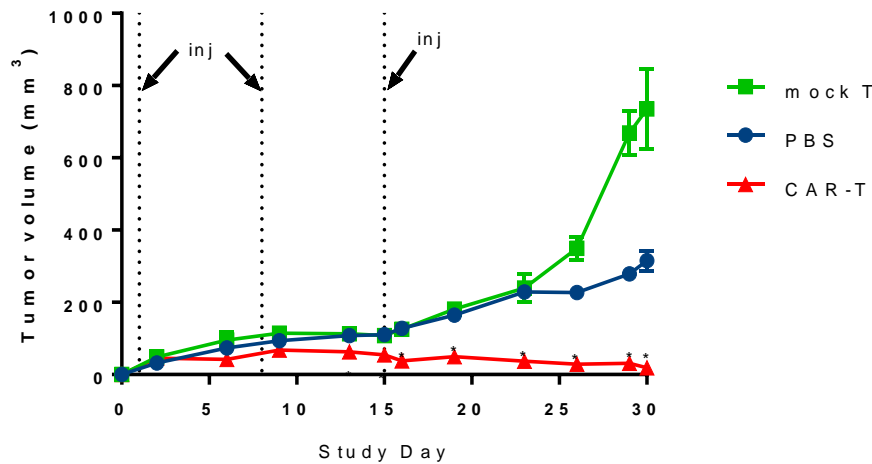


# VHH Based CAR-T

- VHH domains
  - High specificity and affinity
  - Amendable to humanization
  - Target ‘hidden epitope’
  - Easily adapted to CAR construct
- Helix is applying know-how in tumour microenvironment therapeutic development and in VHH antibody design to generate a variety of novel CAR-Ts
  - Solid tumour (POC): anti-CEACAM6 and VEGFR2
  - Hematological cancer: CD19 and others



# Anti-CEACAM6 CAR-T in vivo study In Pancreatic Cancer



- Anti-CEACAM6 CAR-T cells are highly effective against the BxPC3 pancreatic adenocarcinoma xenograft
- VHH CAR-T very effective in a prevention model (top left)
- VHH CAR-T very effective in an 'established' tumour model

# Helix CAR-T Initiatives

- Design novel cell based therapeutics based on unique know-how of tumor microenvironment and VHH single domain antibodies
- New Collaboration with ProMab Biotechnologies, Inc to accelerate CAR-T development with next-generation technologies
- Plans are being reviewed for a possible clinical filing in 2018

# Executive Summary

- Helix develops novel anti-cancer therapies stemming from its proprietary technology platforms
- L-DOS47 is a unique tumour microenvironment immuno-conjugate drug
- L-DOS47 is well tolerated as a single agent in late stage NSCLC patients
- L-DOS47 is being tested in combination with pemetrexed and carboplatin for NSCLC patients with very encouraging early data
- L-DOS47 will be tested in a randomized controlled study in combination of vinorelbine and cisplatin
- Helix CAR-T program may enter the clinic in 2018
- Helix welcomes discussion of partnership and collaboration

# Acknowledgement

- The Maria Sklodowska-Curie Institute of Oncology Poland
- Military Institute of Health Institute Poland
- Mazovian Centre of Pulmonary Diseases and Tuberculosis in Otwock Poland
- Poznan University of Medical Sciences Poland
- National Tuberculosis and Lung Diseases Research Institute Poland
- MD Anderson Cancer Center USA
- Penn State S. Hershey Medical Center USA
- University Hospital Case Medical Center USA
- National Research Council Canada