Impact of Obesity on Immunotherapy: Both the Good and the Bad

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Preclinical Modeling of Cancer Immunotherapy: Issues in “in vivo veritas”

Preclinical modeling needs to better reflect clinical patient demographics

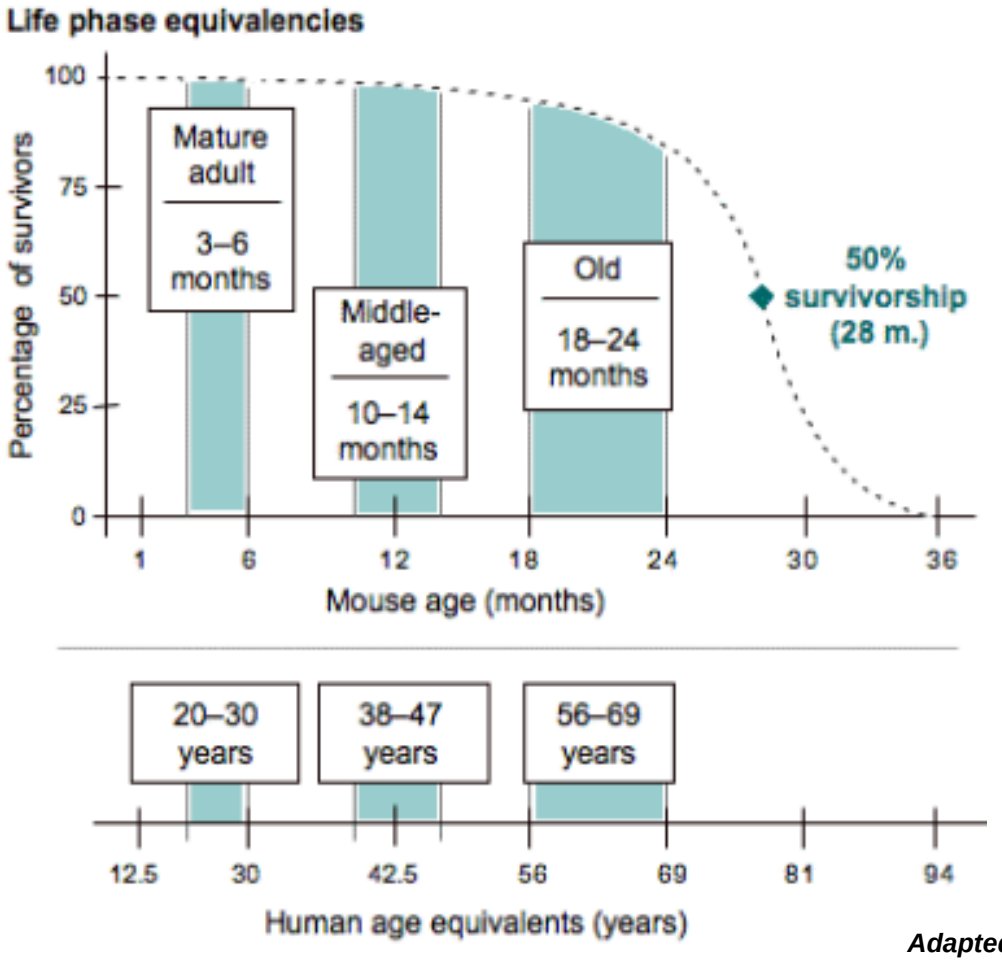
Cancer in the laboratory

https://nobacon.files.wordpress.com/2011/12/diverse_group1.jpg

Variables in Clinical and Preclinical Modeling

Clinical Cancer Patients | **Murine Tumor Models**

Life Phase in Human and Mice



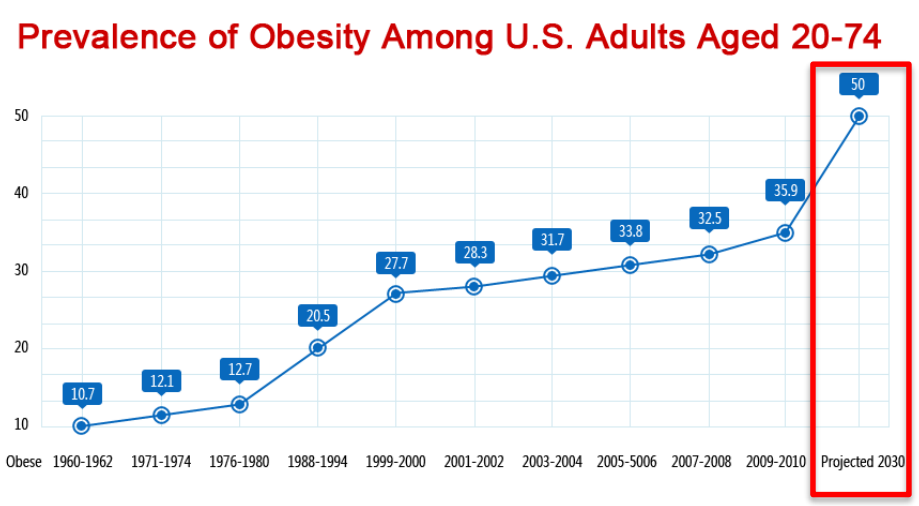
Adapted from The Jackson Laboratory

Obesity Epidemic: Common, Serious, Costly and Still on the Rise

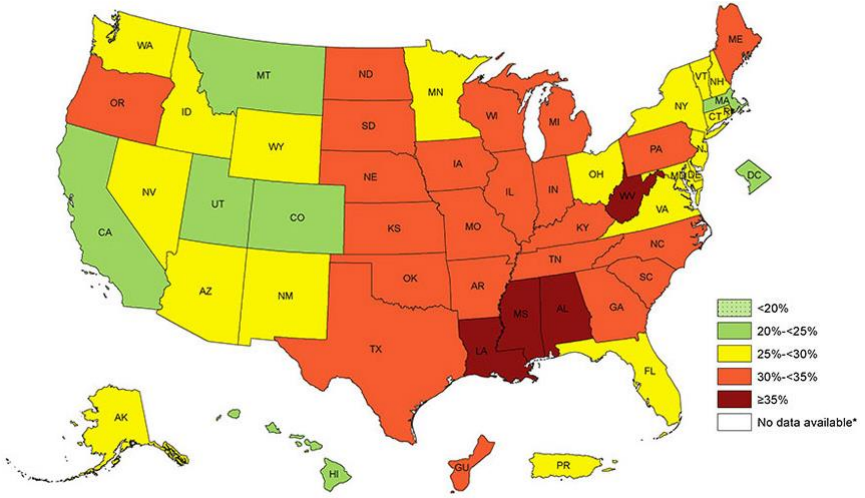
- Prevalence in USA:
  - Nearly 38% in adults
  - Higher among middle-aged (40-59 yrs: 40.2%) and older (>60 yrs: 37.0%)

- Health Risks:
  - Increased risk of morbidity from hypertension, type 2 diabetes, stroke, gallbladder disease, osteoarthritis, sleep

Therefore, the arising pandemic of obesity will likely change the phenotype of a "typical" patient seen in the clinic



Adapted from http://www.cdc.gov/nchs/data/hestat/obesity_adult_09_10/obesity_adult_09_10.html#table1

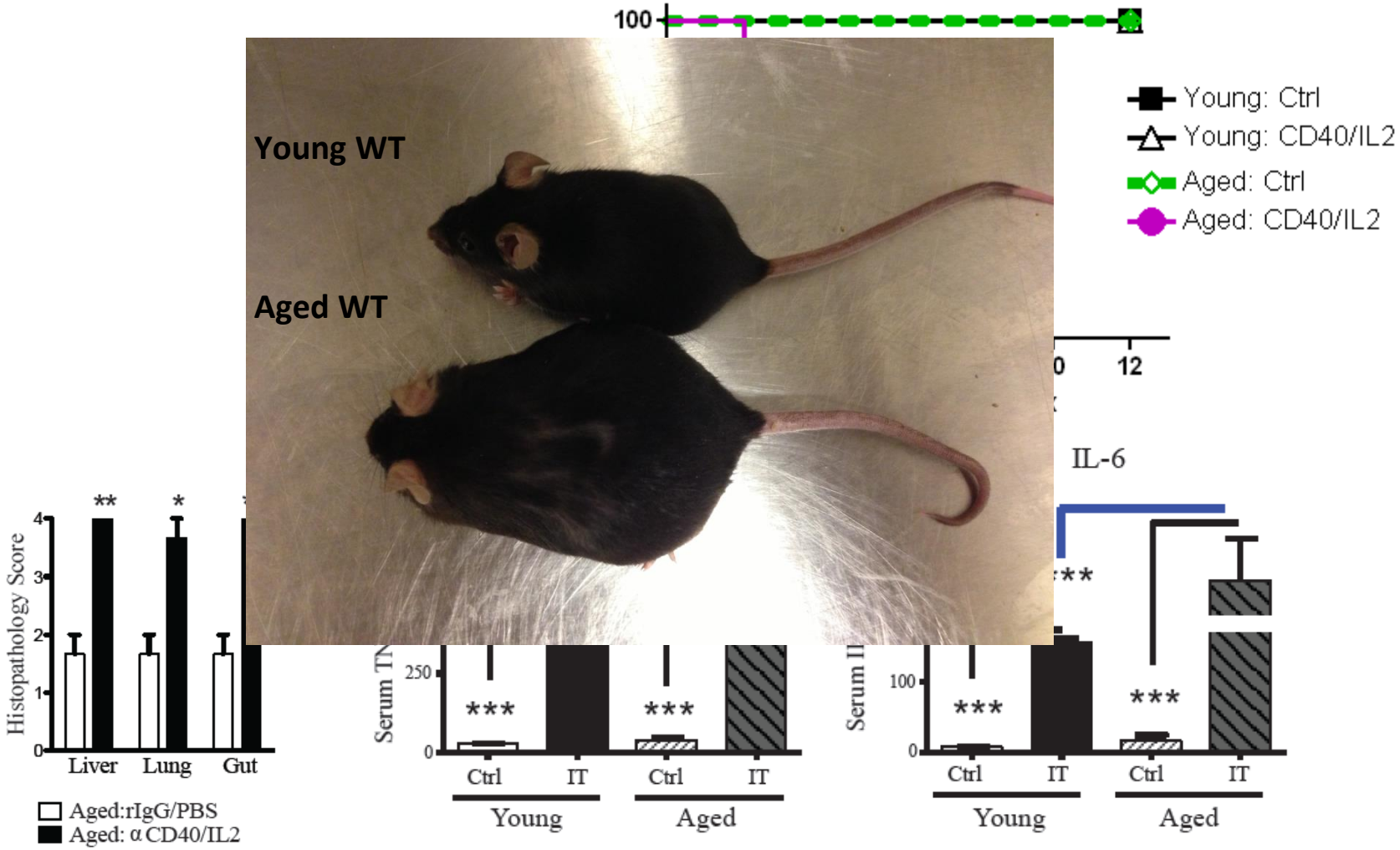


Adapted from https://www.cdc.gov/obesity/data/adult.html

What is the impact of age and obesity on cancer immunotherapy outcome in preclinical mouse models?

What are the immune effects, tumor progression and impact on immunotherapy efficacy/toxicities?

Aged Mice Succumb to Multi-organ Failure and Cytokine Storm Following Systemic Immunostimulatory Therapy



Bouchlaka MN et al. J Exp Med. 2013.

Obesity and Immune Status: “Inflammaging”

- Increased “meta-inflammation” in obesity results in excessive pro-inflammatory responses following systemic immunostimulation (i.e. cytokines, LPS, etc…) which is mediated primarily by macrophages
- What are the effects of obesity on T cell responses when checkpoint blockade to PD1/PDL1 is applied?

Anti-PD-1 Monotherapy Therapy Treatment Schema

Control and DIO
C57BL/6

0 6 8 10 12 14 16

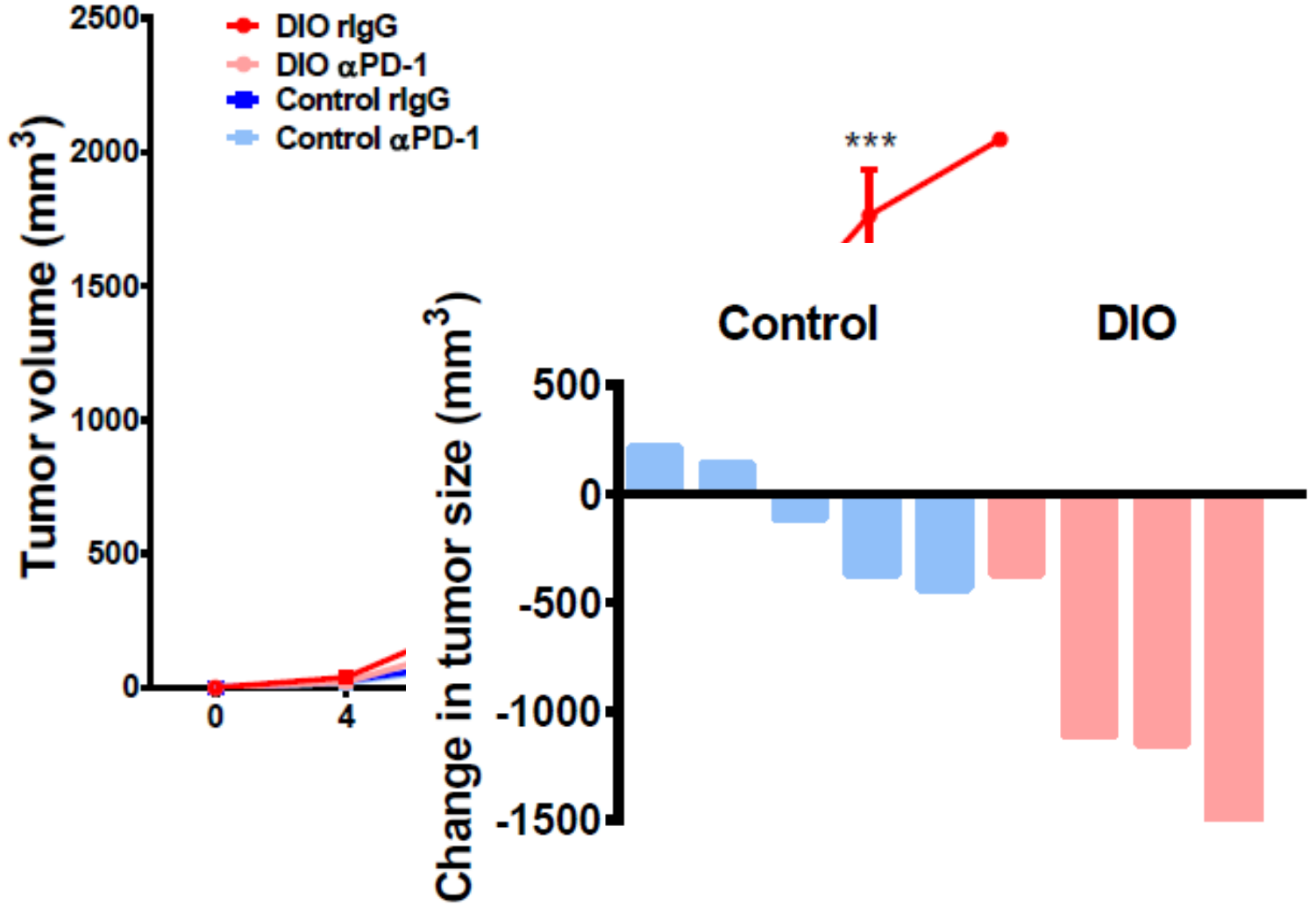
10^6 B16 or 3LL subcutaneously

250ug αPD-1 or isotype control, i.p.

500ug αPD-1 or isotype control, i.p.

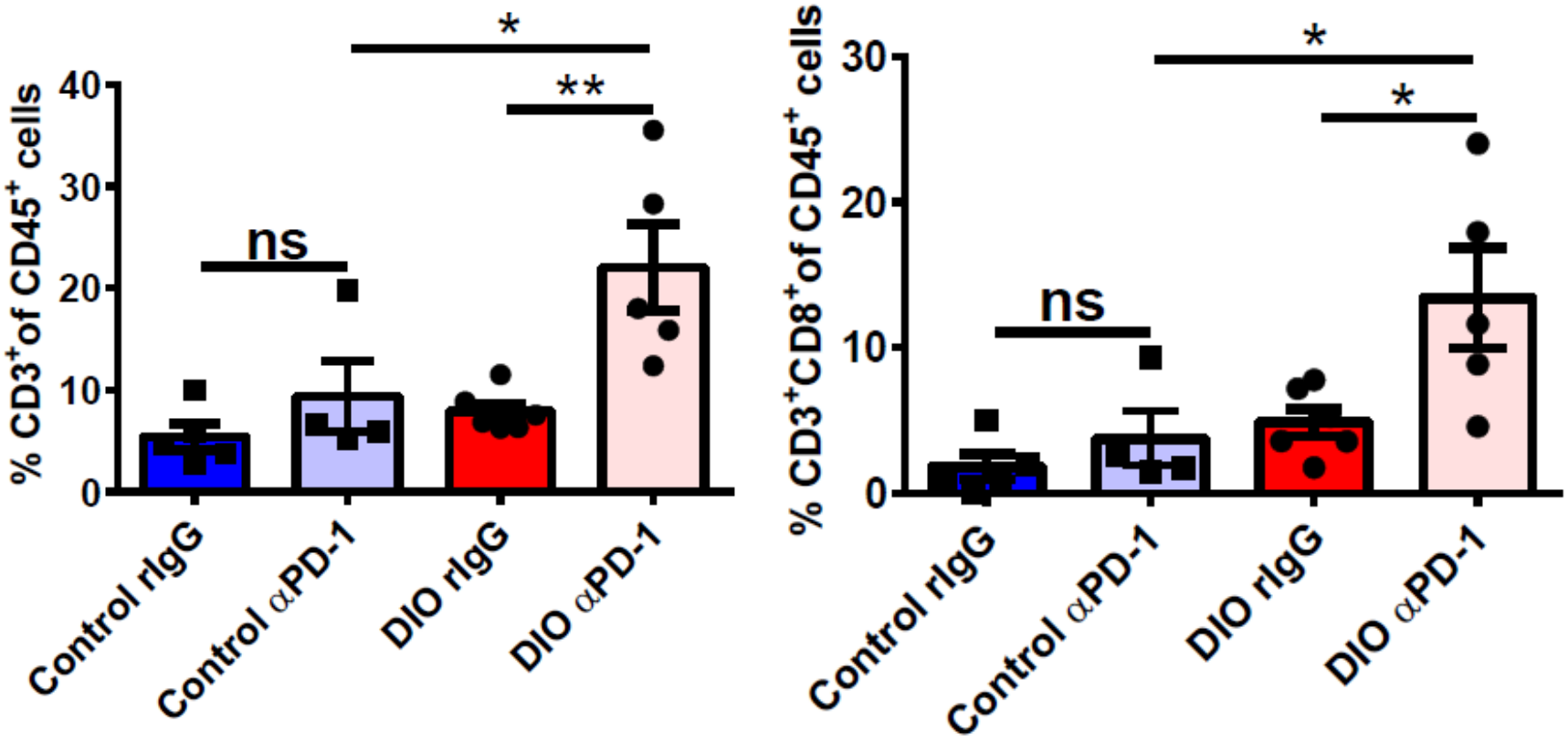
Clone 29F.1A12

Increased Efficacy of PD-1 Blockade in B16-bearing DIO Mice



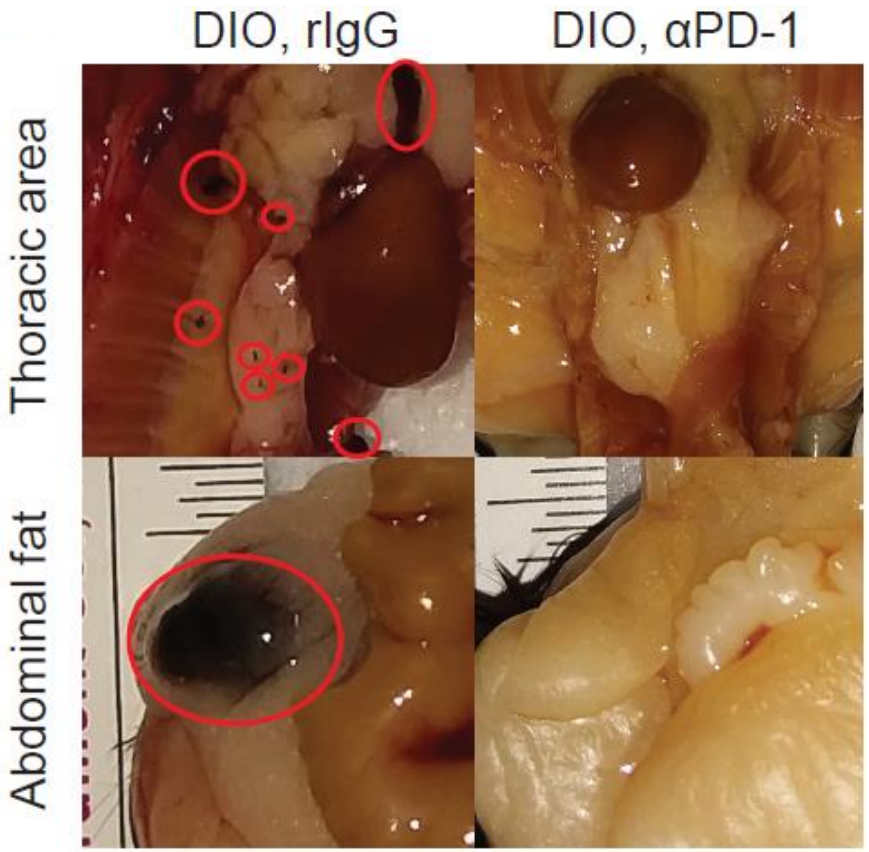
Wang Z. et al. Nature Med. 2019.

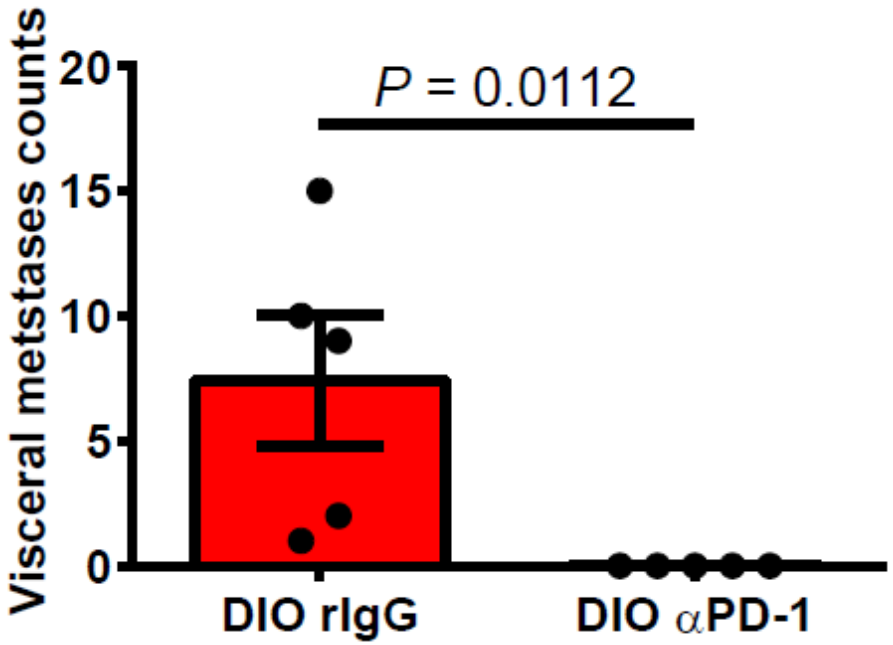
PD-1 Blockade Results in Increased T cell Infiltration in DIO Mice Compared to Tumor-bearing Control Diet Mice



Wang Z. et al. Nature Med. 2019.

PD-1 Blockade Inhibits Visceral B16 Metastases in DIO Mice





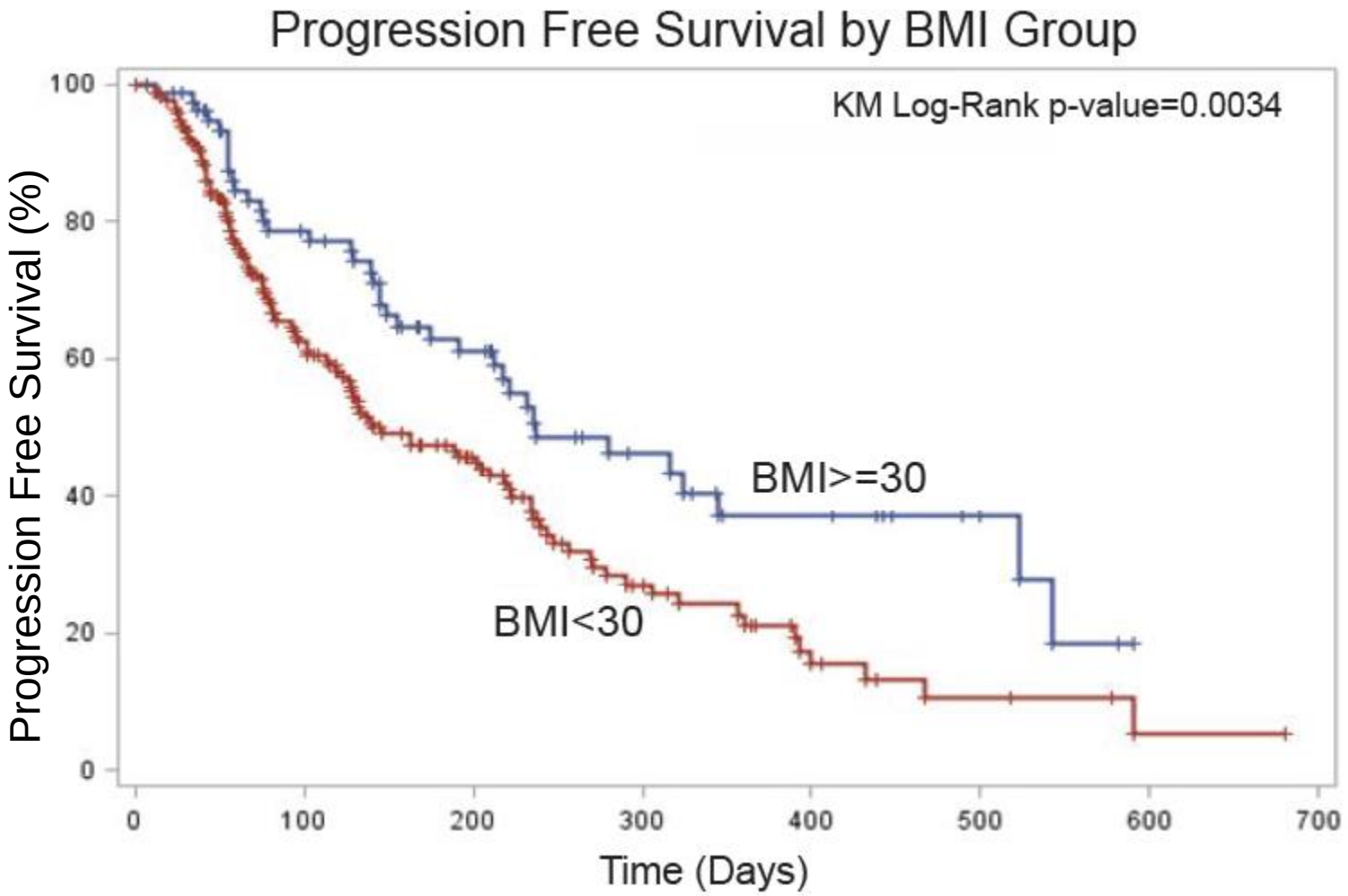
Wang Z. et al. Nature Med. 2019.

Confirming Clinical Findings Across Cancer Types

Variable	Overall (n=250)	BMI < 30 (n=169)	BMI ≥ 30 (n=81)
BMI Mean (SD)	27.4 (7.3)	23.4 (3.6)	35.7 (6.2)
BMI Range	15 -56.6	15 - 29.9	30.0 - 56.6
Age Mean (SD)	61.7 (13.7)	62.6 (14.6)	59.70 (11.52)
Age Range	23, 91	23, 91	36, 87
Sex			
M (%)	114 (45.6)	80 (47.3)	34 (42.0)
F (%)	138 (54.4)	89 (52.7)	47 (58.0)
Cancer Type			
Lung (%)	55 (22.0)	44 (26.0)	11 (13.6)
Melanoma (%)	45 (18.0)	23 (13.6)	22 (27.2)
Ovarian (%)	20 (8.0)	17 (10.1)	3 (3.7)
Other (%)	130 (52.0)	85 (50.3)	45 (55.6)
ECOG			
0 (%)	70 (28.00)	48 (28.4)	22 (27.2)
1 (%)	134 (53.6)	87 (51.5)	47 (58.0)
2 or More (%)	46 (18.4)	34 (20.1)	12 (14.8)
Prior Therapy			
1 (%)	44 (17.6)	24 (14.2)	20 (24.7)
2 (%)	91 (36.4)	66 (39.1)	25 (30.9)
3 or More (%)	115 (46.0)	79 (46.7)	36 (44.4)
irAE (%)	52 (20.8)	32 (18.9)	20 (24.7)
irAE type			
Colitis	23	13	10
Pnuemonitis	11	8	3
Thyroid	14	9	5
Colitis + Thyroid	4	2	2

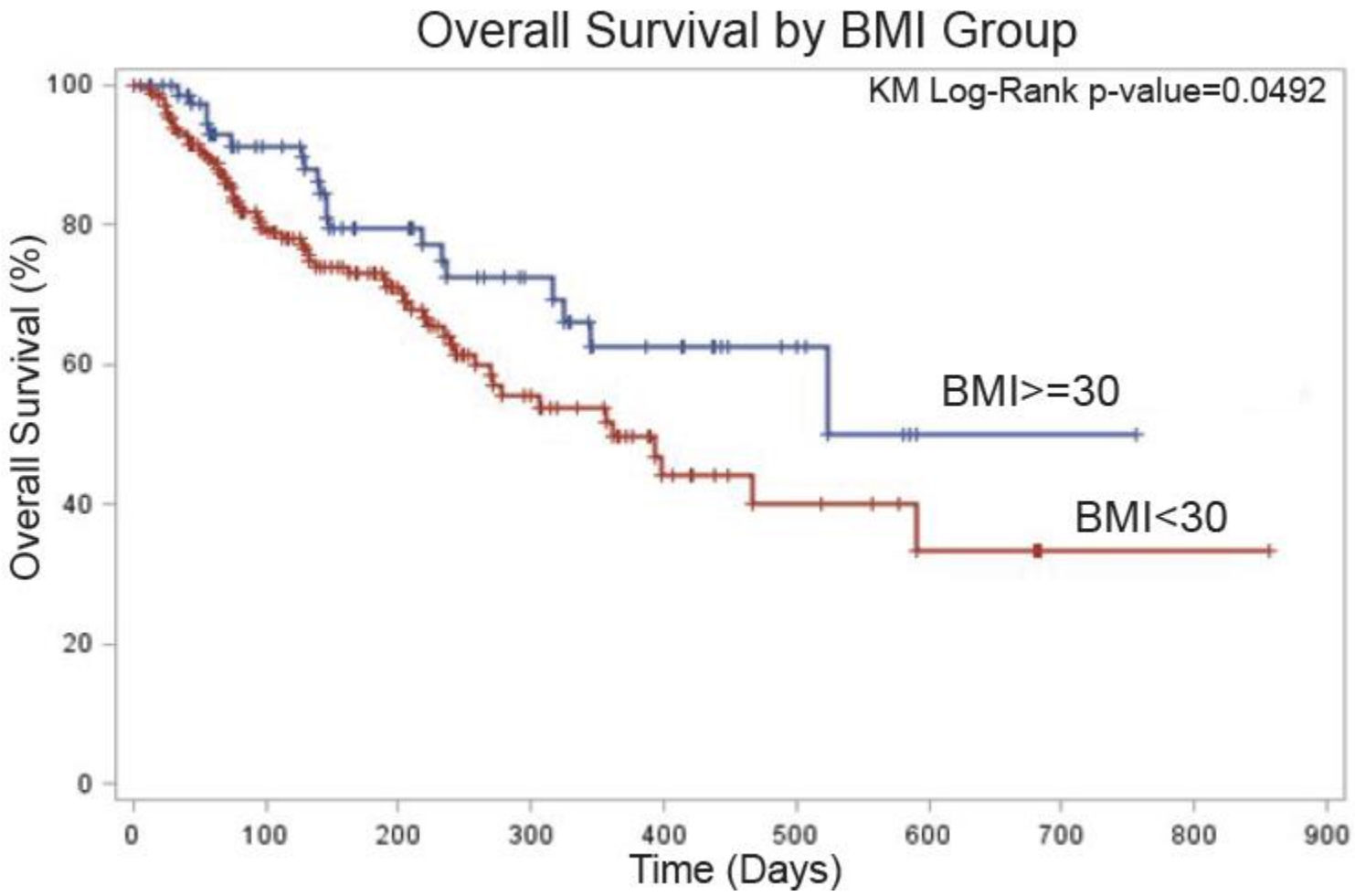
Wang Z. et al. Nature Med. 2019.

Obesity Promotes the Efficacy of PD-1/PD-L1 Blockade



Wang Z. et al. Nature Med. 2019.

Obesity Promotes the Efficacy of PD-1/PD-L1 Checkpoint Blockade in Cancer Patients



Wang Z. et al. Nature Med. 2019.

Hematopoietic Stem Cell Transplantation (HSCT)

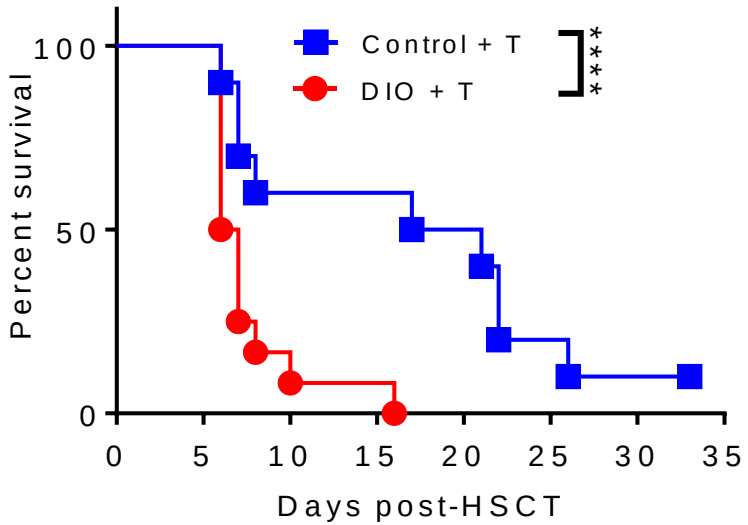
- Hematopoietic stem cell transplantation (HSCT), both autologous and allogeneic, is a potential curative treatment for a variety of hematologic diseases, including leukemias/lymphomas.

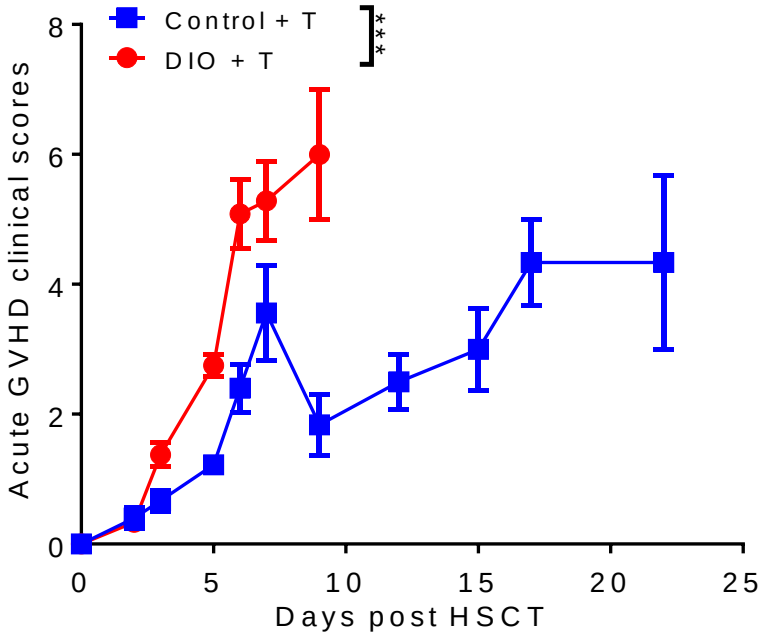
- Allogeneic HSCT is associated with graft-versus-host disease (GVHD) which is a significant cause of morbidity. GVHD results from the immunological attack by donor allogeneic T cells on genetically-disparate and immunocompromised recipient tissues. It is also associated with the beneficial graft-versus-tumor (GVT) effects resulting in lower relapse compared to autologous HSCT

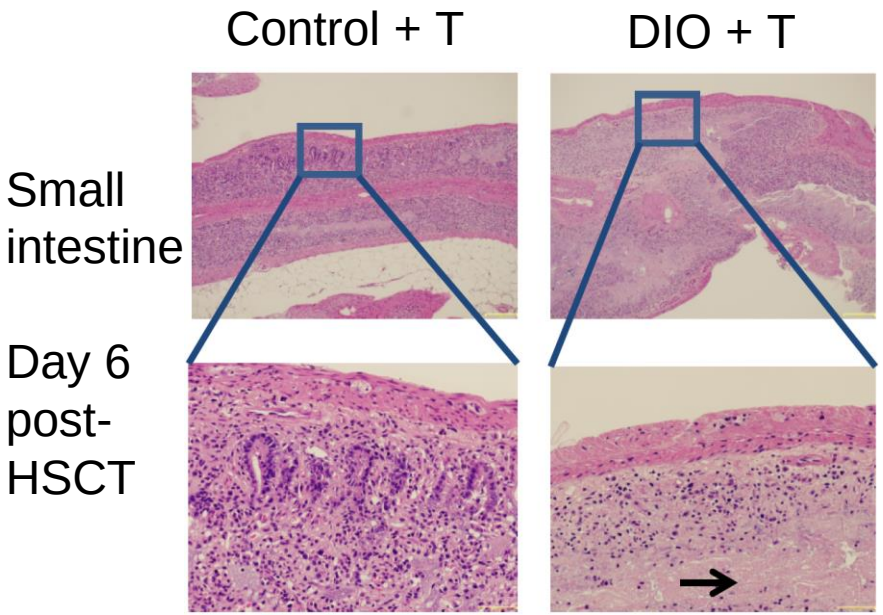
- There are 2 types of GVHD: acute (rapid and inflammatory) and chronic (delayed and fibrotic) with distinct pathogenesis and outcomes.

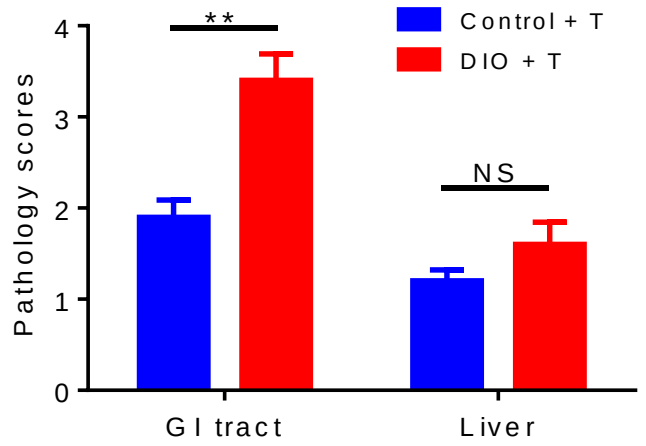
- The impact of obesity on alloHSCT outcomes is not clear.

Obesity resulted in increased acute gut GVHD and mortality in a MHC-mismatched alloHSCT model



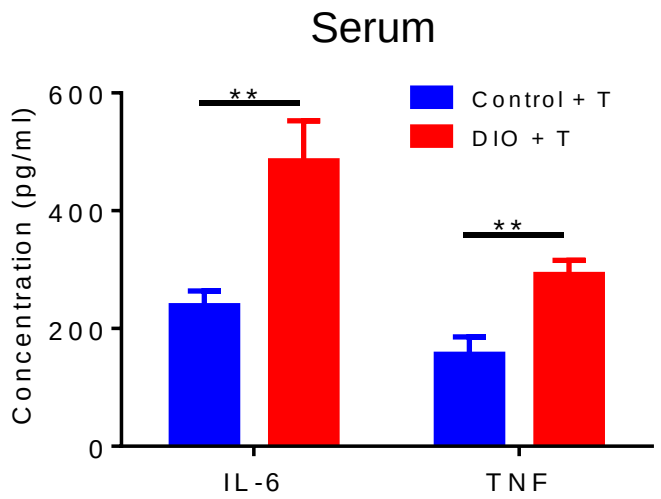


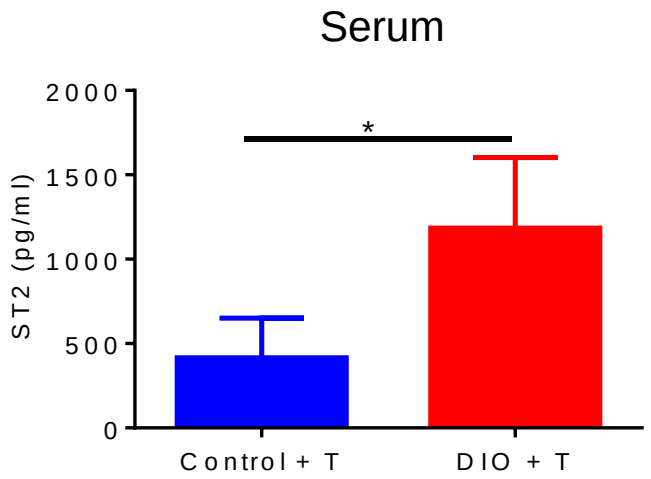




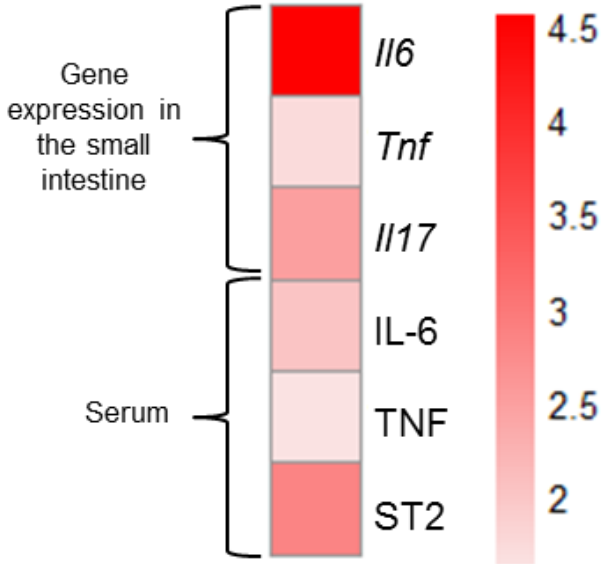
Khuat et al., submitted

Obesity amplifies aGVHD “Cytokine Storm”





DIO vs. control



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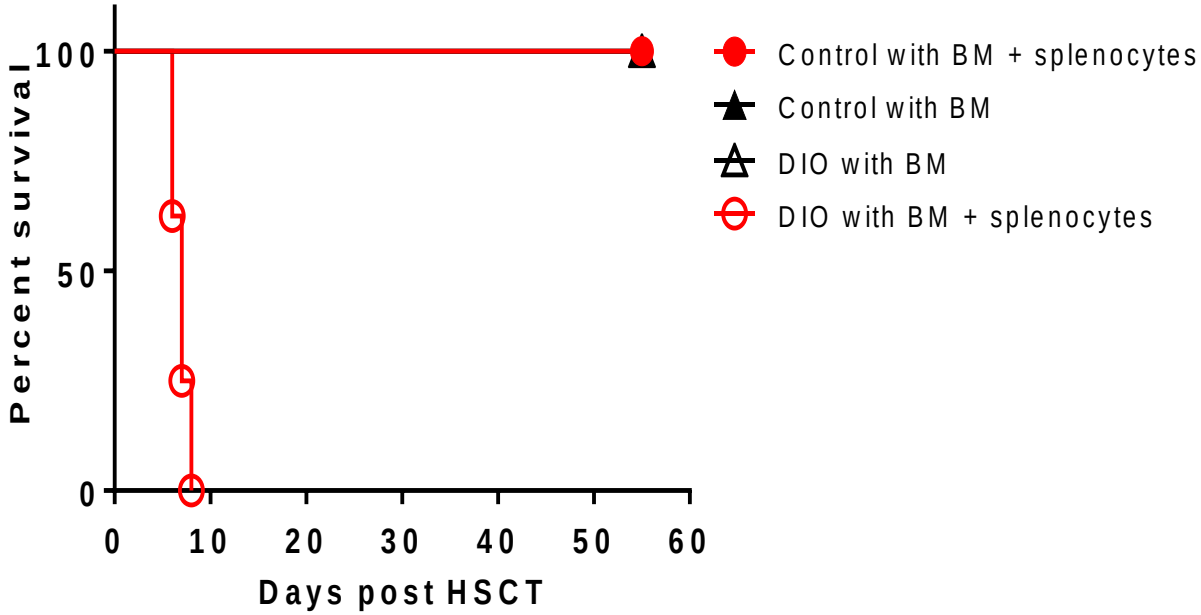
Minor MHC-mismatch chronic skin GVHD model has DIO recipients instead showing lethal aGVHD

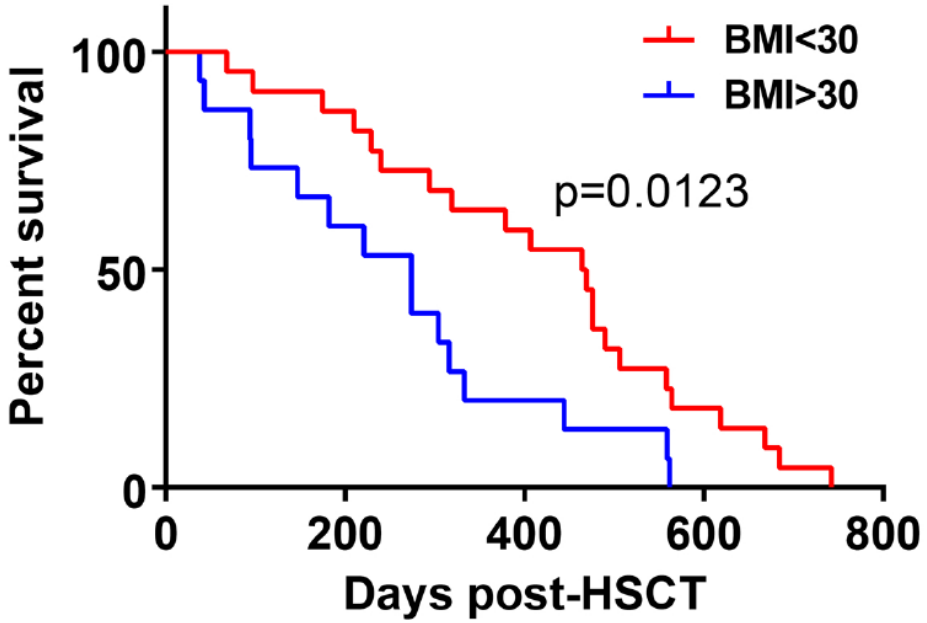


- Control recipients survive and much later develop later cGVHD only in skin.
- DIO recipients succumb to rapid lethal gut aGVHD.

Khuat et al., submitted

Obesity (>30 BMI) results in poorer outcome in adult patients post-alloHSCT

BMI	# patient	Age	Relationship with donors	Conditioning	Disease
< 30	22	18-70	Unrelated	Non-myeloblative (13), Full preparation (9)	Acute myeloid leukemia (10), Acute lymphoid leukemia (2), Myelodysplastic Syndromes (4), non-Hodgkin lymphoma (2), others (4)
> 30	15	31-71	Unrelated	Non-myeloblative (8), Full preparation (7)	Acute myeloid leukemia (6), Acute lymphoid leukemia (3), Myelodysplastic Syndromes (3), Chronic myeloid leukemia (2), B-cell/Small lymphocytic lymphoma (1)



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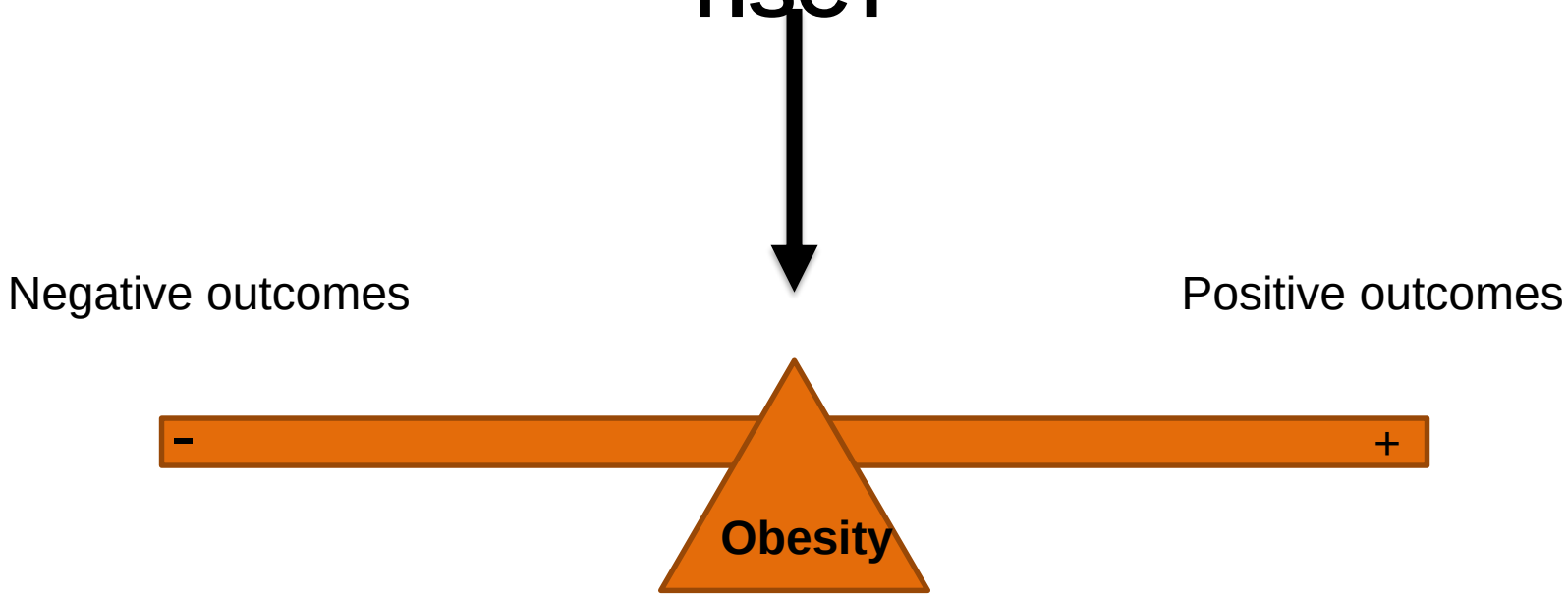
Impact of Obesity on Immunotherapy Efficacy

Systemic Immunostimulation, LPS or Allogeneic HSCT



Systemic Immunostimulation or Allogeneic HSCT

↑ Pro-inflammatory cytokine storm, pathology

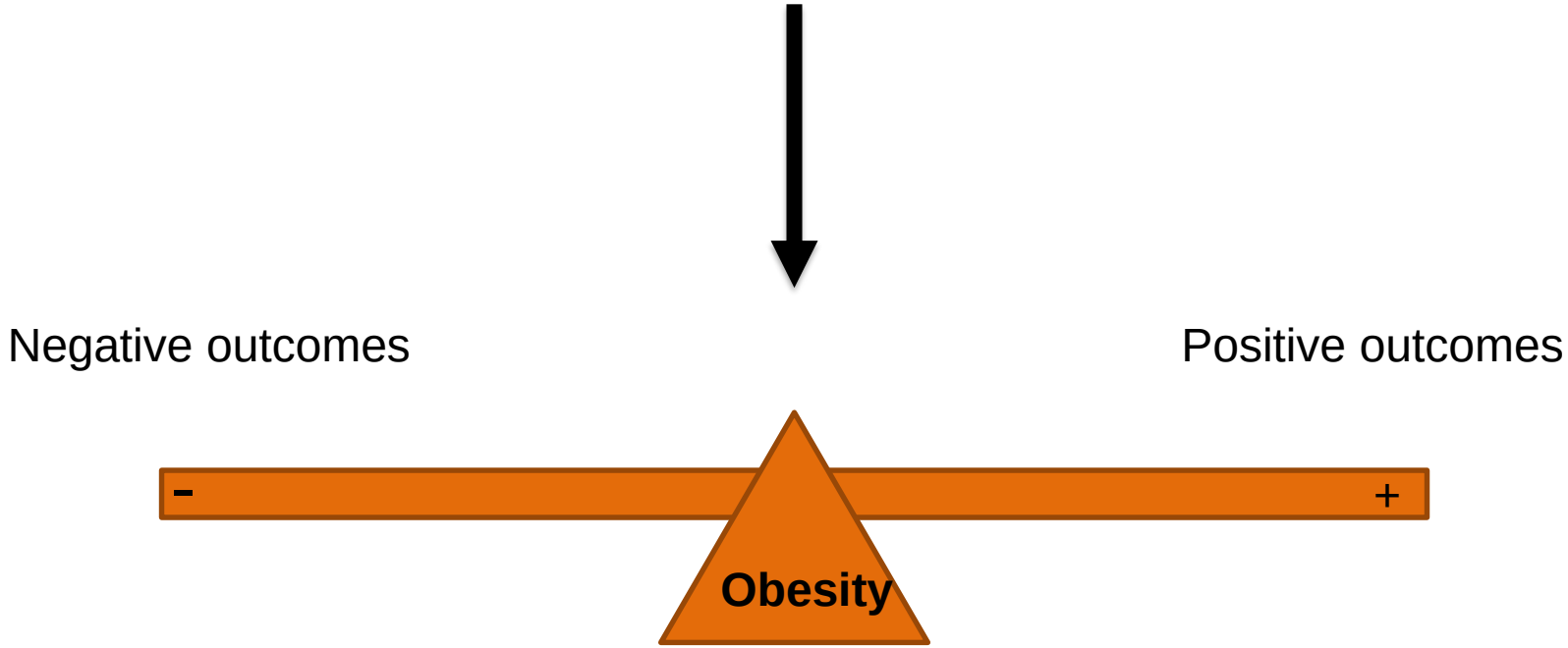
↑ Macrophage dysregulation

↑ Acute gut GVHD

Negative outcomes

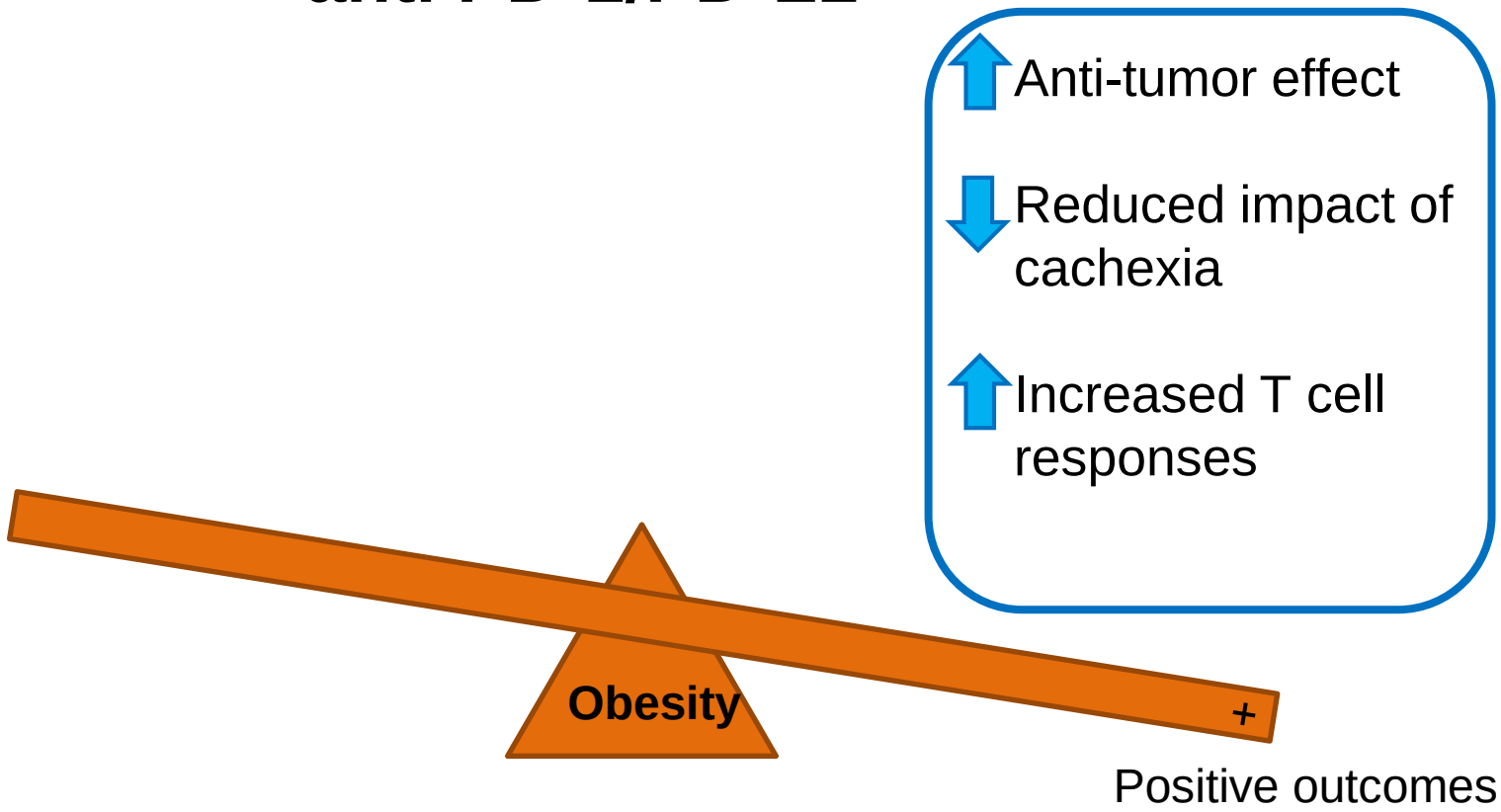
Impact of Obesity on Immunotherapy Efficacy

Cancer immunotherapy targeting PD-1/PD-L1



Impact of Obesity on Immunotherapy Efficacy

Cancer immunotherapy with anti PD-1/PD-L1



CONCLUSIONS: It is essential to incorporate human modifying factors in preclinical modeling as markedly different effects can result depending on the immunotherapy applied.

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