



CAR-T AND MICROBIOME

Rob Jenq, MD

City of Hope National Medical Center

Los Angeles, California

Friday, September 13, 2024

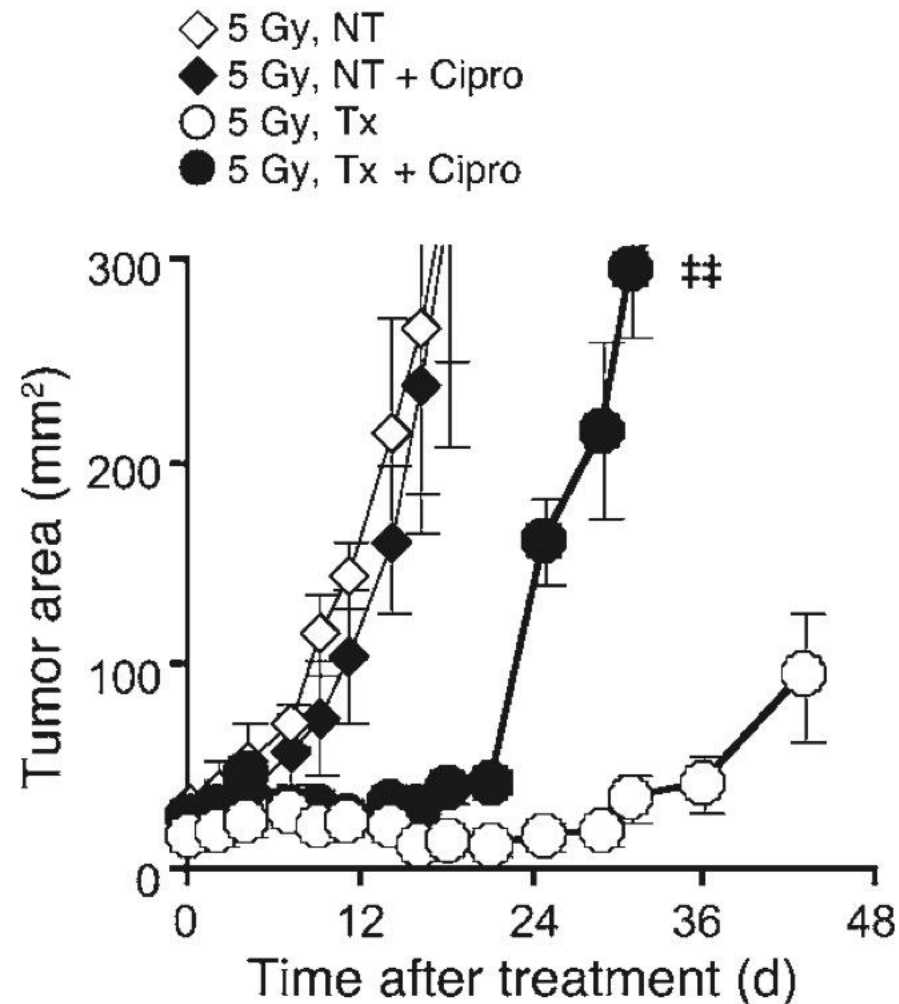
Disclosures

- Advisory board for Probiotics Plus, LIScure Biosciences, MaaT Pharma, Prolacta Biosciences, and Seres Therapeutics
- Royalties from Seres Therapeutics



Microbial translocation augments the function of adoptively transferred self/tumor-specific CD8⁺ T cells via TLR4 signaling

Chrystal M. Paulos,¹ Claudia Wrzesinski,¹ Andrew Kaiser,¹ Christian S. Hinrichs,¹ Marcello Chieppa,² Lydie Cassard,¹ Douglas C. Palmer,¹ Andrea Boni,¹ Pawel Muranski,¹ Zhiya Yu,¹ Luca Gattinoni,¹ Paul A. Antony,³ Steven A. Rosenberg,¹ and Nicholas P. Restifo¹



Paulos, et al, JCI, 2007



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Commensal Bacteria Control Cancer Response to Therapy by Modulating the Tumor Microenvironment

Noriho Iida,^{1*} Amiran Dzutsev,^{1,2*} C. Andrew Stewart,^{1*} Loretta Smith,¹ Nicolas Bouladoux,³ Rebecca A. Weingarten,⁴ Daniel A. Molina,⁵ Rosalba Salcedo,¹ Timothy Back,¹ Sarah Cramer,¹ Ren-Ming Dai,^{1,2} Hiu Kiu,¹ Marco Cardone,¹ Shruti Naik,³ Anil K. Patri,⁶ Ena Wang,⁷ Francesco M. Marincola,^{7,8} Karen M. Frank,⁴ Yasmine Belkaid,³ Giorgio Trinchieri,^{1††} Romina S. Goldszmid^{1††}

Iida, et al, Science, 2013

The Intestinal Microbiota Modulates the Anticancer Immune Effects of Cyclophosphamide

Sophie Viaud,^{1,3} Fabiana Saccheri,¹ Grégoire Mignot,^{4,5} Takahiro Yamazaki,¹ Romain Daillère,^{1,3} Dalil Hannani,¹ David P. Enot,^{7,8} Christina Pfirschke,⁹ Camilla Engblom,⁹ Mikael J. Pittet,⁹ Andreas Schlitzer,¹⁰ Florent Ginhoux,¹⁰ Lionel Apetoh,^{4,5} Elisabeth Chachaty,¹¹ Paul-Louis Woerther,¹¹ Gérard Eberl,¹² Marion Bérard,¹³ Chantal Ecobichon,^{14,15} Dominique Clermont,¹⁶ Chantal Bizet,¹⁶ Valérie Gaboriau-Routhiau,^{17,18} Nadine Cerf-Bensussan,^{17,18} Paule Opolon,^{19,20} Nadia Yessaad,^{21,22,23,24} Eric Vivier,^{21,22,23,24} Bernhard Ryffel,²⁵ Charles O. Elson,²⁶ Joël Doré,^{17,27} Guido Kroemer,^{7,8,28,29,30} Patricia Lepage,^{17,27} Ivo Gomperts Boneca,^{14,15} François Ghiringhelli,^{4,5,6*} Laurence Zitvogel^{1,2,3*†}

Viaud, et al, Science, 2013

Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota

Marie Vétizou,^{1,2,3} Jonathan M. Pitt,^{1,2,3} Romain Daillère,^{1,2,3} Patricia Lepage,⁴
Nadine Waldschmitt,⁵ Caroline Flament,^{1,2,6} Sylvie Rusakiewicz,^{1,2,6}
Bertrand Routy,^{1,2,3,6} Maria P. Roberti,^{1,2,6} Connie P. M. Duong,^{1,2,6}
Vichnou Poirier-Colame,^{1,2,6} Antoine Roux,^{1,2,7} Sonia Becharef,^{1,2,6} Silvia Formenti,⁸
Encouse Golden,⁸ Sascha Cording,⁹ Gerard Eberl,⁹ Andreas Schlitzer,¹⁰
Florent Ginhoux,¹⁰ Sridhar Mani,¹¹ Takahiro Yamazaki,^{1,2,6} Nicolas Jacquelot,^{1,2,3}
David P. Enot,^{1,7,12} Marion Bérard,¹³ Jérôme Nigou,^{14,15} Paule Opolon,¹
Alexander Eggermont,^{1,2,16} Paul-Louis Woerther,¹⁷ Elisabeth Chachaty,¹⁷
Nathalie Chaput,^{1,18} Caroline Robert,^{1,16,19} Christina Mateus,^{1,16}
Guido Kroemer,^{7,12,20,21,22} Didier Raoult,²³ Ivo Gomperts Boneca,^{24,25*}
Franck Carbonnel,^{3,26*} Mathias Chamillard,^{5*} Laurence Zitvogel^{1,2,3,6†}

Vétizou, et al, Science, 2015

Commensal *Bifidobacterium* promotes antitumor immunity and facilitates anti-PD-L1 efficacy

Ayelet Sivan,^{1*} Leticia Corrales,^{1*} Nathaniel Hubert,² Jason B. Williams,¹
Keston Aquino-Michaels,³ Zachary M. Earley,² Franco W. Benyamin,¹ Yuk Man Lei,²
Bana Jabri,² Maria-Luisa Alegre,² Eugene B. Chang,² Thomas F. Gajewski^{1,2†}

Sivan, et al, Science, 2015

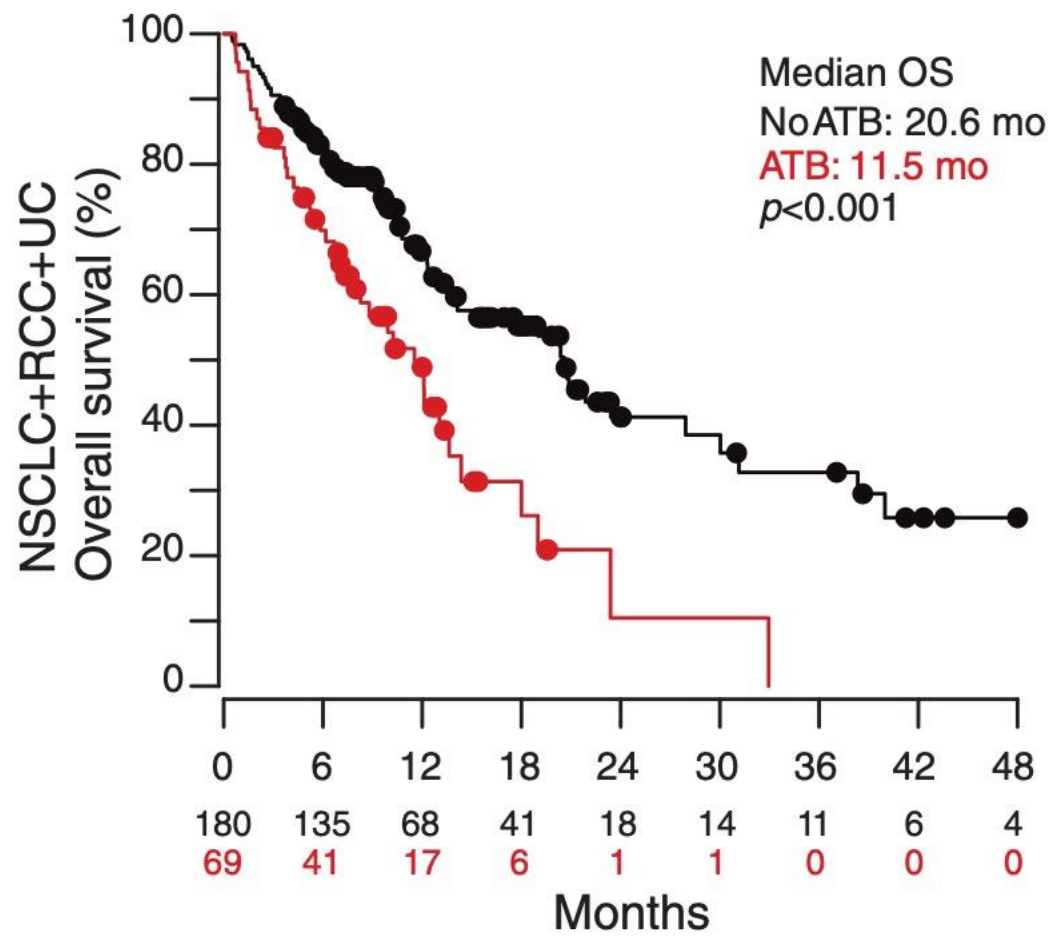
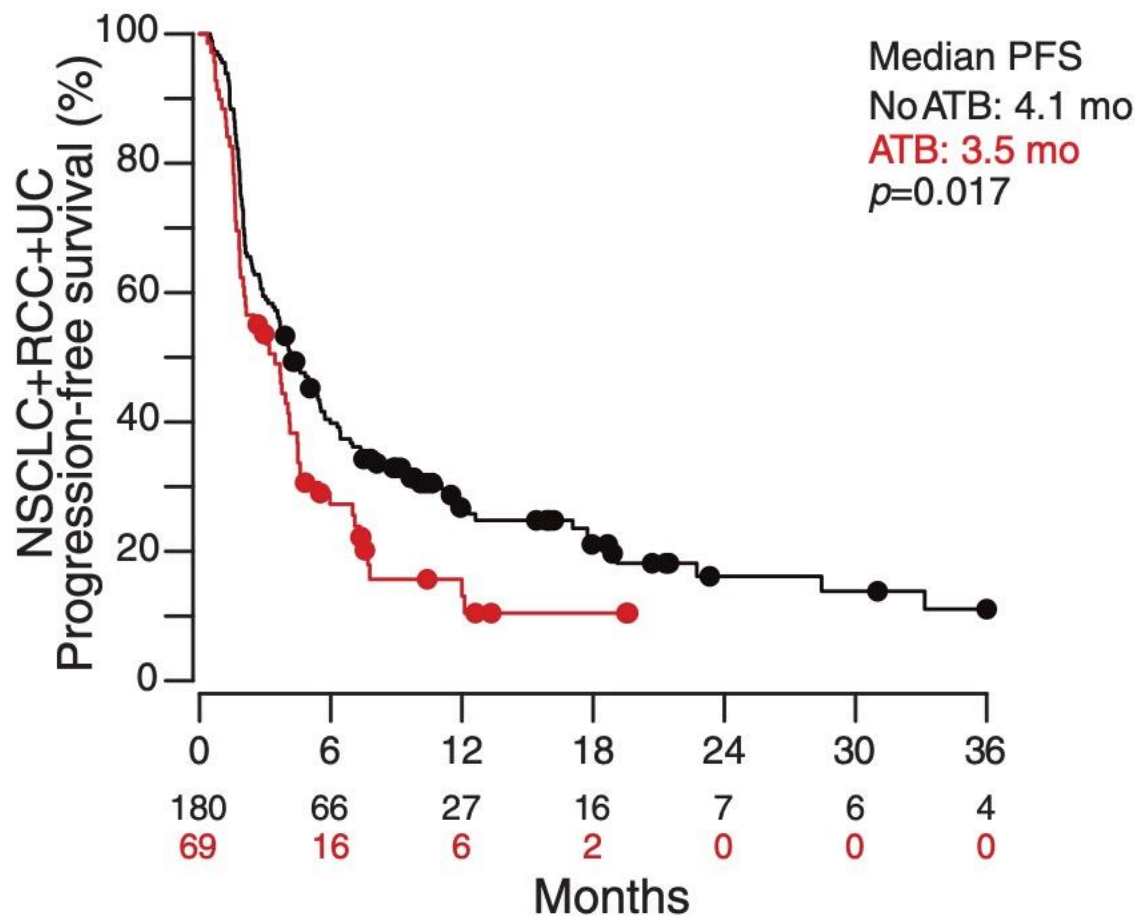
2018 – Microbiome linked to clinical PD1 blockade outcomes

➤ Gopalakrishnan, et al

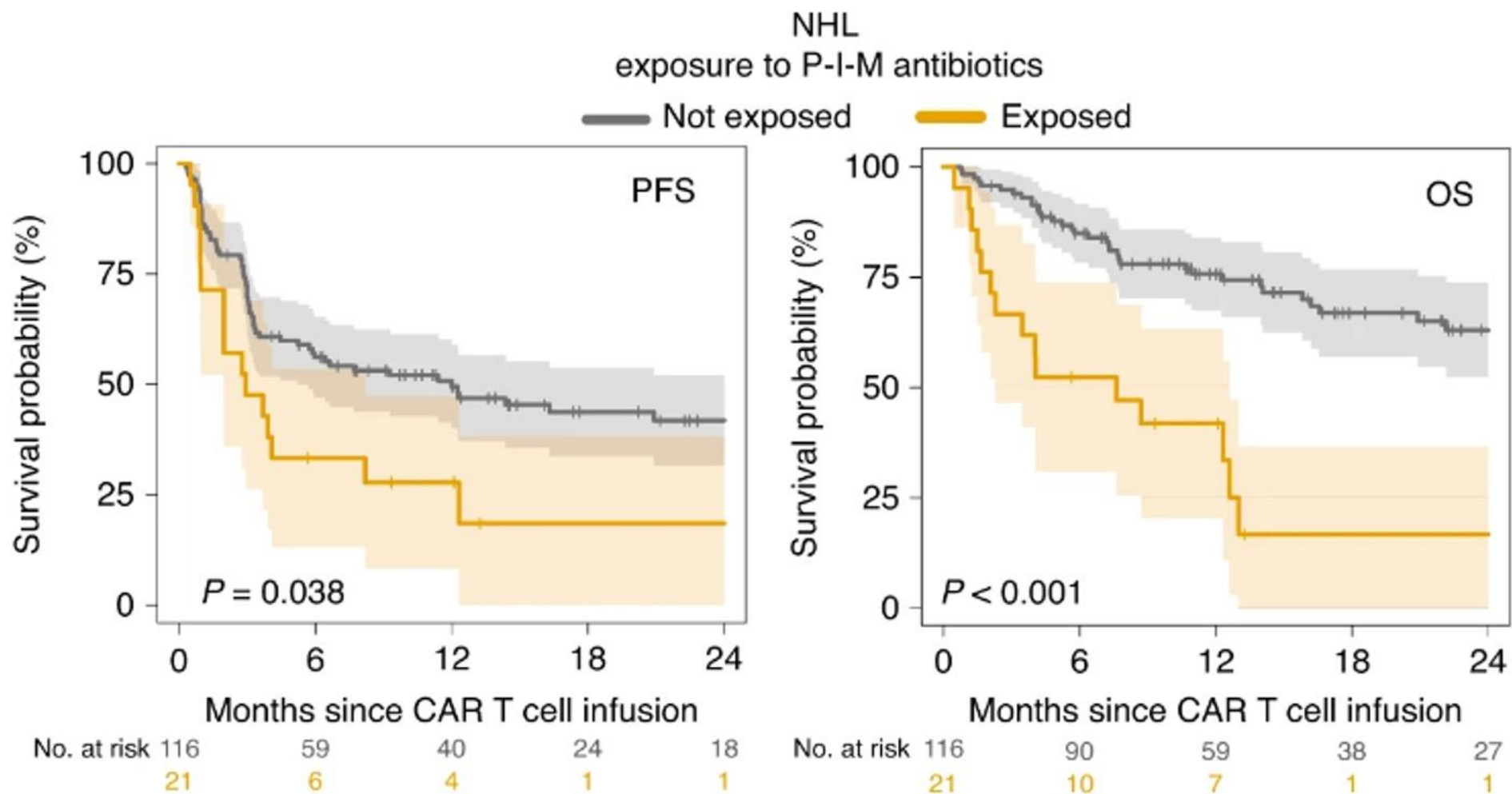
➤ Matson, et al

➤ Routy, et al





PIM antibiotics exposure pre-CAR-T associates with poor survival outcomes



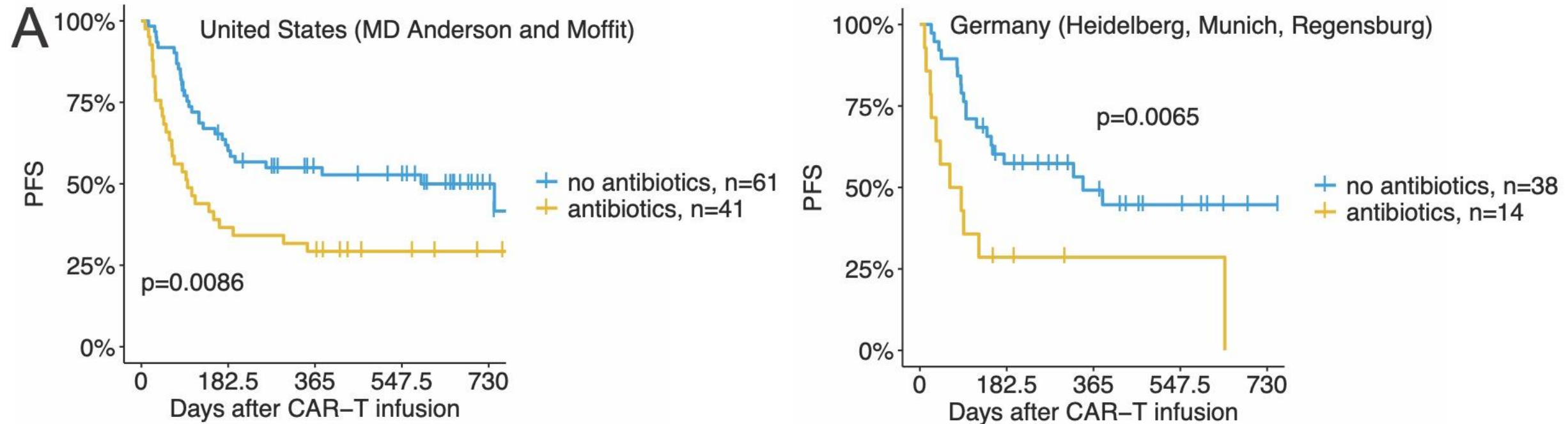
PIM

- Piperacillin-tazobactam
- Imipenem
- Meropenem

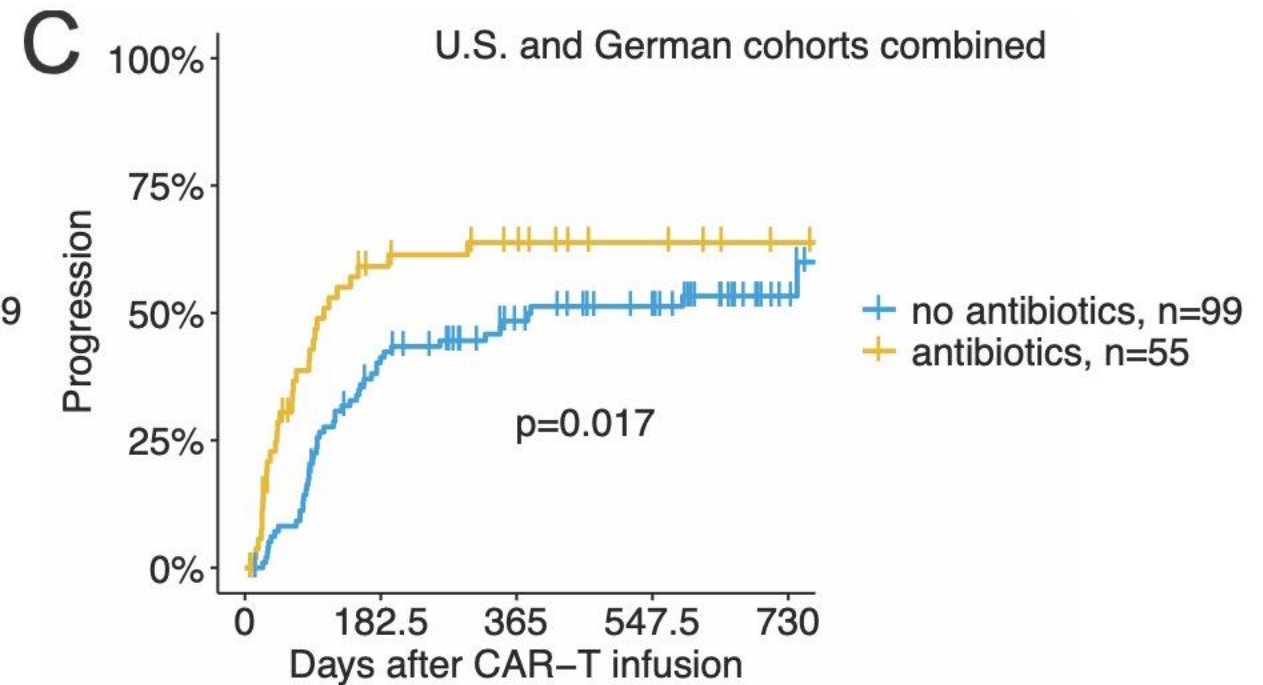
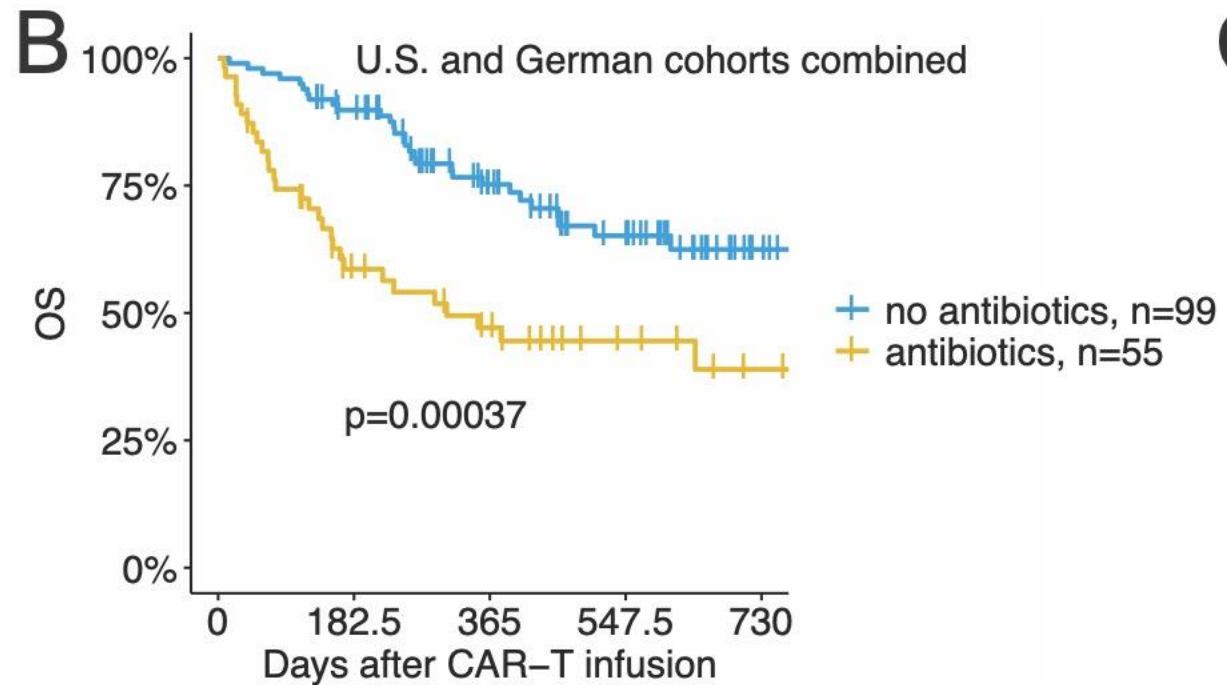
Retrospective multi-center analysis

- Patients undergoing CD19-targeted CAR-T cell therapy (axicabtagene ciloleucel, n=111, or tisagenlecleucel, n=43)
- Treated as standard-of-care
- Participating centers from the United States (MD Anderson, n=58, Moffitt, n=44) and Germany (Heidelberg, n=18, Munich, n=31, Regensburg, n=3)

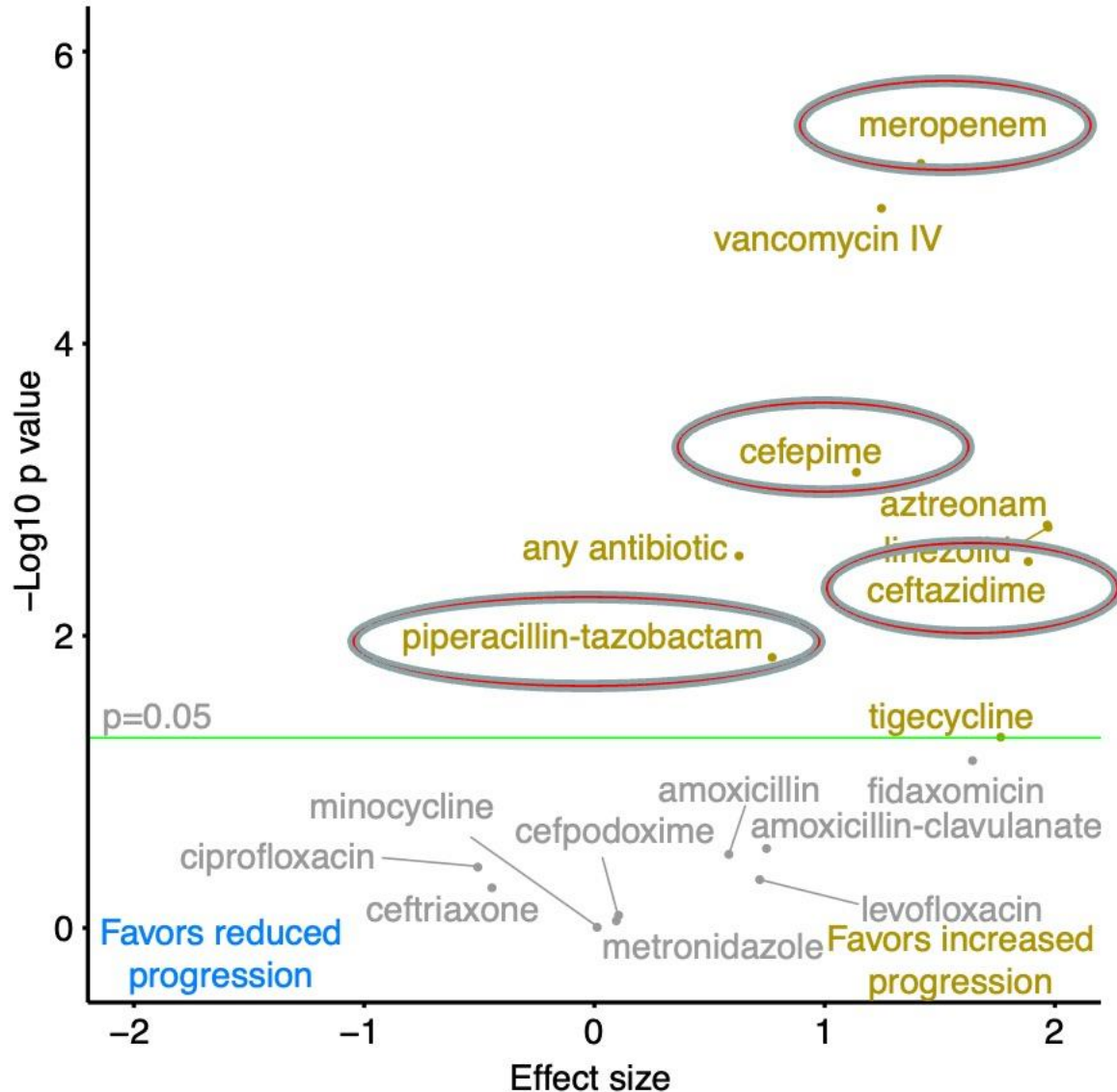
Effects of antibiotics (given within 3 weeks before CAR-T infusion) on progression-free survival



Effects of antibiotics on overall survival and progression incidence



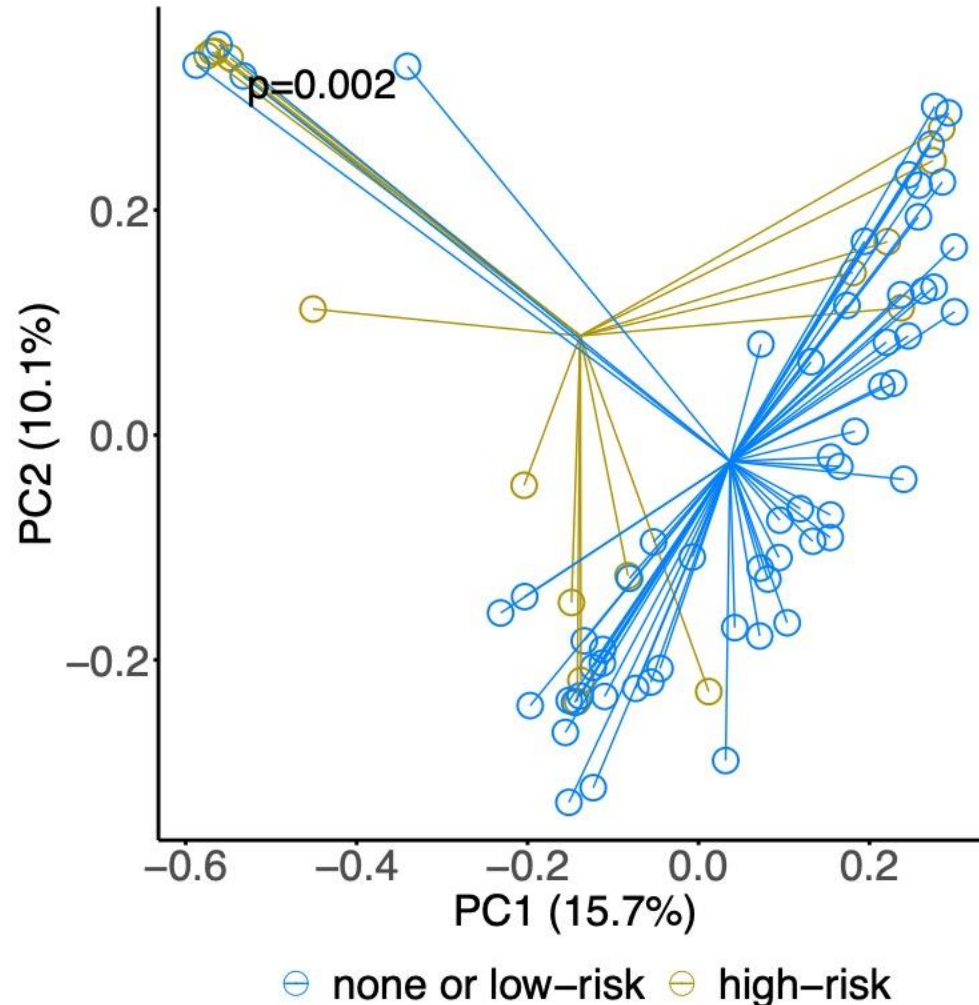
Effects of specific antibiotics on progression



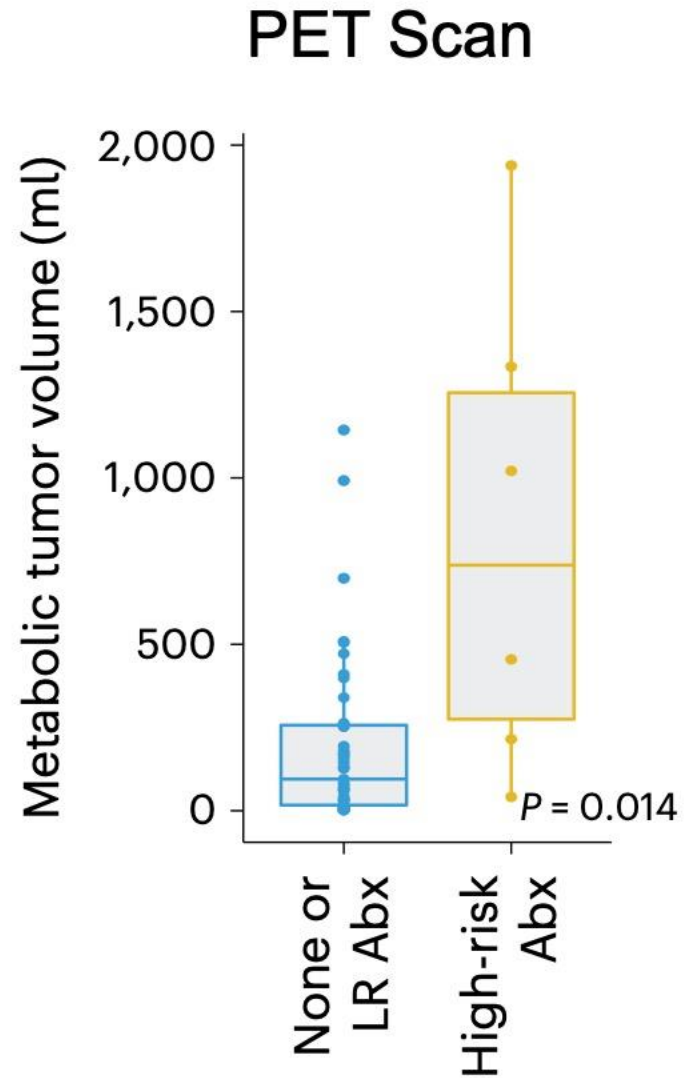
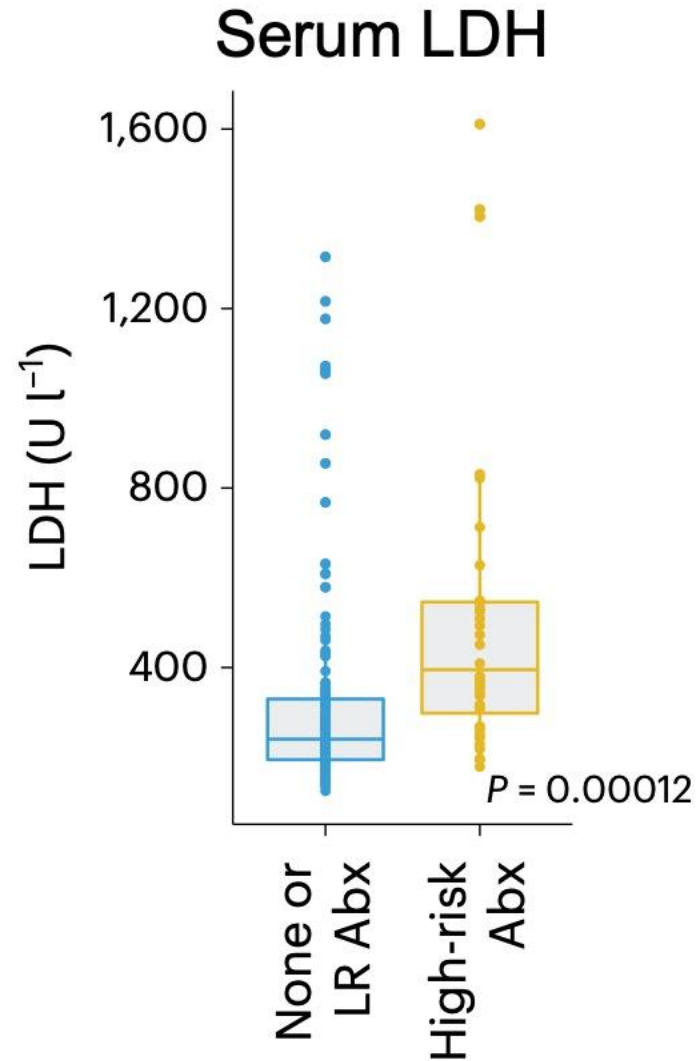
"high-risk antibiotics" –
anti-pseudomonal beta lactams:

- Carbapenems
- Cefepime or ceftazidime
- Piperacillin-tazobactam

Effects of high-risk antibiotics on fecal microbiome composition

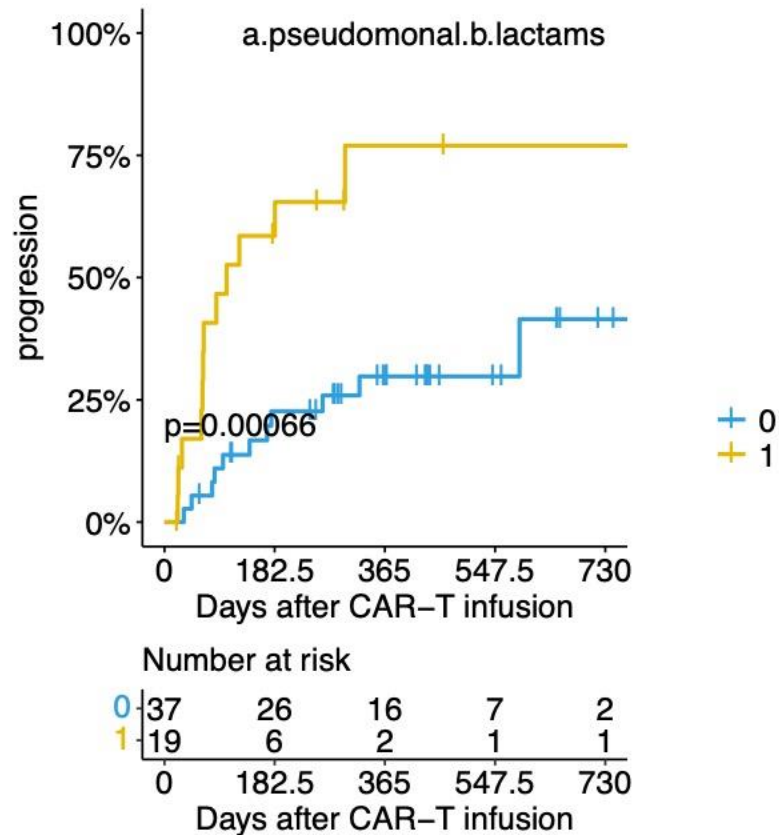


Microbiome skepticism – previous antibiotic use linked to higher disease burden

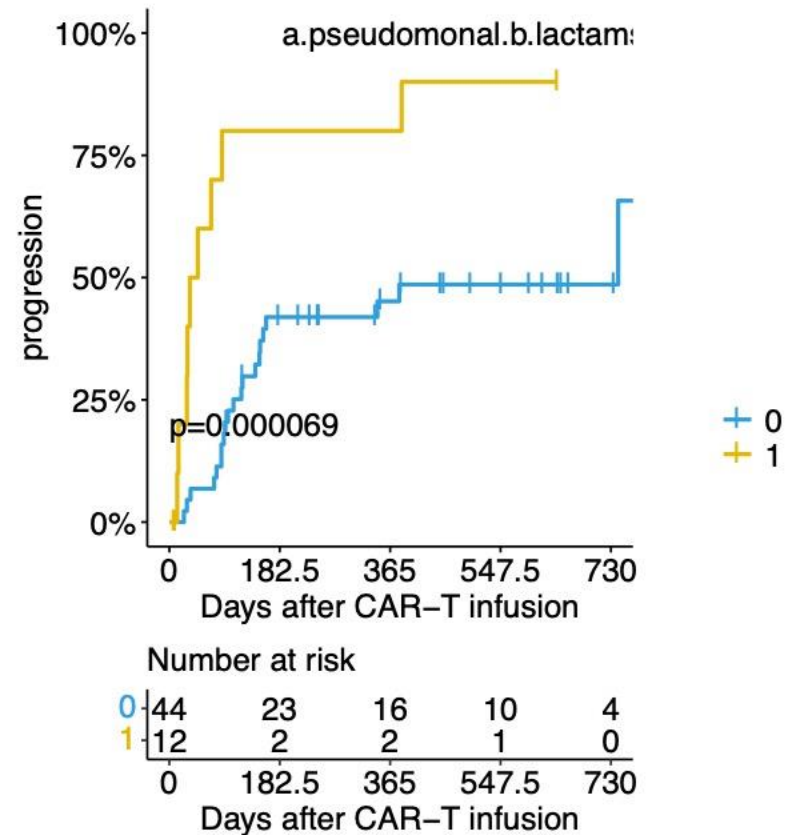


We see an association of antibiotics with disease progression across LDH levels

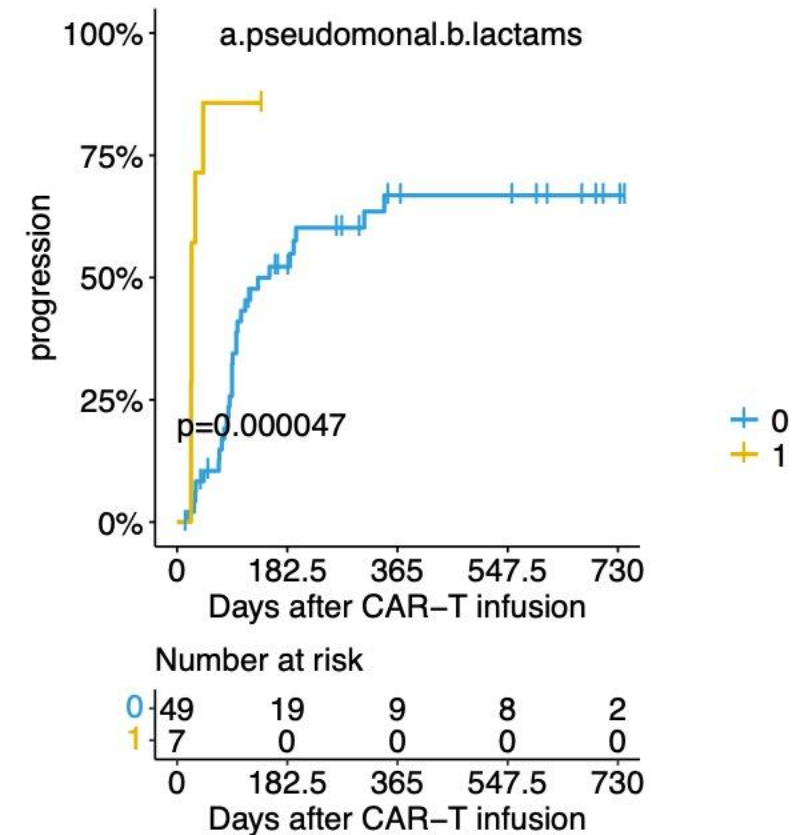
Low LDH tertile



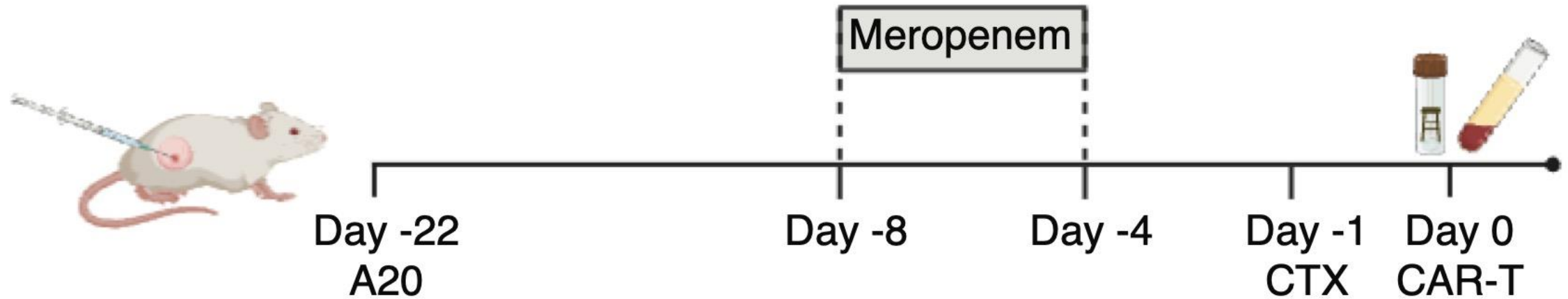
Medium LDH tertile



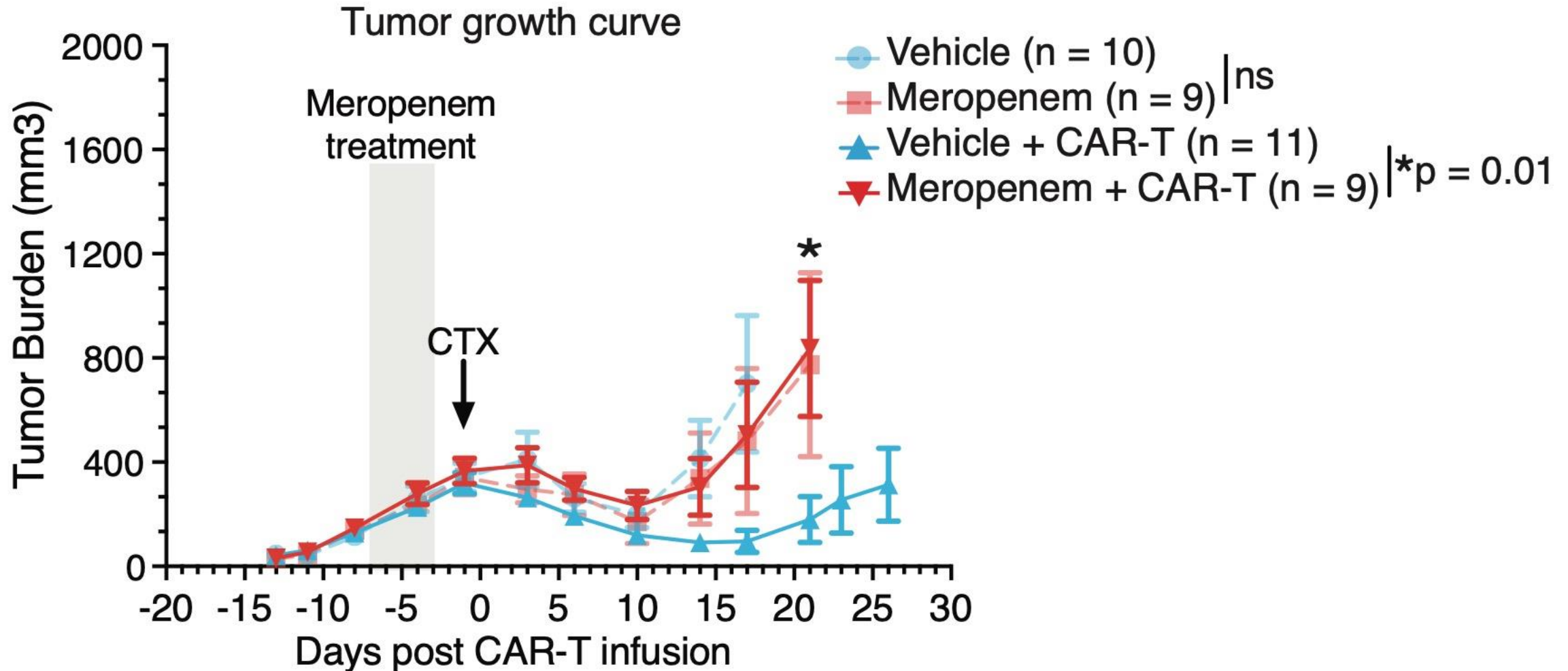
High LDH tertile



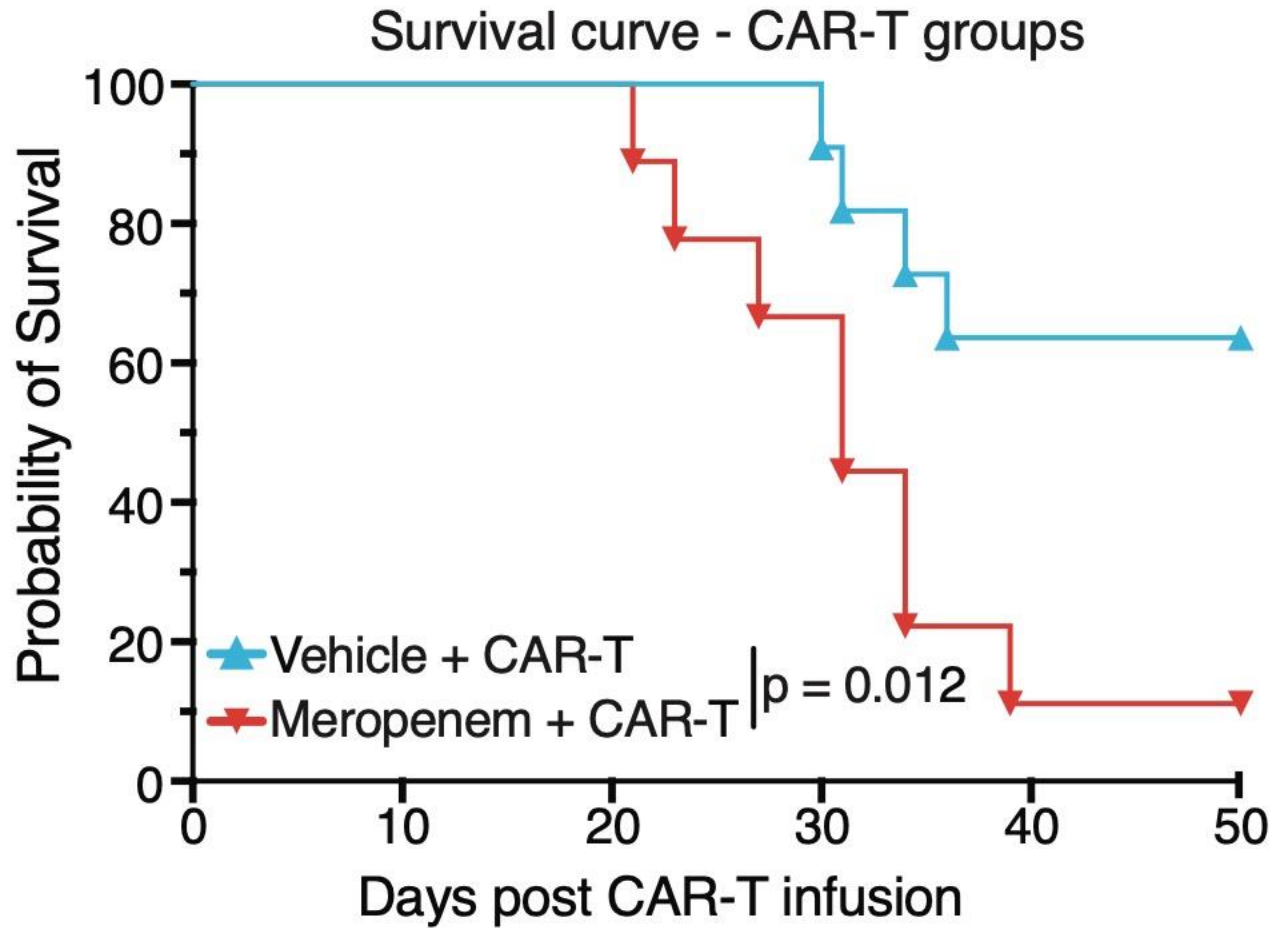
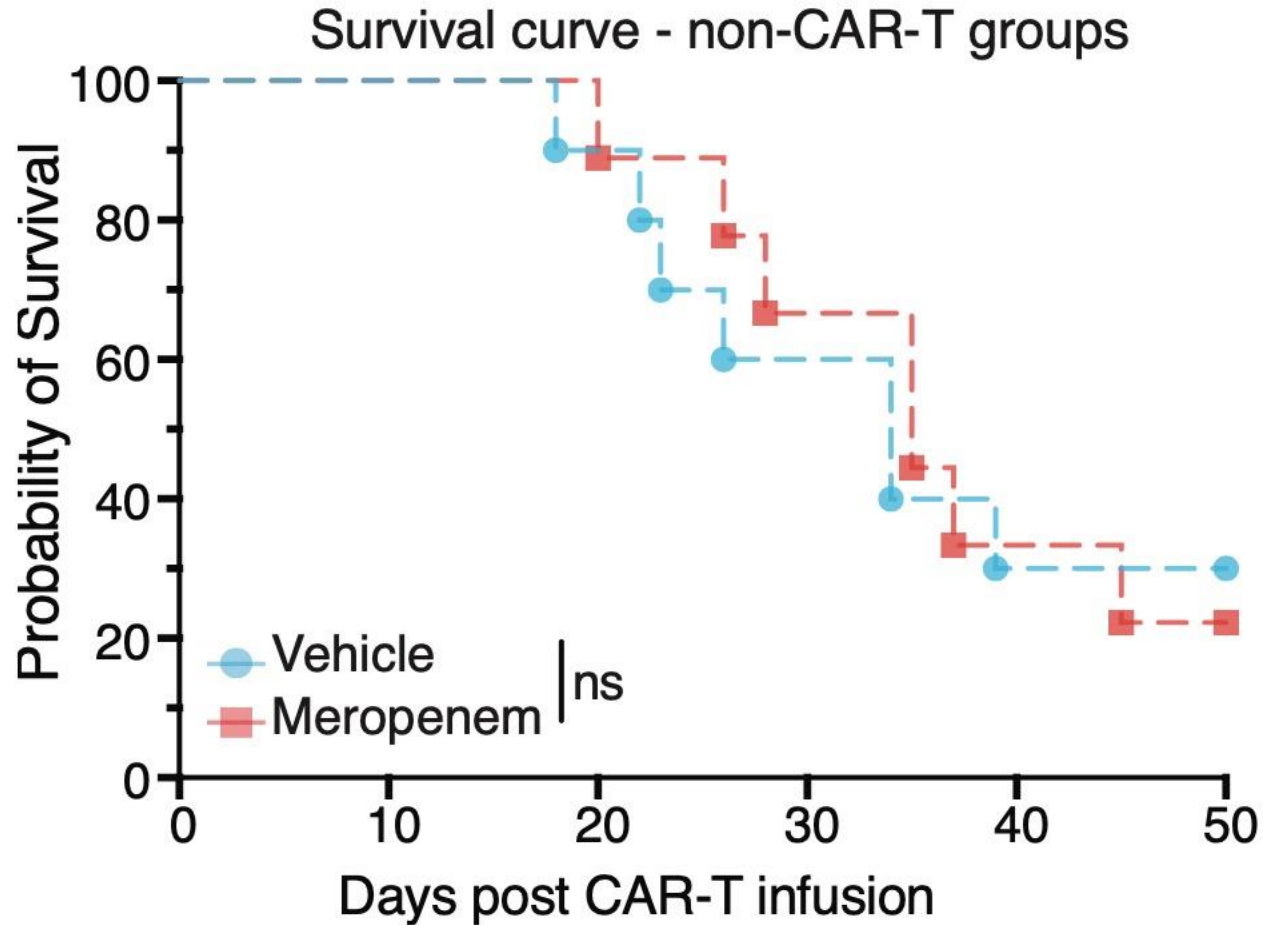
Evaluating effects of antibiotics in an immune-competent model of anti-CD19 CAR-T therapy



Meropenem pre-treatment impairs CAR-T tumor control



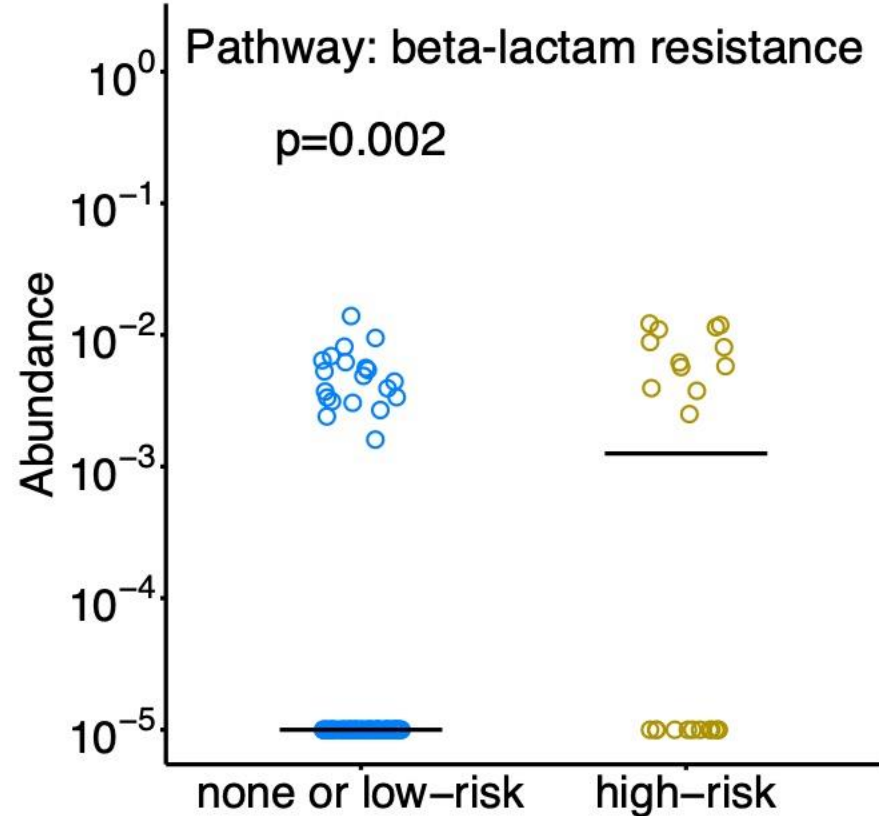
Meropenem pre-treatment impairs CAR-T tumor control



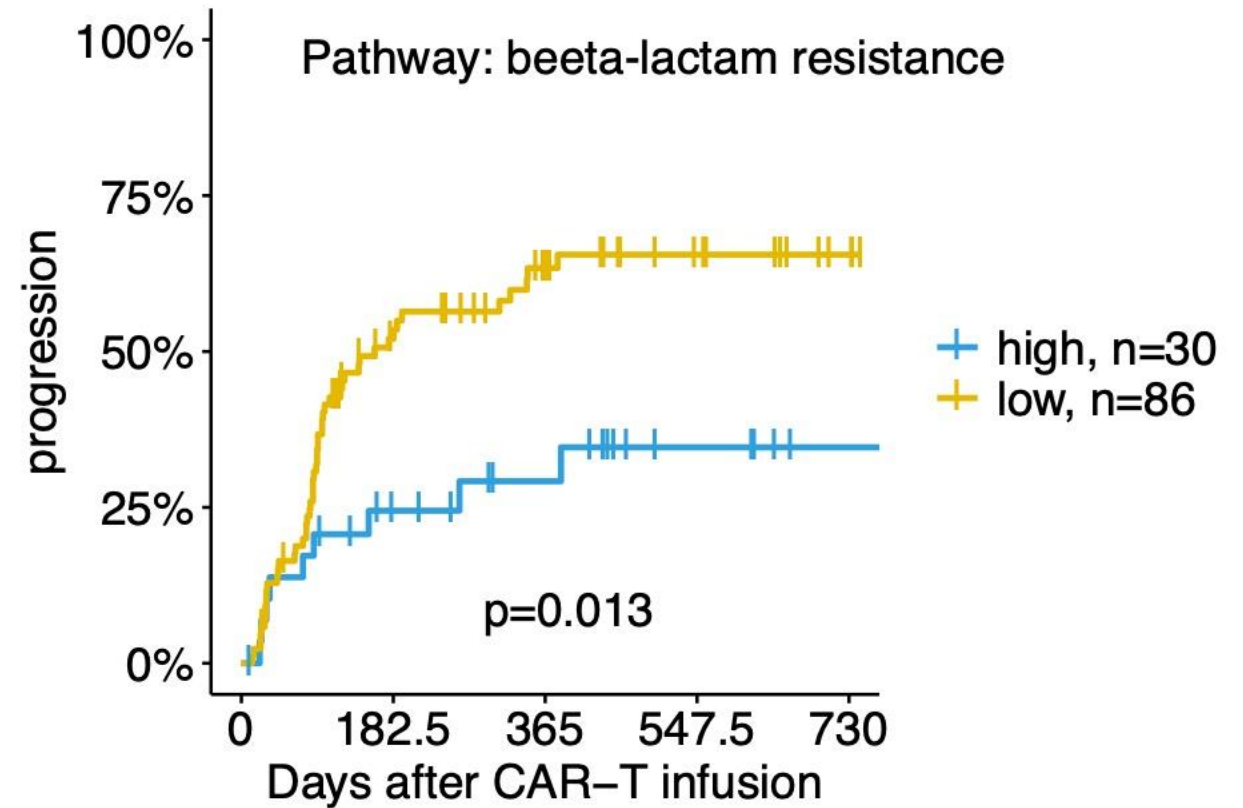
MetaCyc Pathway: peptidoglycan biosynthesis V

(β -lactam resistance)

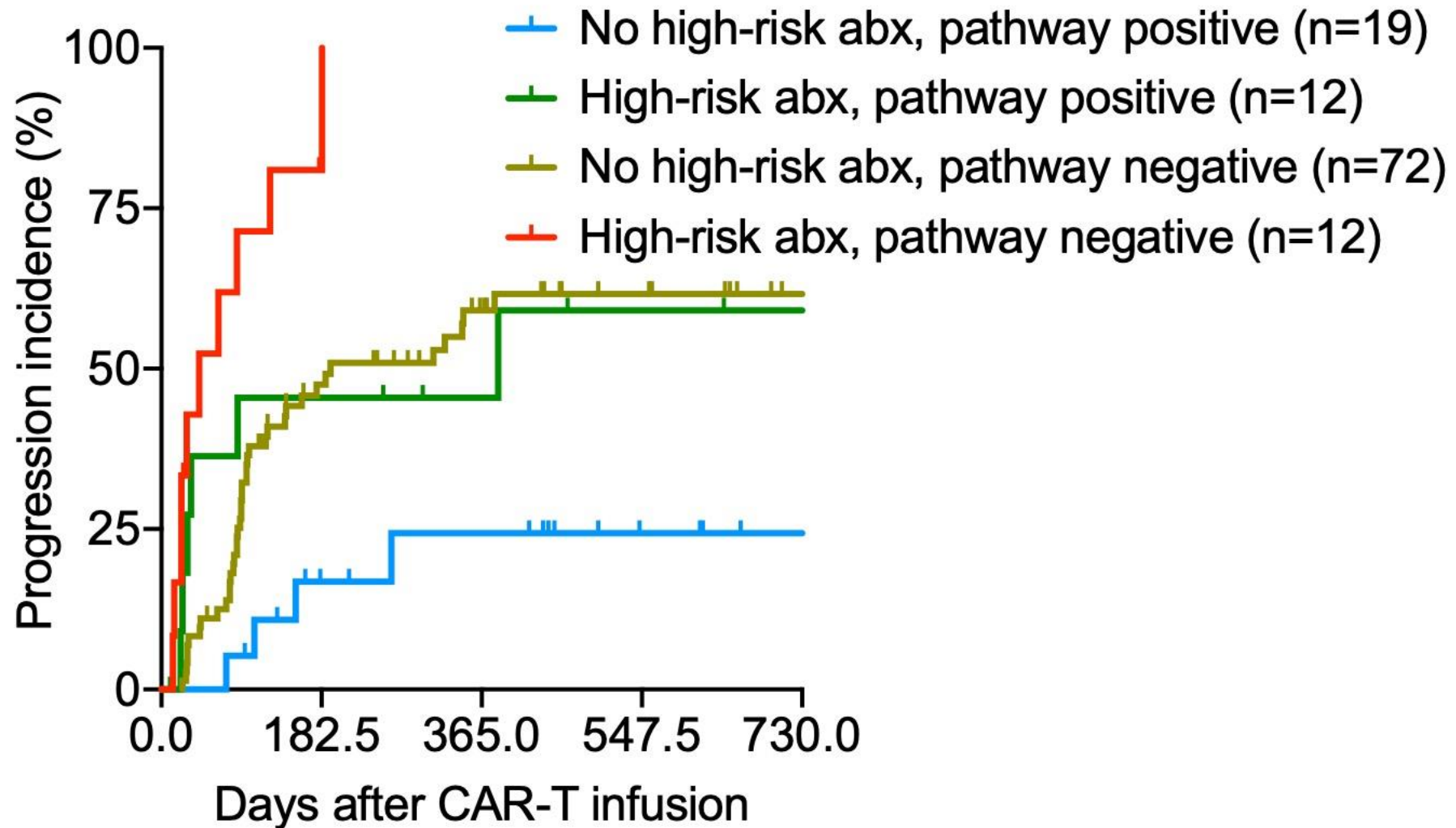
Antibiotics



Progression



MetaCyc Pathway: peptidoglycan biosynthesis V (β -lactam resistance)



MetaCyc Pathway: peptidoglycan biosynthesis V (β -lactam resistance)

Some taxa known to possess this pathway include  : [Enterococcus faecium](#)

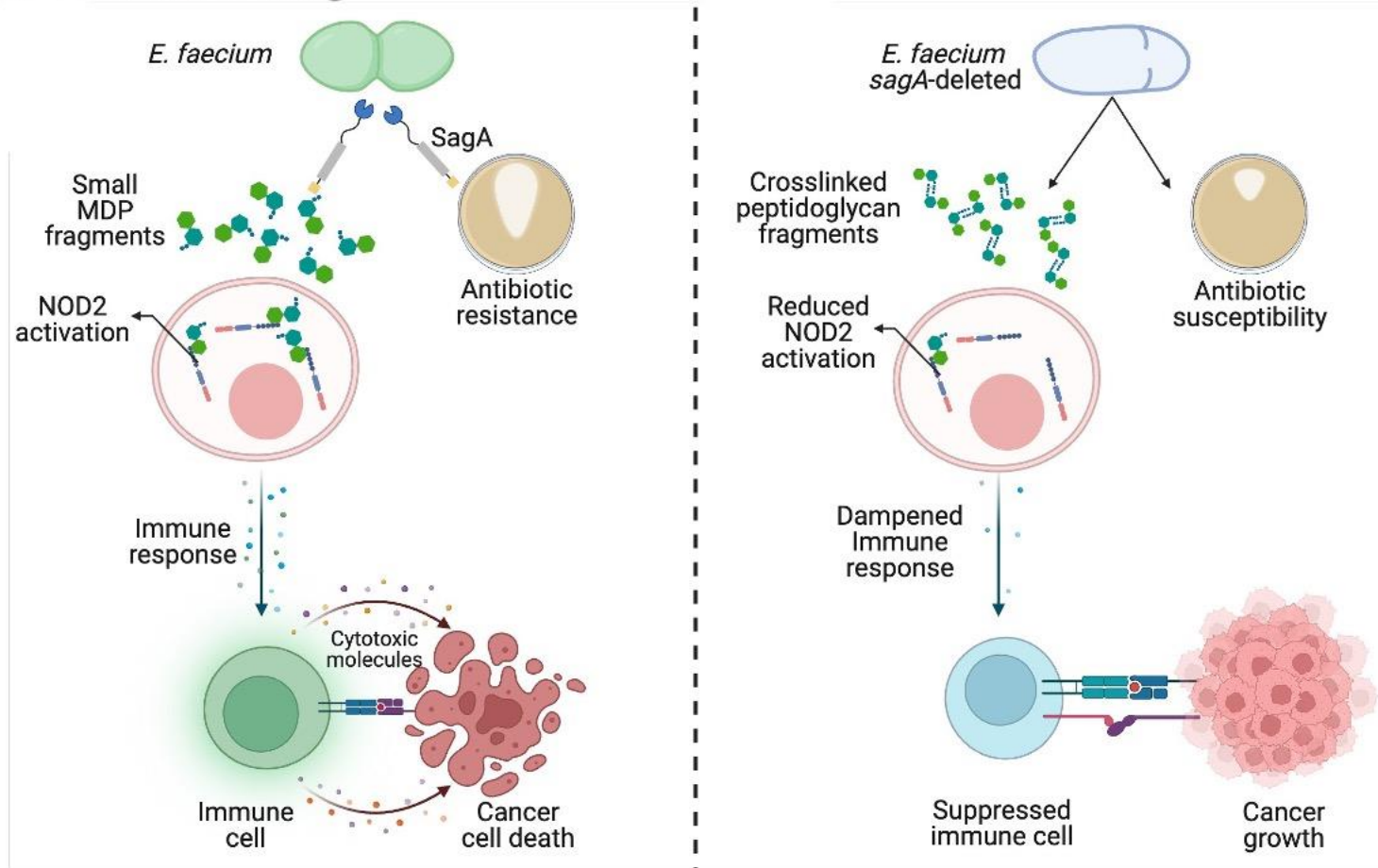
Expected Taxonomic Range: [Actinobacteria](#) <actinobacteria>, [Firmicutes](#)

Synonyms: penicillin resistance; β -lactam resistance

Enterococcus peptidoglycan remodeling promotes checkpoint inhibitor cancer immunotherapy

Griffin, et al, Science, 2021
Klupt, et al, Elife, 2024

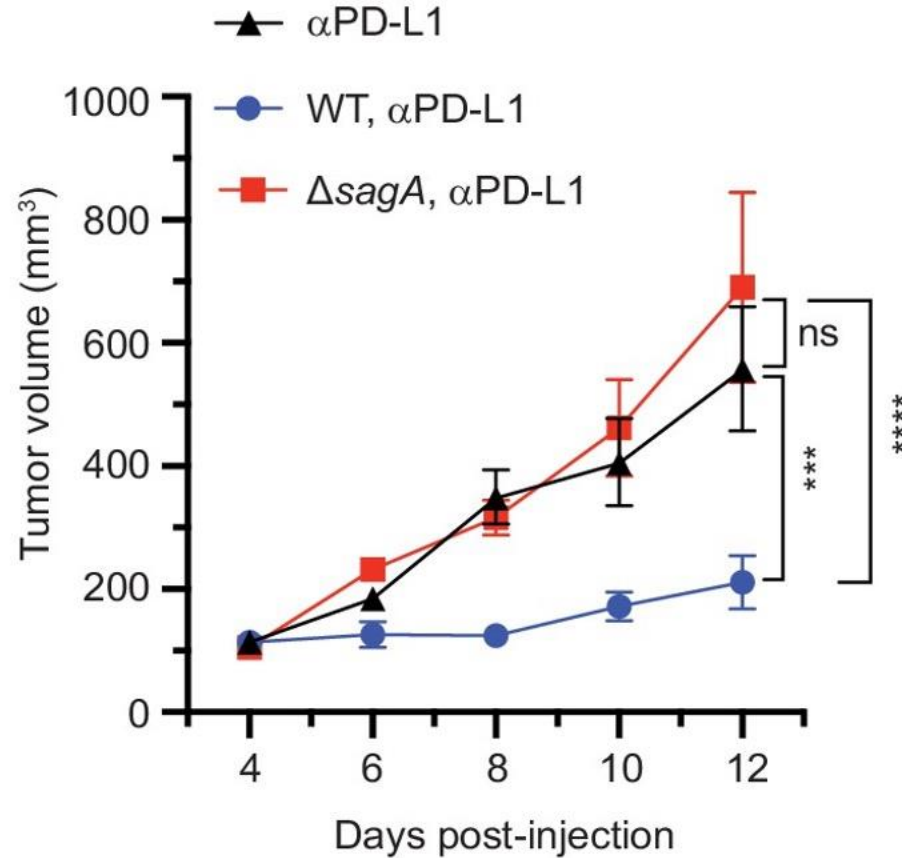
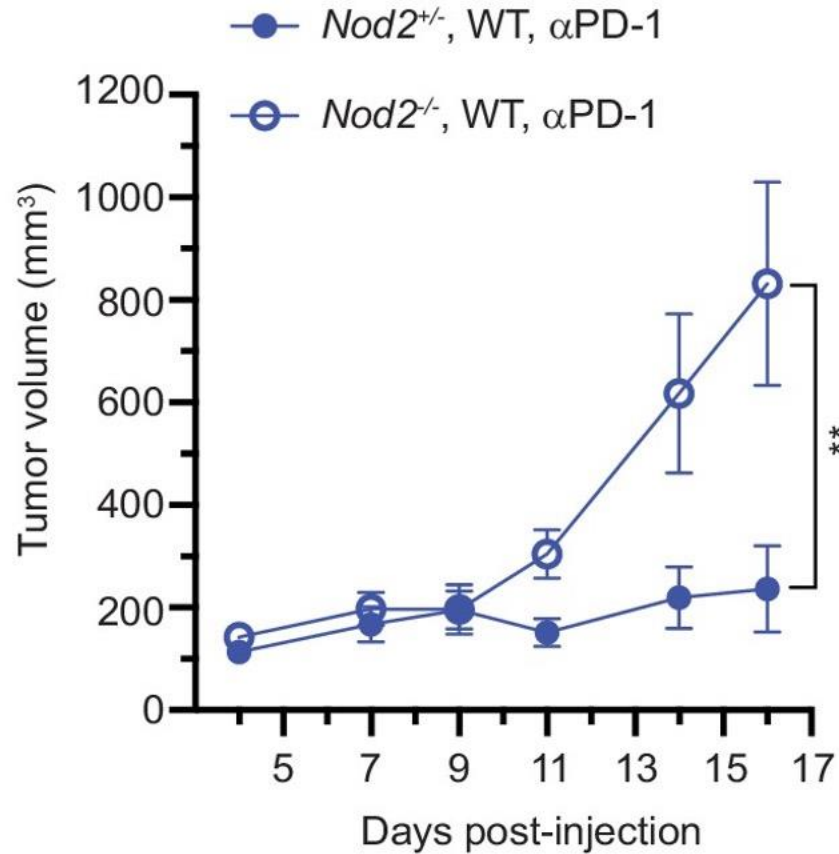
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Jyoti K. Jha⁴, Gary R. Fanger⁴, Howard C. Hang^{1,2,*}



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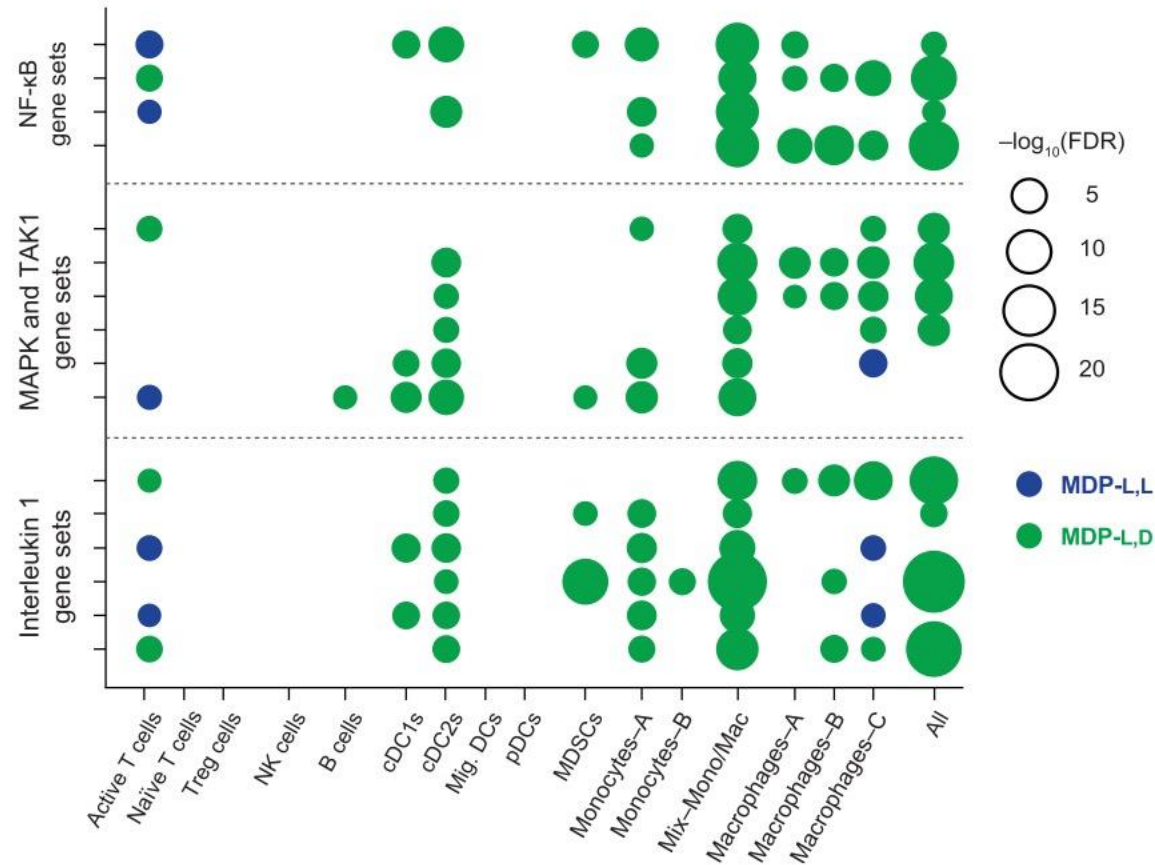
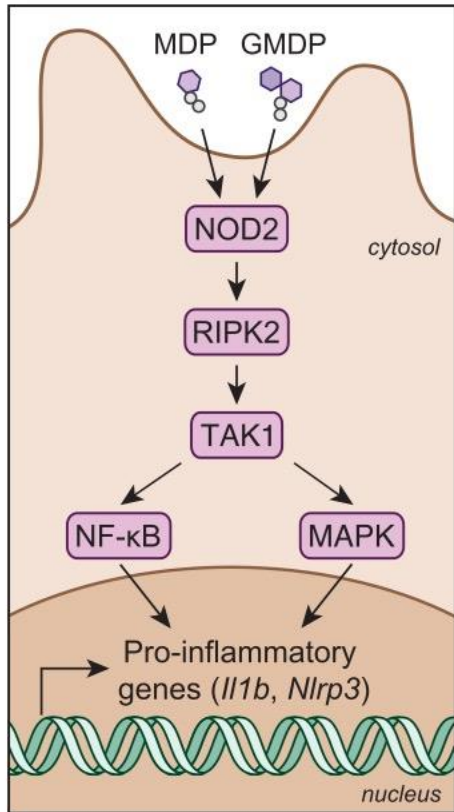
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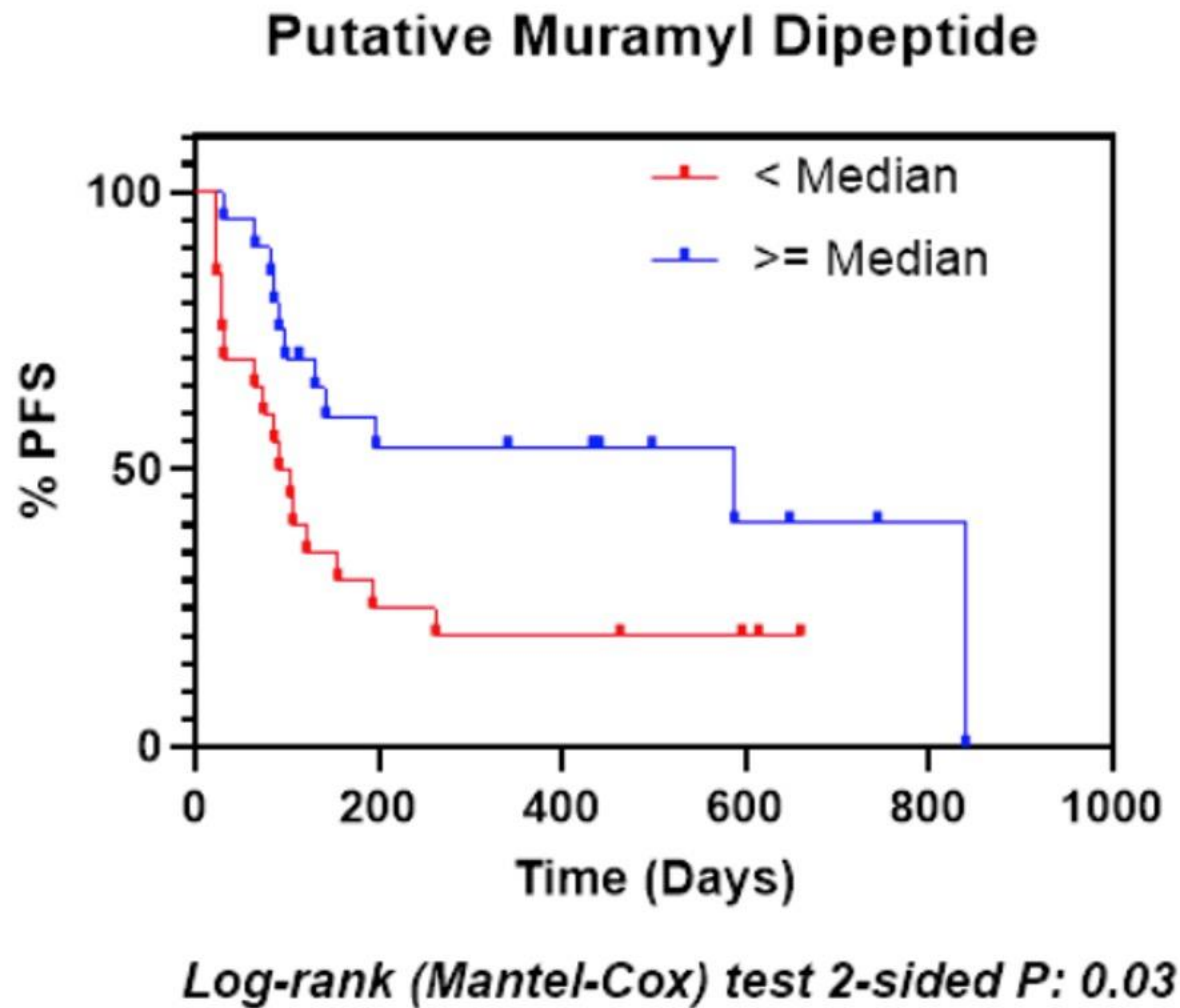
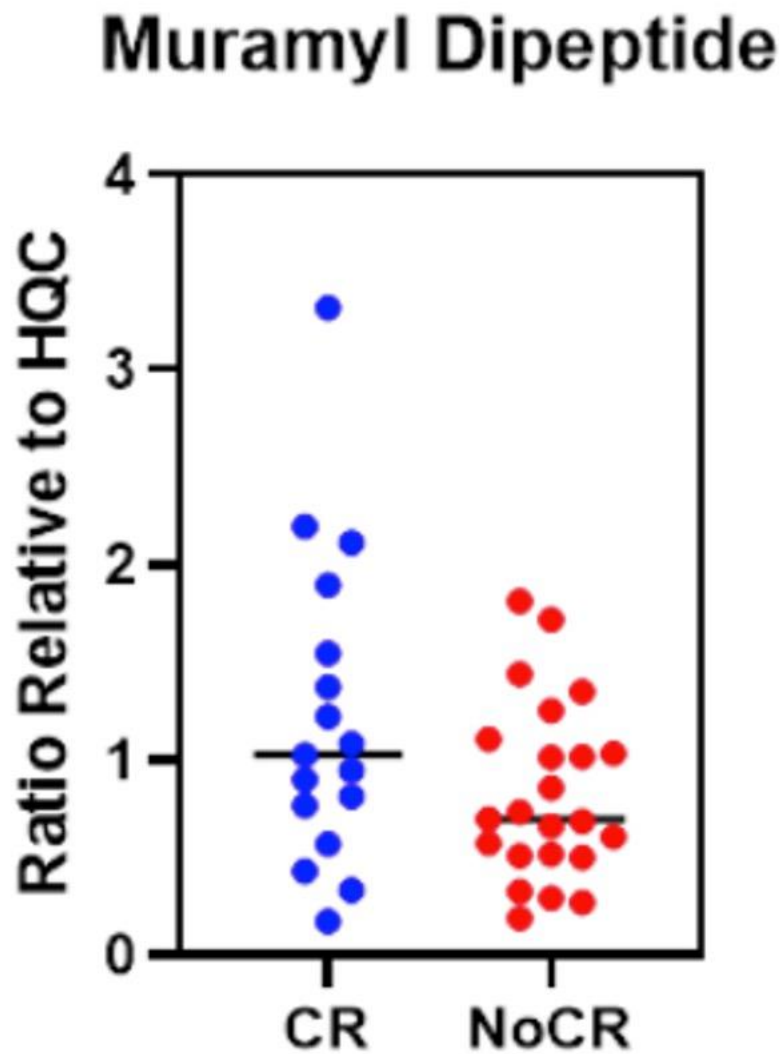
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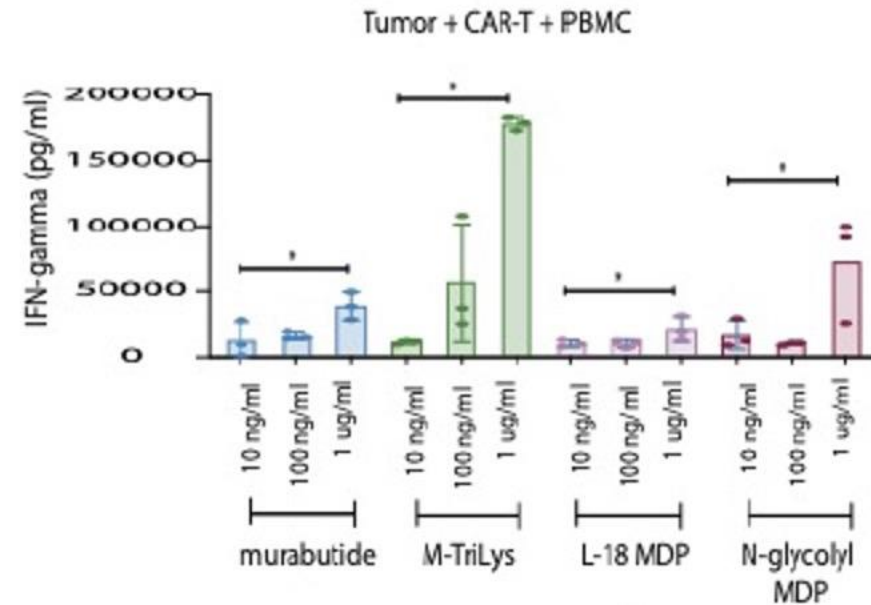
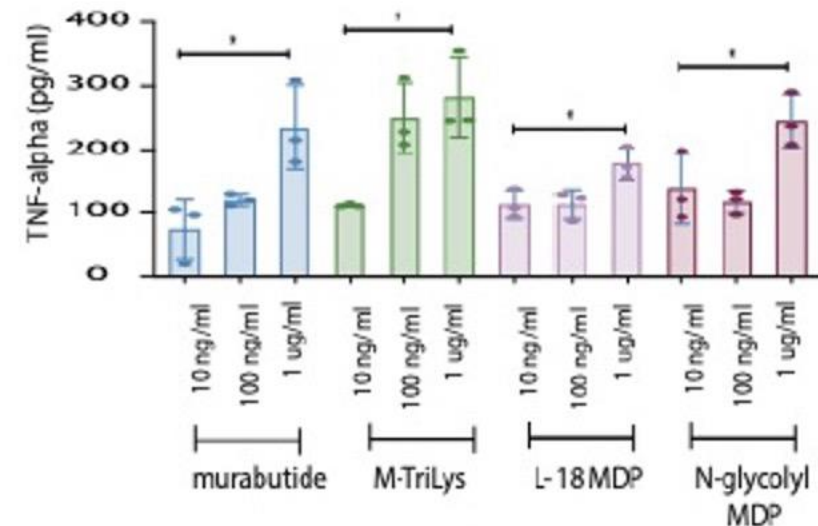
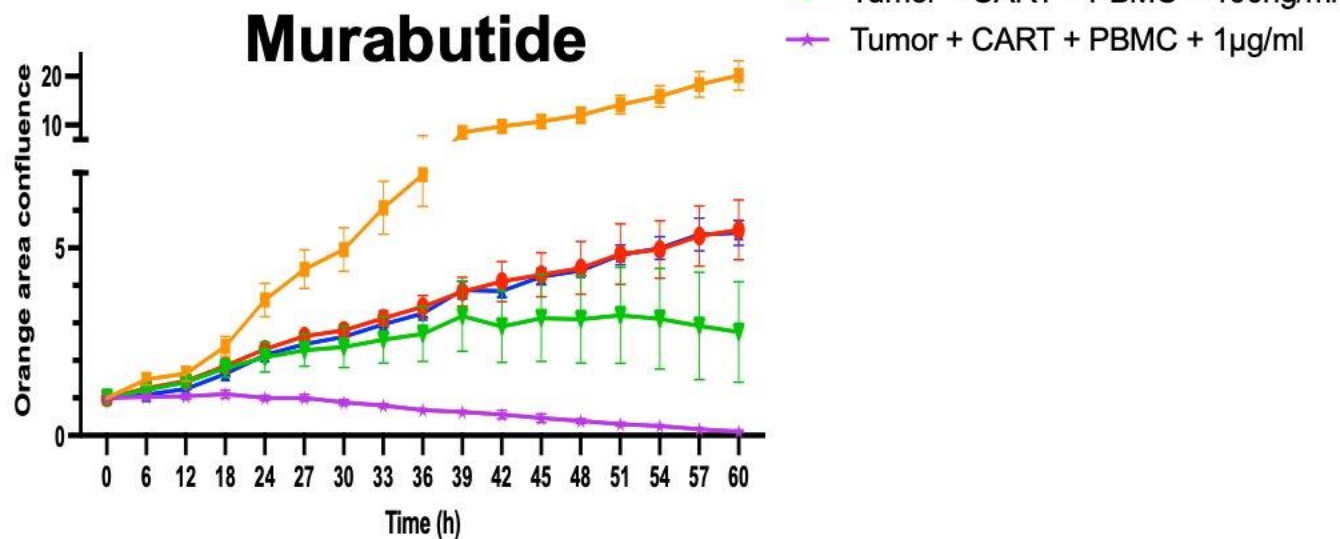
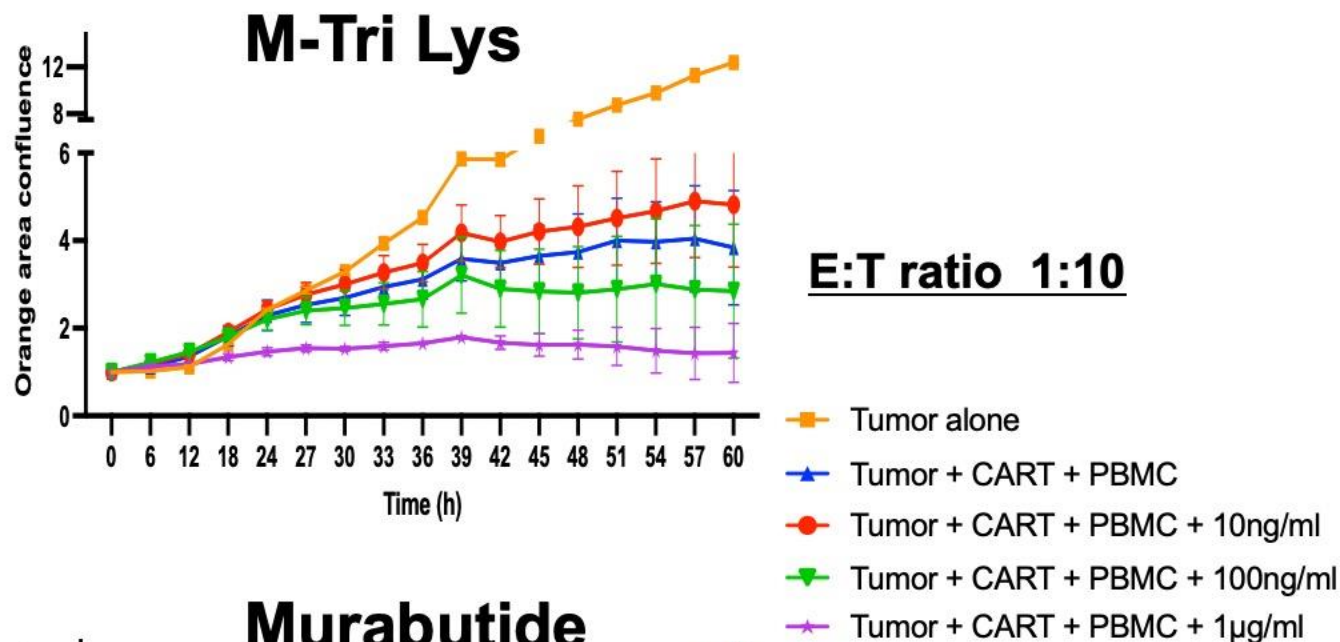
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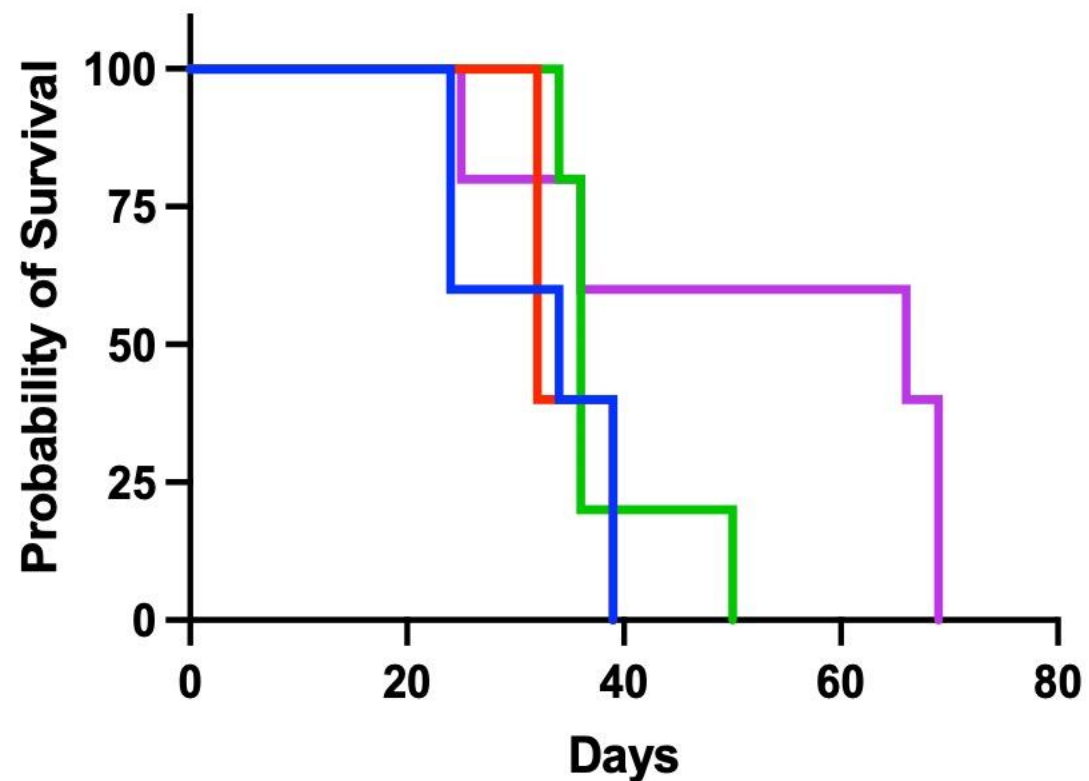
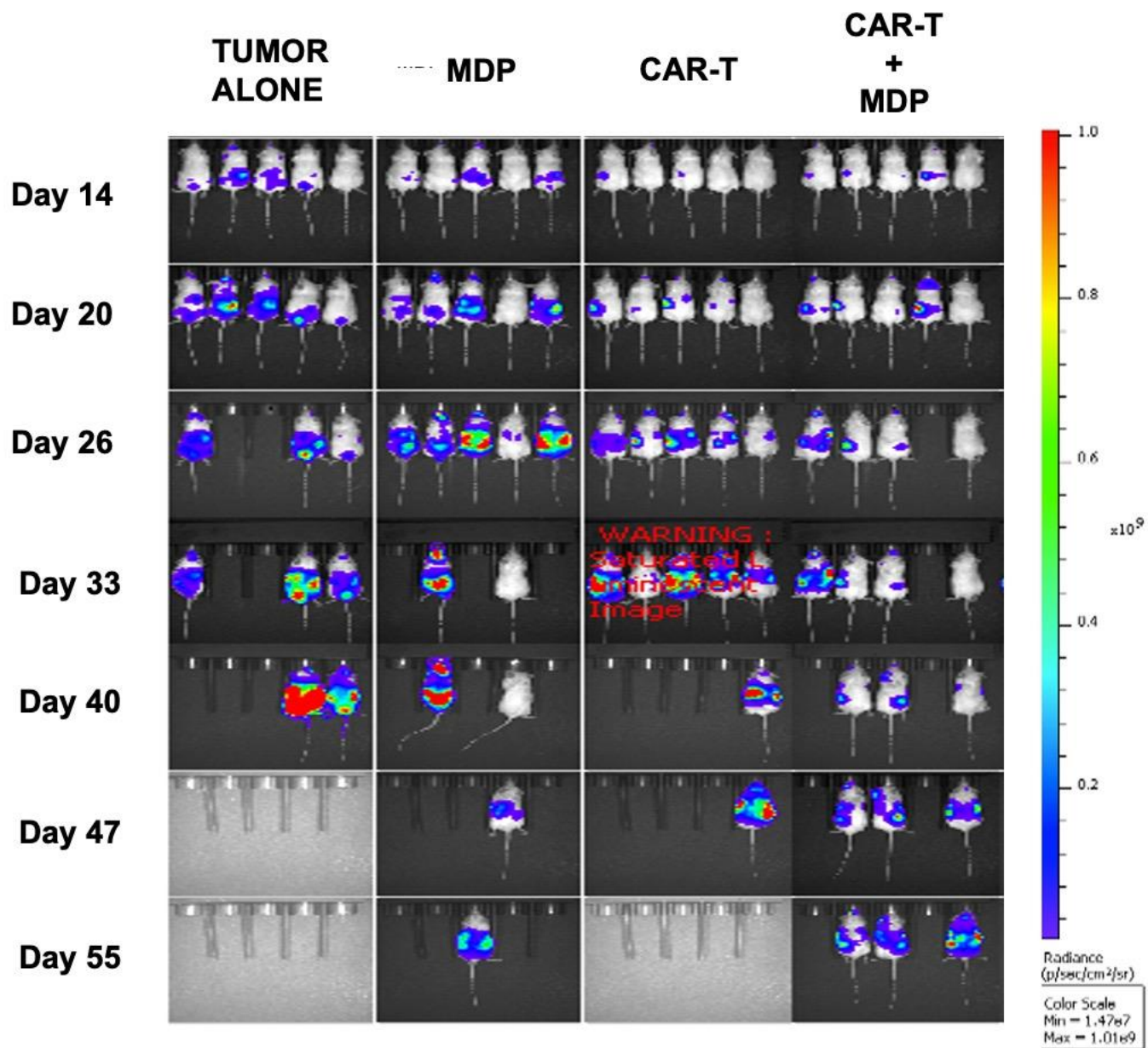


CD19 CAR-T patients: higher plasma MDP levels associated with improved PFS/OS



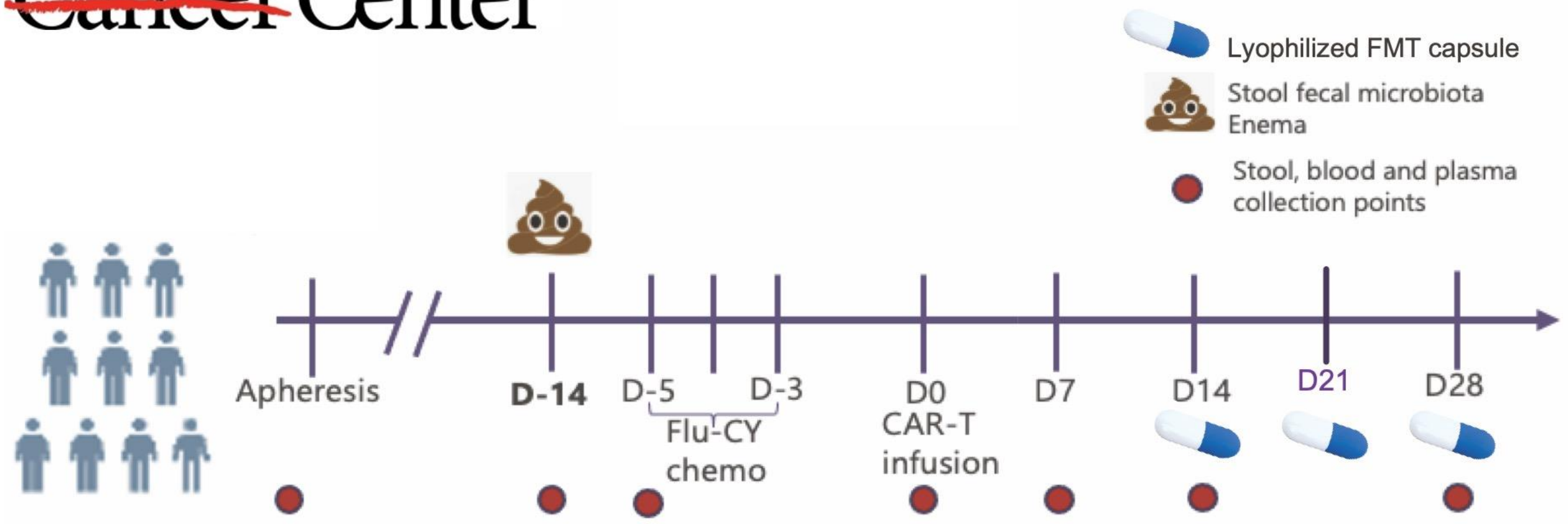
MDP analogs enhance CAR T killing in presence of monocytes





- Tumor alone
- Tumor+MDP
- Tumor+CART
- Tumor+CART+MDP

THE UNIVERSITY OF TEXAS
MD Anderson
Cancer Center[®]



Co-led by Neeraj Saini and Jason Westin

Acknowledgements

MD Anderson

Stem Cell: Neeraj Saini

Lymphoma and Myeloma: Jason Westin, Sattva Neelapu

Prevention?: Johannes Fahrman

Mark Foundation Endeavor Collaborators

Moffitt: Michael Jain

Roswell Park: Marco Davila

Tubingen: Christoph Stein-Thoeringer

DKFZ: Eran Elinav

City of Hope

Rishika Prasad

Altai Enkhbayar

Aqsa Mohammed

Jennifer Karmouch

Maren Schmiester

Karamjeet Sandhu

Elizabeth Budde

Stephen Forman

Larry Kwak

Sandra Thomas

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Joycelyne Palmer

Scott James

Marcel van den Brink

