Checkpoint Blockade in Lymphoid Malignancies

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Tisch Cancer Institute
Icahn School of Medicine at Mount Sinai

Mount Sinai *The Tisch Cancer Institute*

Personal Financial Disclosures

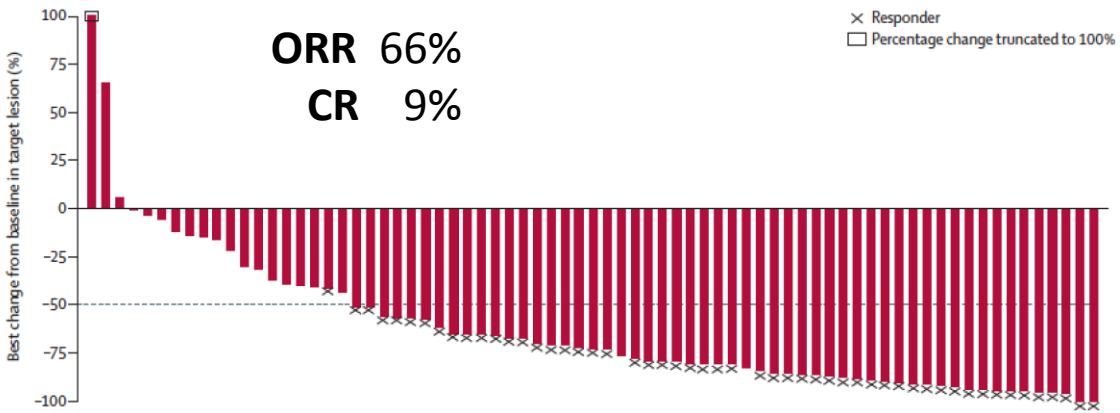
- None

Research Funding

- Bristol-Myers Squibb *(Will discuss off-label use)*
- Merck *(Will discuss off-label use)*
- Regeneron
- CTI Biopharma

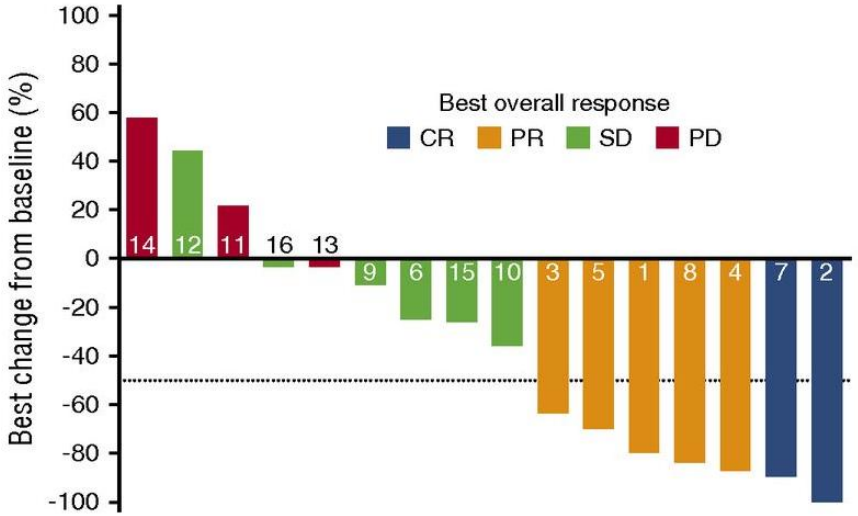
The highest response rates to checkpoint blockade are in PD-L1^{hi} lymphoid tumors

Nivolumab Monotherapy in cHL



CheckMate 205
Younes *et al, Lancet Oncology* 2016

Pembrolizumab Monotherapy in PMBCL



KEYNOTE-170 (ongoing Phase II)
• interim analysis ORR 41%, 14% CR

Adapted from Zinzani *et al* Blood 2017

Efficacy of PD-1 blockade in most B-NHL is poor

CheckMate140
Nivolumab for FL

N	92
ORR	**4.3%**
CR	1.1%
PFS	2.2mo

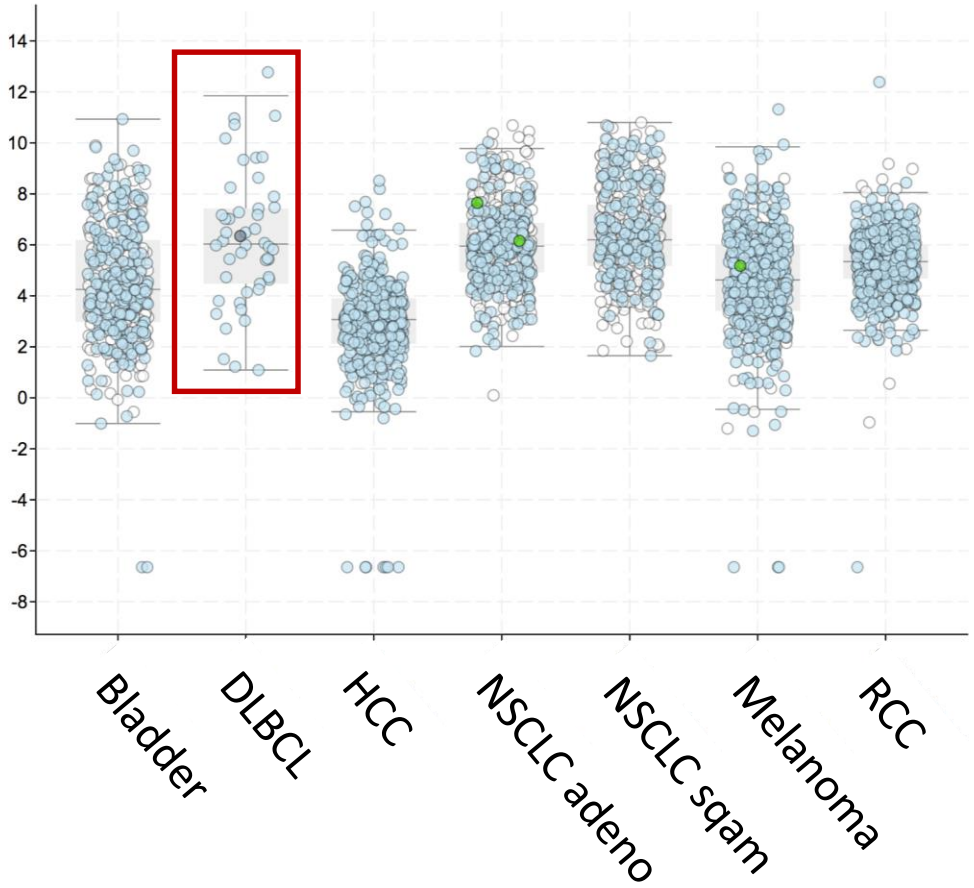
CheckMate139
Nivolumab for DLBCL

	BMT-Failed (n=87)	BMT-ineligible (n=34)
ORR	10.3%	2.9%
CR	**3.4%**	**0%**
PFS	1.87mo	1.41

Clinicaltrials.gov

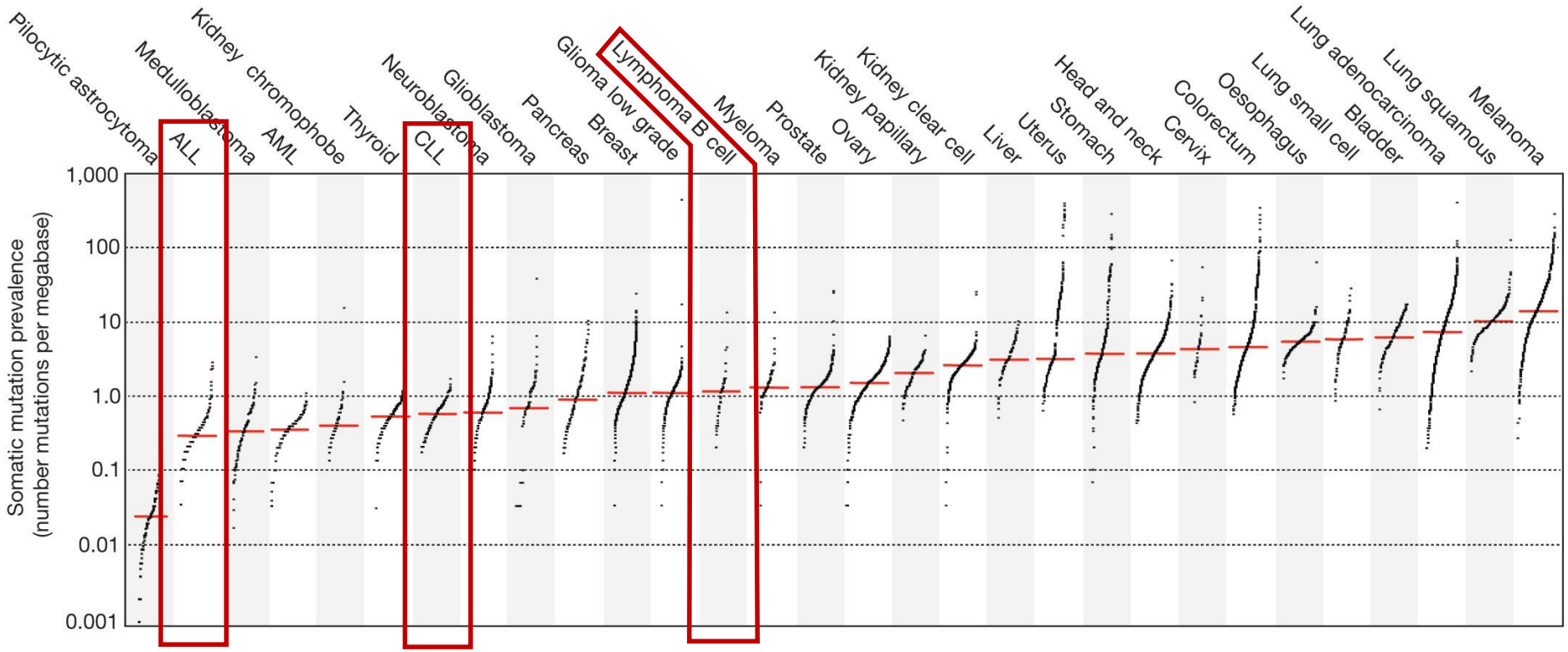
Additionally ”standard” predictors of PD-1 responsiveness are higher in DLBCL

CD274 (PD-L1)



Adapted from cbioportal.org

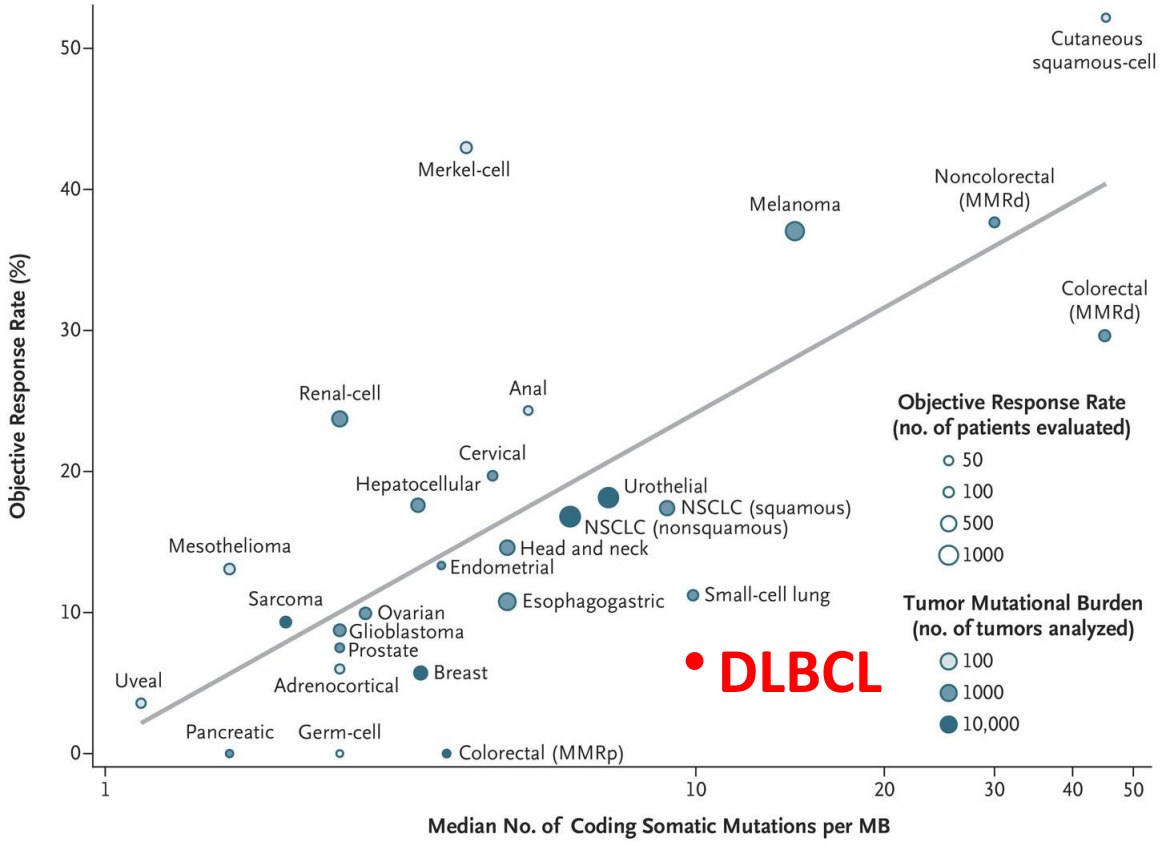
Low TMB may partly explain the poor responsiveness of NHL to IO agents



Alexandrov *et al. Nature* 2013

DLBCL has higher mutational burden but 1/7th ORR of HL

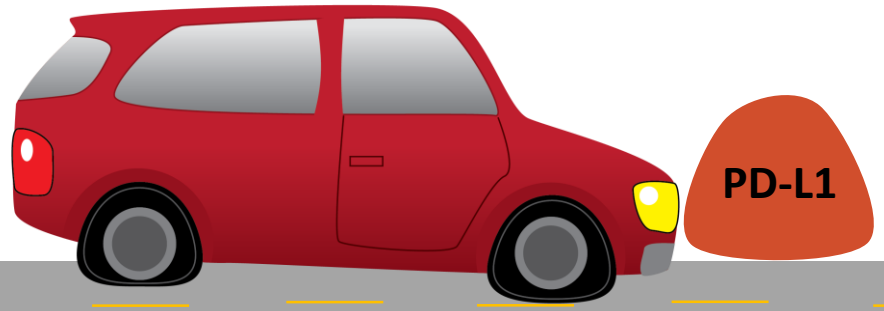
HL •



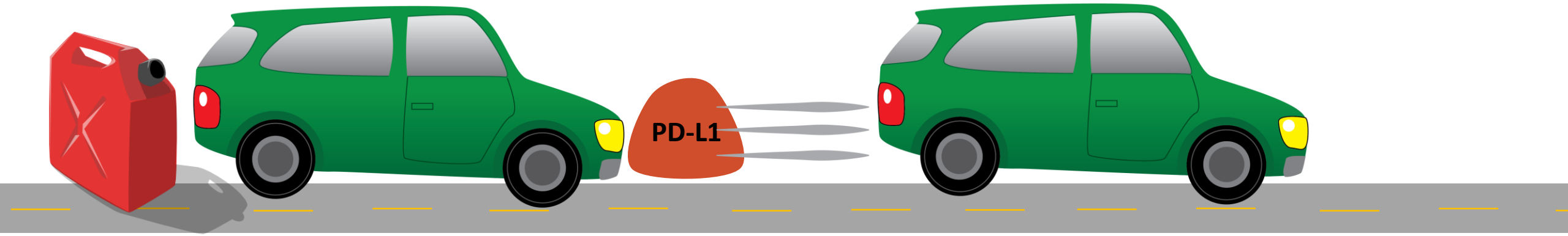
Okosun *et al, Nat Gen*, 2013
Severson *et al, Blood*, 2017
Reichel *et al, Blood*, 2015

Adapted from Yarchoan M *et al. NEJM* 2017

Despite high TMB, PD-L1 expression, checkpoint blockade is not enough in NHL

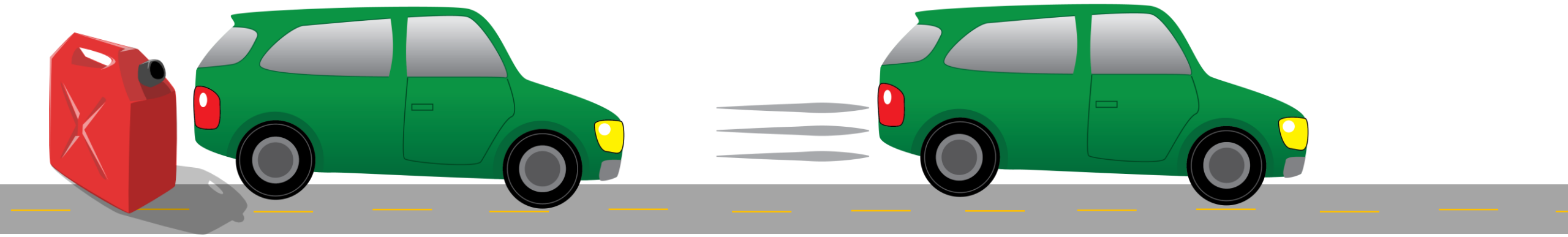


What approaches can gas up our immune system, and allow it to attack NHL?



1) Increase antigen uptake
2) Priming T cell response
3) Promoting T cell expansion

What approaches can gas up our immune system, and allow it to attack NHL?



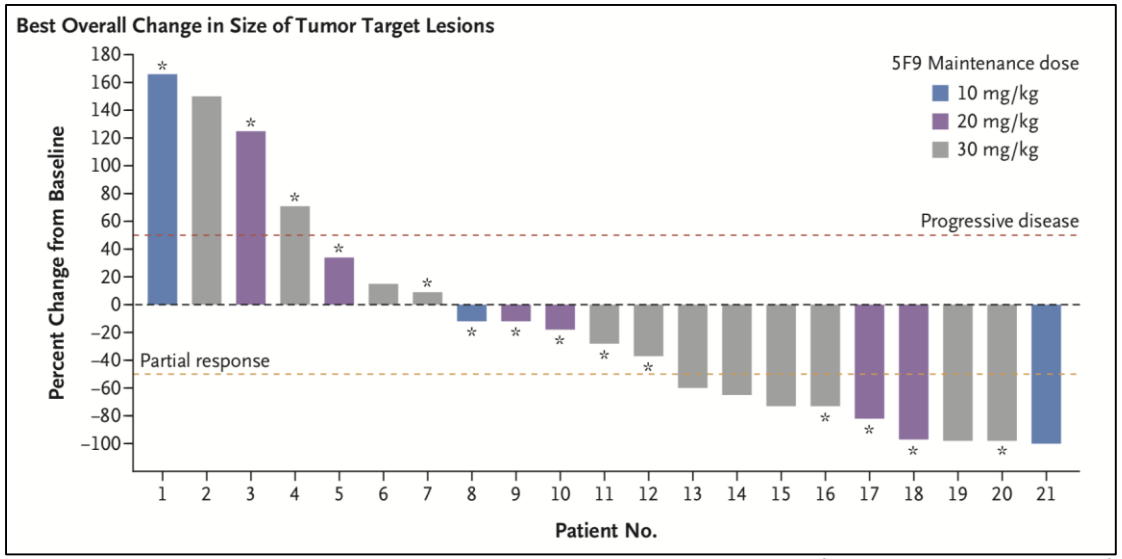
1) Increase antigen uptake
2) Priming T cell response
3) Promoting T cell expansion

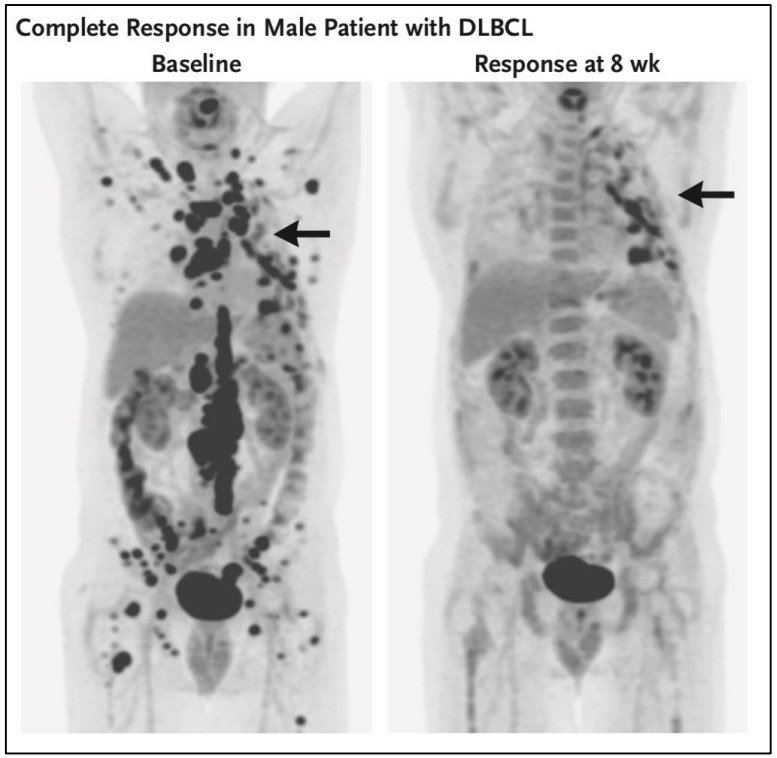
One notable combination from the last few days…

ORIGINAL ARTICLE

CD47 Blockade by Hu5F9-G4 and Rituximab in Non-Hodgkin's Lymphoma

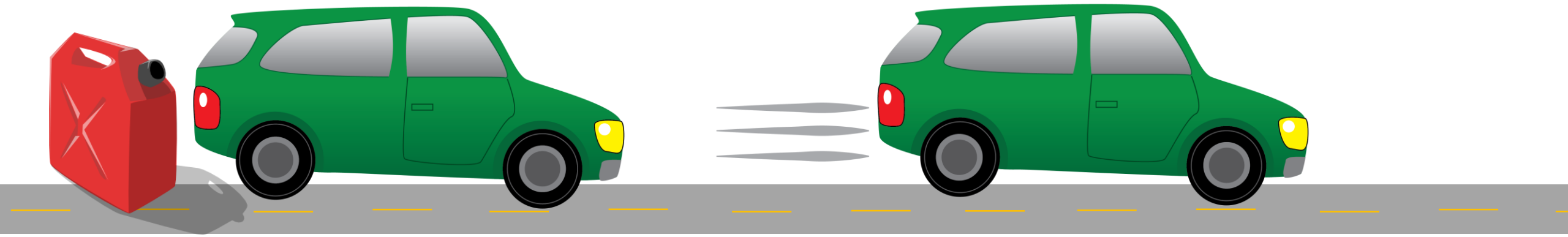
Ranjana Advani, M.D., Ian Flinn, M.D., Ph.D., Leslie Popplewell, M.D.,





NEJM, November 2018

What approaches can gas up our immune system, and allow it to attack NHL?



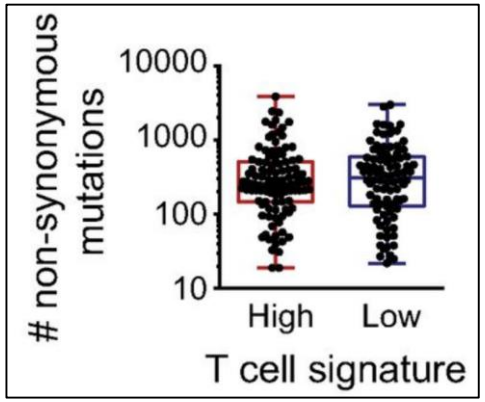
1) Increase antigen uptake
2) **Priming T cell response**
3) Promoting T cell expansion

Neoantigens are not enough, must cross-present them to the effector cells

Density of immunogenic antigens does not explain the presence or absence of the T-cell–inflamed tumor microenvironment in melanoma

Stefani Spranger[a,1], Jason J. Luke[b,1], Riyue Bao[c], Yuanyuan Zha[d], Kyle M. Hernandez[c], Yan Li[c], Alexander P. Gajewski[c], Jorge Andrade[c], and Thomas F. Gajewski[a,b,d,2]

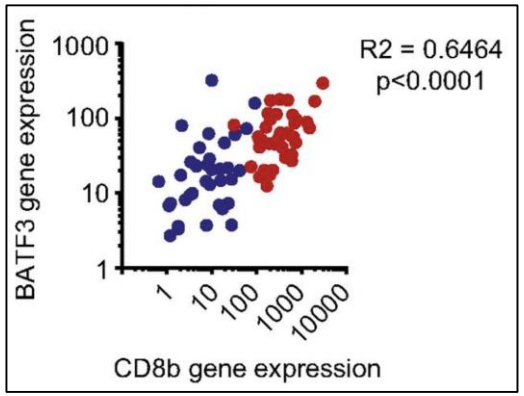
PNAS, 2016



T cell rich TME

≠

presence/absence of tumor antigens



T cell rich TME

~

presence of Batf3 Expression

CD103+ DCs

Batf3+

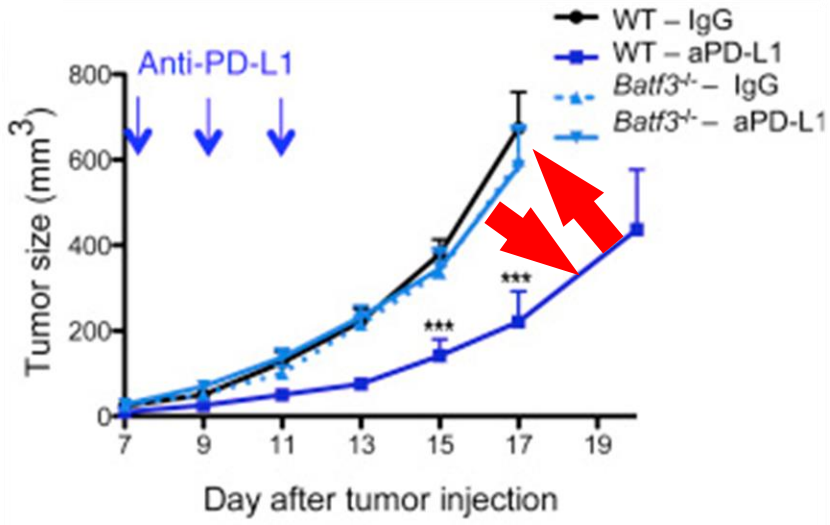
CD141+ DCs

Batf3+

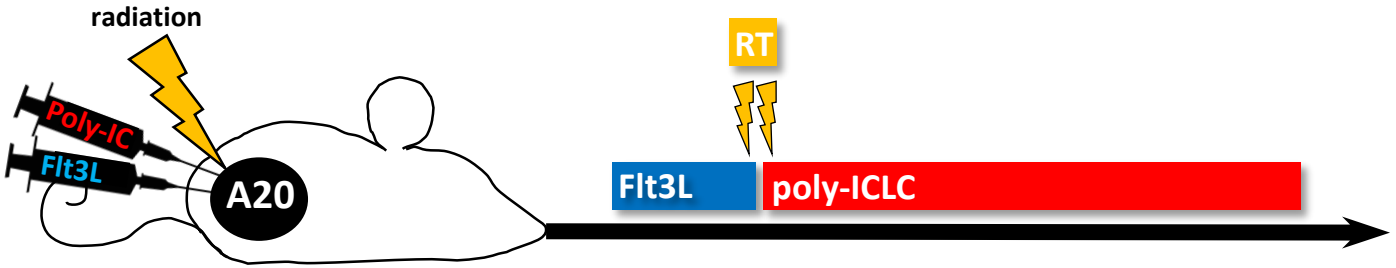
CellPress
Immunity
Article
2016

Expansion and Activation of CD103⁺ Dendritic Cell Progenitors at the Tumor Site Enhances Tumor Responses to Therapeutic PD-L1 and BRAF Inhibition

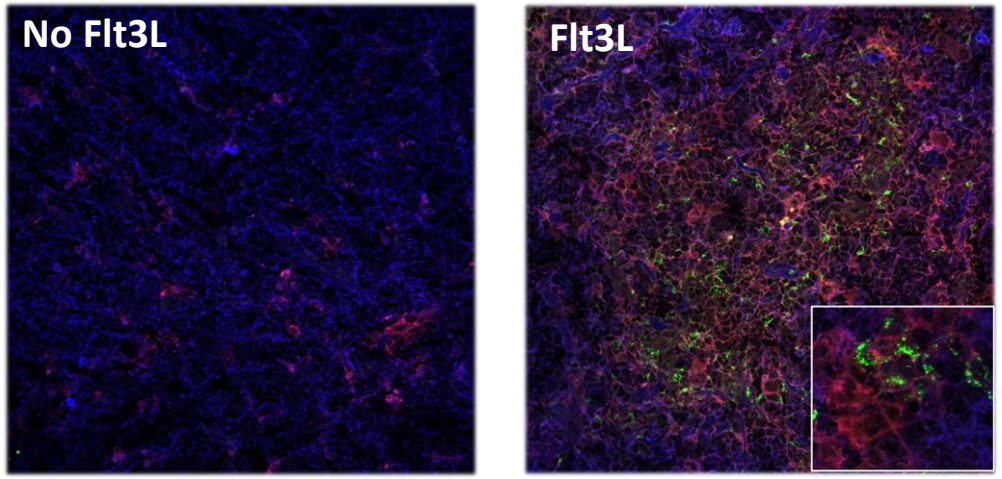
Hélène Salmon,[1,2,3] Juliana Idoyaga,[5] Adeeb Rahman,[4] Marylène Leboeuf,[1,2,3] Romain Remark,[2,3] Stefan Jordan,[1,2,3] Maria Casanova-Acebes,[1,2,3] Makhzuna Khudoynazarova,[1,2,3] Judith Agudo,[2,3,4] Navpreet Tung,[1,2,3] Svetoslav Chakarov,[9] Christina Rivera,[1,2,3] Brandon Hogstad,[1,2,3] Marcus Bosenberg,[6] Daigo Hashimoto,[7] Sacha Gnjatic,[2,3] Nina Bhardwaj,[2,3] Anna Karolina Palucka,[8] Brian D. Brown,[2,3,4] Joshua Brody,[2,3] Florent Ginhoux,[9] and Miriam Merad[1,2,3,*]



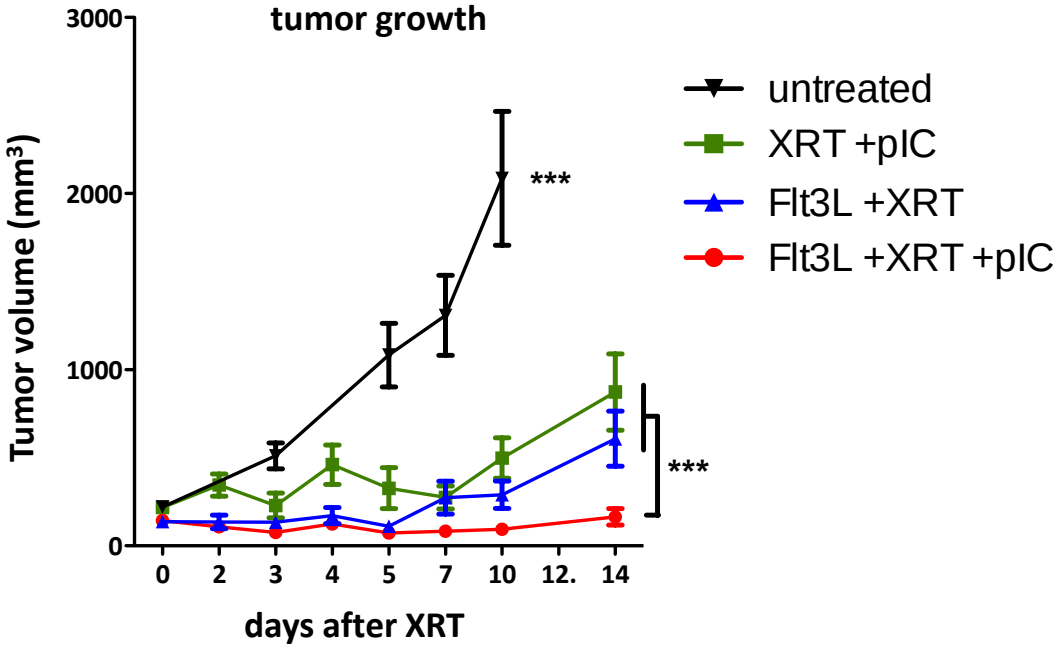
How do we increase cross presentation? Increase the cross-presenters: *In Situ* Vaccine with Flt3L



Linda Hammerich, PhD

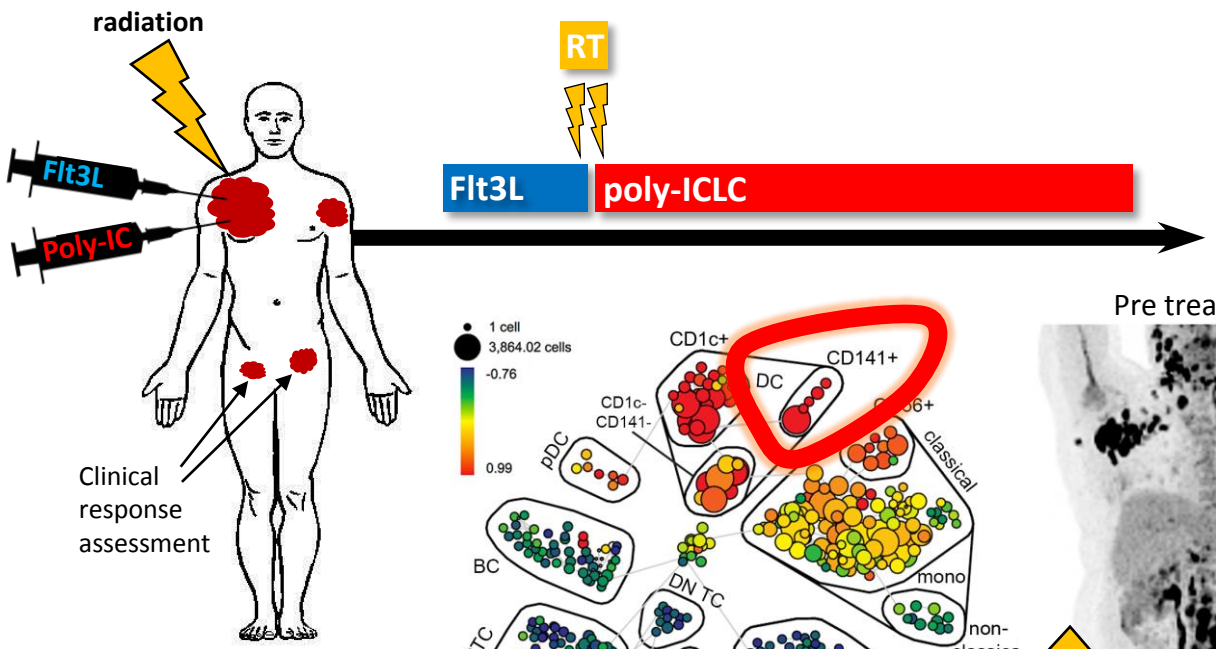


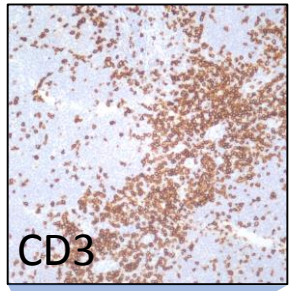
B220
CD11c
TLR3

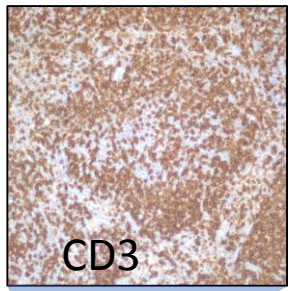


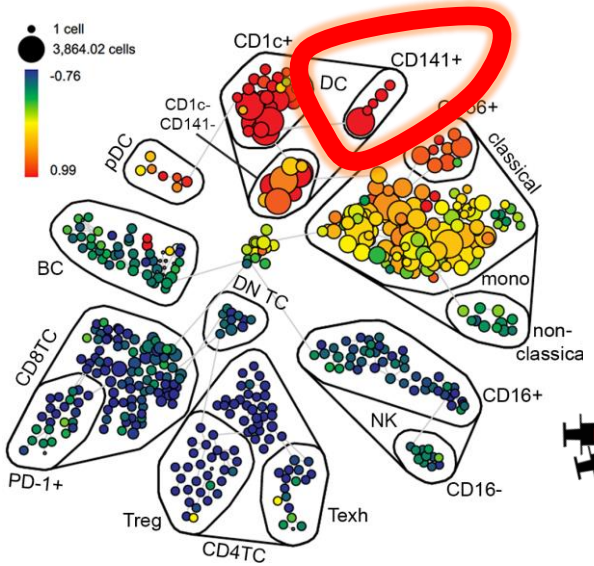
Submitted for publication

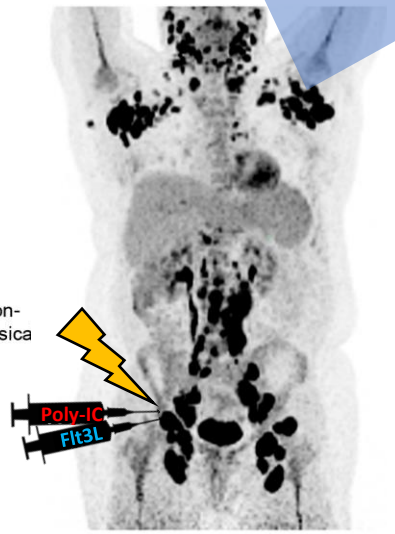
NCT01976585: *In Situ* Vaccine for Low-Grade Lymphoma: Intratumoral Flt3L and Poly-ICLC With Low-Dose Radiotherapy











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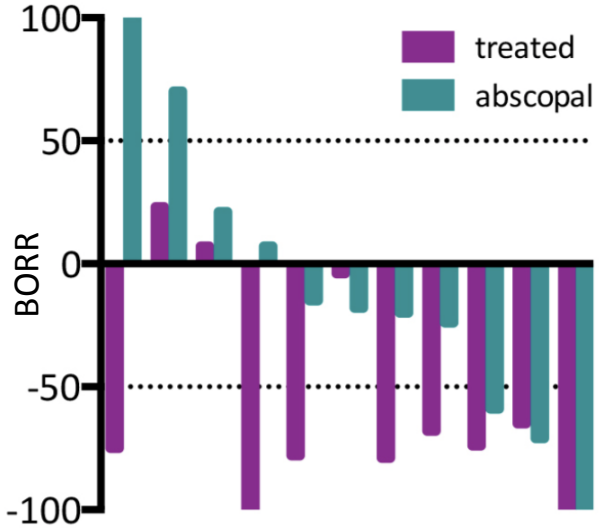
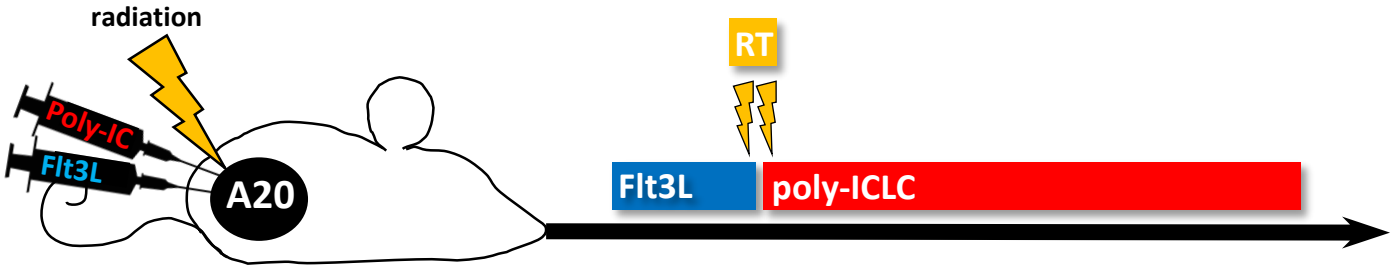


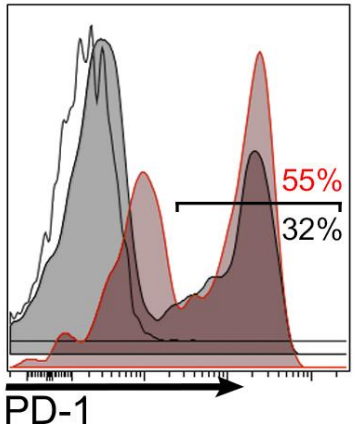
Submitted for publication

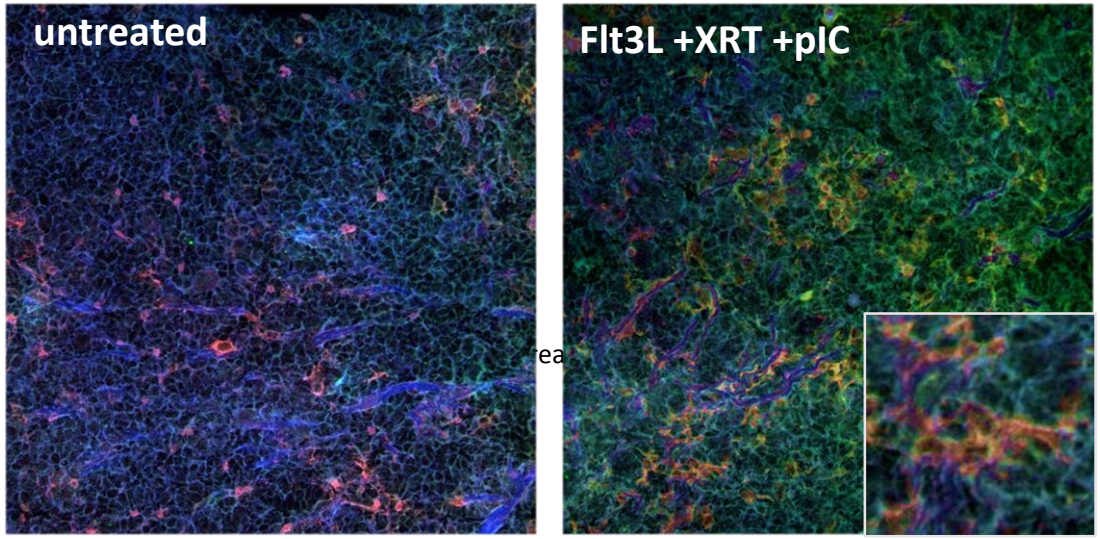
In situ vaccine increases T cell exhaustion and intratumor PD-L1

Linda Hammerich, PhD



Intratumoral CD8+ T cells

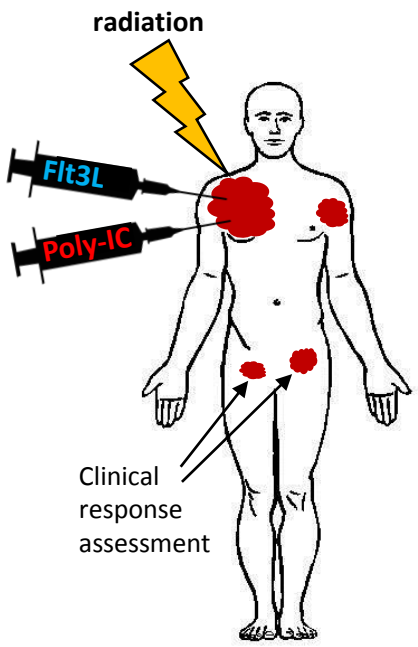


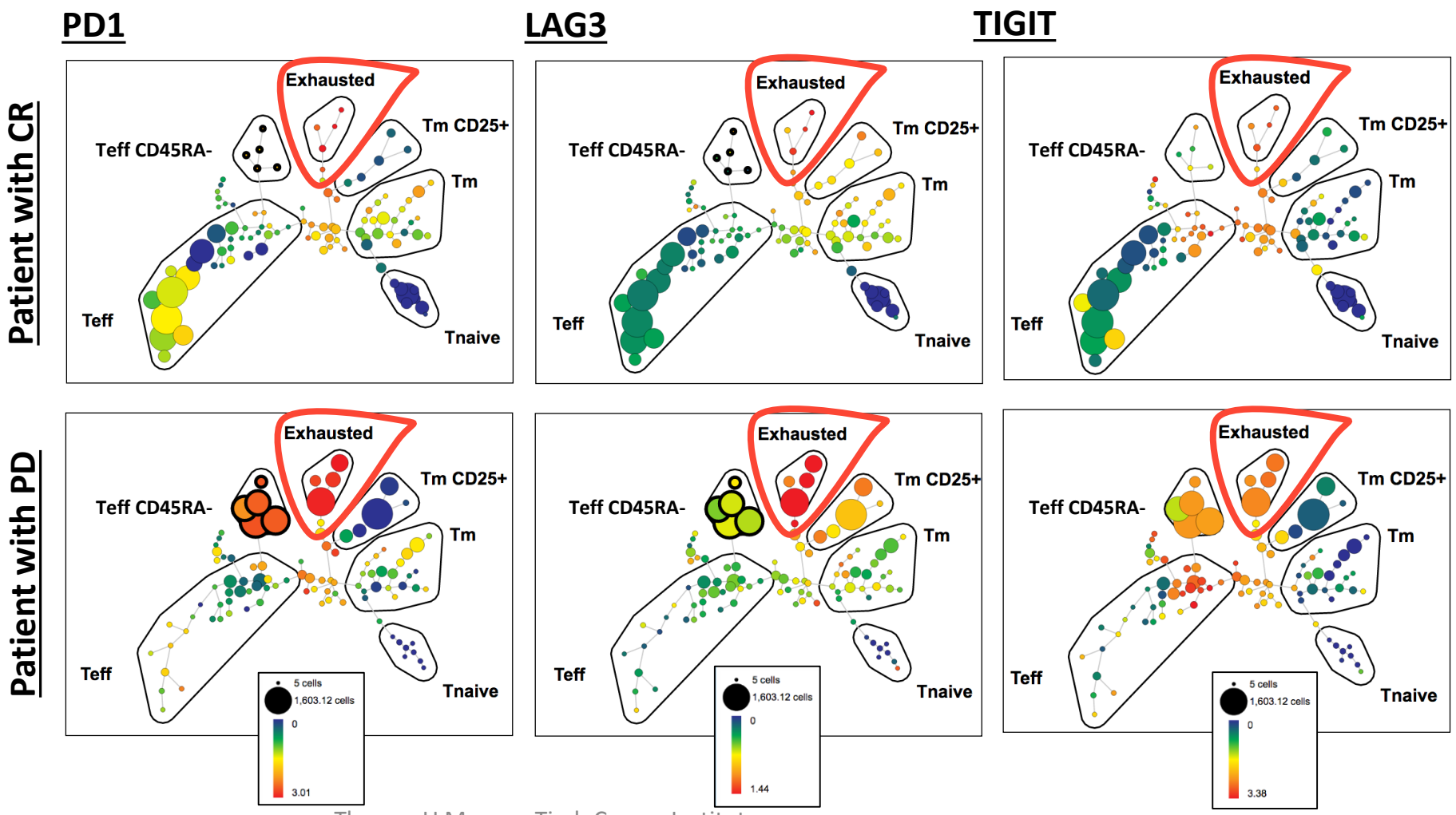


B220
CD11c
PD-L1

Submitted for publication

Non-response to *in situ* vaccine may be due to T cell exhaustion





Week 4

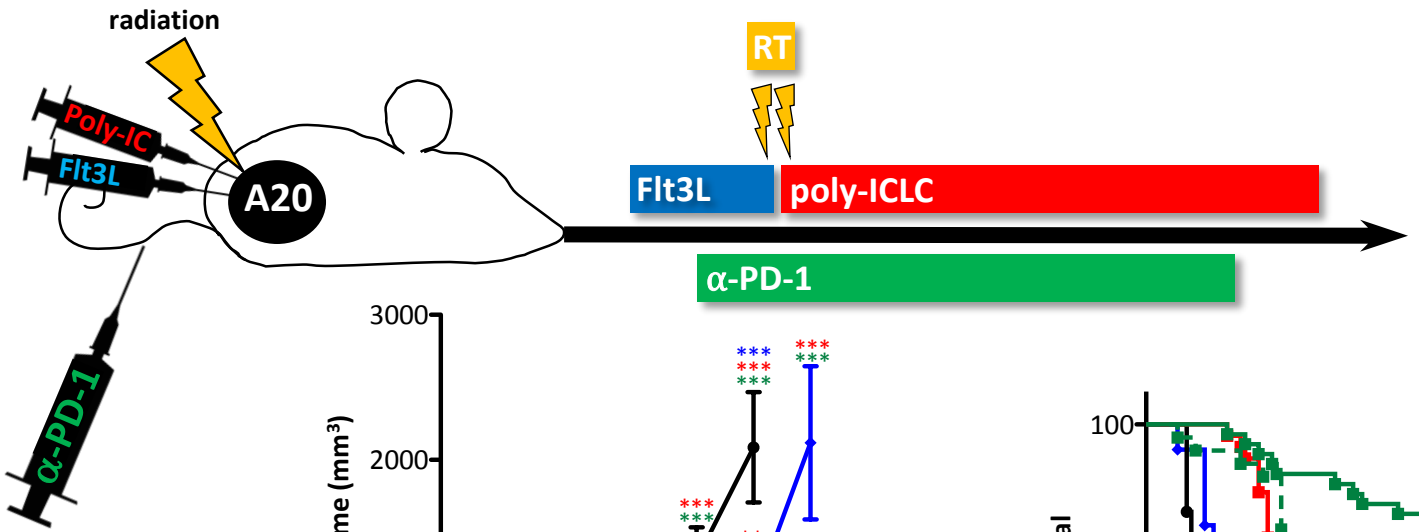
Size = # of cells

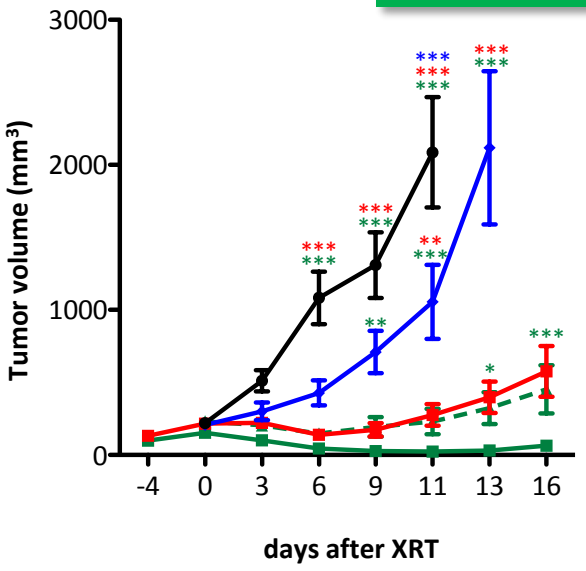
Color = expression level

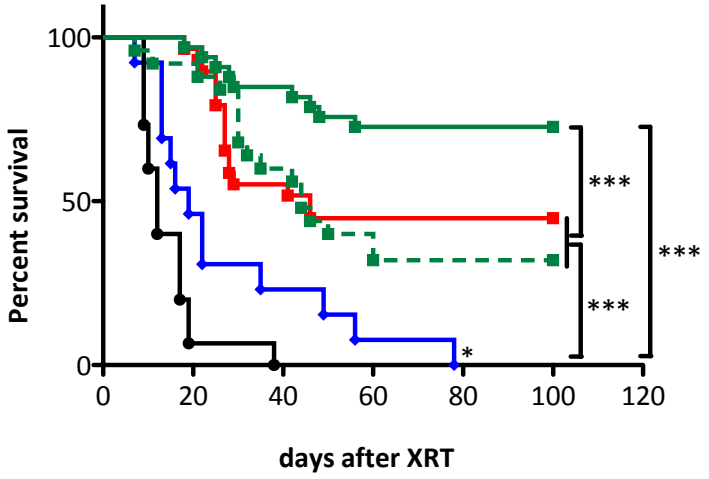
Unpublished data

Adding α-PD-1 to *In situ* vaccine significantly improves response & survival

Linda Hammerich, PhD



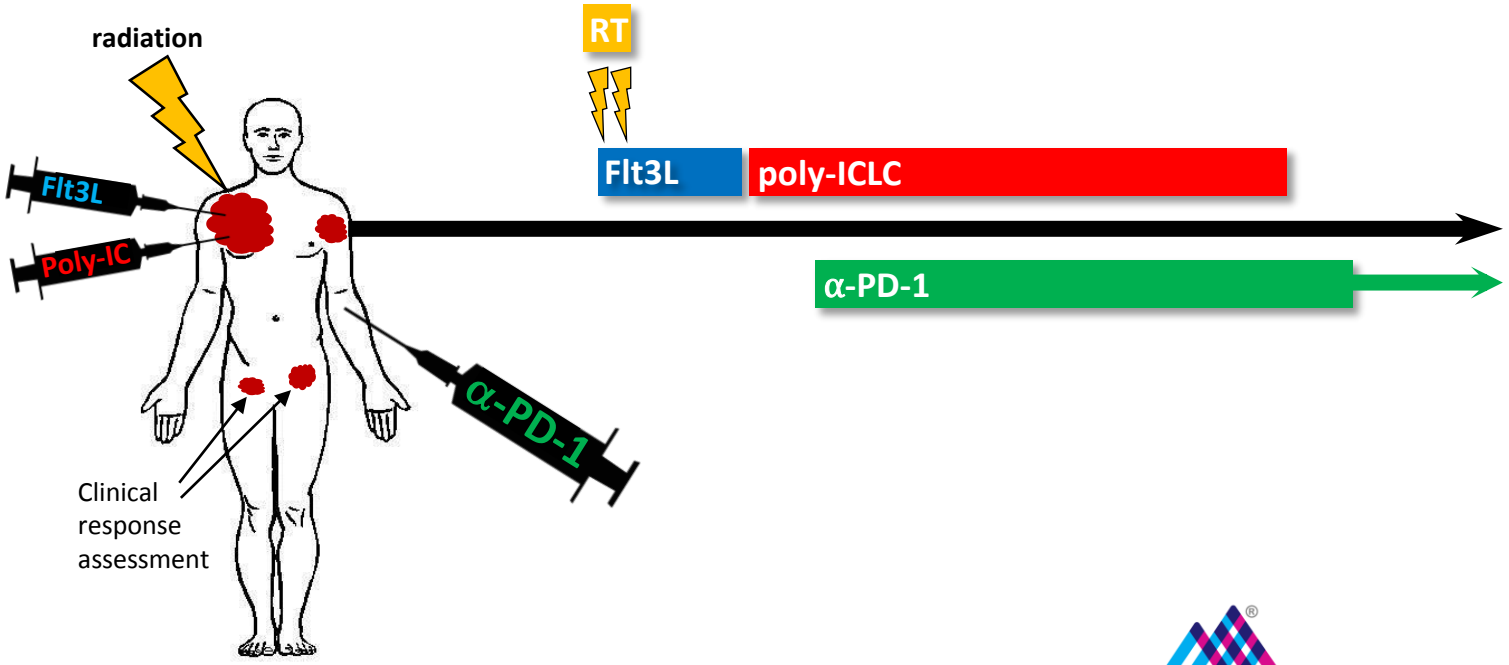




Submitted for publication

IND 140050: Opening December 2018: *In situ* vaccine + pembrolizumab

NHL
MBC
HNSCC



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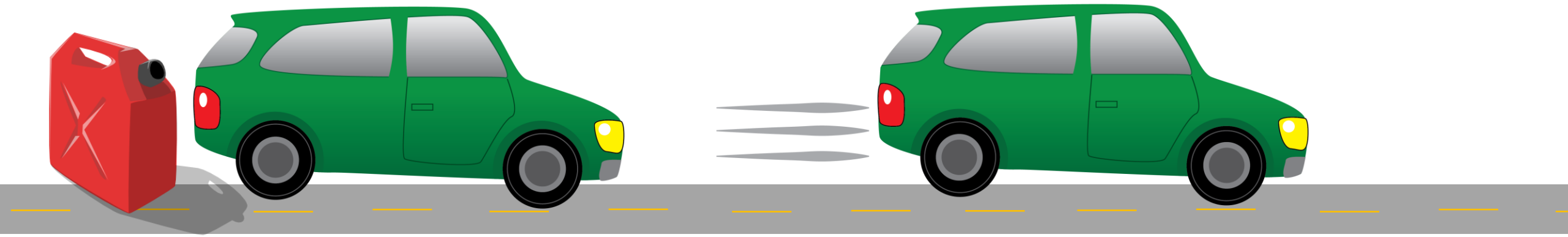
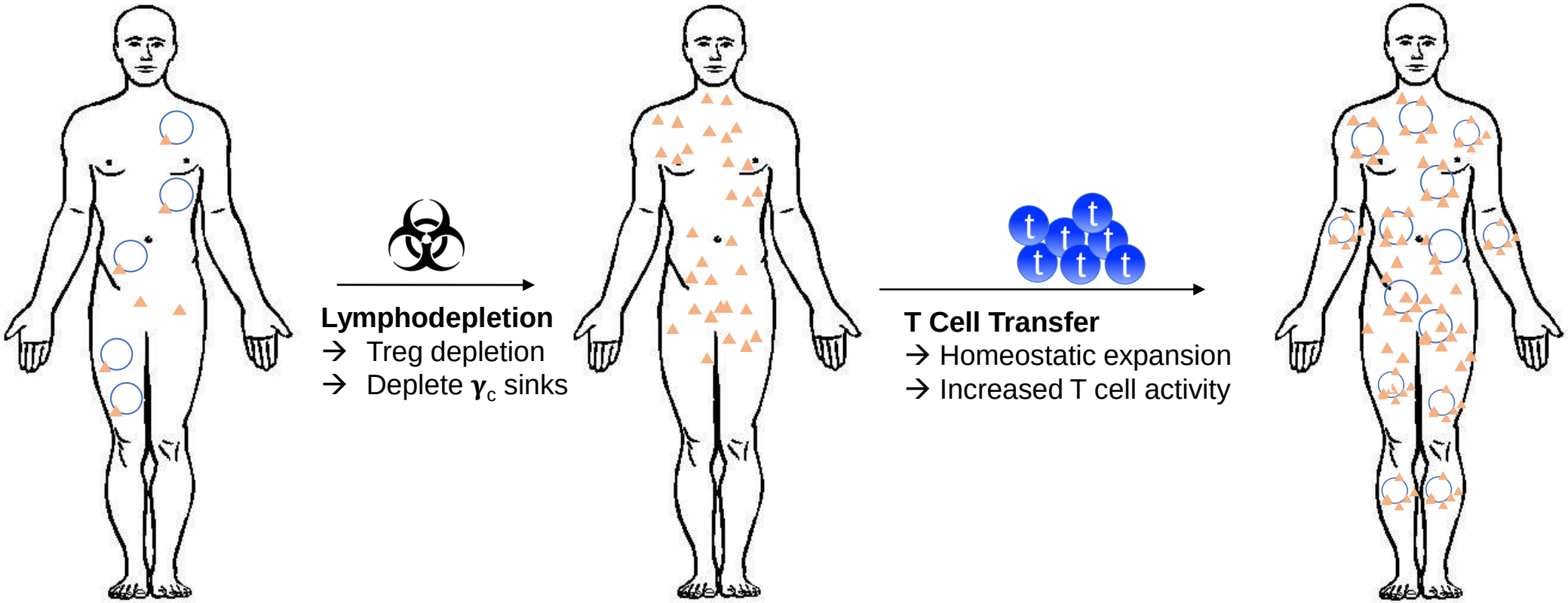
What approaches can gas up our immune system, and allow it to attack NHL?



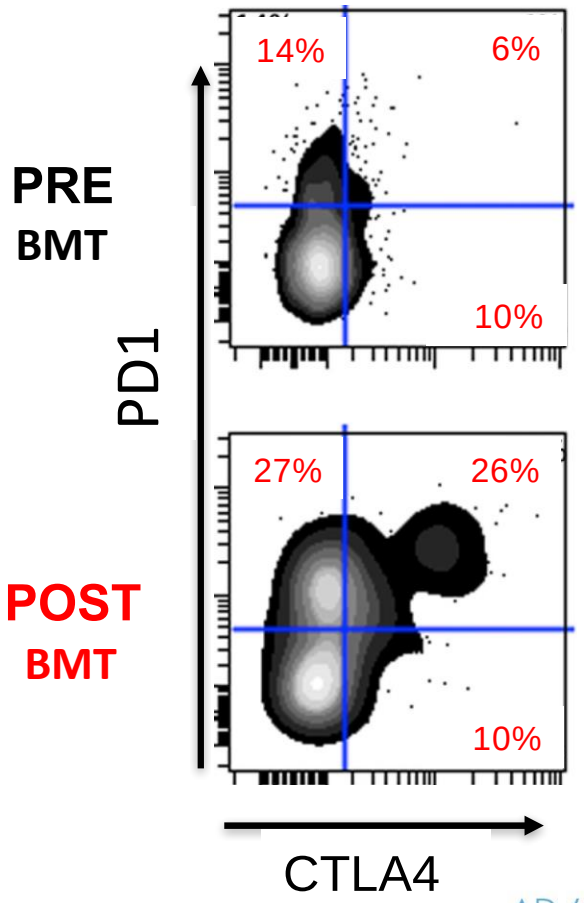
1) Increase antigen uptake
2) Priming T cell response
3) **Promoting T cell expansion**

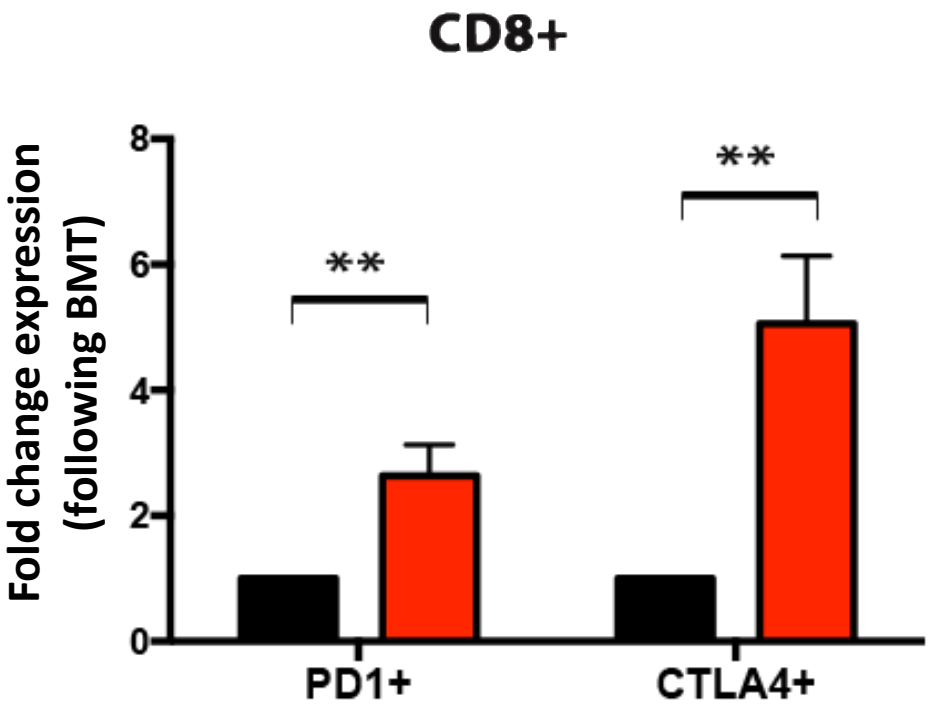
Lymphodepletion promotes homeostatic proliferation and activation of T cells



▲ Homeostatic cytokines (eg IL-7, IL-15)

Following BMT we see homeostatic activation, but also homeostatic inhibition

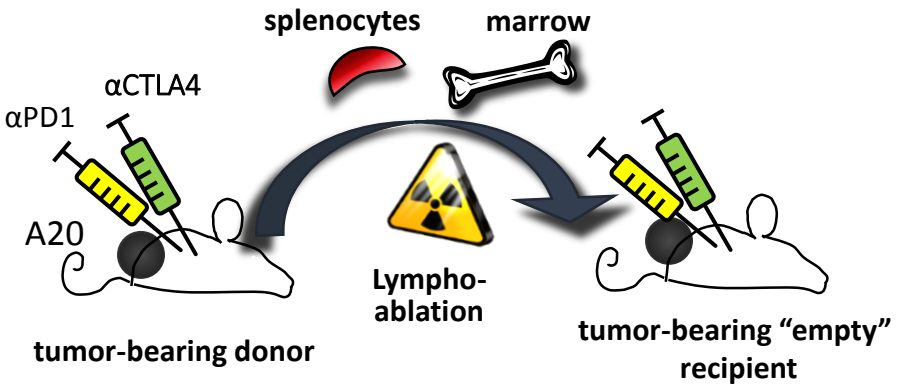


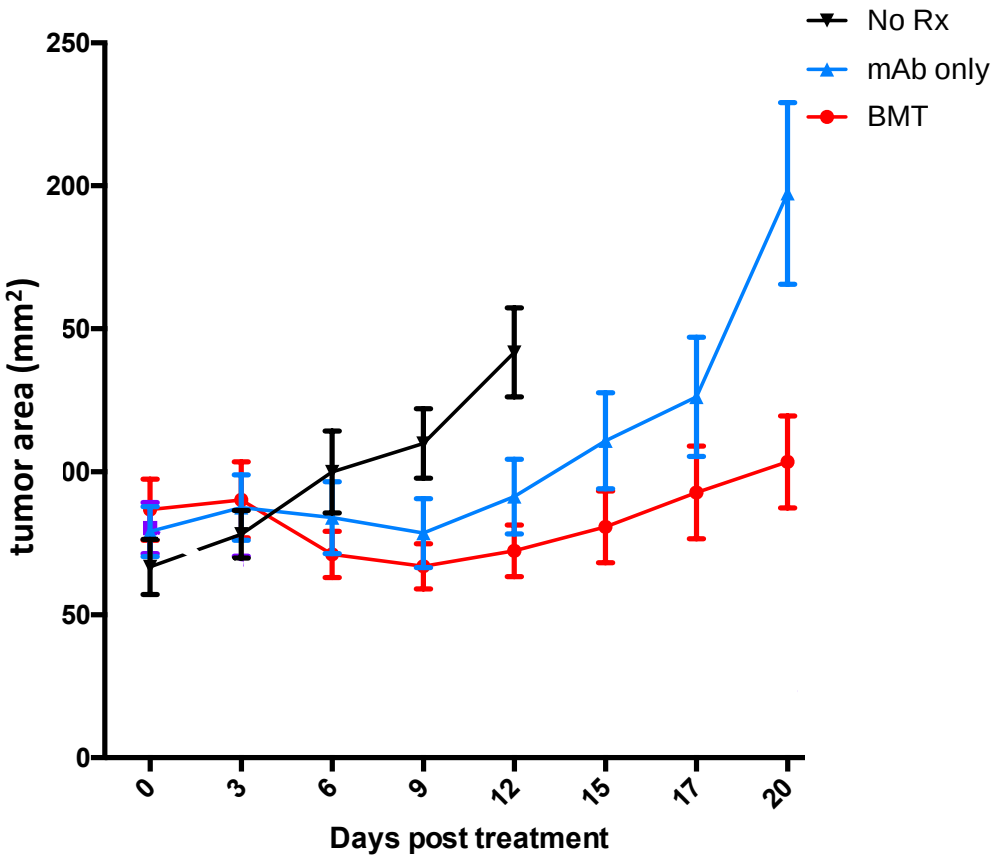


Netonia Marshall, PhD

Submitted for publication

Combining BMT with dual checkpoint blockade improves survival

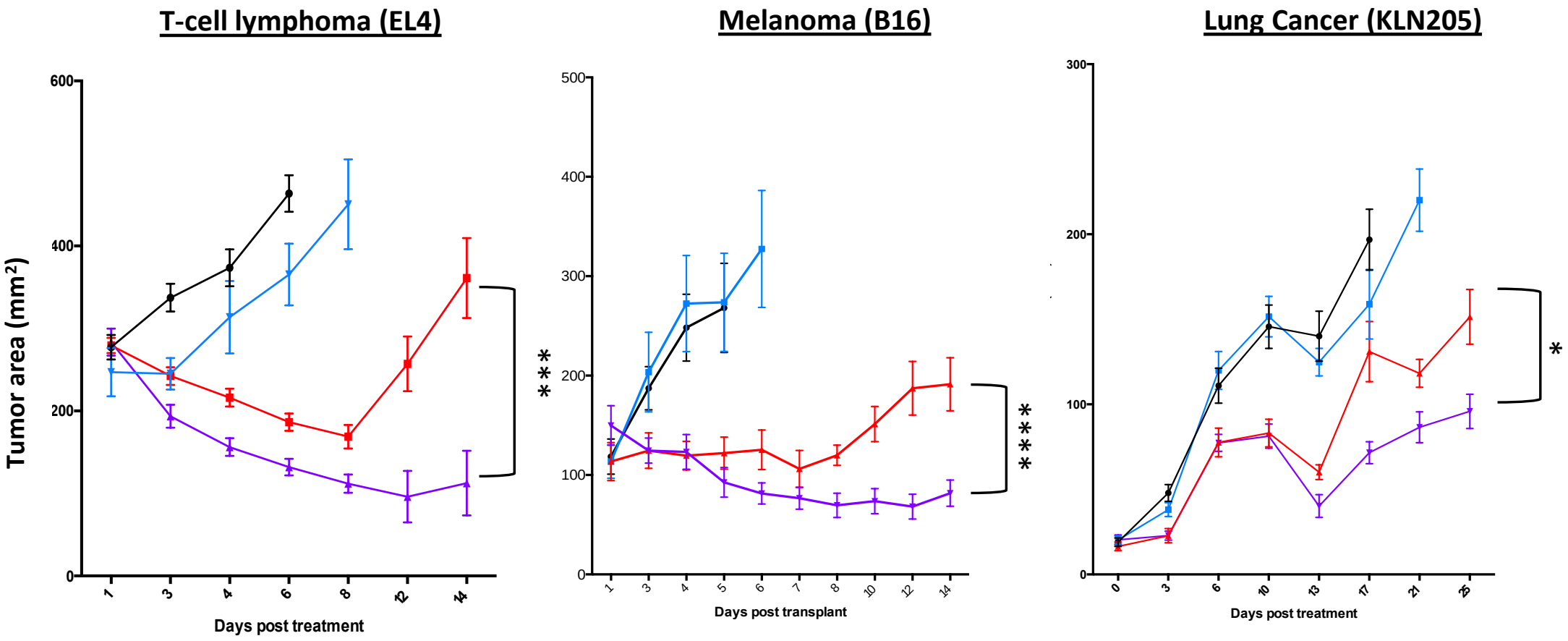




Netonia Marshall, PhD

Submitted for publication

This benefit of immunotransplant is also seen in models of T-NHL, MM and NSCLC

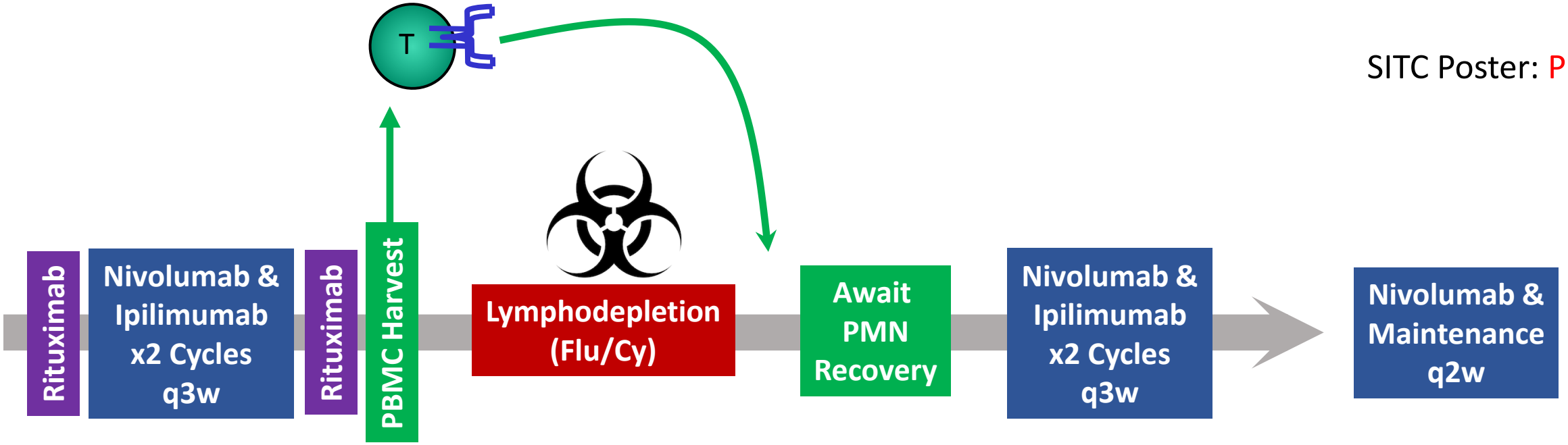


Netonia Marshall, PhD

Submitted for publication

NCT03305445:Nivolumab/Ipilimumab-Primed Immunotransplant for DLBCL

SITC Poster: P330



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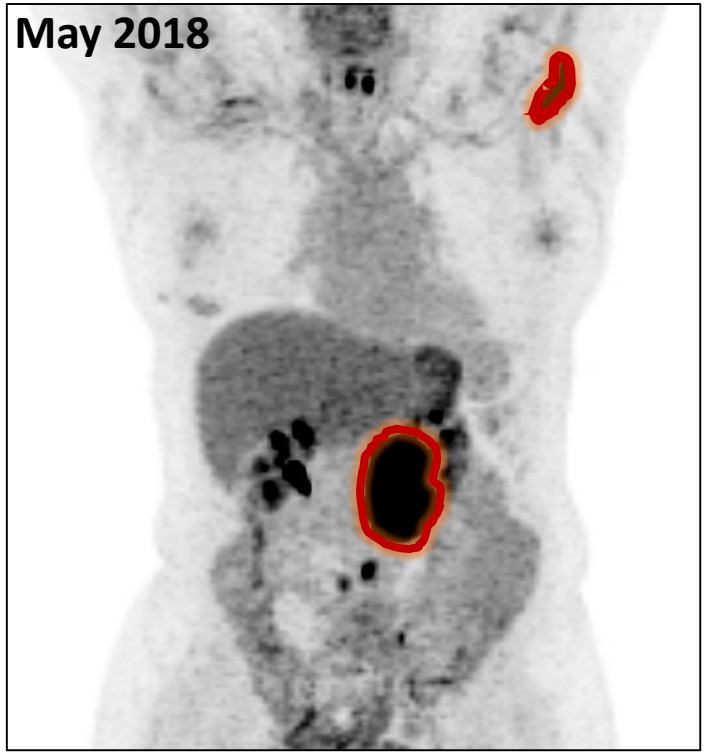
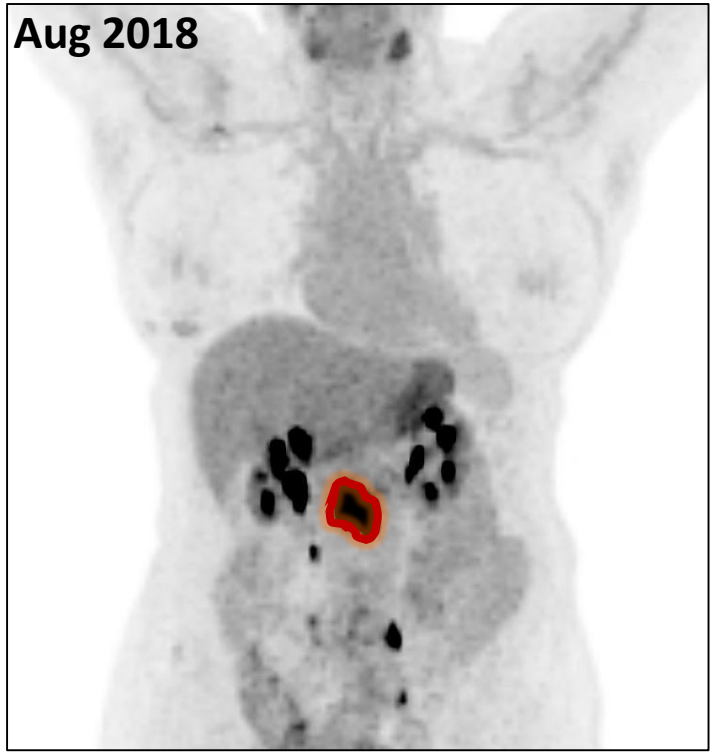
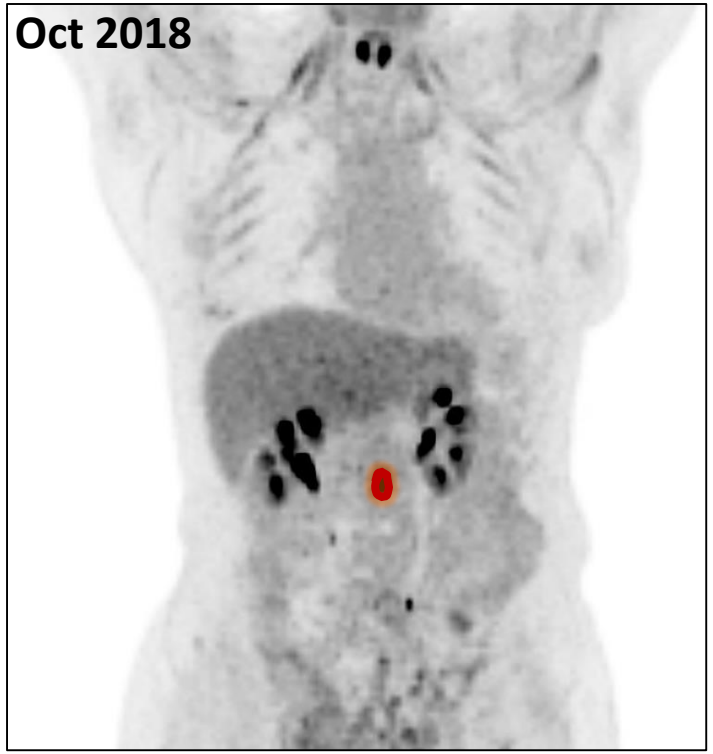
NCT03305445: Nivolumab/Ipilimumab-Primed Immunotransplant for DLBCL







Patient 1: 69F

2009: Dx with 1B DLBCL, Tx with RCHOP x6
2013: recurrence, s/p RICE x3, followed by BEAM/BMT
2017: recurrence, s/p R-Benda x6c → lenalidomide
2018: Relapsed with painful mesenteric mass

No irAE to date

Acknowledgements

Patients & Families

Our Nurses

Joshua Brody & Lab
Linda Hammerich
Netonia Marshall

Nina Bhardwaj & Lab
Miriam Merad & Lab

Sacha Gnjatic
Brian Brown
Ben Greenbaum
Jeremiah Faith
Human Immune Monitoring Core

Mount Sinai *The Tisch Cancer Institute*

Icahn School of Medicine at Mount Sinai *Precision Immunology Institute*