INTEGRATING IMMUNOTHERAPY INTO LYMPHOMA

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Ronald Levy, MD, has affiliations with Abpro, Apexigen, BeiGene, Checkmate, Corvus, Dragonfly, Five Prime, 47 Inc., Gigagen, Immune Design, Innate Pharma, Nohla, Nurix, Sutro, Teniobio, Viracta (*Consulting Fees*); BMS, Dynavax, Pfizer, Pharmacyclics (*Contracted Research*)

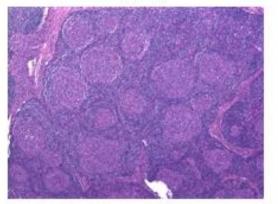
Note:

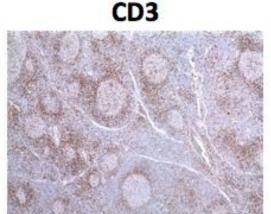
I will discuss as yet unapproved or off label uses of various immunotherapies



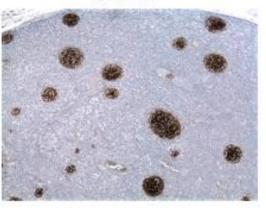
Immune Cells are Prevalent at Sites of Lymphoma but Do Not Eradicate It

H+E





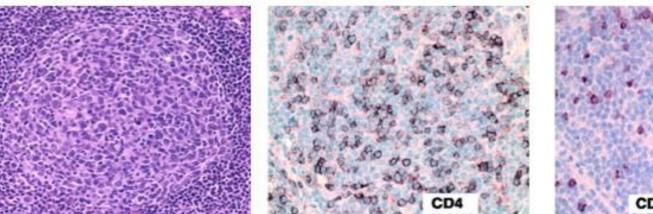
CD21



H+E



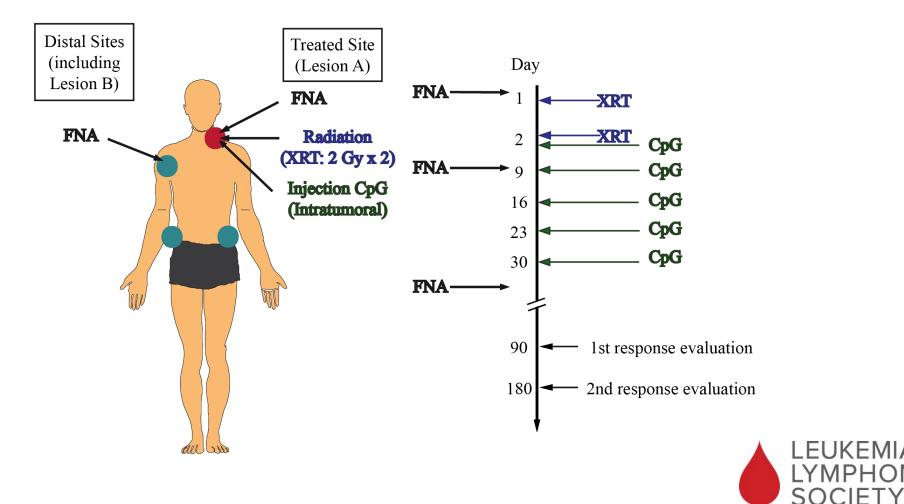






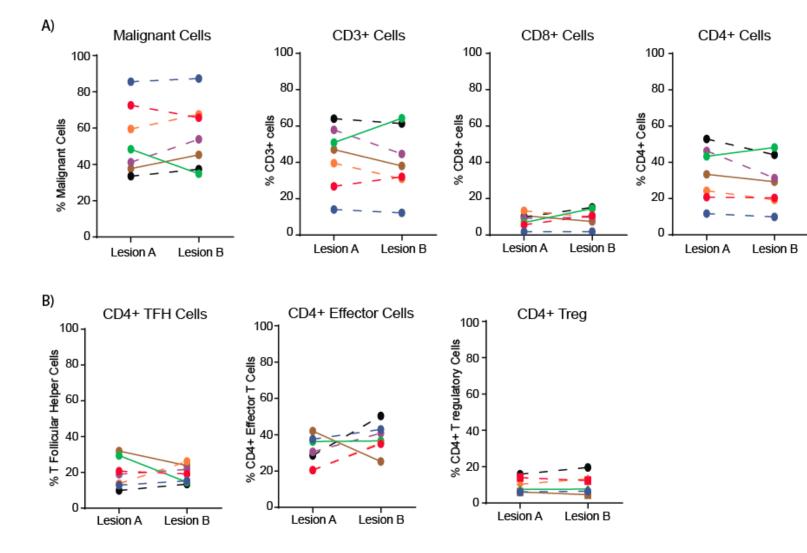
Stephen Ansell

Trial Schema: Patients with Untreated Indolent Lymphoma



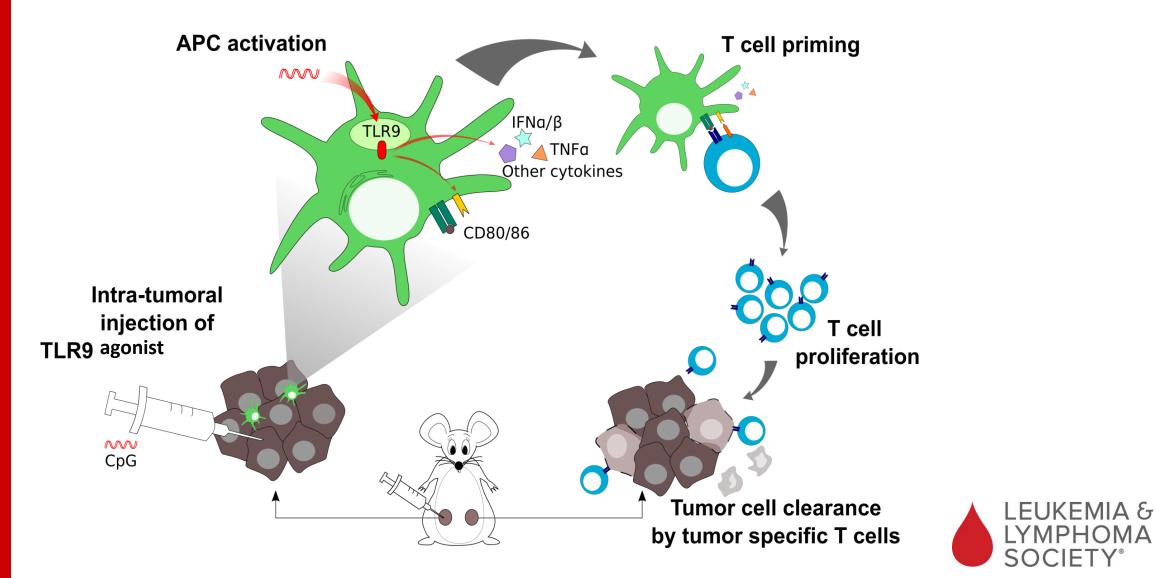
Frank MJ, et al. Cancer Discov. 2018;8(10):1258-1269.

Lesion A to Lesion B Comparison Before Treatment

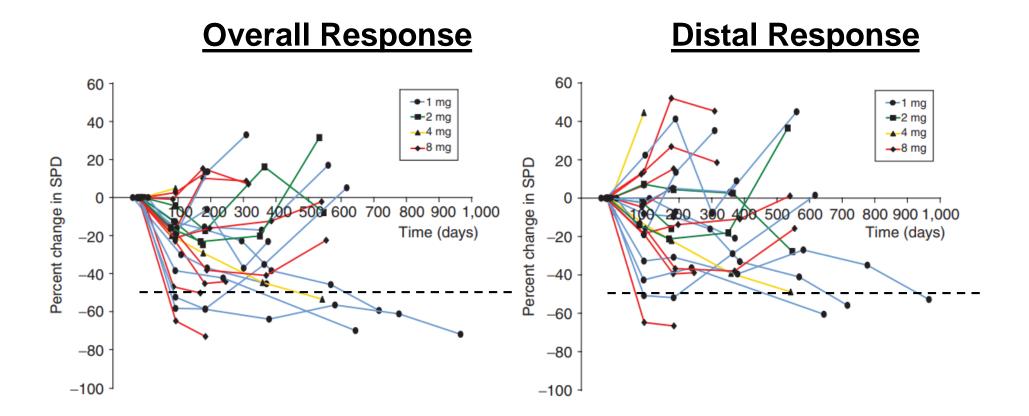




Mechanism of CpG (TLR9 Agonist)

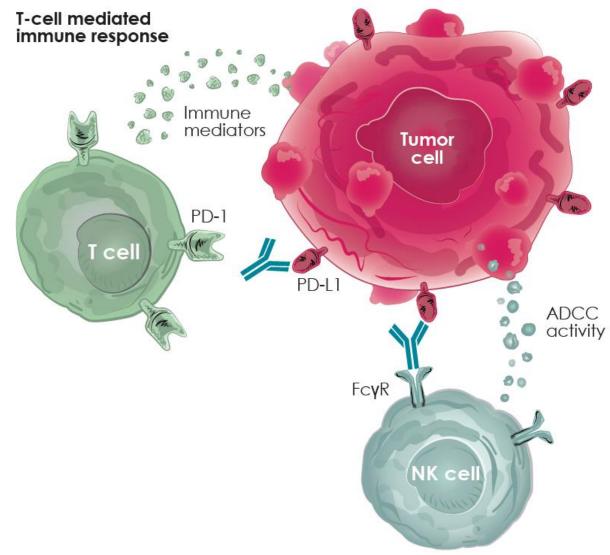


Clinical Responses Were Durable; Can Deepen Over Time





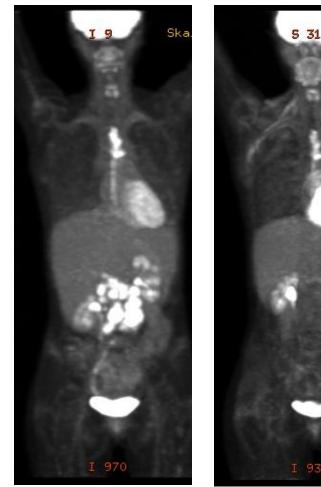
Approaches to Enhance Immune Therapy



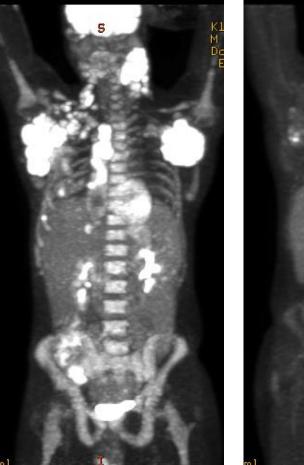


Chen R, et al. Hematol Oncol. 2017:35:67.

Does Blocking PD-1 signaling work? Highly Effective in Hodgkin Lymphoma



42-year-old female – Hodgkin lymphoma

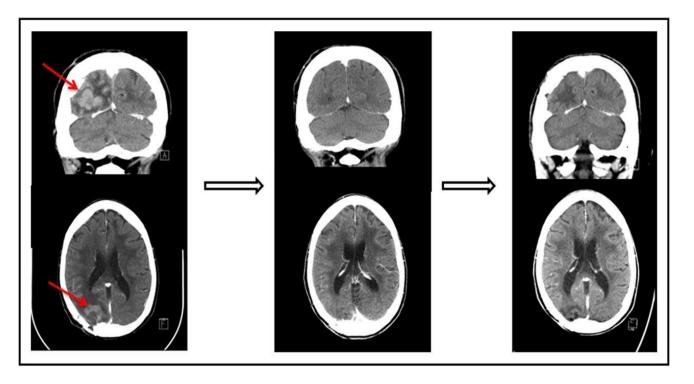




26-year-old male – Hodgkin lymphoma

Courtesy of SM Ansell, Mayo Clinic

Promising Results with Anti-PD1 in Patients with Primary Refractory PCNSL



- 13% of PCNSL patients have translocations at 9p24.1
- 67% have copy number gains
- All 4 patients responded



Nayak L, et al. Blood. 2017;129(23):3071-3073.

Scorecard for PD-1 Blockade in Lymphoma

- Hodgkin's Disease: FDA approved fourth line, 65% ORR
- PMBCL: FDA approved third line, 45% ORR
- PCNSL: Impressive results in small series
- NK/T Cell: Positive anecdotes
- Mediastinal Grey Zone: Positive anecdotes
- Richter's Transformation: Positive anecdotes
- FL: Disappointing
- DLBCL: Disappointing



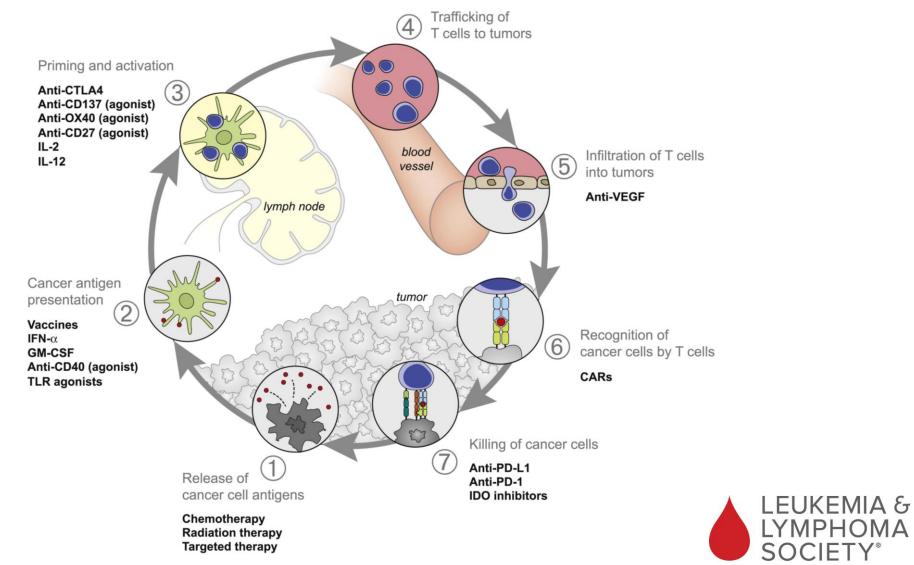
Other Interesting Antibody Targets

Naked Antibodies	Bispecific Antibodies	Antibody-Drug Conjugates
CD 40	CD 3-19*	CD 79b
CD 137	CD 3-20	CD 30*
CD 27	CD 3-BCMA	
CD 47		
CD 22		
CCR 4*		
CD38*		
SlamF7 (CD319)*		



*FDA Approvals

Combination Approaches



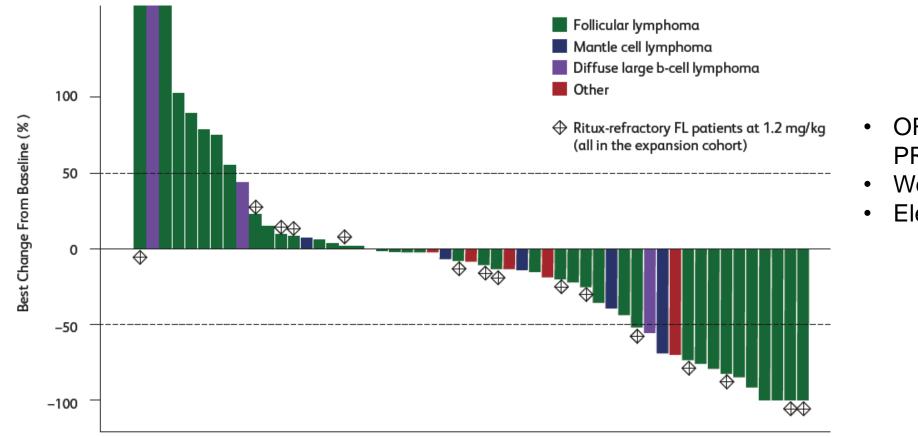
Chen DS, et al. Immunity. 2013;39(1):1-10.

Increasing Complexity > 800 CT with PD-L1/PD1

SCLC
Marketed Pembro+crizotinib Atezo+cobimetinib Melanoma
Phase III Nivo+erlotinib Pembro+epacadostat Atezo+CPI-444 Pembro+epacadostat Durva+tremelimjumab Atezo+CPI-444 Nivo+irilumab
Prinduc in Nvo+epacadostat Permbro+gefitinib Anton VEN/r 2b Nivo+urelumab Permbro+LV305
Priase For // II Pembro+GSK-3174998 Pembro+GSK-3174998
Ave+PF-04518600 Nivo+iniumab Pembro+ienvatinib Nivo+ Alezo+vaniumab Pembro+ipilimumab Pembro+pexidartinib Ave+utomilumab Nivo+urelumab Pembro+encitumumab Volcupiumab Ave+PF-04518600 Pembro+AM0010 Pembro+SD-101
Durva+AZD6738 Nivo+variliumab Pembro+PEGPH20 Ave+utomilumab Pembro+CAVATAK Pembro+X4P-001
Atezo+CP1444 Durva+epacadostat PDR001+LAG525 Pembro+pexidarlinib Nivo+ Durva+dabrafenib+brametinib PDR001+LAG525 Pembro+zmuclinumab Rivo T Durva+epacadostat PDR001+LAG525 Pro+Zmuclinumab Rivo T Durva+epacadostat PDR001+LAG525 Pembro+Zmuclinumab Rivo T Durva+epacadostat PDR001+LAG525 Pro+Zmuclinumab Rivo T Durva+epacadostat PDR001+LAG525 PR001+LAG525 Pro+Zmuclinumab Rivo T Durva+epacadostat PDR001+LAG525 PR001+LAG525
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Durva+IMC-C54 Durva+IV/S10324 Durva+MED0650
Durva+MEDI0562 Durva+MEDI9447 Durva+monalizumab Nivo+pilimumab Nivo+pilimumab Atezo+chemo Atezo+chemo Atezo+chemo
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Nivo+mogamulizuna Pennin-HK.1248 Pennino+HK.1466 Pennino+HK.1
Pembro+MK-4280 Pembro+demoizumab Pembro+MCP/444 Durva+AZD9150 Pembro+MCP/-elotuzumab Pembro+MK-42B0 Pembro+demoi /T-VEC
PDR001+GWN323 Pembro+utomilumab Durva+/AMD Atezo+accitidine Durva+/AMD Atezo+colometinit Atezo+chemo Atezo+chemo Atezo+chemo Atezo+chemo Durva+AXAL Pembro+chemo Durva+AXAL Pe
PURUIT-MICS/TIU Atezo+daratumumab+/JMID Atezo+daratumumab+/JMID Atezo+daratumumab+/JMID Atezo+daratumumab+/JMID
Durva+rituximab+MD Atezo+Obinutuzumab+polatuzumab Polatuzumab Personal Pers
Pembro-acalabrutinib Durva+AZD9150 Alezo+tazemetostat Pembro-acateminib Durva+
Pembro+AFM13 Durva+rituximab+bendamustine Durva+/femelimumab /emelimumab /emel
Pembro-dinacicilio Nivo-brentuzimab vedotin Alezo+GDC-0919 Alezo+bevacizumab Alezo+GDC-0919 Alezo+CDC-0919 Alezo+Varillumab PDR001-CJM112
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Nivo+varillumab Nivo+varillumab Nivo+earaizumab Durva+
Pembro+enadenotucirev Nivo+plimumab ramucirumab Pembro+margetuximab Pembro+PEGPH20 Pembro+miretuximab soravtansine
PDR001 + BL2945 Alezo+bevacizumab Pembro-pexidartinib Pembro-pexidartinib
CRC Pembro-yelareoprep Atezo+codrituzumab Pembro-yamucirumab Ovarian
PDR001+capmelinib PDR001+capmelinib
Pancreas Liver Gastric



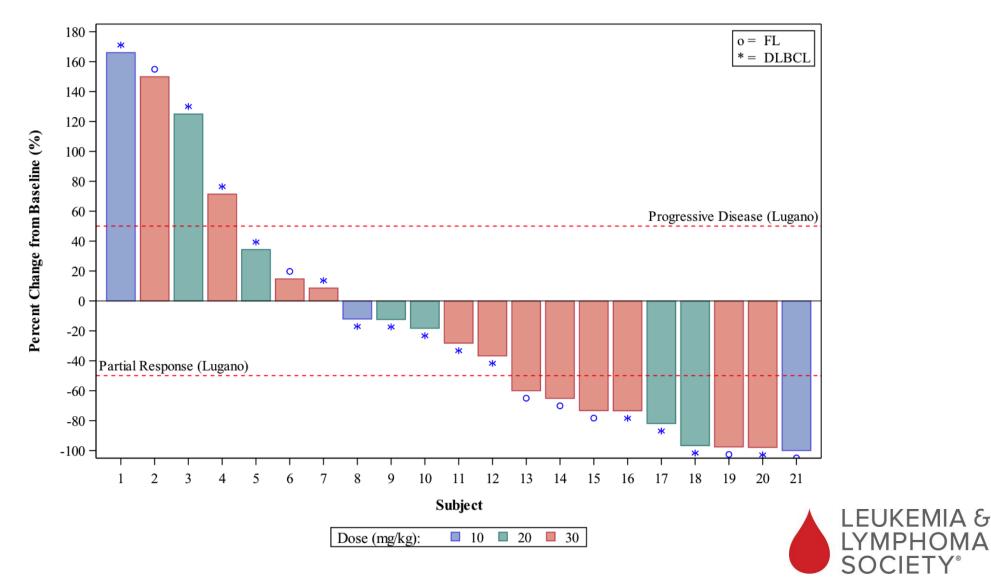
Anti-CD 137 Plus Rituximab in Relapsed Lymphoma



- ORR 23%, CR 8%, PR - 15%
- Well tolerated, no DLTs
- Elevated LFTs



Anti CD47 plus Rituximab

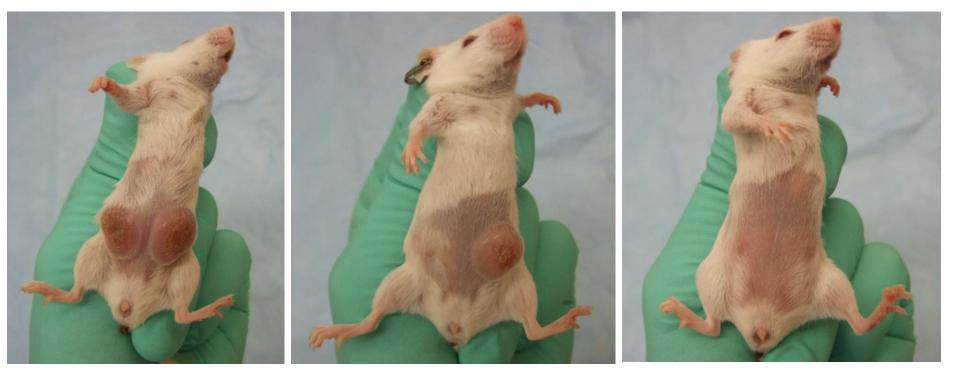


Search for Synergy: Two-Tumor Model

No Treatment

CpG Alone

CpG + Effective Ab





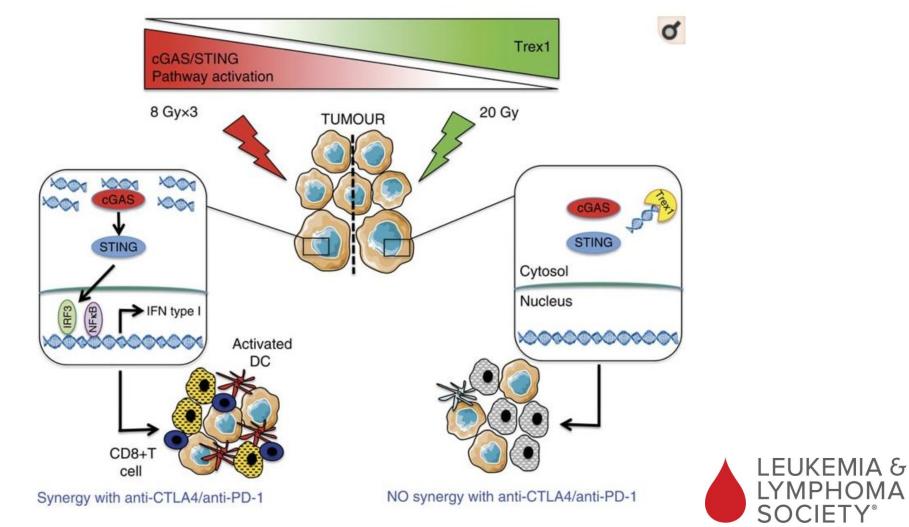
Houot R, et al. Blood. 2009;113(15):3546-3552.

Ongoing Clinical Trials of *in situ* Vaccination at Stanford

- Ibrutinib + intratumoral TLR9 + low-dose radiation in previously treated patients with indolent lymphoma (NCT02927964)
- Anti-Ox40 monoclonal antibody + intratumoral TLR9 + lowdose radiation in patients with indolent lymphoma (NCT03410901)



Combining Low-Dose XRT with Immunotherapy



Conclusions

- The immune system interacts with lymphoma potentially either to aid or impede the tumor.
- Locally injected immune modulators can trigger systemic antitumor immune responses.
- Checkpoint blockade works well in HD and perhaps in other lymphomas with amplified PDL1 genes.
- Antibodies against other targets are promising.
- Synergistic combinations of immune modulators with other therapies are actively being sought.



PANEL DISCUSSION/Q&A SESSION

Integration of Immunotherapy into Treatment for Hematological Malignancies





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