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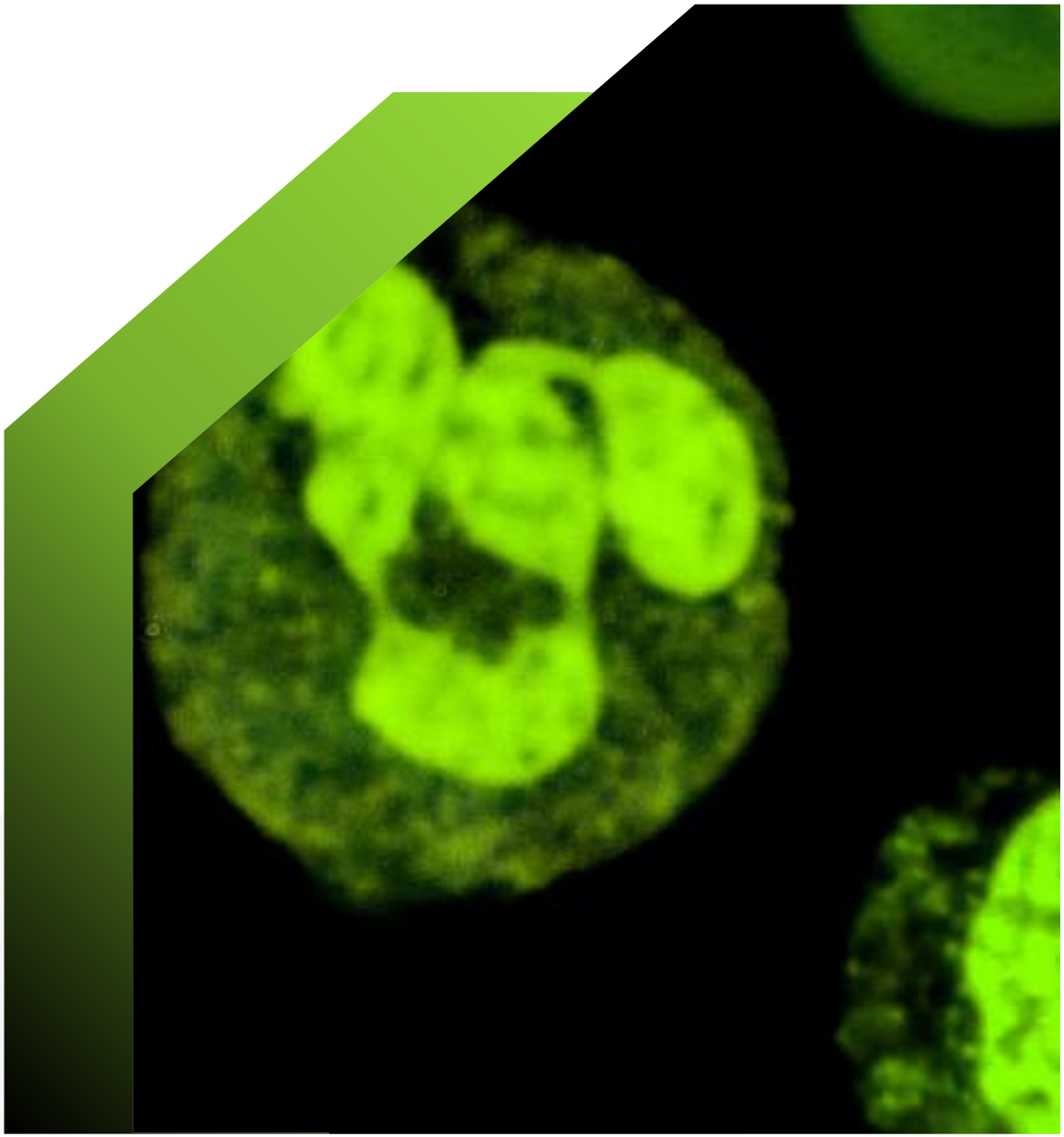
Off-the-shelf, universal, macrophage reprogramming cell therapies for life-threatening diseases



NASDAQ Ticker: ENLV

Forward-Looking Statements

These slides and the accompanying oral presentation contain forward-looking statements and information. Forward-looking statements are subject to known and unknown risks, uncertainties, and other factors that may cause our or our industry's actual results, levels or activity, performance or achievements to be materially different from those anticipated by such statements. The use of words such as "may", "might", "will", "should", "could", "expect", "plan", "anticipate", "believe", "estimate", "project", "intend", "future", "potential" or "continue", and other similar expressions are intended to identify forward looking statements. For example, all statements we make regarding (i) the initiation, timing, cost, progress and results of our preclinical and clinical studies and our research and development programs, (ii) our ability to advance product candidates into, and successfully complete, clinical studies, (iii) the timing or likelihood of regulatory filings and approvals, (iv) our ability to develop, manufacture and commercialize our product candidates and to improve the manufacturing process, (v) the rate and degree of market acceptance of our product candidates, (vi) the size and growth potential of the markets for our product candidates and our ability to serve those markets, and (vii) our expectations regarding our ability to obtain and maintain intellectual property protection for our product candidates, are forward looking. All forward-looking statements are based on current estimates, assumptions and expectations by our management that, although we believe to be reasonable, are inherently uncertain. All forward-looking statements are subject to risks and uncertainties that may cause actual results to differ materially from those that we expected. Any forward-looking statement speaks only as of the date on which it was made. We undertake no obligation to publicly update or revise any forward-looking statement, whether as a result of new information, future events or otherwise, except as required by law. This presentation is not, and nothing in it should be construed as, an offer, invitation or recommendation in respect of our securities, or an offer, invitation or recommendation to sell, or a solicitation of an offer to buy, any of our securities in any jurisdiction. Neither this presentation nor anything in it shall form the basis of any contract or commitment.

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Immune rebalancing

Enlivex: next-generation cell therapies

PAST

- Autologous
- Not scalable
- High COGS

- Engineered T-cells

FUTURE

- Off-the-shelf
- Scalable
- Low COGS

&

- New cell modalities
  - NKs
  - RBCs
  - Macrophages

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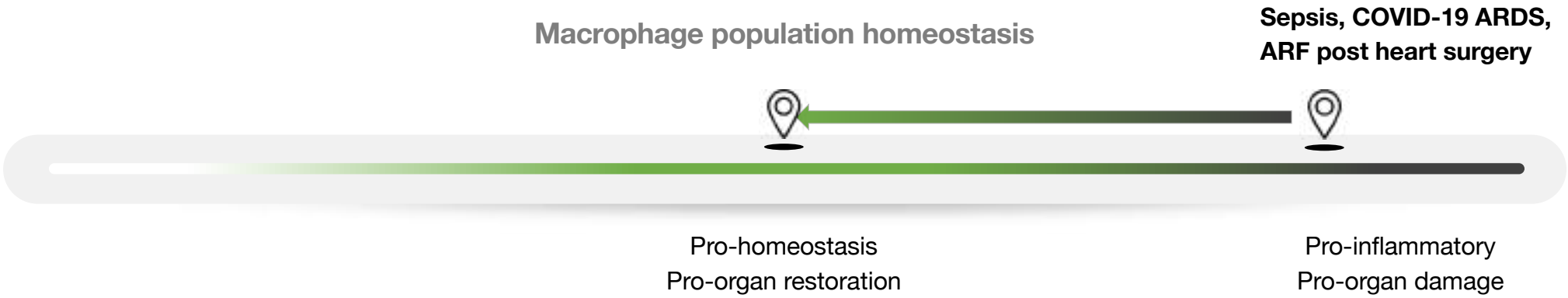
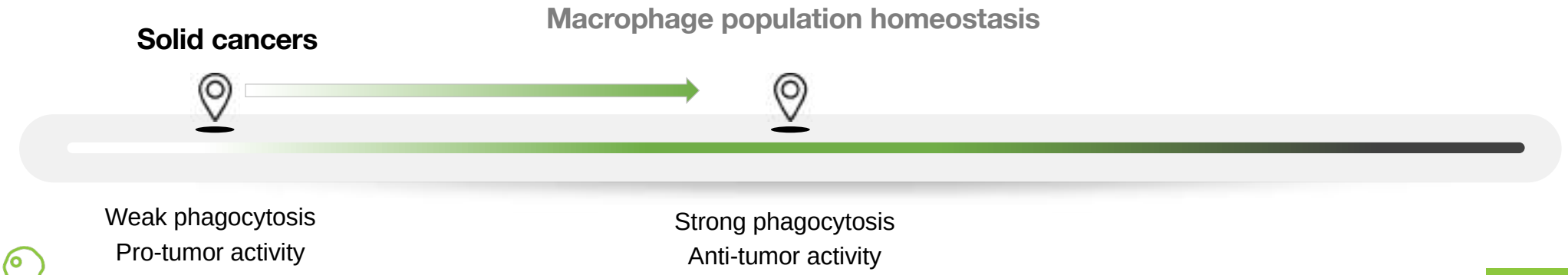
Macrophage homeostasis implies proper function for its specific tissue, environment and challenge

Reprogramming imbalanced macrophage populations can lead to disease resolution





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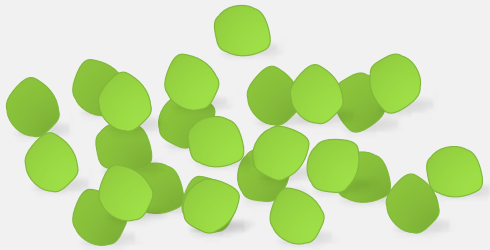
Allocetra™ Mechanism of Action

Restoring immune homeostasis through reprogramming of macrophages

Allocetra™ for macrophage reprogramming

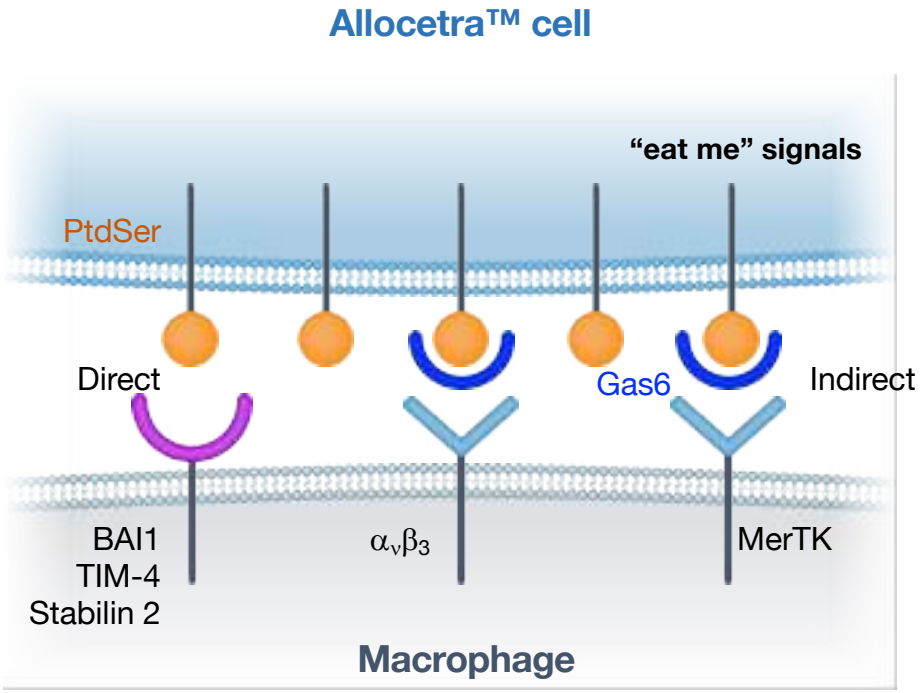
Proprietary, universal, off-the-shelf, macrophage-reprogramming cells

Allocetra™ characteristics



- Mononuclear cells collected from healthy donors
- Modified through a proprietary process to:
  - Express PtdSer (“eat me” signal) on their surface
    - Enabling engulfment into macrophages via binding to BAI, TIM4, and stabilin 2, annexin V
  - Yet maintain their membrane in-tact
- Universal, off-the-shelf

Allocetra™ delivery into macrophages via engulfment



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Allocetra™ for macrophage reprogramming

Pipeline of reprogrammable macrophage-modulated indications

Indication	Global Market Size	Pre-Clinical	Phase Ib	Phase IIb	Support for EU Conditional Marketing Approval Submission	Post EU Marketing US Phase 3
Organ failure associated with Sepsis	$33B		Completed	Phase II Initiated Q1 2021	Completion of Phase II Q3 2023	
Advanced-stage solid tumors with peritoneal metastases, in combination with chemotherapy	$4B		Phase I/II Q2 2022			
Advanced-stage solid tumors with peritoneal metastases, stand-alone + in combination with anti-PD1	$4B		Phase I/II Q3 2022			

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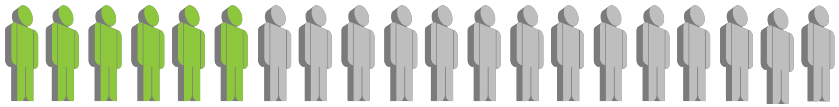
Reprogramming macrophages responsible for organ failure in sepsis

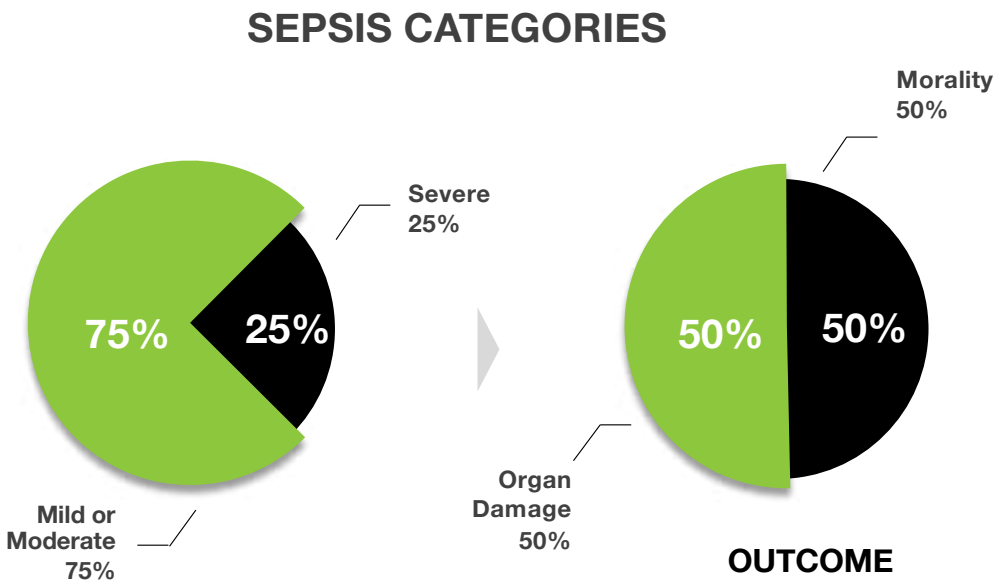
Sepsis is the 3rd leading cause of death in the U.S. – $33B target market*

There are currently no FDA approved drugs for the treatment of sepsis



Each year, at least **1.7 million** adults in America develop sepsis. Nearly **270,000** Americans die as a result of sepsis each year.

1 in 3 One in three patients who die in a hospital have sepsis.



$50,000 x 675,000 Patients PA (global) = $33B Total Addressable Market

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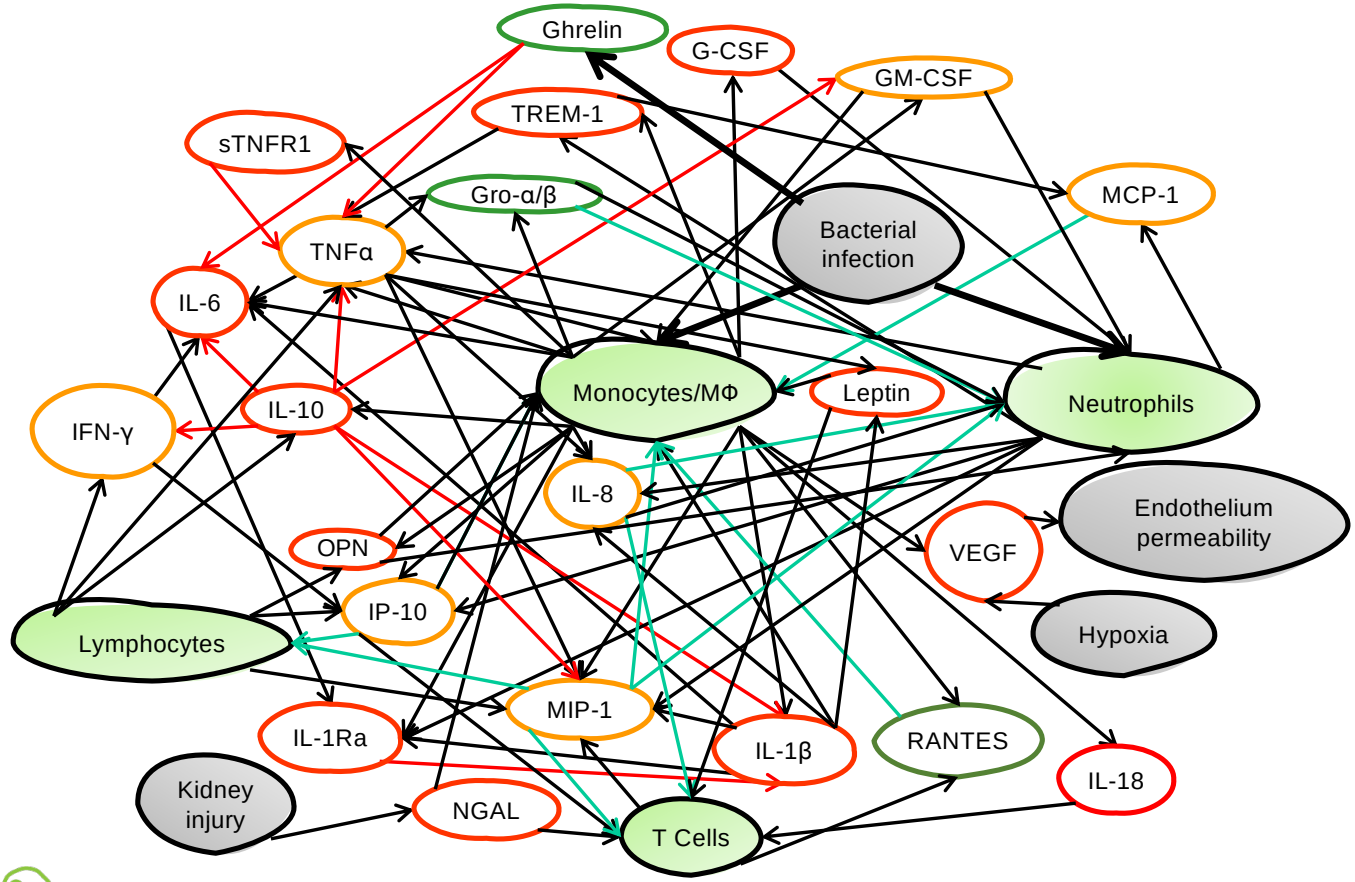
* U.S. & EU

Cytokine/Chemokine network in sepsis: the impossible task of resolving sepsis with inhibition of a certain cytokine or signaling pathway



MΦ: Macrophages

- Activation
- Inhibition
- Chemotaxis
- Downregulated in most of the patients
- Downregulated in 50% of the patients
- Upregulated in most patients

Macrophage reprogramming to "manufacturer settings" is required to obtain sepsis resolution

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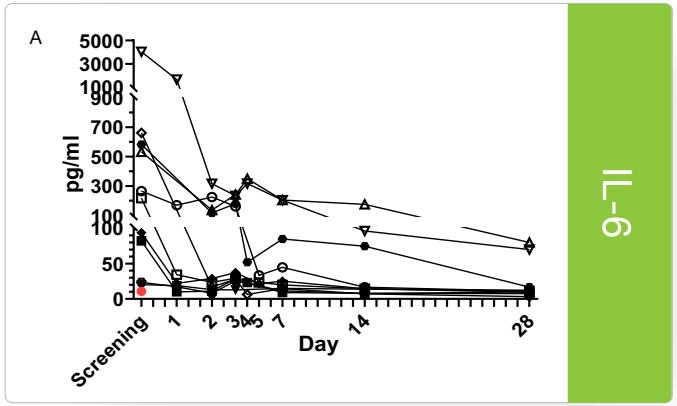
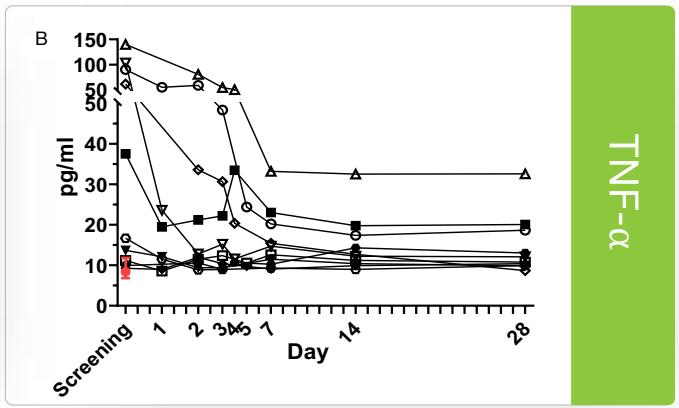
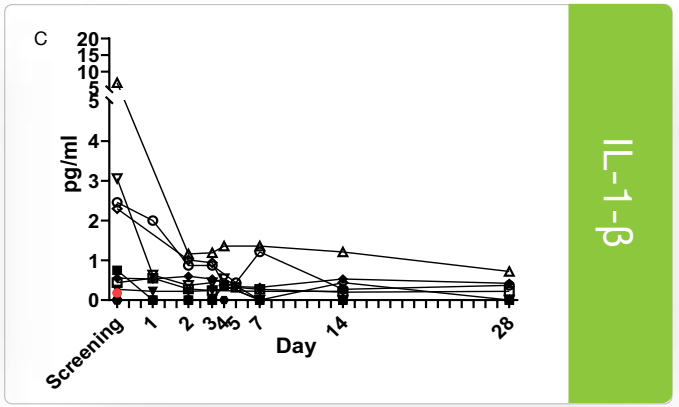
Phase Ib clinical trial of macrophage reprogramming in sepsis patients

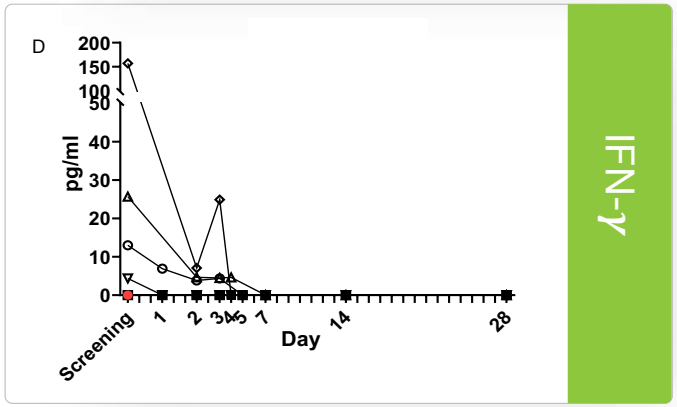
Reprogrammed macrophages in sepsis patients return to homeostatic state (1)

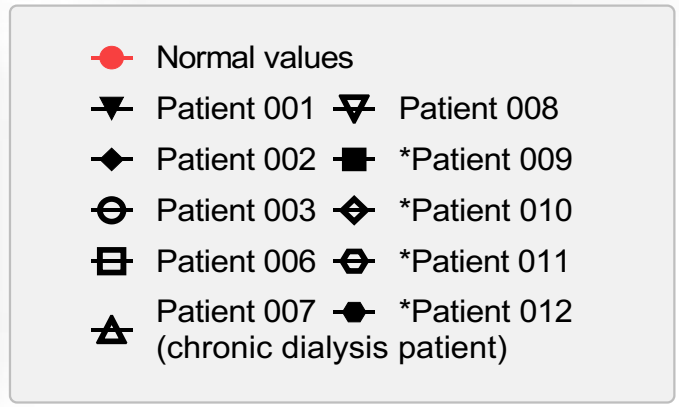
Phase Ib clinical trial data, change from screening, pro-inflammatory cytokines











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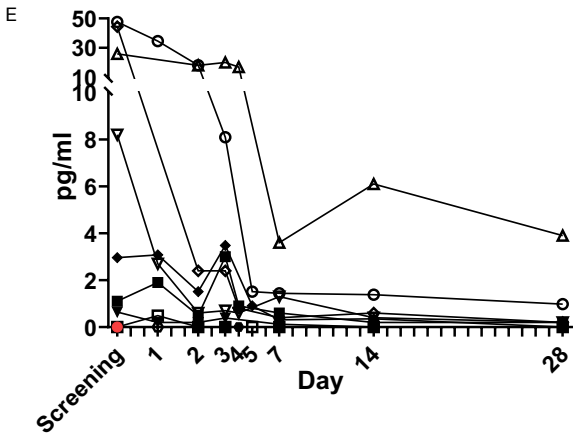
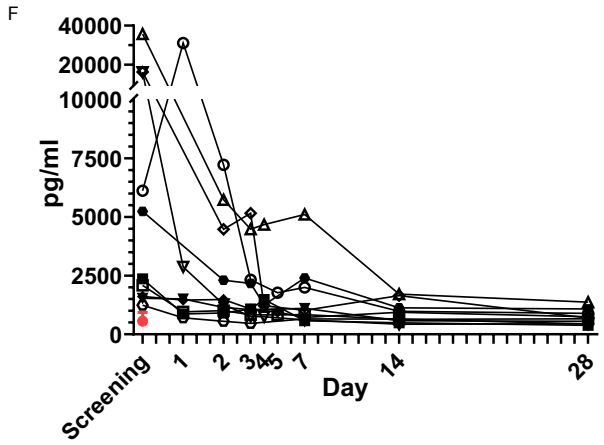
Reprogrammed macrophages in sepsis patients return to homeostatic state (2)

Phase Ib clinical trial data, change from screening, anti-inflammatory cytokines

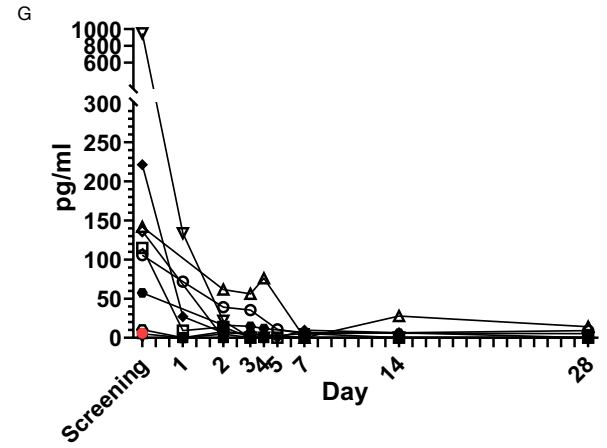
IL-10

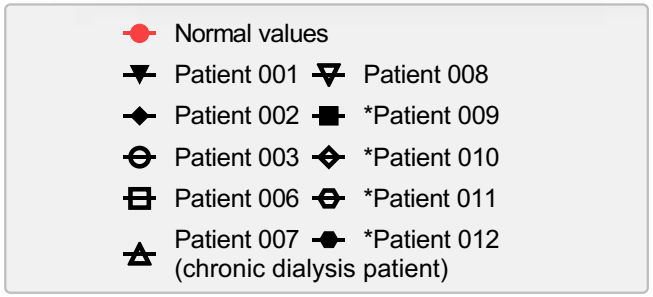


IL-1Rα



G-CSF





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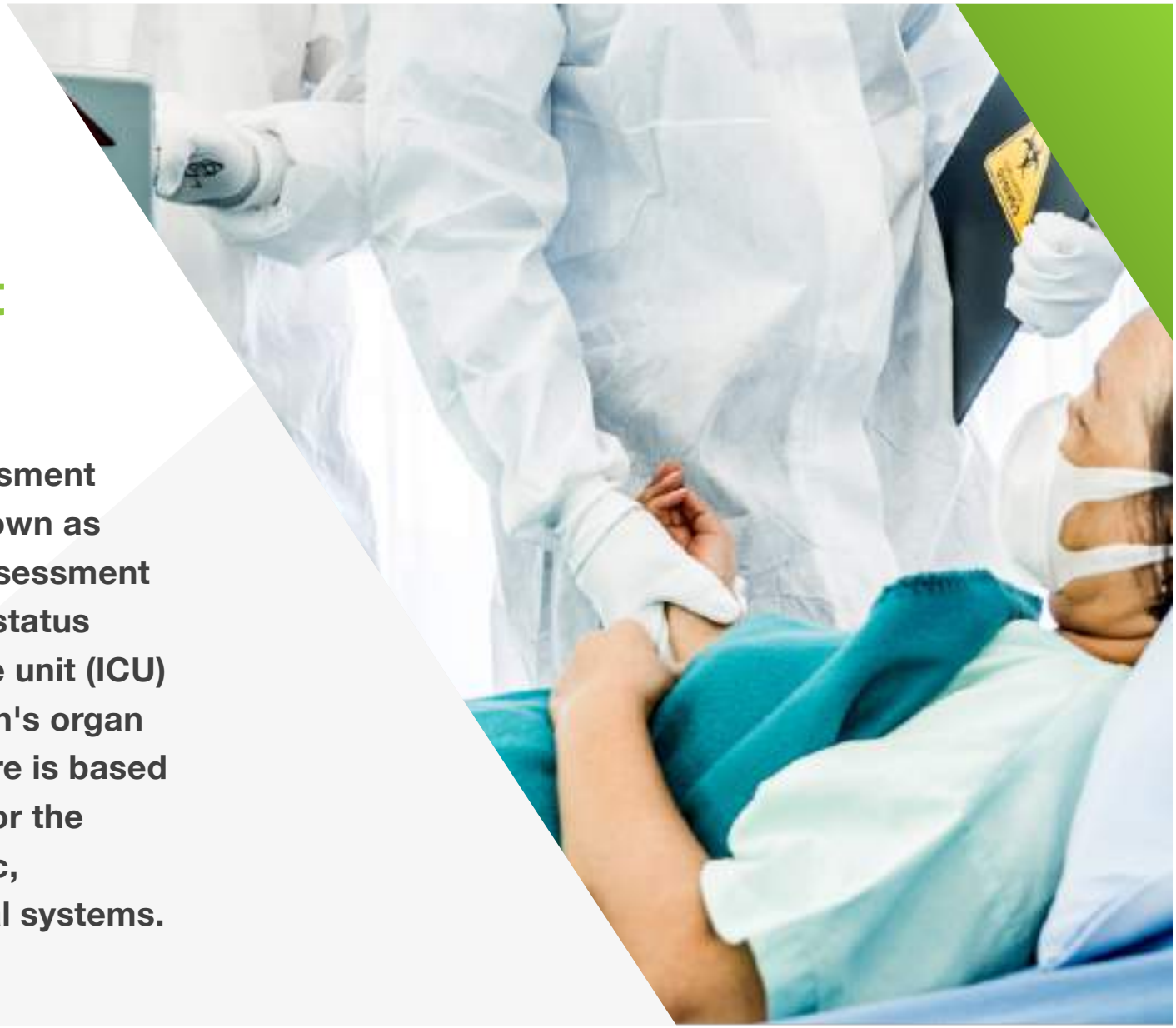
Sequential Organ Failure Assessment (SOFA) Score

The sequential organ failure assessment score (SOFA score), previously known as the sepsis-related organ failure assessment score, is used to track a person's status during the stay in an intensive care unit (ICU) to determine the extent of a person's organ function or rate of failure. The score is based on six different scores, one each for the respiratory, cardiovascular, hepatic, coagulation, renal and neurological systems.



High degree of matching: treated vs controls

	Treated (n=10)	Matched Controls (n=37)
Average age	71.5 (51-83)	71.25 (50-83)
Male/female	80/20	80/20
Average diagnosis SOFA	3.4 (2-6)	3.47 (2-7)
Average diagnosis Apache II score	12.3 (8-21)	14.25 (5-24)

Sepsis source		
Pneumonia	50%	53%
Biliary infections	30%	25%
Endovascular	10%	8.3%
UTI	10%	14%

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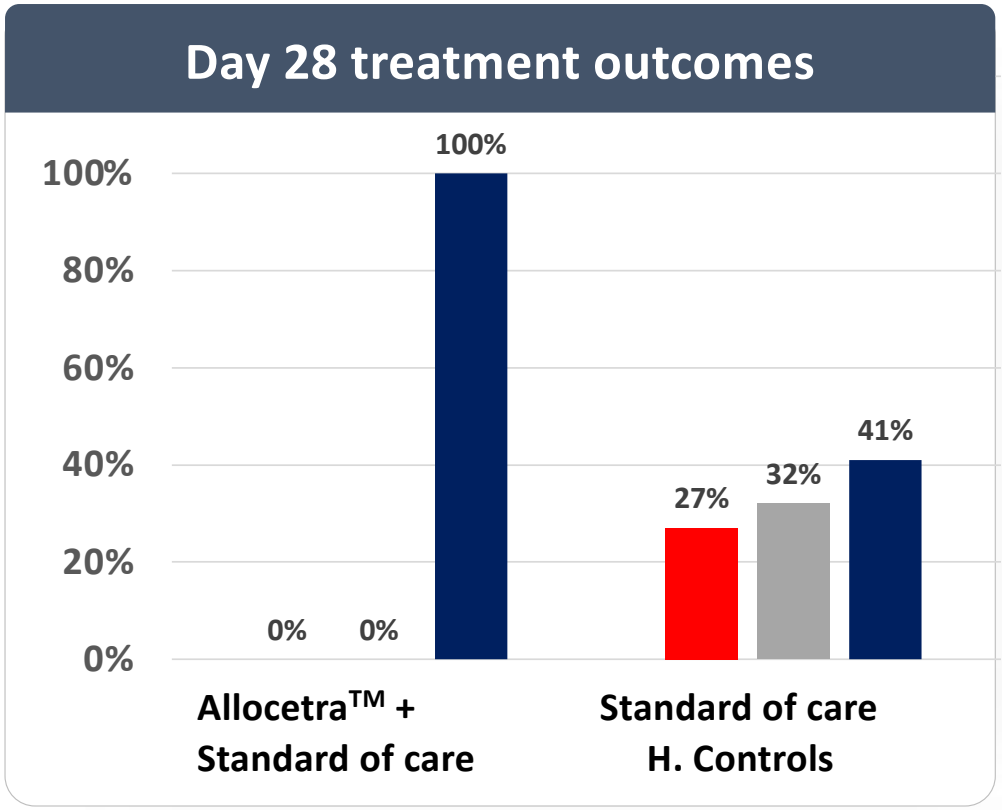
Allocetra™ macrophage reprogramming leads to improved outcomes for sepsis patients

Alive and organs recovered on day 28: 100% vs 41%

- Day 28 mortality
- Day 28 still with organ failures
- Hospital discharge



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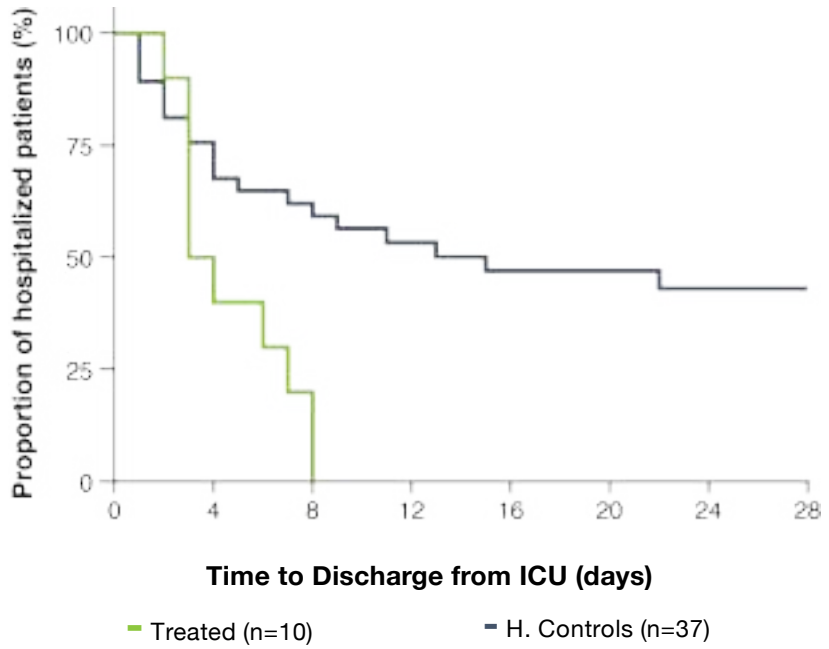
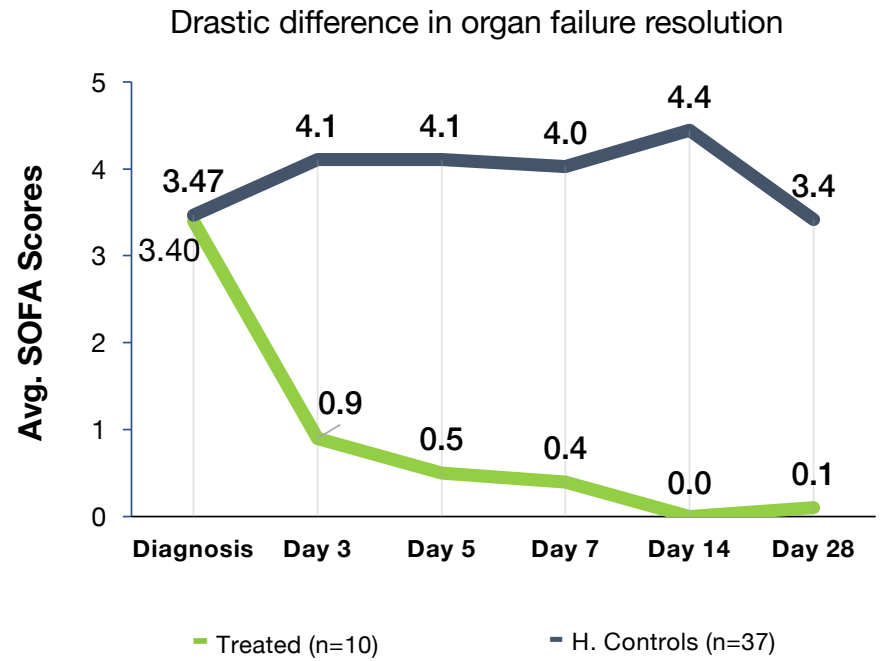
Allocetra™ macrophage reprogramming leads to improved outcomes for sepsis patients

Statistically significant improvement in hospitalization and SOFA vs. matched controls

Time to ICU discharge



Average SOFA score during 28 days



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Clinical summary of macrophage reprogramming in sepsis Phase Ib: complete recovery from any organ failure for all 10 patients and 100% 28-day survival

Sepsis clinical characteristics and organ recovery

Organ Dysfunction	Each patient had at least 2 organ dysfunctions, maximum of 5
Kidney	3/9 patients (33%) had new-onset acute kidney injury, all have completely recovered to baseline kidney function
Lungs	5/10 (50%) of patients had lung involvement, no patient required mechanical ventilation, all patients recovered to normal saturation and no oxygen supplement upon discharge
Cardiovascular	3/10 (30%) of patients had mean arterial pressure <70 but none needed vasopressors
Hematological	8/10 patients (80%) had significant thrombocytopenia, with complete recovery in all.
Liver	4/10 patients (40%, of which 3 had biliary tract infection) had hyperbilirubinemia, with complete recovery in all. 5/10 patients had elevated liver enzymes (AST ALT) >3 above normal range, with complete recovery in all.

Sepsis

Allocetra™ macrophage reprogramming Phase IIb clinical plan

	Sepsis Phase IIb
Addressable global market	$33 Billion market (severe Sepsis only)
Type	Controlled, randomized, multi-center (10 centers)
Patients	80-160, SOFA < 10, Source: pneumonia, biliary, urinal tract, and peritoneal infections
Duration	28 days / patient
Recruitment	12 Months
End-points	Safety, Change in SOFA score
Secondary	Mortality
First patient dosed	Q2/2021

- **COVID-19 BUSINESS OPPORTUNITY IS DE-PRIORITIZED**
- **CLINICAL DATA PROVIDED TO DEMONSTRATE SAFETY AND EFFECT IN ANOTHER INFECTIOUS DISEASE INDICATIONS**

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Phase Ib & II Clinical Trials in COVID-19 Patients in Severe or Critical Condition

Despite strong clinical results, COVID-19 business opportunity is de-prioritized

- Primary reasons:
  - Availability of therapeutics for mild/moderate patients
  - Dominance of Omicron variants, who seem to cause less severe disease in most patients
  - Regulators “step-back” and reluctance to provide emergency use authorizations, requirements for large Phase IIIs

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Patient classification as defined by the NIH classification guide

Allocetra™: Positive Phase Ib and top line Phase II results in COVID-19

Clinical Trial	# Patients enrolled	Disease Severity	Clinical Outcome		Hospitalization Post Administration of Allocetra™	
			Recovered Day 28	Mortality Day 28	Discharged Day 28	Duration (days, avg.)
Phase Ib	5	2 Severe, 3 Critical	5/5 (100%)	0/5 (0%)	5/5 (100%)	6.6
Phase II	16	9 Severe, 7 Critical	14/16 (87.5%)	0/16 (0%)	14/16 (87.5%)	5.3
Total	21	11 Severe, 10 Critical	19/21 (90.5%)	0/21 (0%)	19/21 (90.5%)	5.6

- 0/21 (0%) mortality on day-28
- 19/21 (90.5%) patients recovered and were discharged from the hospital by day-28
- Average duration of hospitalization post administration of Allocetra™ for discharged patients was 5.6 days
- 2/21 (9.5%) patients, both of whom had critical illness at the time of Allocetra™ treatment, were hospitalized in the ICU on a respirator on day-28

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Patient classification as defined by the NIH classification guide

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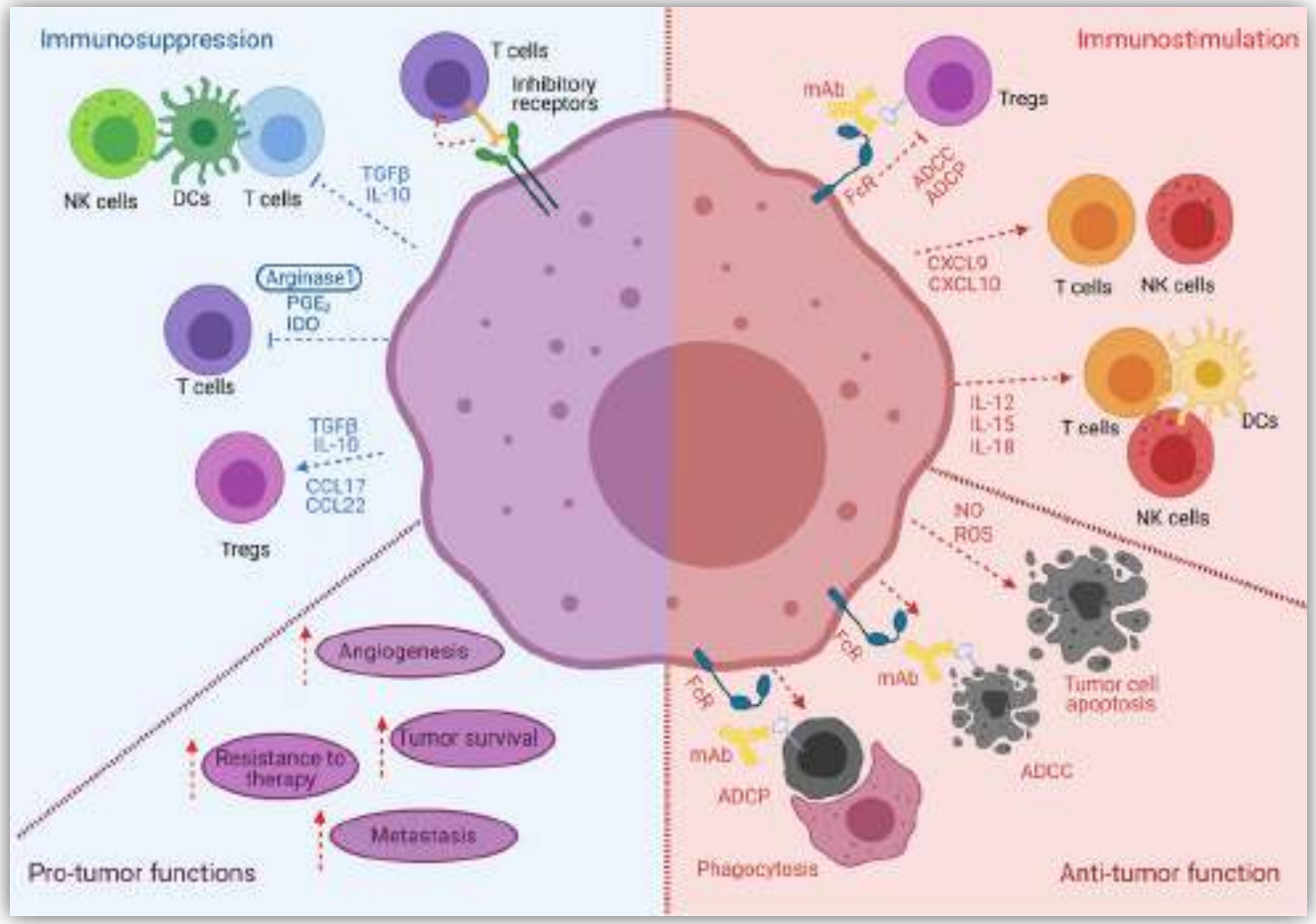
Macrophage reprogramming in solid tumor microenvironment

Unique & differentiated value proposition

Tumor-associated macrophages: pro-tumor, immunosuppressive activities

Immunosuppressive functions[1]
- inhibit T cell, DC and NK cell activation
- suppress anti-tumor T cell functions through inhibitory

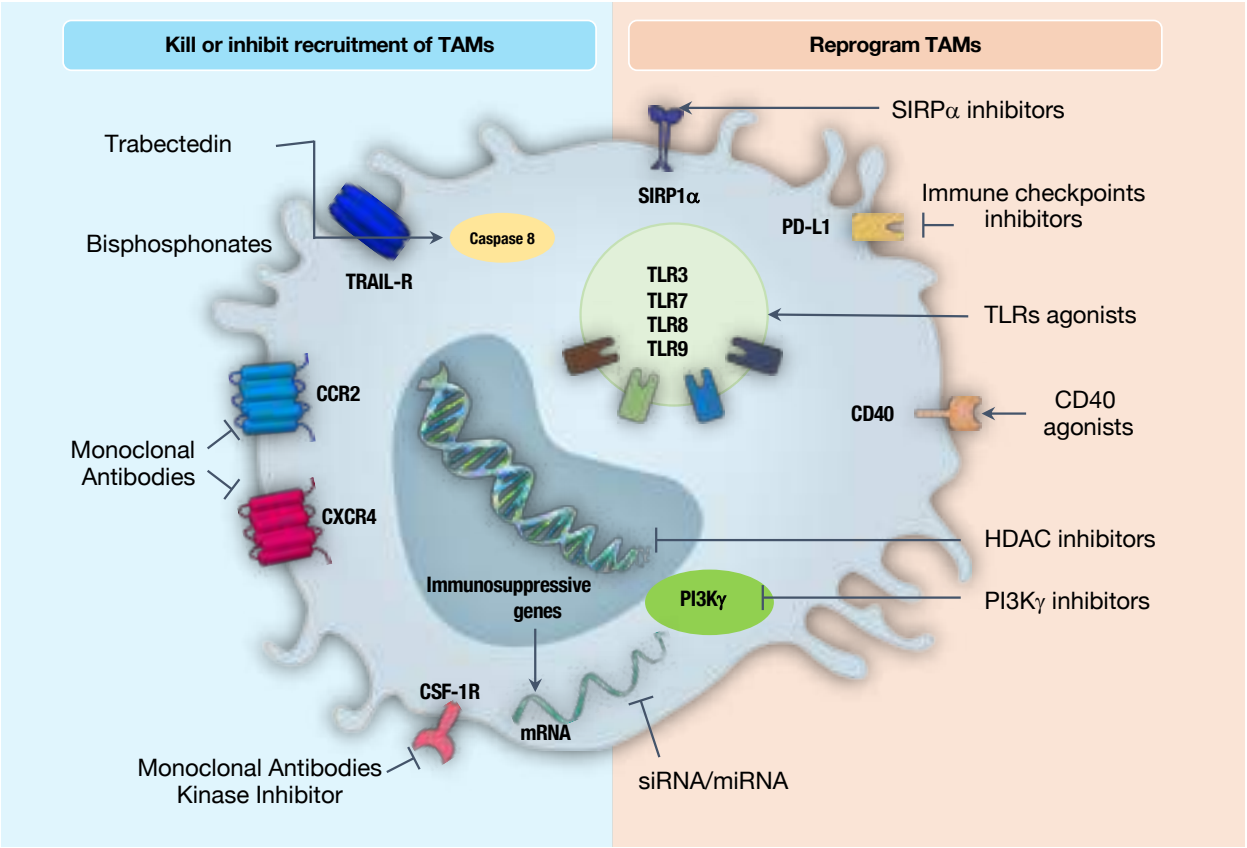
Direct pro-tumor functions
- Promote resistance to therapy, angiogenesis, tumor cell survival and metastasization



[1] Turning enemies into allies-reprogramming tumor-associated macrophages for cancer therapy, Molgora et al., Med (N Y). 2021 June 11;

Effective solid cancer therapy requires changes to macrophages in the TME

Multiple strategies to kill or reprogram non-homeostatic, pro-tumor macrophages (TAMs)[1]



[1] Adapted from Current Strategies to Target Tumor-Associated-Macrophages to Improve Anti-Tumor Immune Responses, Anfray et al., Cells 2020, 9, 46

The Enlivex differentiation: Balance of resident macrophages vs bloodborne infiltrating macrophages and the effect on anti-tumor activity

Cancer-induced changes to macrophage sub-populations:

- **Elimination of resident macrophages**
- **Accumulation of pro-tumor TAMs originating from infiltrating macrophages**

Allocetra™ therapy, in combination with anti-cancer agents/therapies

- **Repopulation of resident macrophages**
- **Depletion of pro-tumor TAMs originating from infiltrating macrophages**

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Macrophage reprogramming in solid tumor microenvironment

Preclinical data

Studies for evaluating the synergistic effect of Allocetra™ + anti-cancer drugs in solid tumors

	Model	Anti-cancer drug used
1.	Syngeneic peritoneal mesothelioma (AB12) in immunocompetent mice	Anti-CTLA4
2.	Syngeneic peritoneal mesothelioma (AB12) immunocompetent mice	Anti-PD1
3.	Syngeneic peritoneal mesothelioma (AB12) immunocompetent mice	Cisplatin
4.	Syngeneic ovarian cancer (ID8) in immunocompetent mice *	Anti-PD1
5.	Peritoneal human HeLa-CD19-luciferase in SCID-Bg mice	CD19 CAR-T

* Study conducted at Yale Cancer Center

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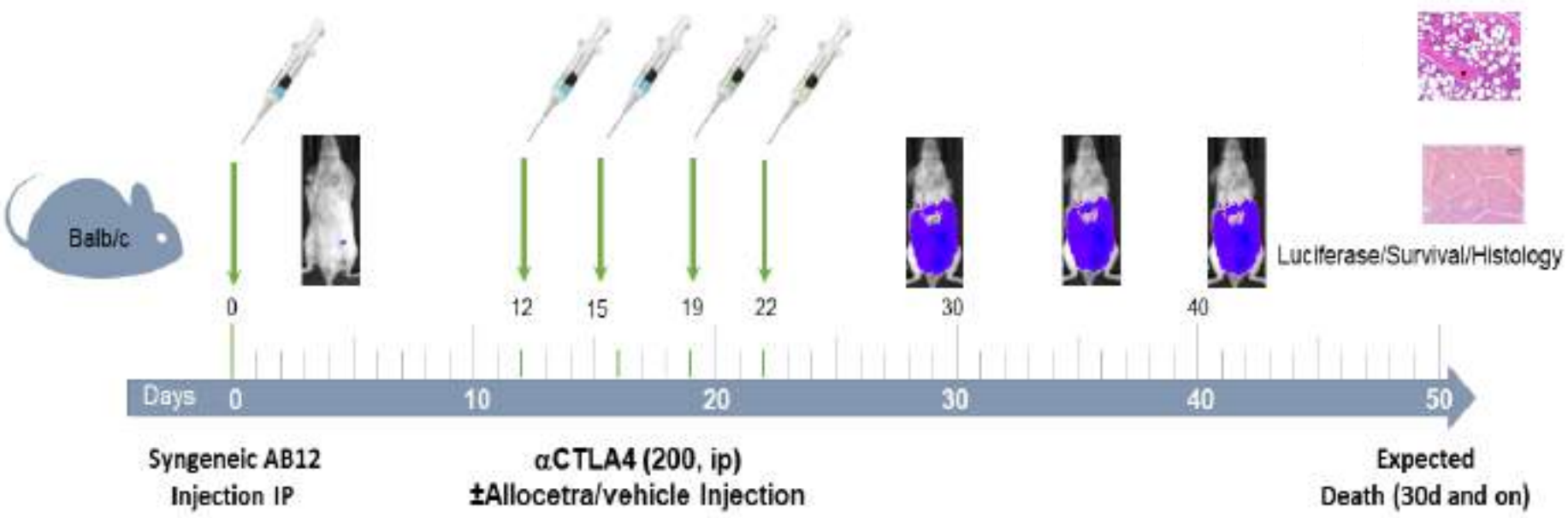
Synergistic effect of Allocetra™ + anti-CTLA4 in peritoneal mesothelioma solid tumor



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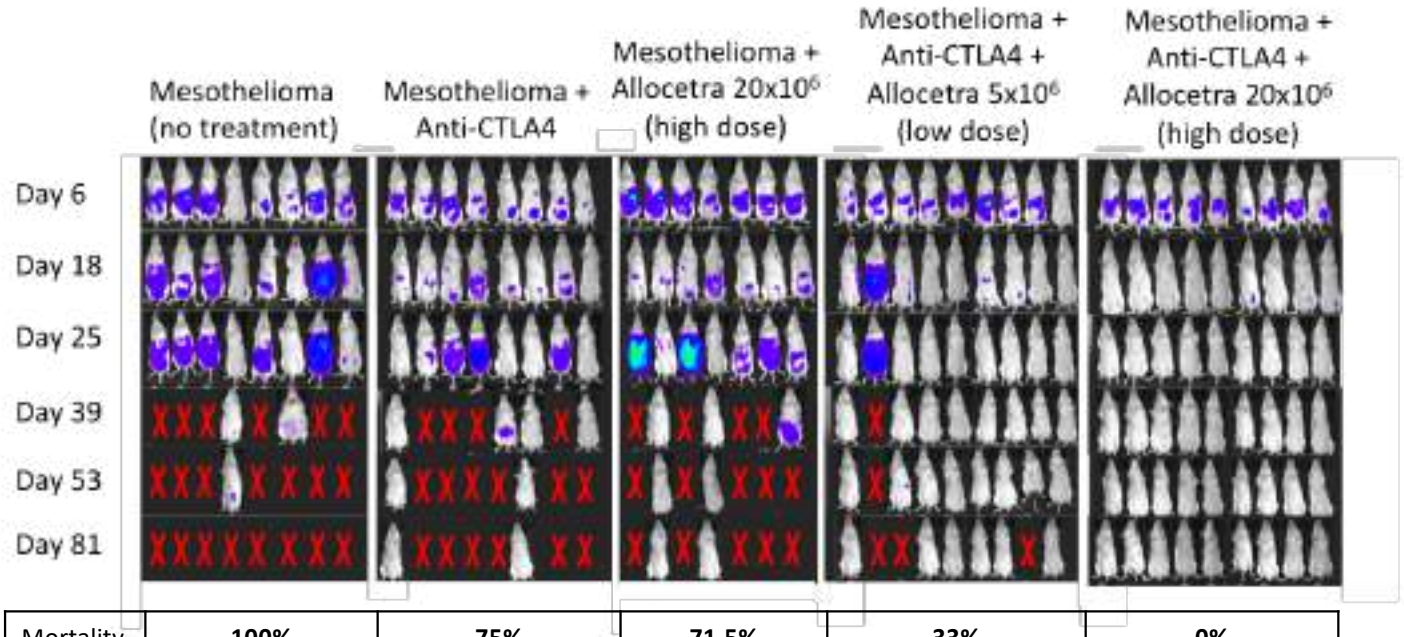
Synergistic effect of Allocetra™ + anti-CTLA4 in peritoneal mesothelioma solid tumor



Mortality	**100%**	**75%**	**71.5%**	**33%**	**0%**
Survival	0%	25%	28.5%	67%	100%
Complete cure	0%	25%	28.5%	67%	100%

Legend

Initial cancer spread

advanced cancer spread

mouse dead ✗

mouse alive

IVIS imageing, AB12-137 study

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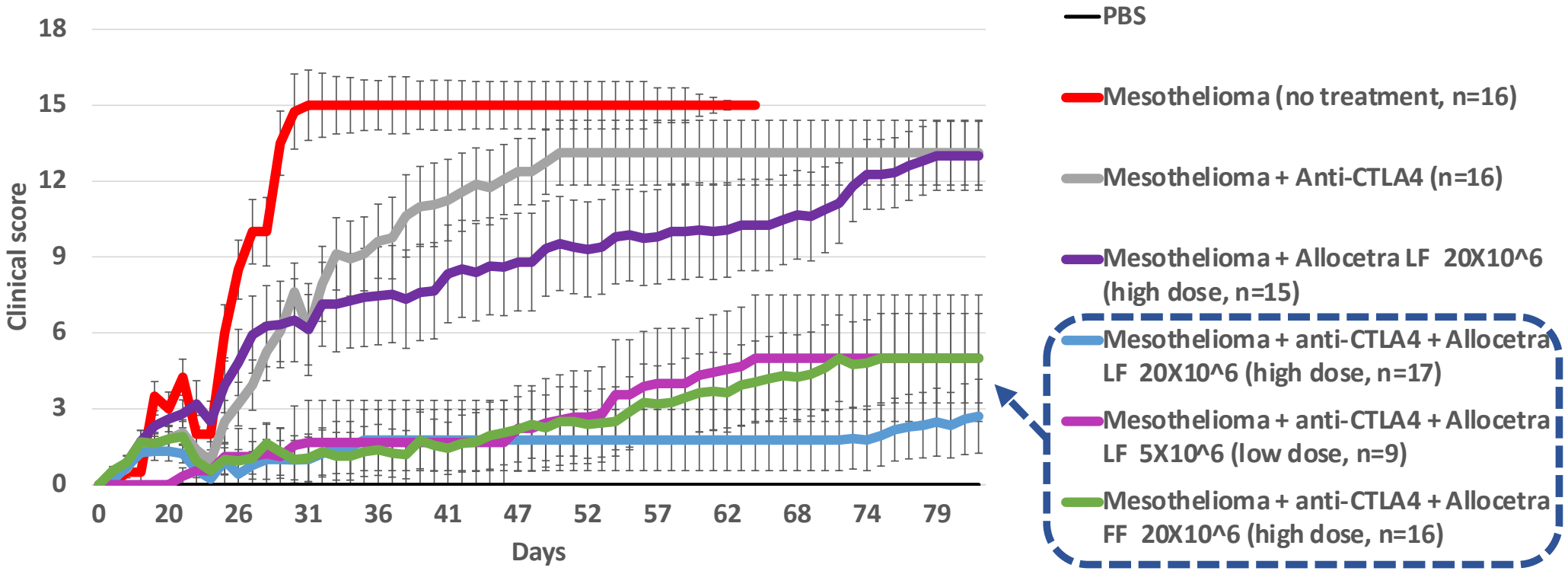
Synergistic effect of Allocetra™ + anti-CTLA4 in peritoneal mesothelioma solid tumor

- **Clinical score observations support superior clinical and survival effect of the anti-CTLA4+Allocetra combinations**



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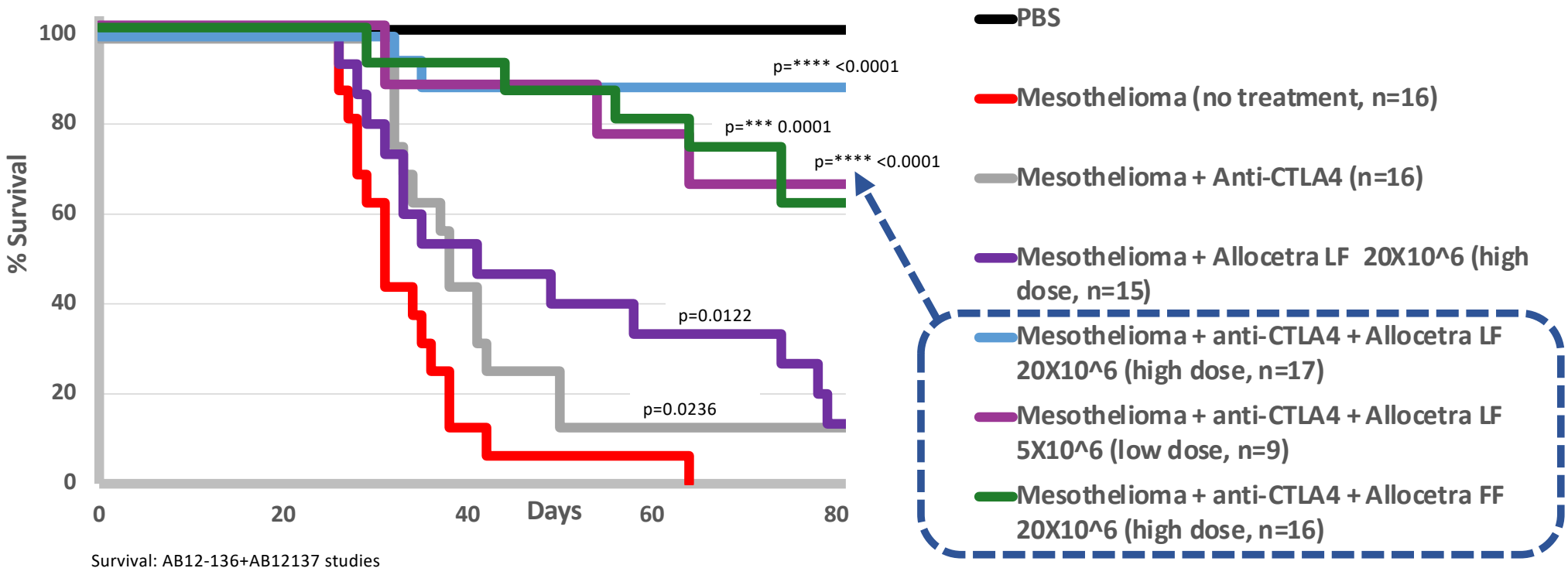
Clinical scores: AB12-136+AB12137 studies

Synergistic effect of Allocetra™ + anti-CTLA4 in peritoneal mesothelioma solid tumor

- **Superior survival of the anti-CTLA4+Allocetra combinations, dose response demonstrated**
- **Weak, although statistically-significant, survival effect of stand-alone anti-CTLA4, Allocetra**



Survival: AB12-136+AB12137 studies

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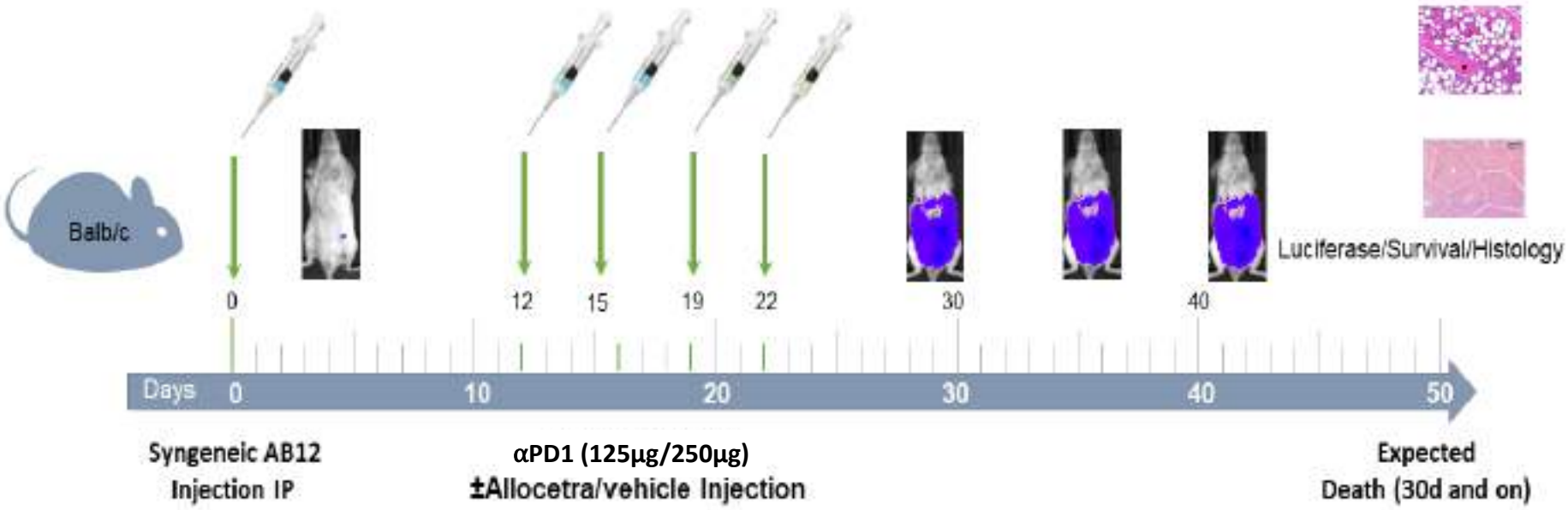
Synergistic effect of Allocetra™ + anti-PD1 in peritoneal mesothelioma solid tumor



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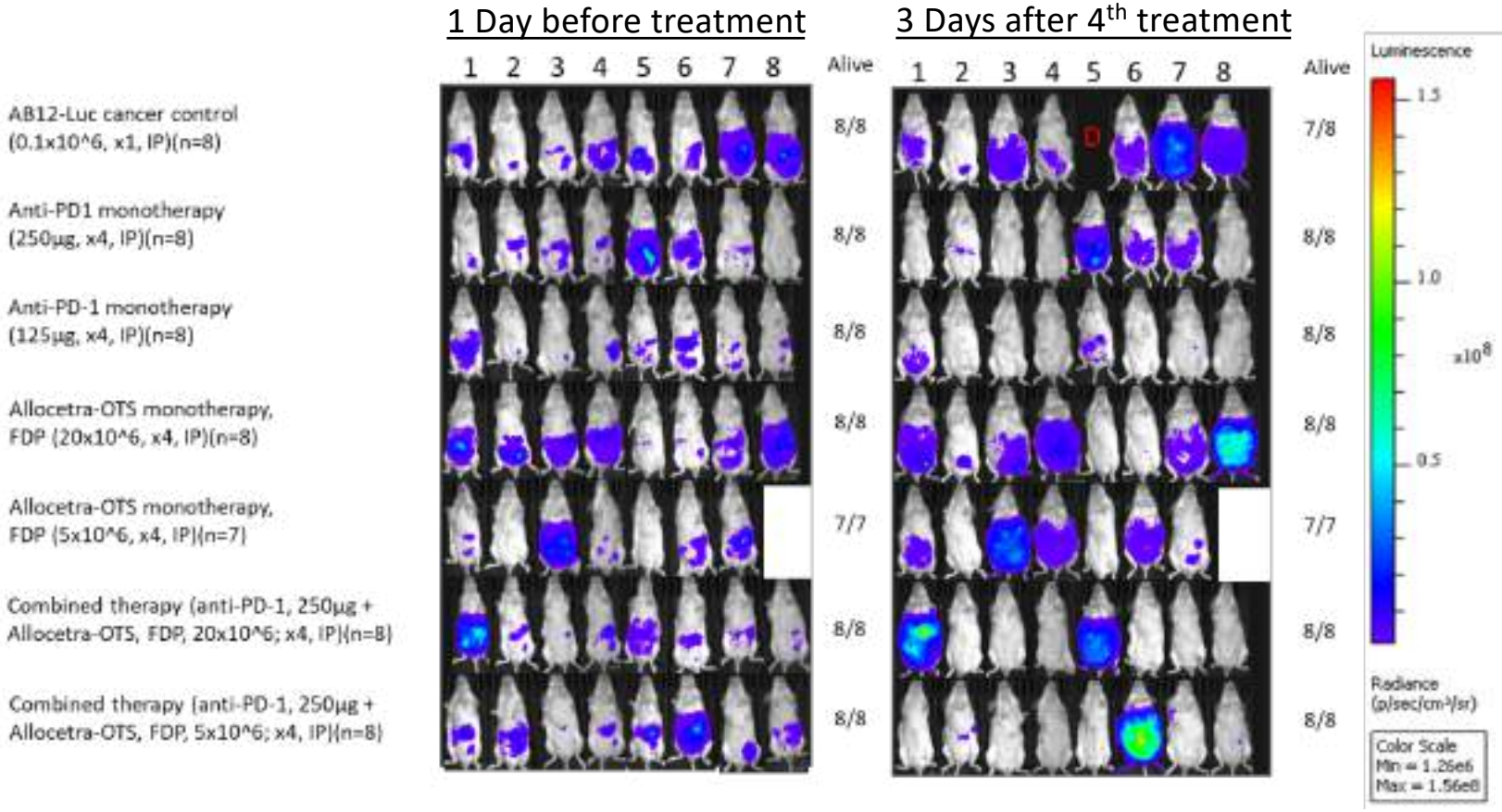
Synergistic effect of Allocetra™ + anti-PD1 in peritoneal mesothelioma solid tumor



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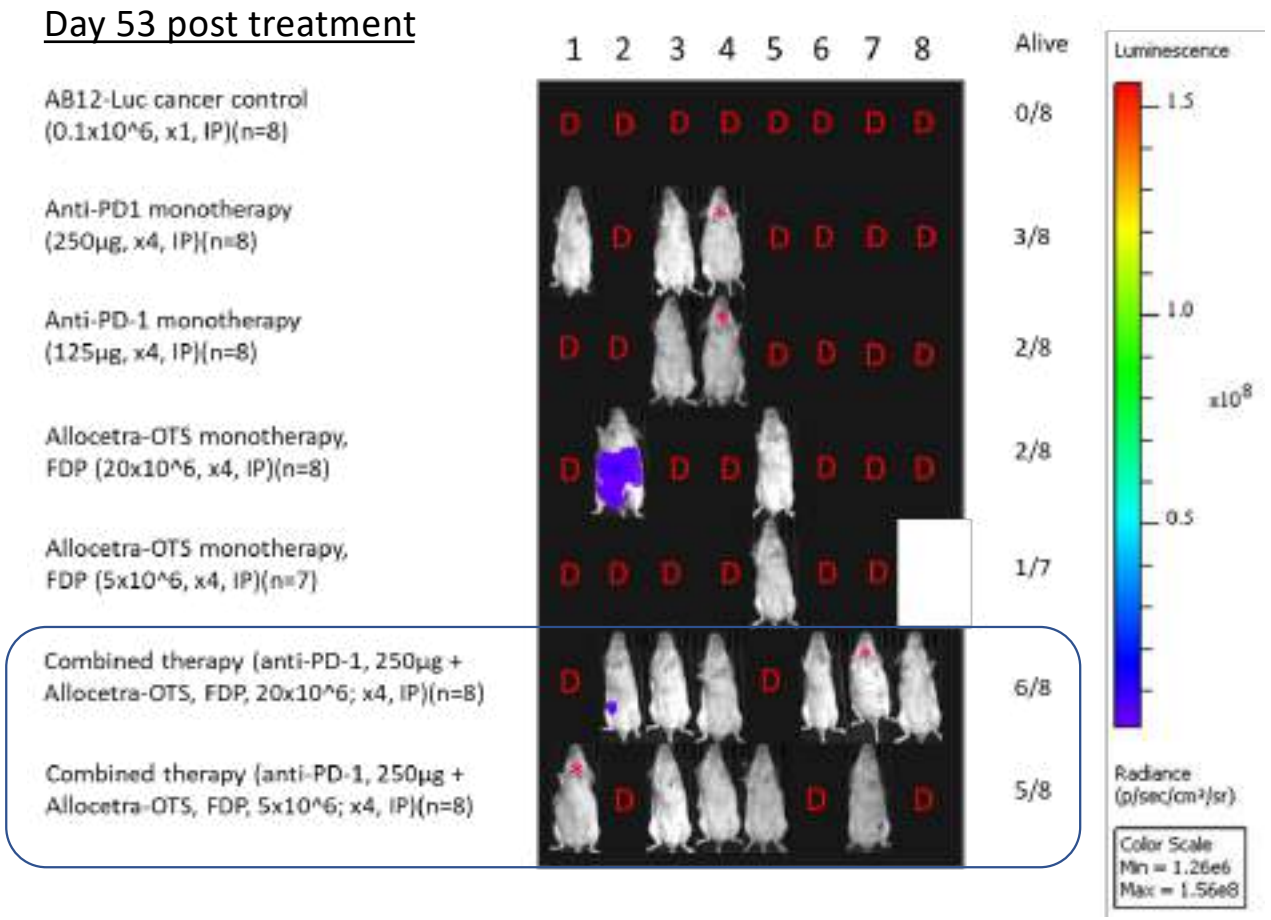
Synergistic effect of Allocetra™ + anti-PD1 in peritoneal mesothelioma solid tumor



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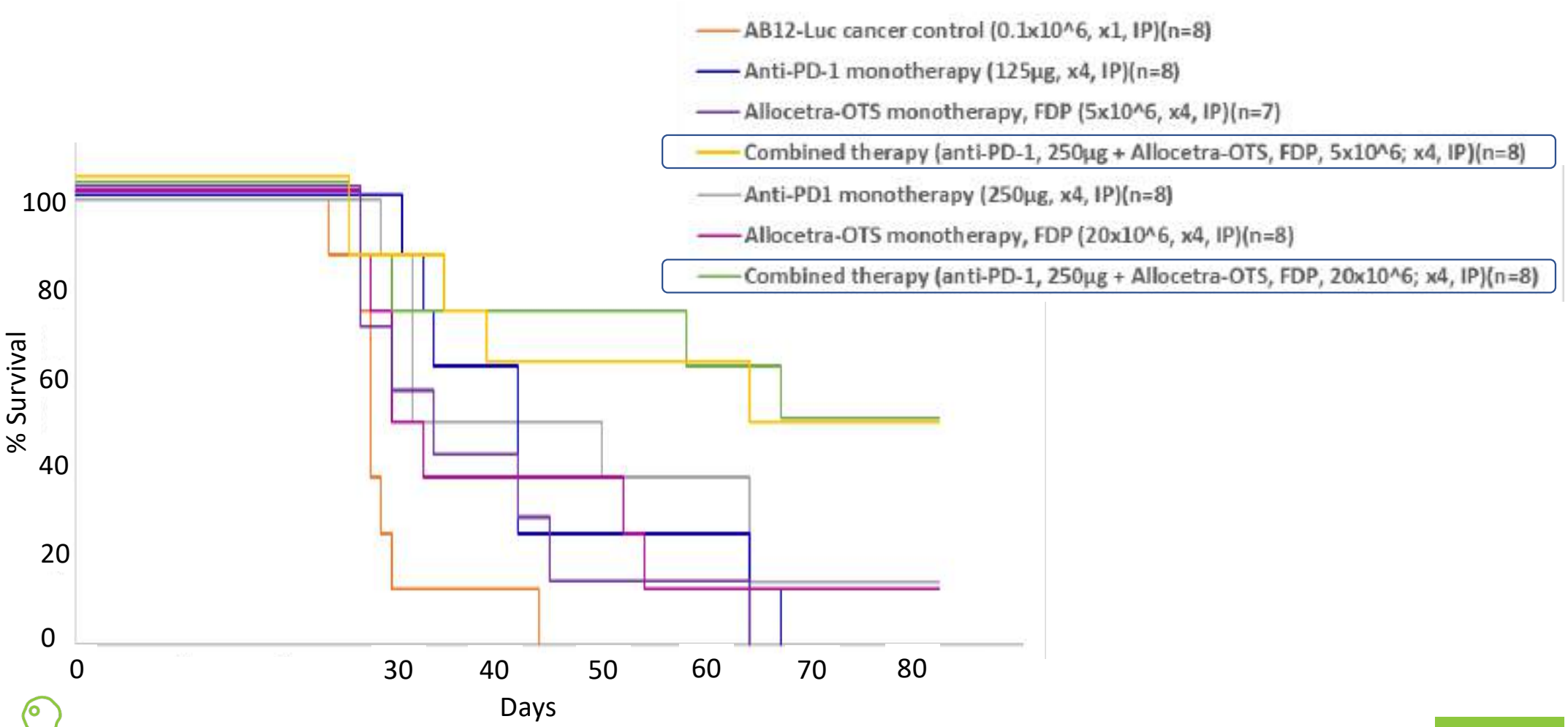
Synergistic effect of Allocetra™ + anti-PD1 in peritoneal mesothelioma solid tumor



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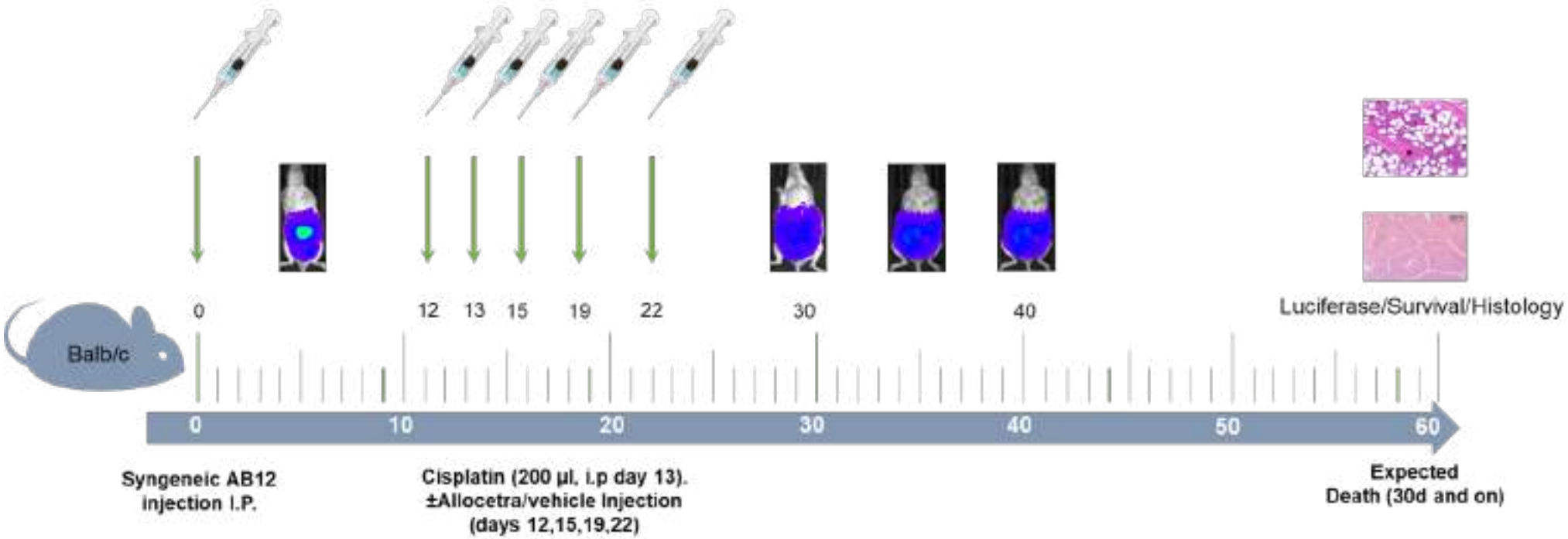
Synergistic effect of Allocetra™ + cisplatin in peritoneal mesothelioma solid tumor



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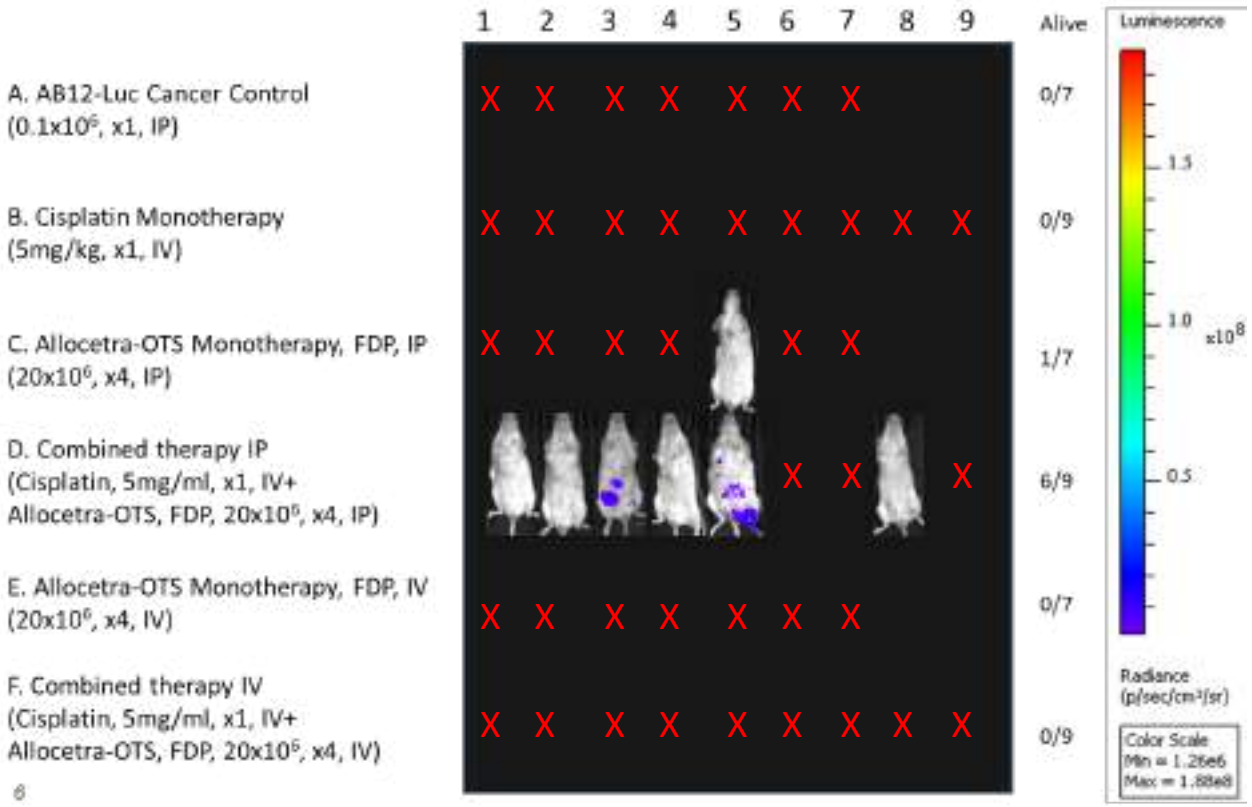
Synergistic effect of Allocetra™ + cisplatin in peritoneal mesothelioma solid tumor

Day 54 post treatment



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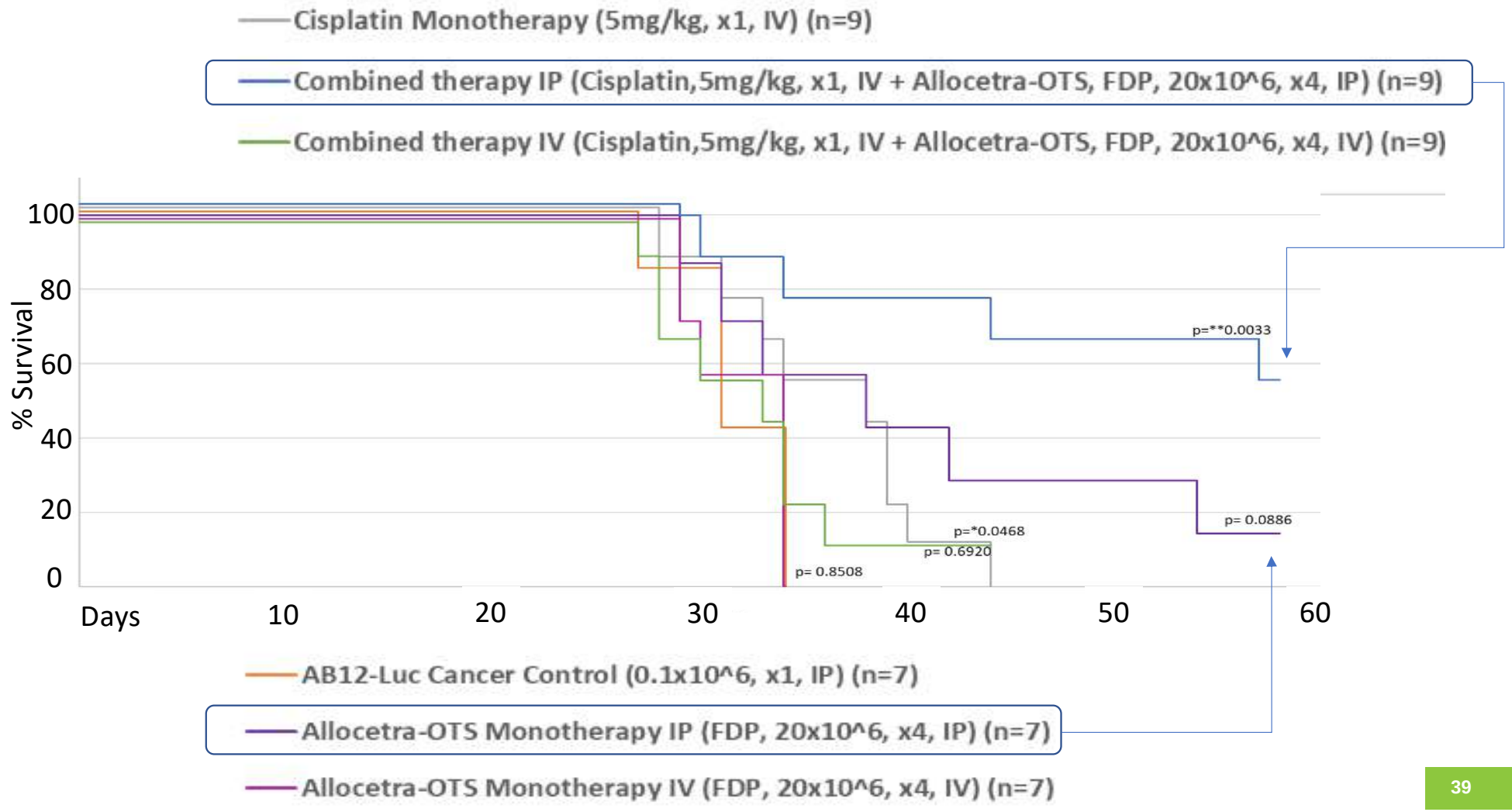
Synergistic effect of Allocetra™ + cisplatin in peritoneal mesothelioma solid tumor



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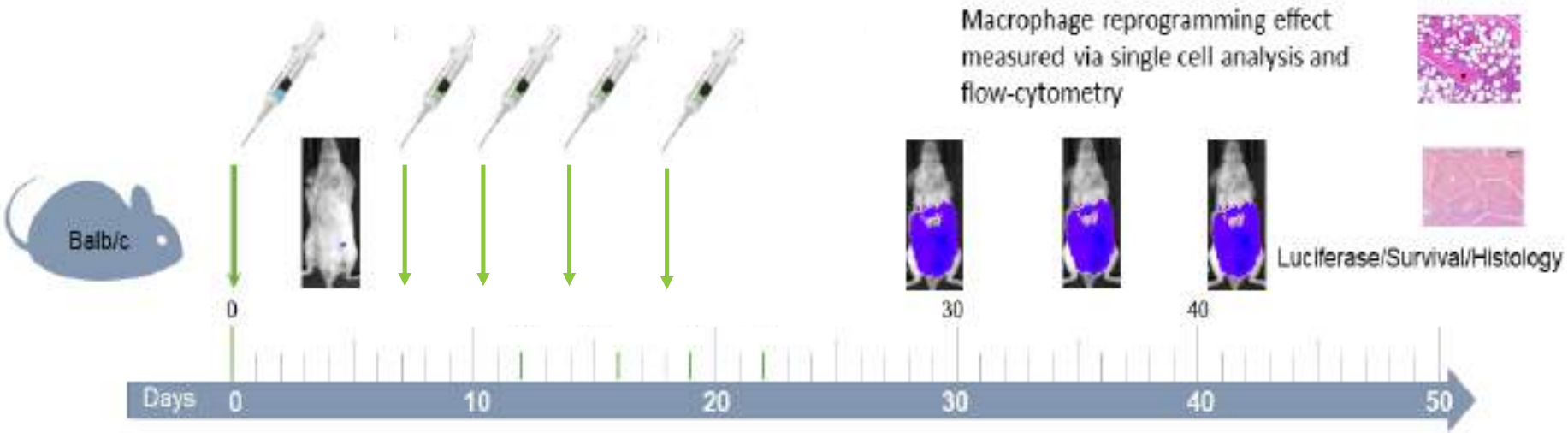
Synergistic effect of Allocetra™ + anti-PD1 in ovarian cancer solid tumor model



Immunocompetent C57BL/6 Injection IP

αPD1 (1.25 mg/kg) ±Allocetra/vehicle Injection ip

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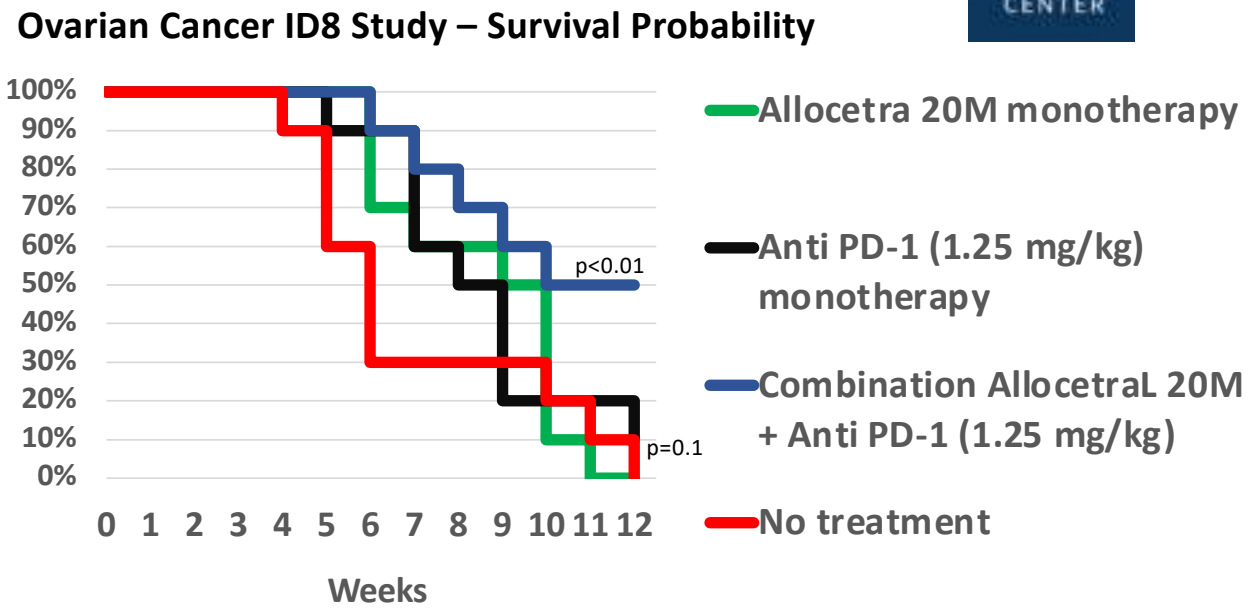
Synergistic effect of Allocetra™ + anti-PD1 in ovarian cancer

(study conducted in collaboration with Yale Cancer Center)

- Superior overall survival, survival duration and lower rate of tumor progression with the anti-PD1+Allocetra combination
- Noticeable and comparable effect on survival duration, weak overall survival effect of stand-alone anti-PD1, Allocetra



	No treatment	Anti PD-1 (1.25 mg/kg) monotherapy	Allocetra 20M monotherapy	Combination AllocetraL 20M + Anti PD-1 (1.25 mg/kg)
Median survival duration (weeks)	6	8.5	9.5	11
% Survival duration increase vs untreated	--	42%	58%	83%
Overall survival percent	0%	10%	0%	50%

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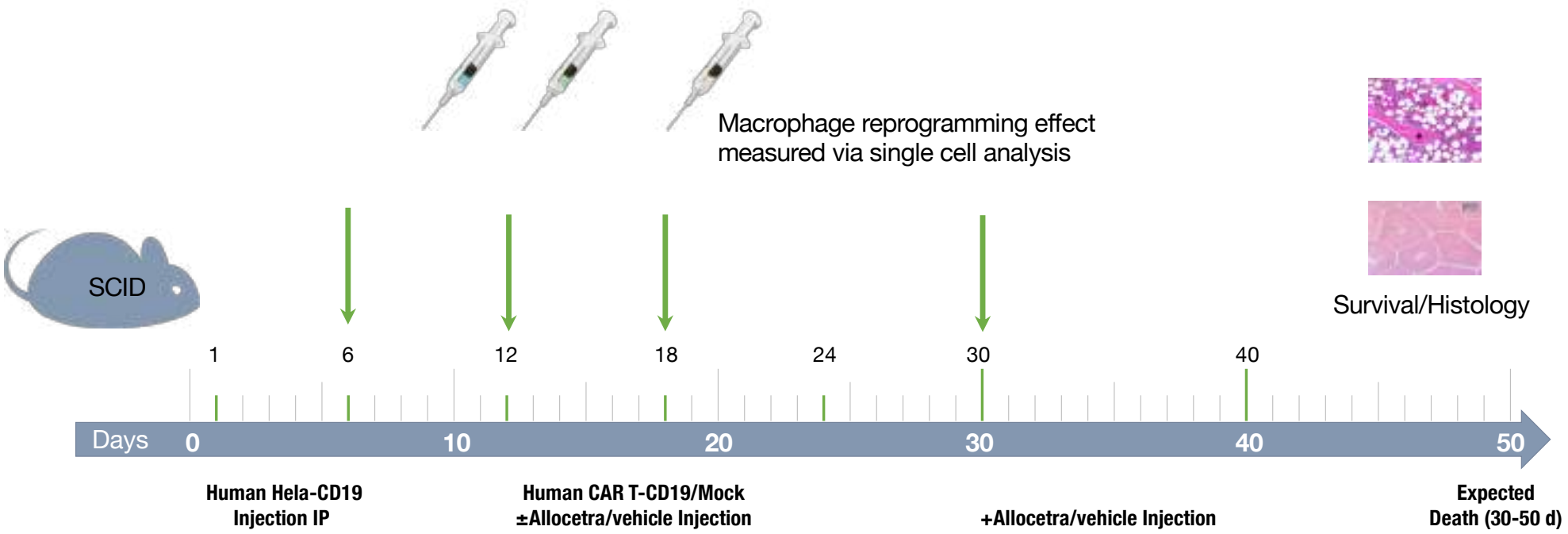
Allocetra™: reprogramming of peritoneal pro-tumor macrophages

Preclinical study model: solid tumor engineered to express CD19, making it potentially responsive to CD19 CAR-T



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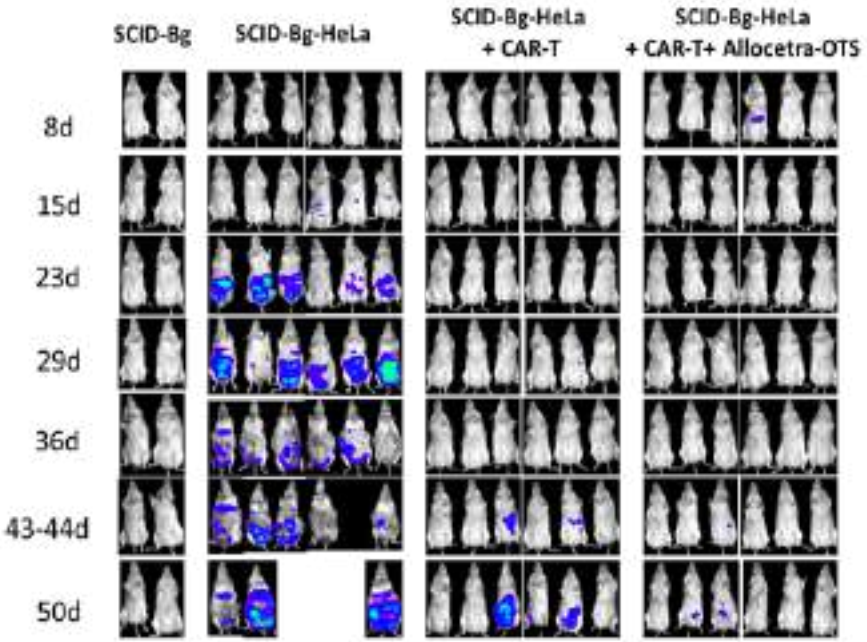
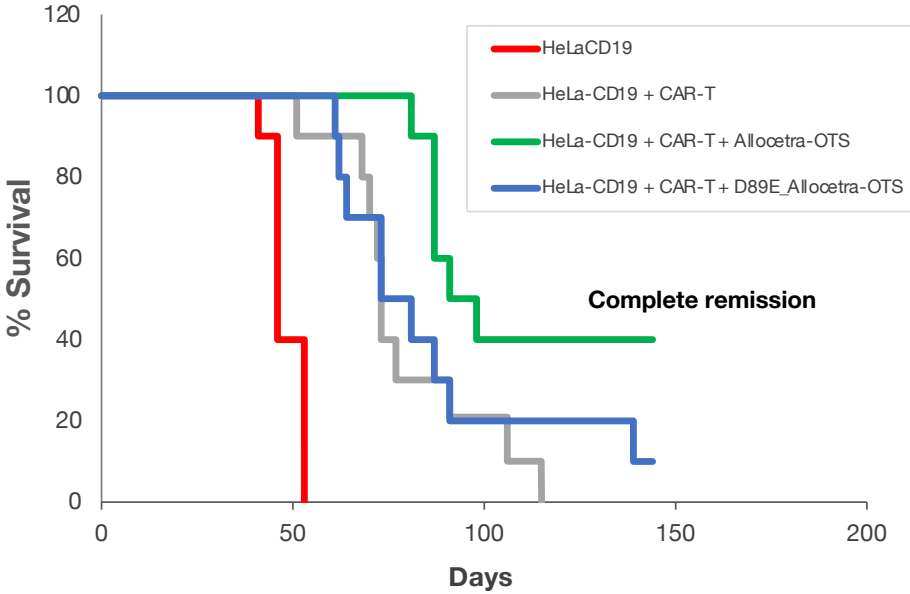
Allocetra™ macrophage reprogramming synergistic with CD19 CAR-T

D89* Allocetra (opsonized, not engulfed by macrophages) has no programming nor clinical effect





Avg. survival, days		
No therapy	CAR-T	CAR-T + Allocetra™
30±5	55±11 (p<0.001)	74±10 (p<0.01)

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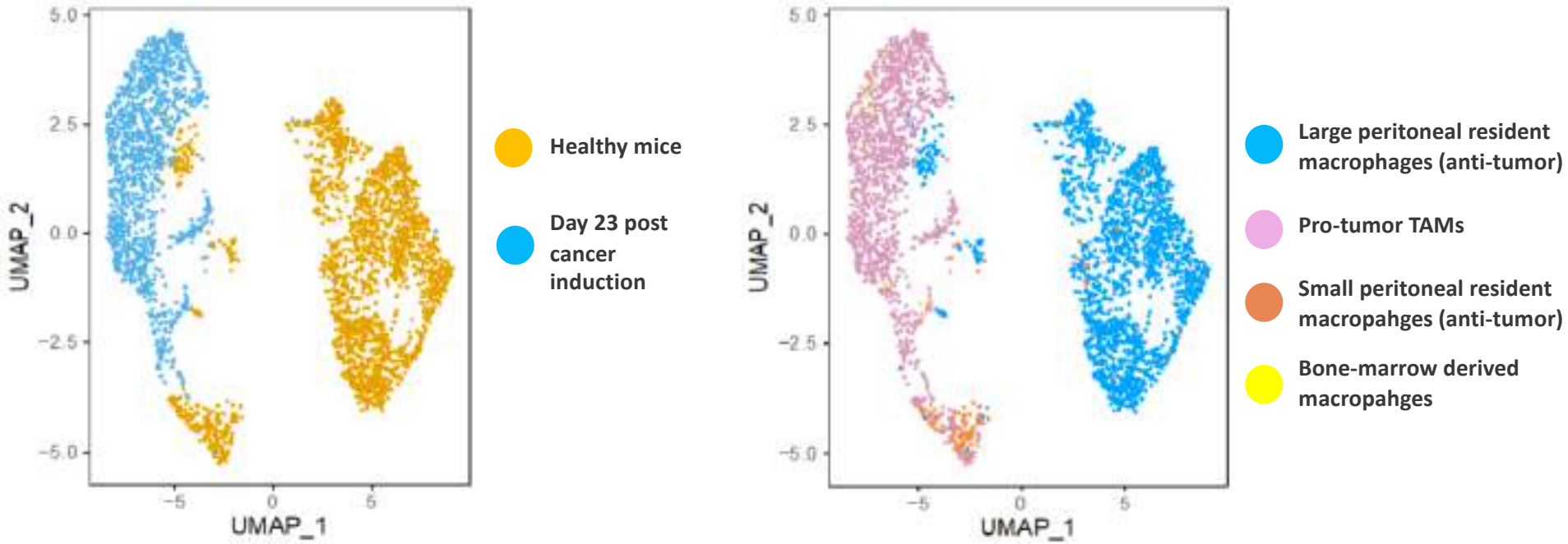
* D89E mutant plasmid was received from N. Nagata, transfected using Lenti X HEK293T cells (Clontech-Takara), and the protein was generated and added to apoptotic cells before intra-peritoneal injection

Balance of resident macrophages vs bloodborne infiltrating macrophages and the effect on anti-tumor activity

Peritoneal fluid myeloid cells populations pre/post induction of peritoneal cancer, SCID-bg mice



In the presence of cancer cells, large and small resident macrophages (anti-tumor) almost disappear, and are replaced with pro-tumor macrophages

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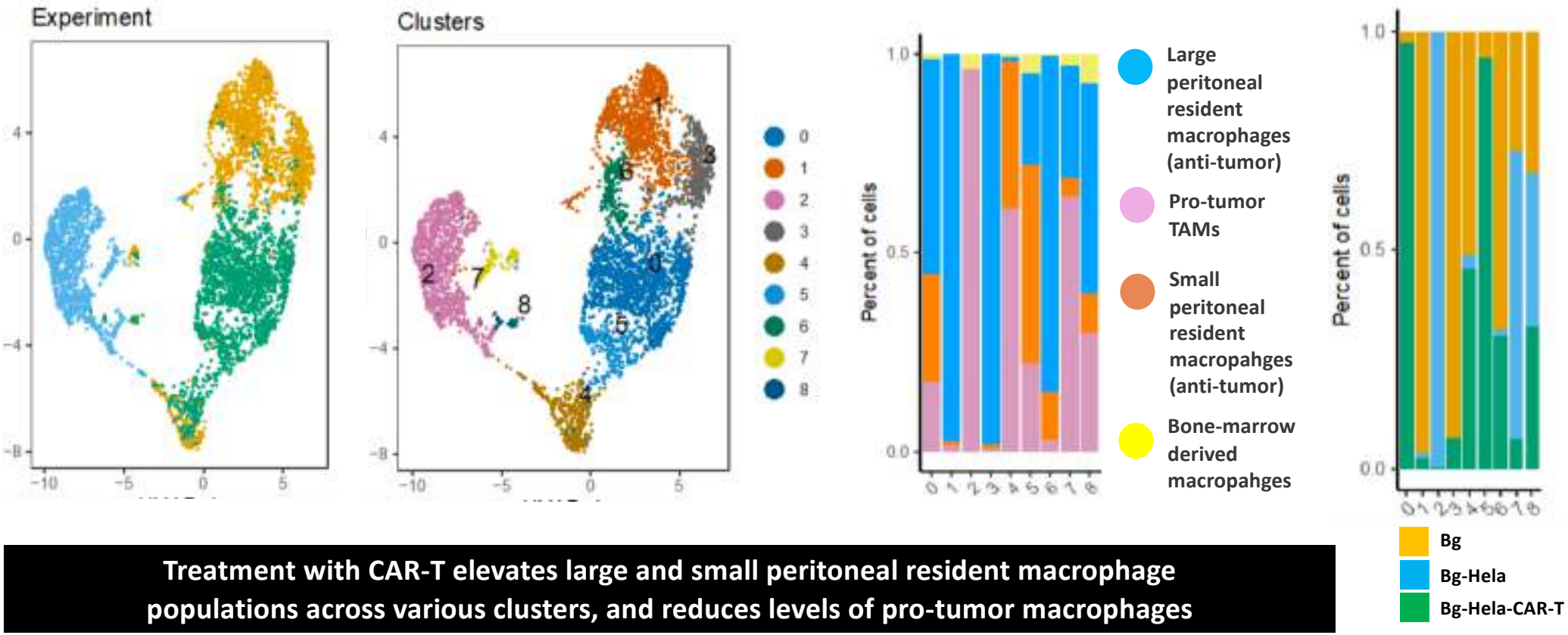
CAR-T treatment restores resident macrophage populations, and depletes pro-tumor infiltrating macrophages

Peritoneal fluid myeloid cells populations pre/post induction of peritoneal cancer, SCID-bg mice



Treatment with CAR-T elevates large and small peritoneal resident macrophage populations across various clusters, and reduces levels of pro-tumor macrophages

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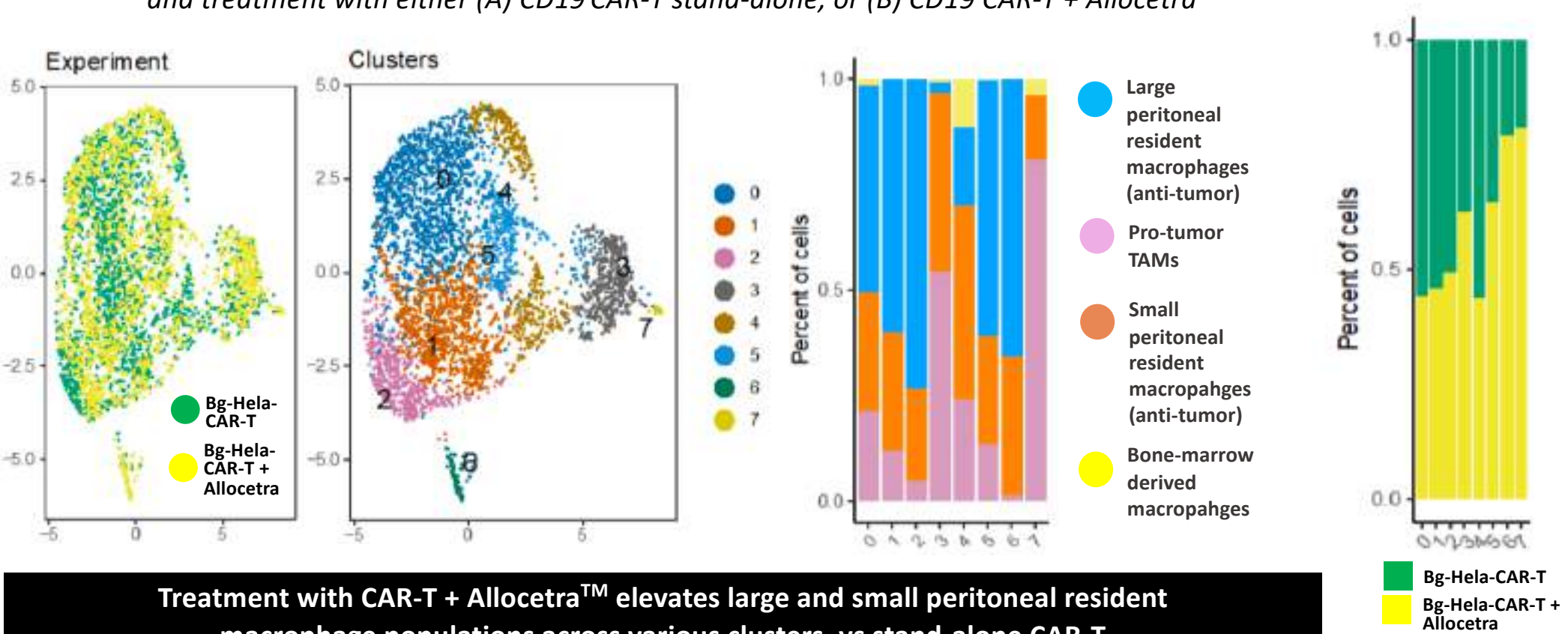
Allocetra's MOA under characterization, single cell analysis

- *Peritoneal fluid myeloid cells populations post induction of CD19⁺ peritoneal cancer in SCID-bg mice and treatment with either (A) CD19 CAR-T stand-alone, or (B) CD19 CAR-T + Allocetra*



Treatment with CAR-T + Allocetra™ elevates large and small peritoneal resident macrophage populations across various clusters, vs stand-alone CAR-T

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Allocetra™

Macrophage reprogramming in solid tumor microenvironment

Clinical programs

Phase I/II Clinical Trial Evaluating Allocetra™ + Chemotherapy in Patients with Peritoneal Metastases Arising from Solid Tumors

	Phase I/II
Addressable global market	$4 Billion market
Type	Open-label, single center
Patients	12, all-comers with peritoneal metastases
Duration	90 days / patient
Expected recruitment	12 Months
End-points	Safety
Secondary	ORR
First patient dosed	Q3/2022

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Phase I/II Clinical Trial Evaluating Allocetra™ + anti-PD1 in Patients with Solid Tumors

	Phase I/II
Addressable global market	$4 Billion market
Type	Open-label, multi-center
Patients	36-48, ~all-comers with solid tumors
Duration	90 days / patient
Expected recruitment	24 Months
End-points	Safety
Secondary	ORR
First patient dosed	Q4/2022

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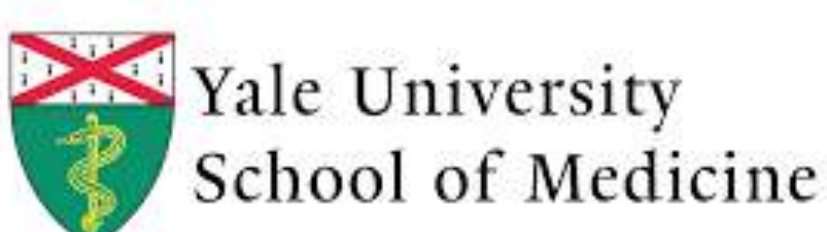
Allocetra macrophage reprogramming research collaborations



Collaborations aim to evaluate the potential of Allocetra™ in combination with immune-checkpoint inhibitors in solid cancer patients that do not respond to stand-alone checkpoint inhibitor therapies

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Planned milestones (24 months)

Q1 2022

Completion of development of frozen formulation Allocetra™

Q3 2022

Regulatory approval for the integration of frozen formulation Allocetra™ into Phase II sepsis and oncology studies

Q4 2022

Initiation of Phase I/II in advanced-stage solid tumors patients with peritoneal metastases, stand-alone + in combination with anti-PD1

Q3 2022

Initiation of Phase I/II in advanced-stage solid tumors patients with peritoneal metastases, in combination with chemotherapy

Q1 2023

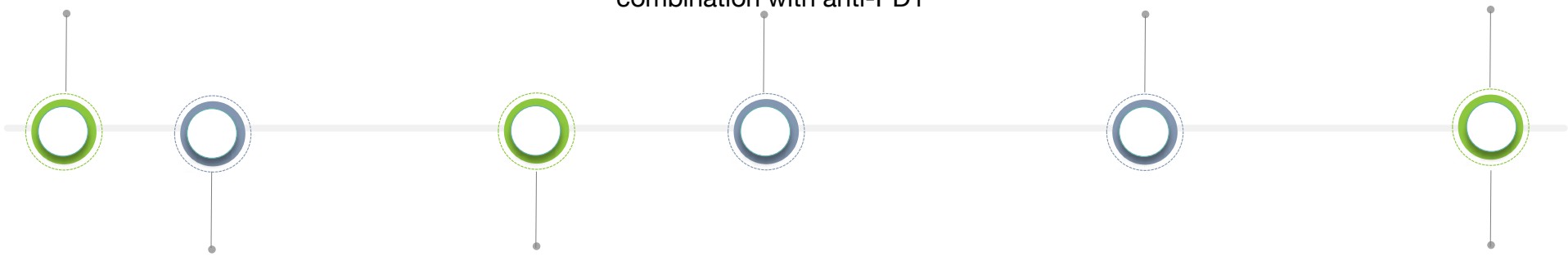
Interim data macrophage reprogramming sepsis Phase II

Q3 2023

Top line data macrophage reprogramming sepsis Phase II

Q3 2023

Top line Allocetra™ Phase I/II studies



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Financial Summary

NASDAQ GS	ENLV
Cash	$62MM (Jun 30, 2022)
Debt	None
Shares Outstanding	18.2 MM
Funded Through	Q3 2024

Management

Shai Novik Executive Chairman	Founder and President of PROLOR Biotech, Sold in 2013 ($560mm transaction). Lead product partnered to Pfizer, $295 million down payment, $275 upon FDA & other regulatory approvals. BLA filed by Pfizer late 2020.
Oren Hershkovitz CEO	Former Director of CMC, VP R&D and General Manager of OPKO Biologics (PROLOR Biotech). Led multiple clinical programs in Phase I, II and III. Ph.D. in Immunology.
Dror Mevorach Chief Scientific Officer	Director, Rheumatology Research Centre and Molecular Immunology; and Director, Centre for Rare diseases, Hadassah Medical Center, Jerusalem.
Einat Galamidi VP Medical	10 years at Gamida Cell Ltd., where Dr. Galamidi most recently served as Vice President of Clinical Development, She led clinical development for omidubicel (rolling-BLA submission in 2022).
Iris Tavor Senior Director of RA/QA	13 years of experience in Quality and Regulatory Affairs in at Pluristem Ltd, where most recently Iris served as the Head of Regulatory Affairs and led submissions of several INDs and CTAs.
Veronique Amor-Baroukh Senior Director of Operations	Extensive experience as manager of Allocetra development department, CMC and operation at Enlivex, Ph.D., Molecular Neurobiology, Weizmann Institute of Science.
Shachar Shlosberger CFO	~Former PROLOR Biotech Ltd Finance Director where she was responsible for the overall financial operations in Israel and US. A C.P.A., and holds a M.B.A. in Accounting and Business Administration.
Chen Ankri Director of Pre-Clinical & Clinical pharmacology	Ph.D., Cancer Immunotherapy, Bar-Ilan University, Israel. Former Immunology research manager in CTG Pharma. Several years of experience in immunotherapy R&D in various biotech companies

Board Of Directors

Shai Novik Executive Chairman	Founder and President of PROLOR Biotech, Sold in 2013 ($560mm transaction). Lead product partnered to Pfizer, $295 million down payment, $275 upon FDA & other regulatory approvals. BLA filed by Pfizer late 2020.
Roger Pomerantz Vice Chairman	Former Worldwide Head of Licensing and Acquisition and Knowledge Management at Merck & Co., where he led the completion of more than150 business development transactions. Former Global Head of Infectious Diseases for Johnson & Johnson Pharmaceuticals. Former Venture Partner at Flagship Pioneering, as well as the former President, CEO, and Chairman of the Board of Seres Therapeutics
Sangwoo Lee Director	Executive Director of the Investment Department & Head of U.S. Branch at Korea Investment Partners Co. Ltd
Bernhard Kirschbaum, PhD Director	Former Executive Vice President & Member of the Board at Merck Serono, and Head of Global Research & Early Development
Gili Hart, Ph.D Director	Formerly with PROLOR Biotech, led the pre-clinical, clinical and pharmacological activities. CEO of Mitoconix Bio, a biopharmaceutical company developing disease modifying therapies addressing unmet medical needs
Brian Schwartz, M.D. Director	Former CMO of Arqule through its $2.7 billion acquisition by Merck in 2020. Previously, responsible for the global clinical development of sorafenib (Nexavar®) at Bayer Healthcare.
Abraham Havron, Ph.D. Director	Former CEO of PROLOR Biotech. Founding team and Director of R&D of Interpharm (Merck Serono) ,VP CMC of BioTechnology General Ltd., and VP of Clal Biotechnology Industries Ltd.
Michel Habib Director	Managing partner of ALIVE, a medical device VC fund; Former CEO of HBL, former Managing Partner of Agate-MaC Fund, a healthcare VC

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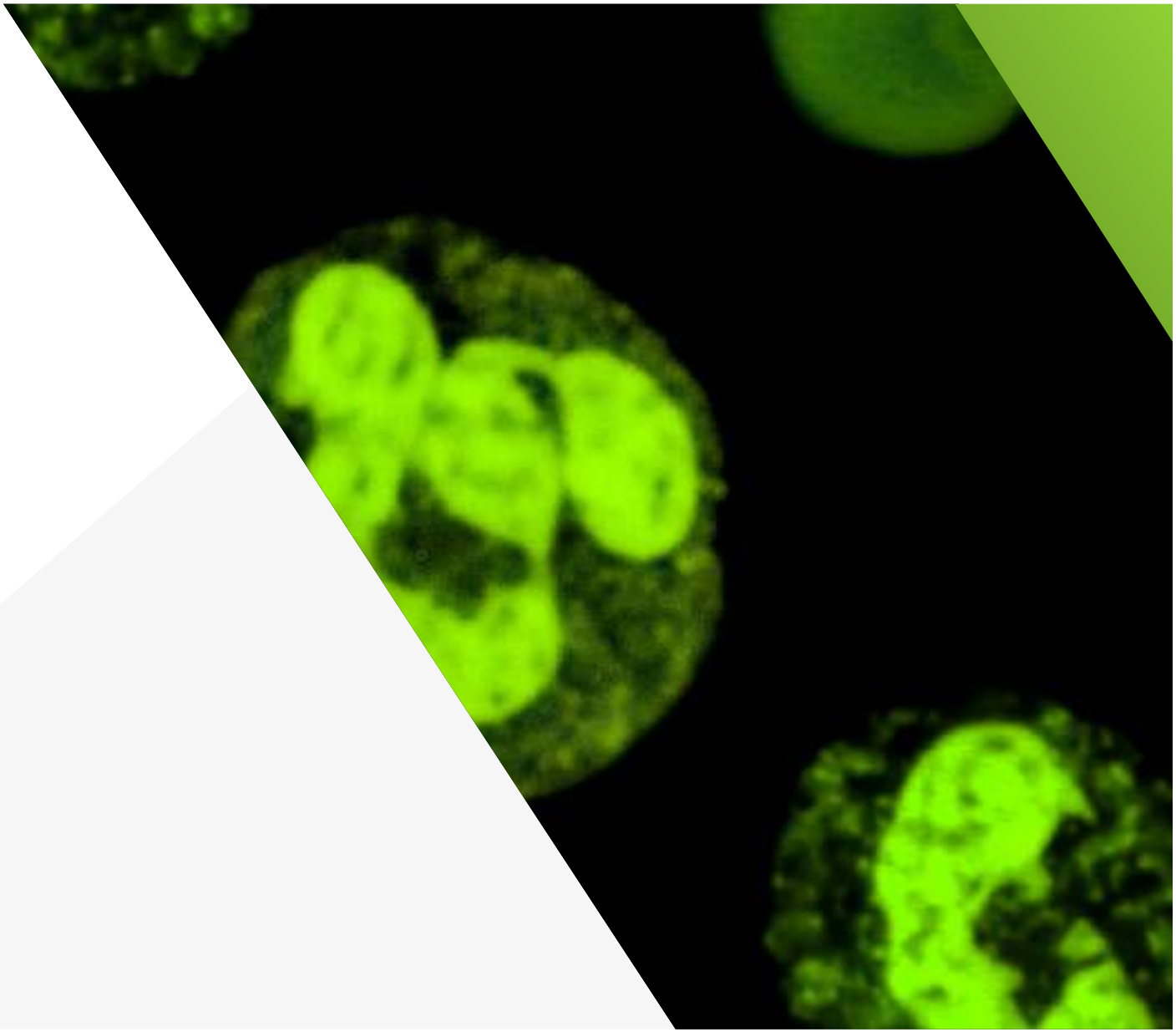
Thank You