LDOS002

Phase I/II dose escalation study of immunoconjugate L-DOS47 as a monotherapy in non-squamous non-small cell lung cancer patients

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CLINICAL SESSION 8. PRECISION/PERSONALIZATION OF TARGETED THERAPY

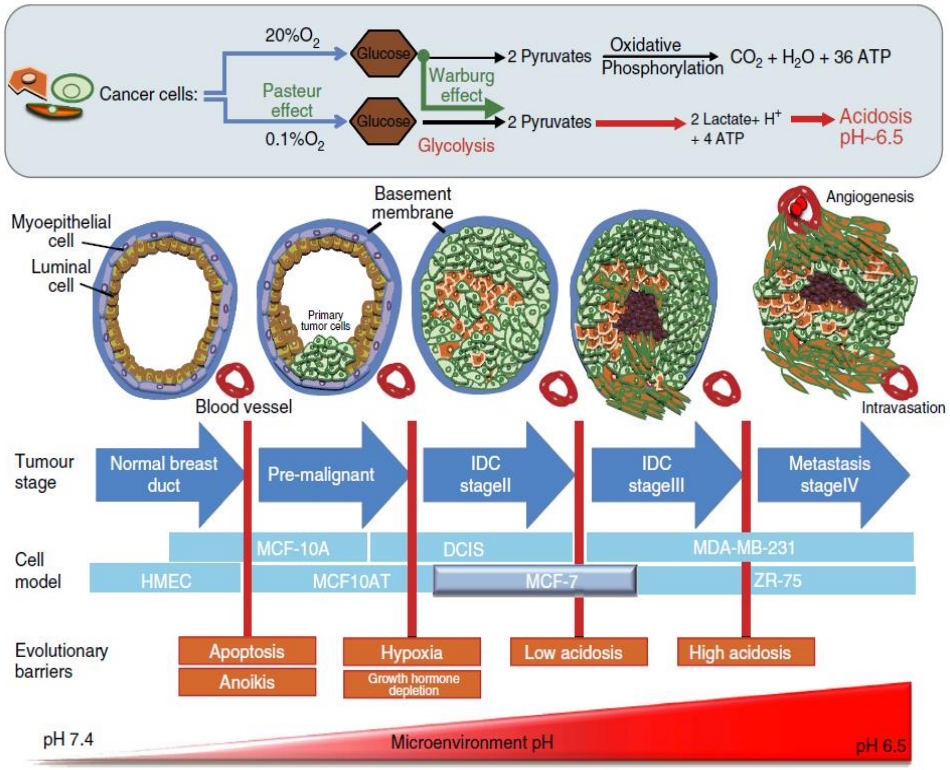
(KWO17-00034-2017-01)

March 24th, 2017

Summary

- L-DOS47 is safe and well tolerated at doses up to 13.55µg/kg.
- At doses between 5.76 to 13.55µg/kg, 53% of patients in the response evaluable population were progression free greater than 16 weeks.
- L-DOS47 may be effective an treatment of CEACAM6 expressing tumors in combination with other therapies that may benefit from the pH-modulating effects of L-DOS47.
- Phase II monotherapy study currently ongoing in Poland.

Acidosis and Hypoxia

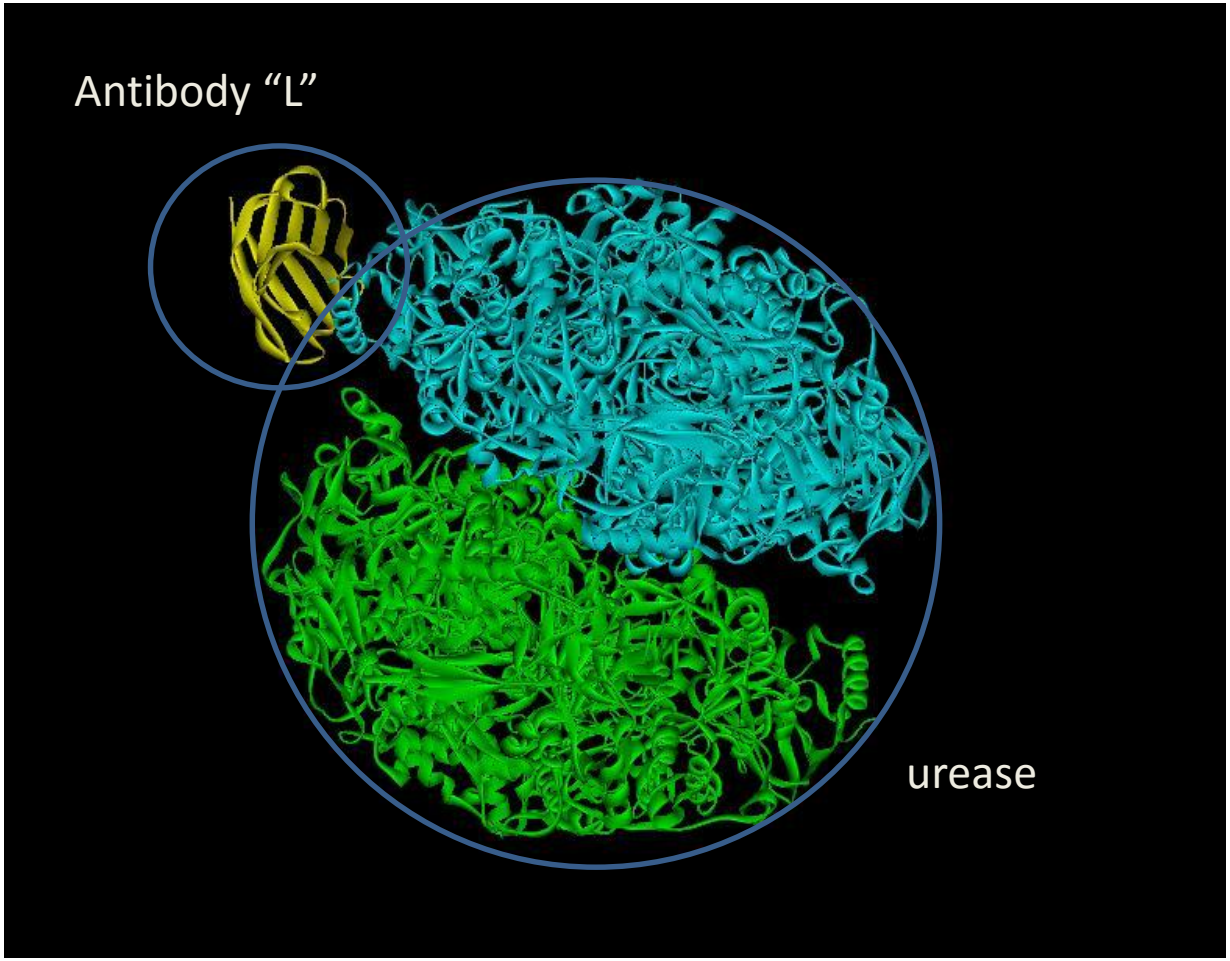


- Hypoxia, poor vasculature and increased flux of carbons through fermentative glycolysis leads to extracellular acidosis in solid tumors (Pasteur effect).
- Cancer cells can maintain the glycolytic phenotype even in the presence of oxygen (Warburg effect) causing further and constant acidification of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

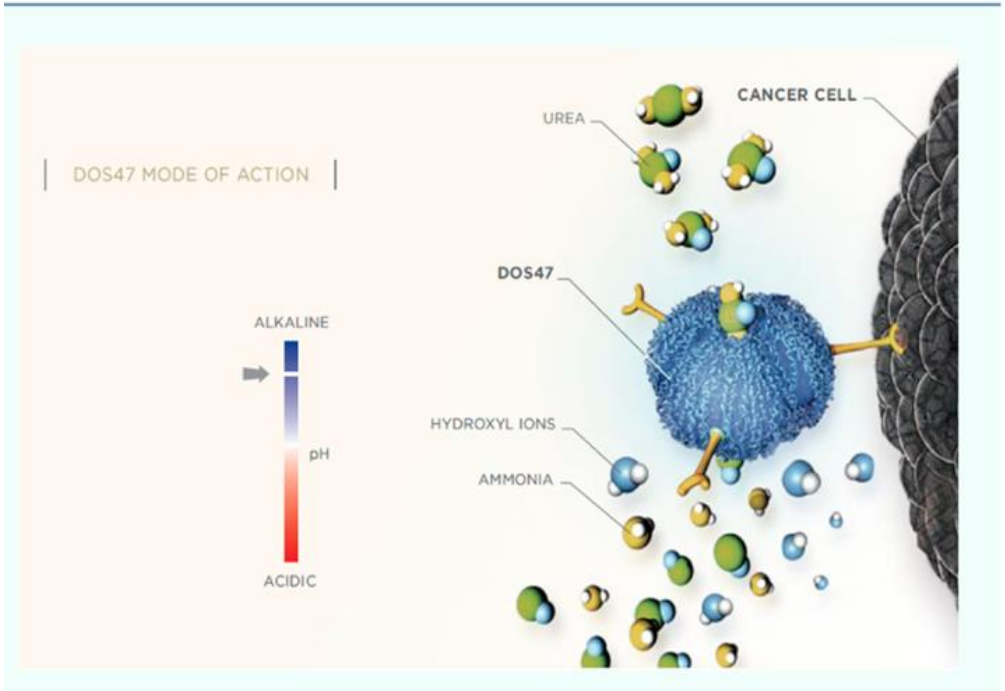
This figure illustrates how acidosis increases during cancer progression from DCIS to Stage IV metastasis and how acid adapted cells (orange cells) become more aggressive and invasive (breast cancer model).

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

L-DOS47



L-DOS47 Mechanism of Action



- L-DOS47 is an immune conjugate that binds lung cancer cells specifically
- L-DOS47 converts urea into ammonia and raises pH
- Acidity reversal may augment and repair immune function

L-DOS47 action in combination of other immune-related therapeutics (e.g. checkpoint inhibitors) are currently being planned

LDOS002 Primary Objectives

- Phase I
  - To define the MTD of multiple doses of L-DOS47 administered i.v. to patient with non-squamous non-small cell lung cancer when given monotherapy. MTD is defined as the highest dose level which ≤ 2 dose limiting toxicities are observed in patients in a dosing cohort ≤ 3 weeks after commencing L-DOS47 treatment
- Phase II
  - To make a preliminary assessment of the efficacy of L-DOS47 in patients with non-squamous non-small cell lung cancer

LDOS002 Study Design

- Dose Escalation, modified Fibonacci, 3 + 3 Design
- The starting dose of L-DOS47 for the first cohort will be 0.12 µg/kg; further possible dose levels that may be assessed are 0.21, 0.33, 0.46, 0.59, 0.78, 1.04, 1.38, 1.84, 2.45, 3.26, 4.33, 5.76, 7.66, 10.19 and 13.55µg/kg.
- A dose-limiting toxicity (DLT) defined as any NCI CTCAE v4.0, ≥ Grade 3 non-hematologic and any ≥ Grade 4 hematologic AE that is at least possibly related to L-DOS47 occurring ≤ 3 weeks after commencing L-DOS47 treatment.
- L-DOS47 is administered weekly over 14 days followed by 7 days rest (one treatment cycle is 3 weeks).

LDOS002 Patient Inclusion

- Male or female aged ≥ 18 years old;
- Have histologically confirmed non-squamous NSCLC;
- Refractory Stage IIIb or IV non-squamous NSCLC (or chemo-naïve who refused standard therapy);
- Have at least a single measurable lesion in accordance with the RECIST v1.1 criteria;
- Eastern Cooperative Oncology Group (ECOG) performance status: 0-2.
- Have a life expectancy of ≥ 3 months
- Have adequate organ function

Study Accrual and Patient Disposition

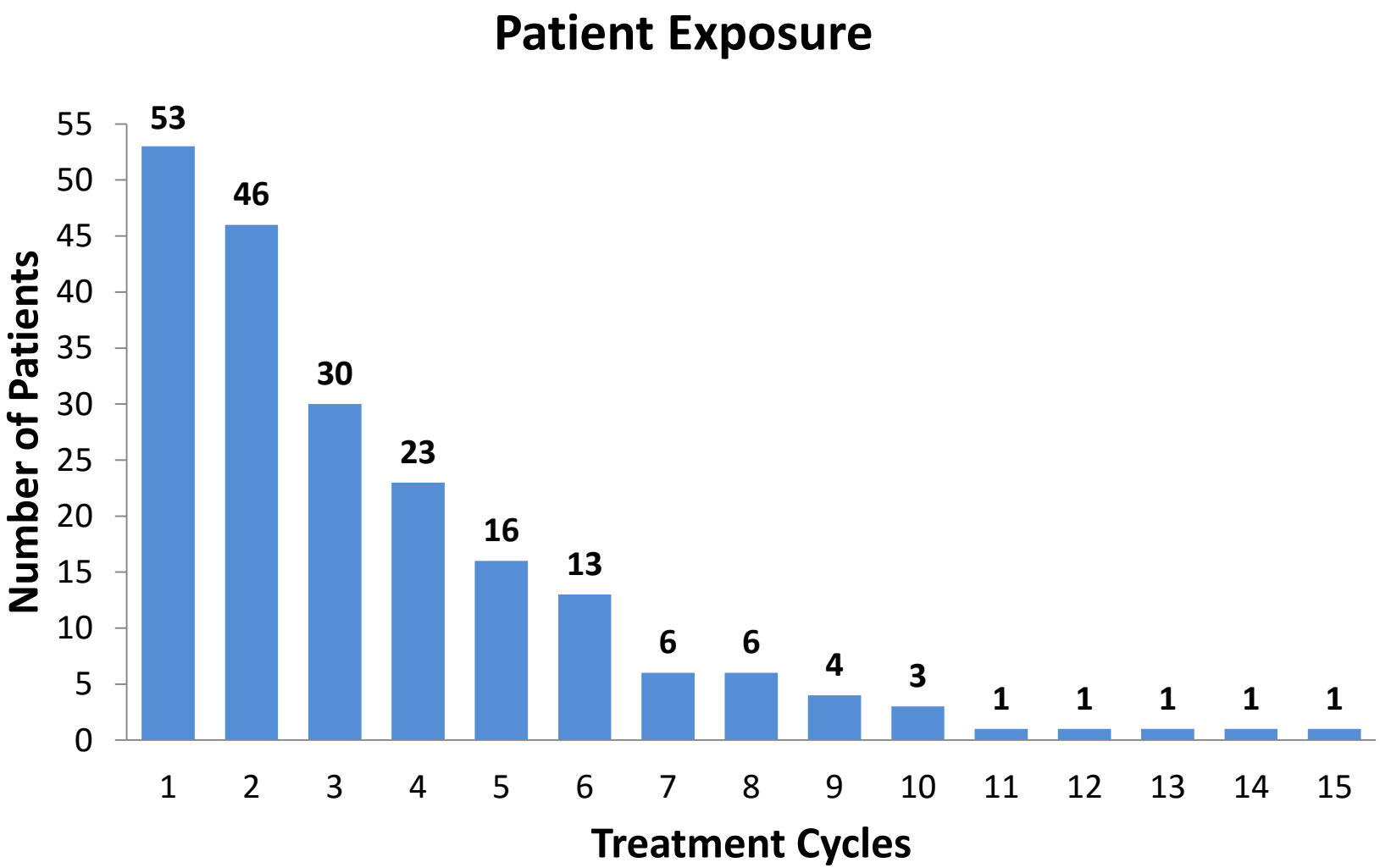
Study Status [n (%)]	Total
Screened	*90*
Screen Failures	*35*
Treated	*55*
Completed 4 Cycles	*21*
Additional Cycles	*16*

Demography and Baseline Characteristics

Parameters	Total
Age	N = 55 Mean = 60.9 Min, Max (34, 83)
Weight (kg)	N = 55 Mean = 68.4 Min, Max (48, 95)
Gender Male Female	 *N = 29 (53%)* *N = 26 (47%)*
Race Caucasian	 *N = 55 (100%)*
Stage IIIB IV	 *N = 7 (13%)* *N = 48 (87%)*
ECOG 0 1 2	*N = 13 (24%)* *N = 40 (73%)* *N = 2 (3%)*

Prior Cancer Therapies

Parameters	Total (n=55)
Prior Therapy	*None = 8 (16%)* *Chemo/Target = 47 (85%)* *Radiation = 26 (47%)* *Surgery = 17 (31%)*
Prior Chemo/Target Therapy	*Adjuvant = 4 (7%)* *Locally Advanced = 3 (5%)* *Metastatic Disease = 37 (67%)* *Palliative = 3 (5%)* *Unknown = 4 (7%)*
Best Response	*Unknown = 4 (8.5%)* *CR = 1 (4%)* *PR = 14 (30%)* *Stable = 20 (43%)* *PD = 8 (17%)*


Patient Exposure
Number of Patients
55
50
45
40
35
30
25
20
15
10
5
0
53
46
30
23
16
13
6
6
4
3
1
1
1
1
1
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
Treatment Cycles

Number of Patients Retreated, Dose Delay and Dose Modification

Parameter	Total	(n=55)
No. of patients Retreated	*53[1,2]*	*96%*
No. of patients with Dose Delay	*11*	*20%*
No. of patients with Dose Modification	*0*	*0%*
Treatment Duration (Cycles)	*190*	*3.5 Cycles*
Study Drug Compliance (%)	*390*	*96%*

1. ***Patient 05-055 – Patient decision to withdraw***
2. ***Patient 05-059 – Protocol violation (low hemoglobin)***

Patients with Treatment Emergent AEs ≥ 5%

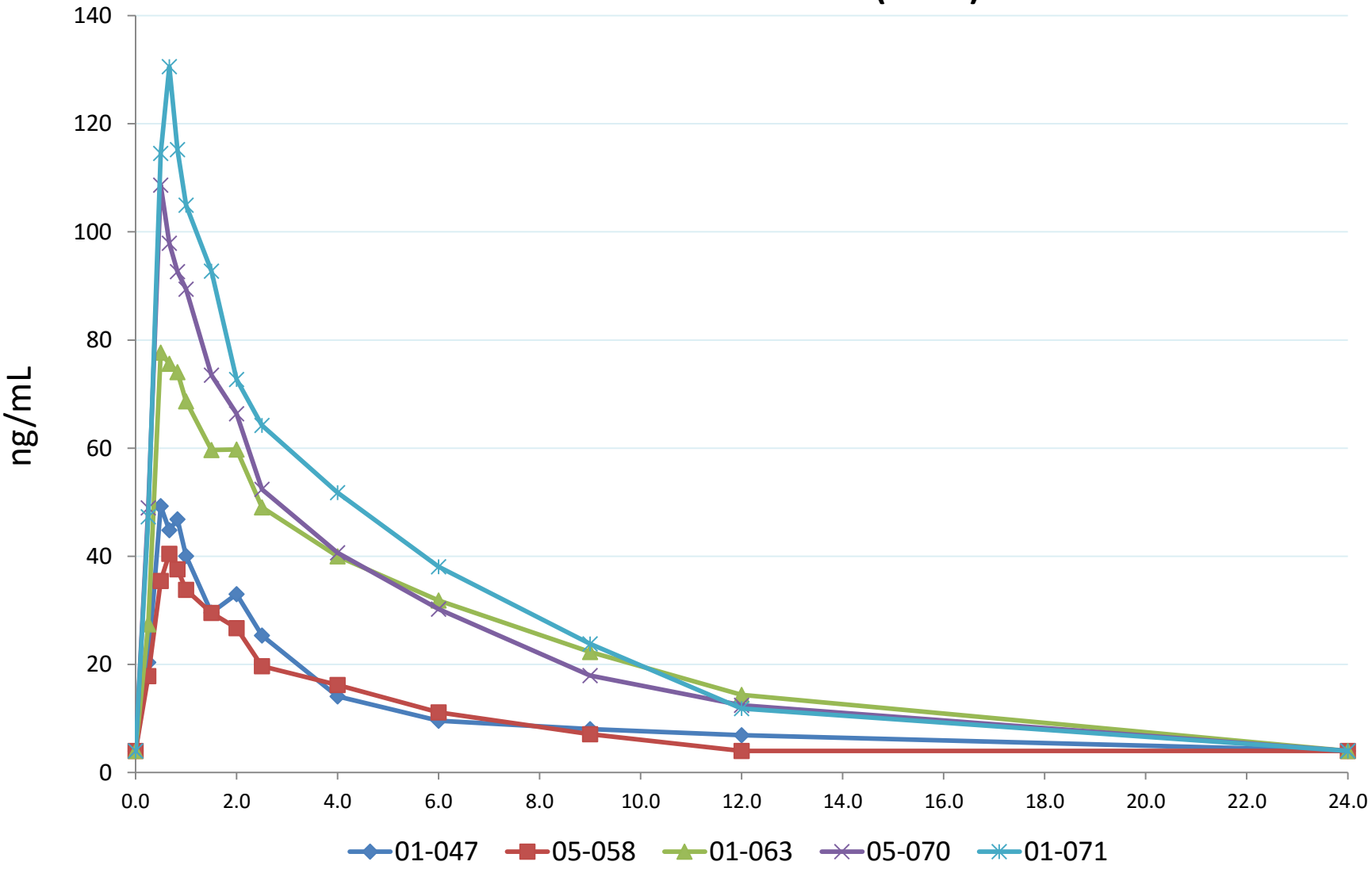
System Organ Class Preferred Term	Toxicity Grade (No. of pts)					Cohort(s)	No. of pts (N=55)	(%) pts
	1	2	3	4	5			
Blood and Lymphatic System Disorders						1,10,11,12,15	5	9%
Anemia		1	4			1,10,11,12,15	5	9%
Gastrointestinal Disorder						1,2,3,4,6,10,11,12,14,15	11	20%
Abdominal pain	2	1				1,2,11	3	5%
Nausea	3	5				2,3,6,10,11,14,15	8	16%
Vomiting	4		1			6,10,11,15	5	9%
General Disorder and Admin Site Cond						1,2,3,4,5,6,7,8,9,10,11,13,15,16	20	36%
Asthenia	2	2	1			5,7,10,11,16	5	9%
Edema Peripheral	1	2				1,3,11	3	5%
Fatigue	4	3				1,2,6,8,13,15	7	13%
General physical health deterioration		2		1	1	1,2,8,11	4	7%
Non-cardiac chest pain	2	1				1,7	3	5%
Infections and infestations						1,2,3,7,9,14,15	7	13%
Pneumonia		2	2			1,2,7,14	4	7%
Metabolism and Nutritional Disorder						1,6,7,10,11,15	7	13%
Decreased Appetite	1	4				6,7,10,11,15	5	9%
Musculoskeletal and connective tissue						3,4,6,7,10,13,15	8	16%
Bone pain		2		1		10,13,15	3	5%
Neoplasms benign, malignant						1,8,9,10,11,12	7	13%
Non-small cell lung cancer				1	4	8,9,10,11	5	9%
Psychiatric disorders						1,2,5,10,11,12,15	8	16%
Insomnia	3	3				1,2,11,12,15	6	11%
Respiratory, thoracic and mediastinal						1,2,4,5,7,8,10,11,12,13,14,15,16	21	38%
Cough	4	2				1,4,13,15,16	6	11%
Dyspnea	4	7	1	2	1	1,2,4,5,7,10,12,13,14,15	15	27%

Patients with Treatment Emergent Serious Adverse Events

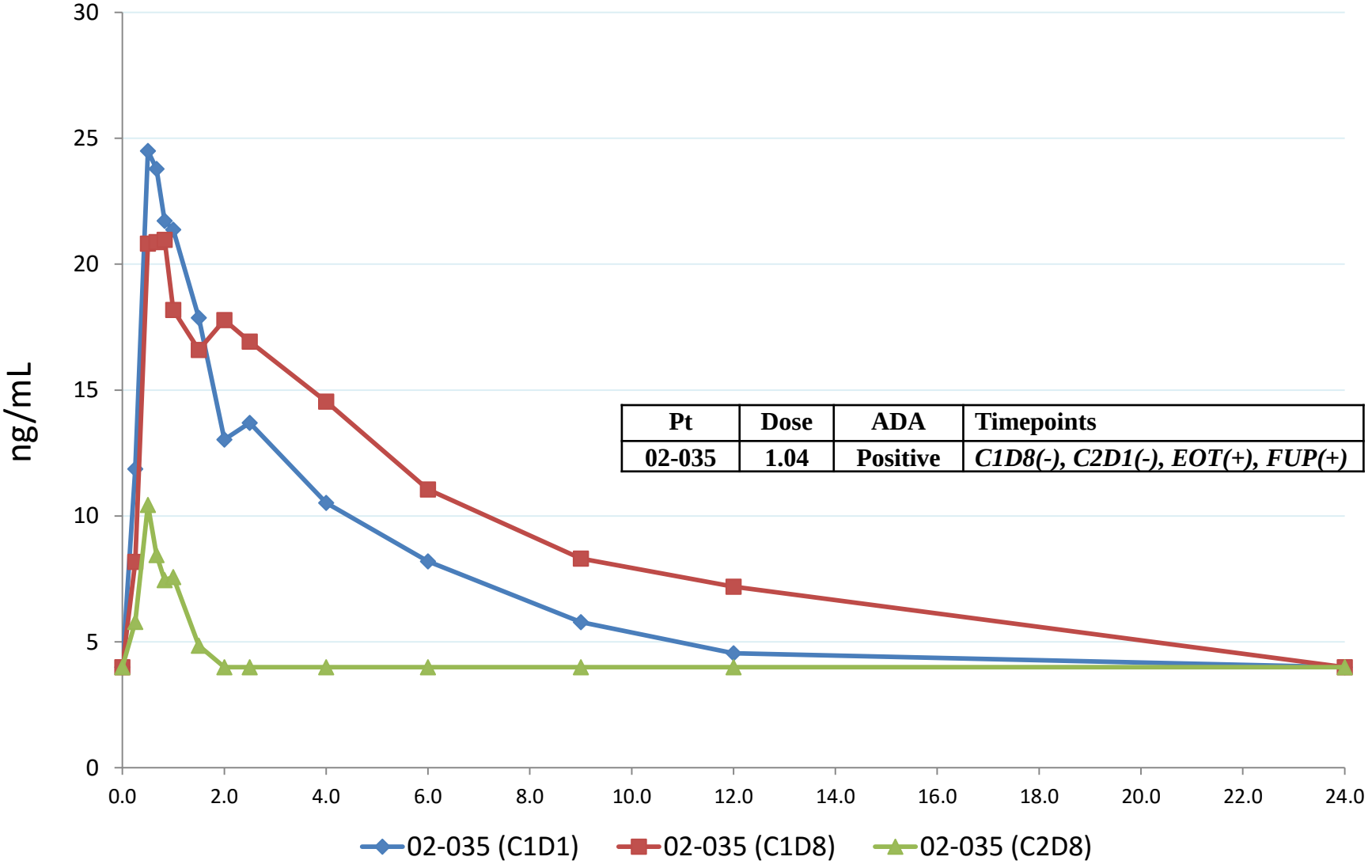
System Organ Class Preferred Term	Toxicity Grade (No. of pts) 1	2	3	4	5	Cohort(s)	No. of pts (N=55)	(%) pts
Blood and Lymphatic System Disorders						1,8,11,15	4	7%
Anemia			3			1,8,11,15	4	7%
Gastrointestinal Disorder						10	1	2%
Vomiting			1			10	1	2%
General Disorder and Admin Site Conditions						1,8,9,11	4	7%
General physical health deterioration				1	1	8,11	2	4%
Pain			1			9	1	2%
Sudden Death					1	1	1	2%
Infections and infestations						1,2,7,8	4	7%
Pneumonia		1	2			1,2,7,8	4	7%
Upper Respiratory Tract Infection			1			1	1	2%
Injury, poisoning and procedural complications						1,10	2	4%
Contrast media reaction			1			1	1	2%
Humerus Fracture		1				10	1	2%
Investigations						11	1	2%
ECOG performance status improved			1			11	1	2%
Musculoskeletal and connective tissue disorders						13	1	2%
Bone pain				1		13	1	2%
Neoplasms benign, malignant and unspecified						7,8,9,10,11	6	11%
Non-small cell lung cancer				1	5	7,8,9,10,11	6	11%
Renal and urinary disorders						12	1	2%
Renal failure acute			1			12	1	2%
Respiratory, thoracic and mediastinal disorders						1,7,13,14,15	5	9%
Dyspnea		1	1	2	1	1,7,13,14,15	5	9%
Pleural effusion			1			7	1	2%

Concentration Time Curves

Cohorts 9 to 13 (C1D1)

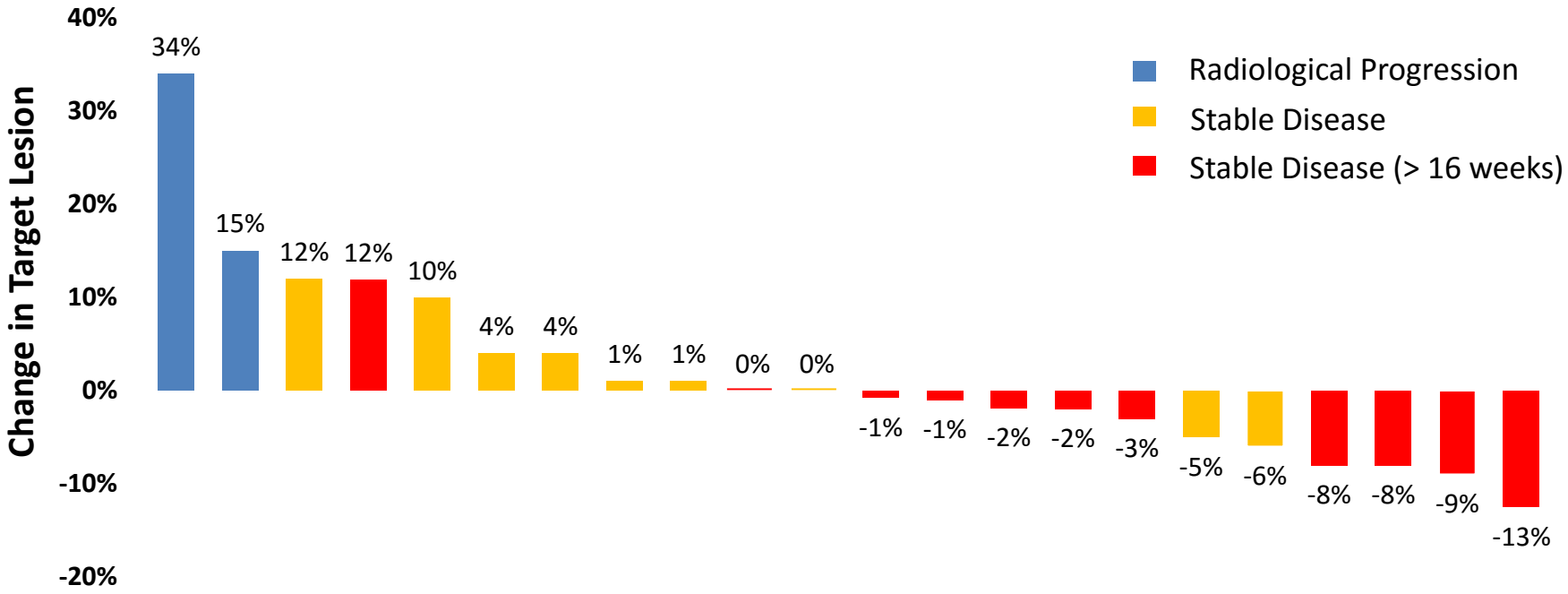


Effect of anti-LDOS47 antibodies on PK parameters



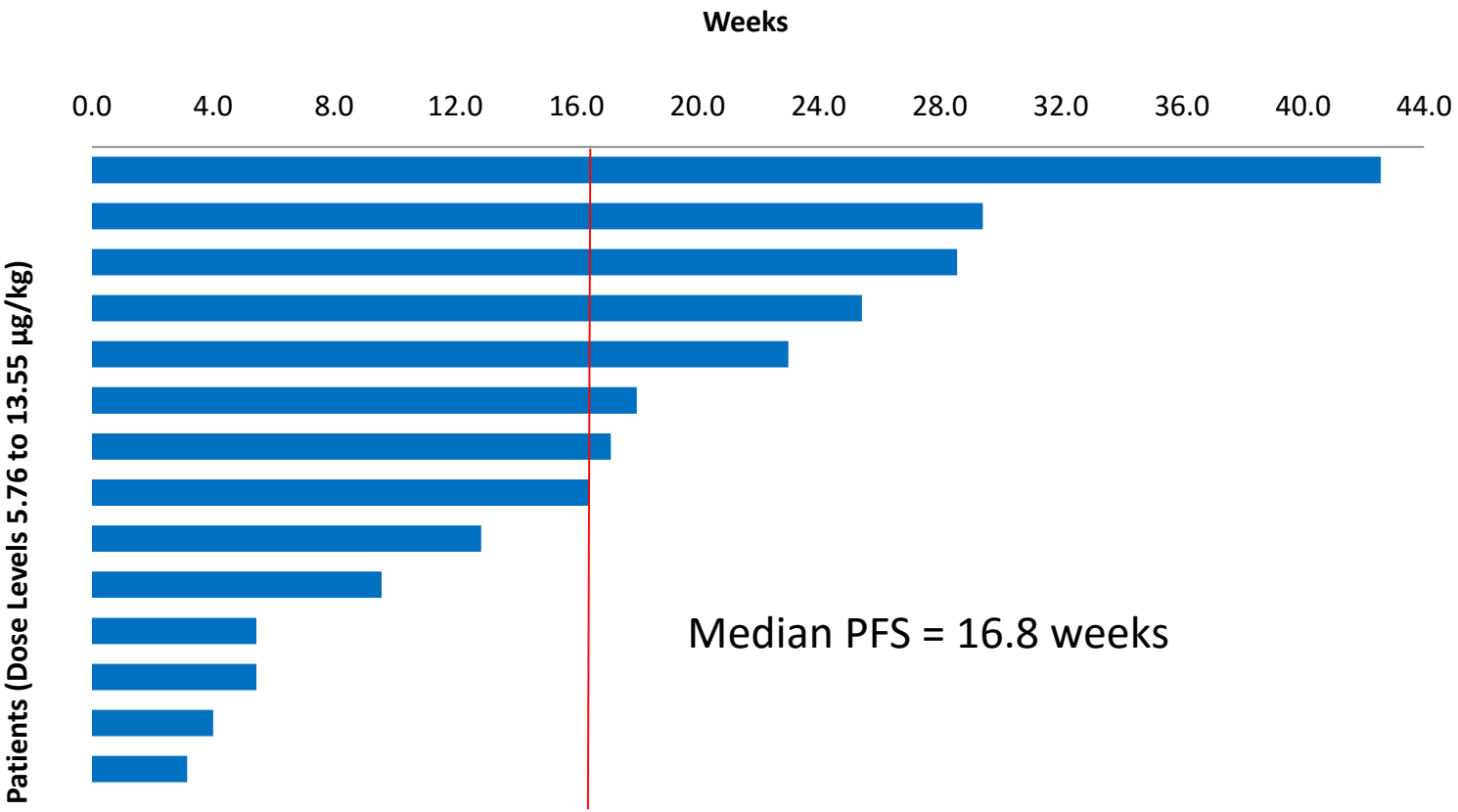
Pt	Dose	ADA	Timepoints
02-035	1.04	Positive	*C1D8(-), C2D1(-), EOT(+), FUP(+)*

Waterfall Plot: Target Lesion Response (Cohorts 9 to 16)

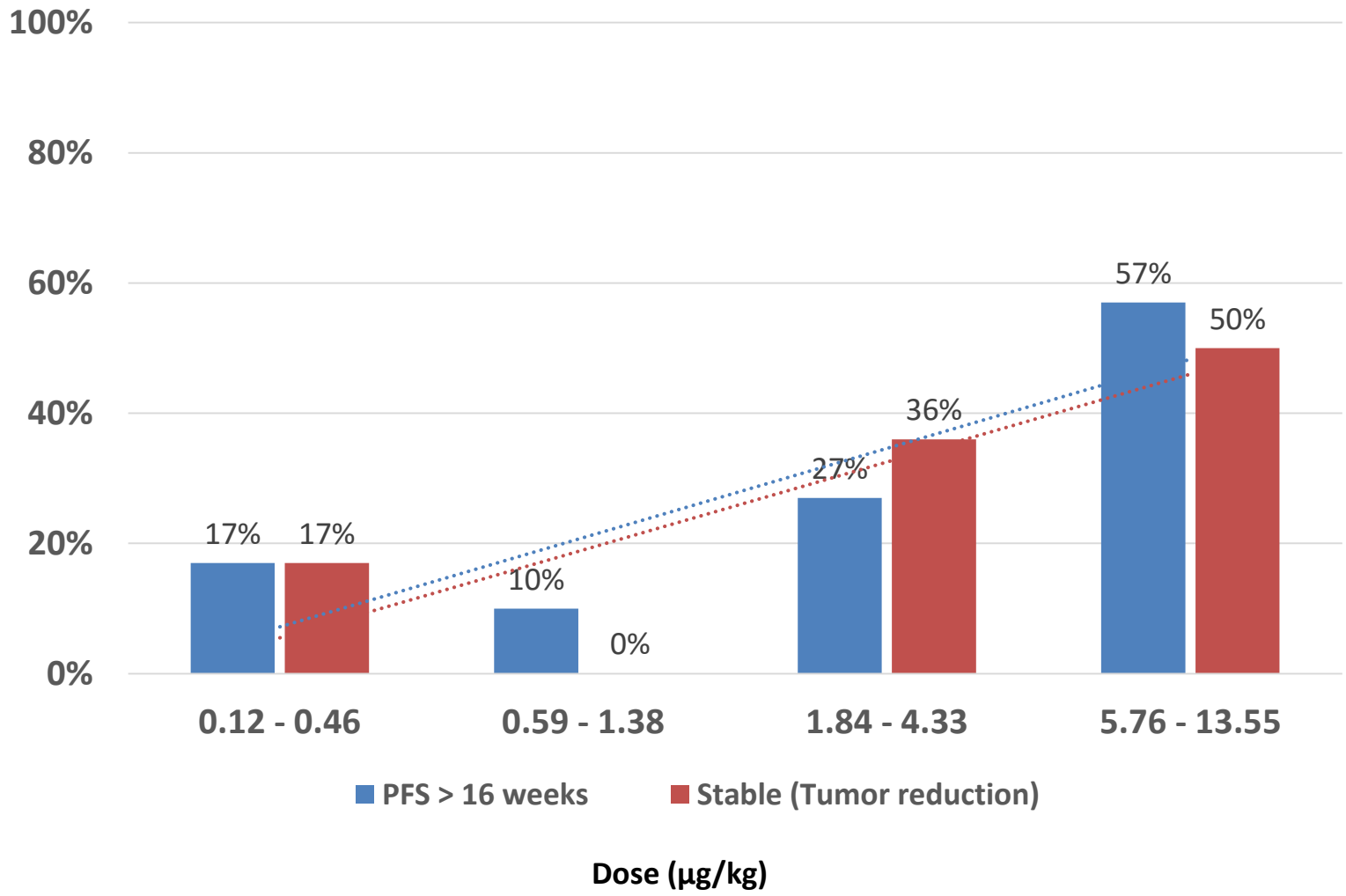


L-DOS47 Monotherapy (Cohorts 13 to 16) LDOS002
Swimmer Plot

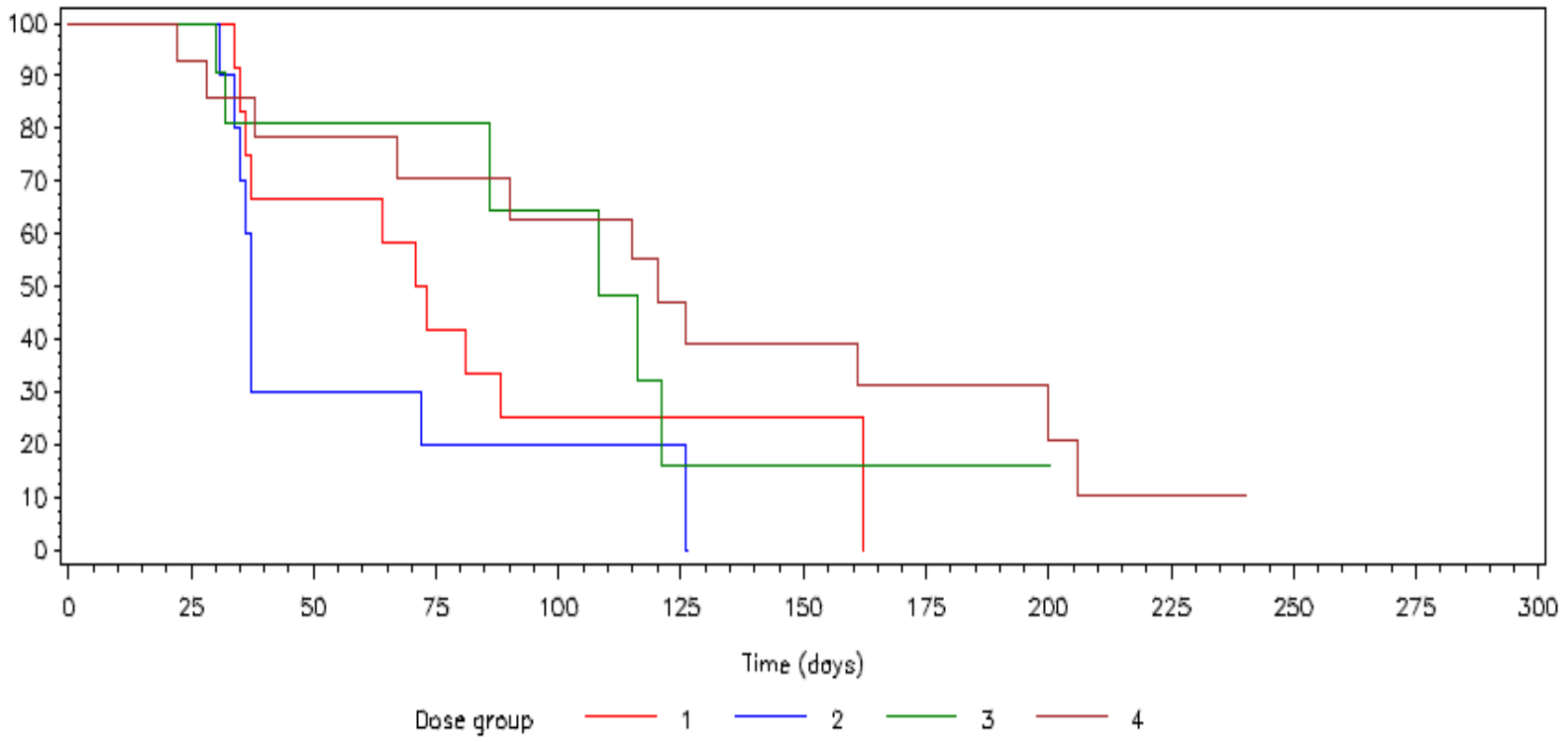
Response Evaluable Population



L-DOS47 Dose – Response
(Response Evaluable Population)



Kaplan Meir Plot by dose group
(Response Evaluable Population)



1. Dose groups: 1 = 0.12 ug/kg – 0.46 ug/kg, 2 = 0.59 ug/kg – 1.38 ug/kg, 3 = 1.84 ug/kg – 4.33 ug/kg, 4 = 5.76 ug/kg – 13.55 ug/kg
2. Progression–free survival is derived as [minimum (Date of PD or Date of Death or Date of Last Response Assessment) – Study Day 1)] +1
Date of Death is used if a responding patient has not progressed but died during the treatment period.
Date of Last Response Assessment is used if a responding patient has not progressed and has not died during the treatment period.
3. Censored = 0 if patient has been known to meet criteria of Progressive Disease or to have died (any cause); Censored = 1 otherwise

Safety Evaluation

- One DLT reported to date in Cohort 13 (5.76 µg/kg) – spinal pain (grade 4);
- Mild infusion reactions reported as early as Cohort 2 (0.21 µg/kg) – chills, dyspnea;
- Adverse reactions reported consistent with what was observed pre-clinically – dyspnea, fatigue, vomiting, decreased appetite;
- Unexpected adverse reactions not reported pre-clinically – anemia, AV block, erythroderma, infusion site reactions;
- Excluding the reported DLT and anemia (grade 3), adverse reactions were mild and patients recovered soon after onset;
- Many of the adverse events reported to-date expected for the population under study;
- L-DOS47 is safe and well tolerated at doses up to 13.55µg/kg.

Efficacy Evaluation

- Exposure response trend observed over the 16 dose levels studied;
- Fewer patients with radiological progression following Cohort 8 (1.38 µg/kg);
- At doses between 5.76 to 13.55µg/kg, 53% of patients in the response evaluable population were progression free greater than 16 weeks.

Conclusion

- L-DOS47 may be effective an treatment of CEACAM6 expressing tumors in combination with other therapies that may benefit from the pH-modulating effects of L-DOS47.

Phase II Study Design

- Same patient population;
- The protocol was amended to take the cohort 16 dose (13.55µg/kg) into Phase II;
- L-DOS47 currently administered twice weekly over 14 days (Days 1, 4, 8, 11) followed by a 7 day rest.
- Simon Two-Stage: Seventeen (17) evaluable patients will be enrolled in the first stage of the Phase II component of the study. If there is/are ≥ 1 response(s) out of these initial seventeen evaluable patients, 22 additional evaluable patients will be enrolled.

Acknowledgments – Investigative Sites

- **Prof. Dariusz Kowalski, MD, PhD**, The Maria Sklodowska-Curie Memorial Cancer Centre & Institute of Oncology
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