Immunotherapy in Heme Malignancies

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UCDAVIS
COMPREHENSIVE
CANCER CENTER
Radiation Oncology

Disclosures

- Research Funding and / or Advisory Boards
  - Genetech
  - BMS
  - Merck
  - Incyte
  - Dynavax
  - Transgene
  - Astra Zeneca

Immunotherapy for Leukemia

Targeted Antibodies

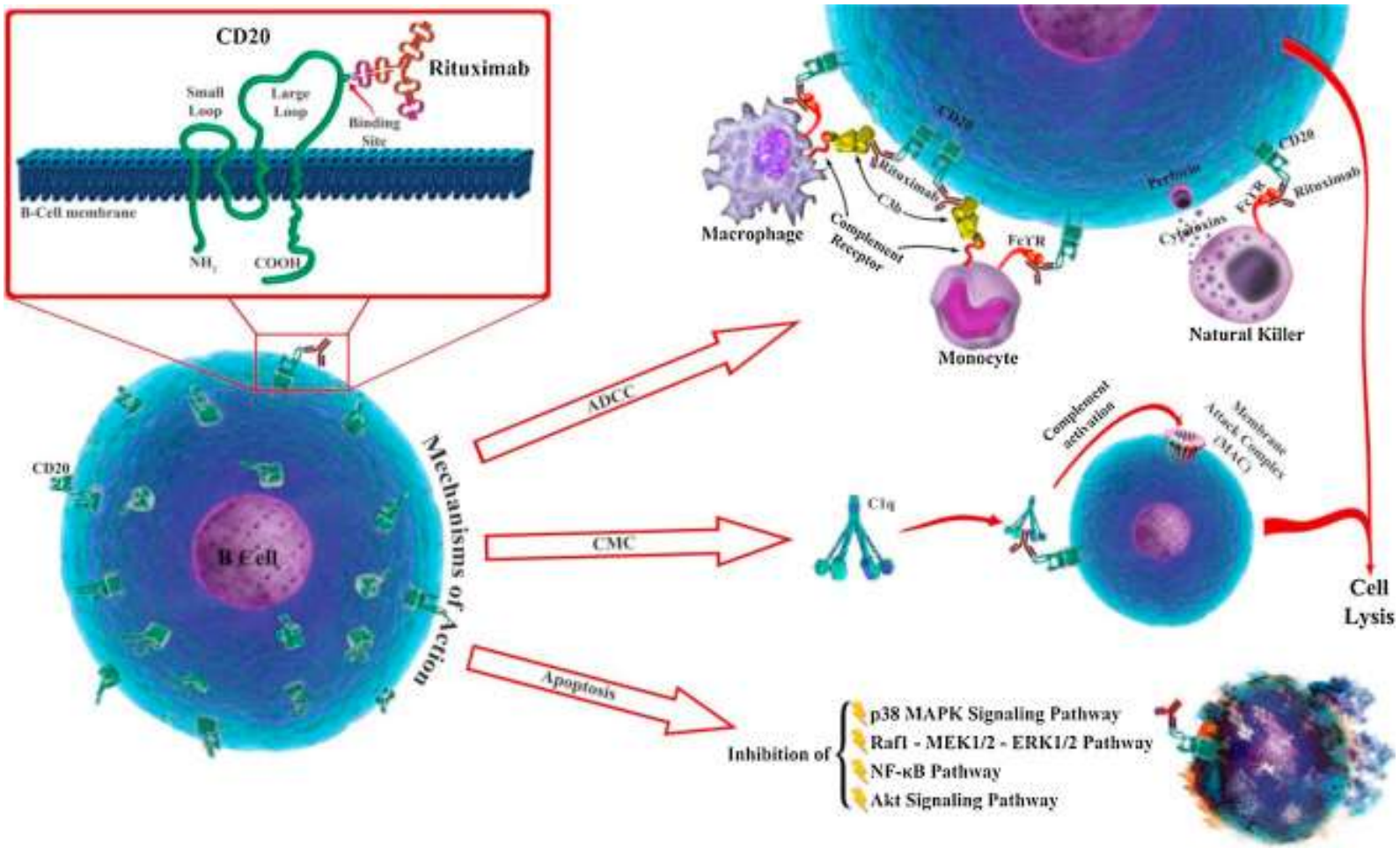
- **Alemtuzumab (Campath®):** a monoclonal antibody that targets the CD52 pathway; approved for subsets of patients with chronic lymphocytic leukemia (CLL)
- **Blinatumomab (Blincyto®):** a bispecific antibody that targets CD19 on tumor cells as well as CD3 on T cells; approved for subsets of patients with acute lymphoblastic leukemia (ALL)
- **Gemtuzumab ozogamicin (MyloTarg®):** an antibody-drug conjugate that targets the CD33 pathway and delivers toxic drugs to cancer cells; approved for subsets of adult and pediatric patients with CD33-positive acute lymphoblastic leukemia (ALL)
- **Inotuzumab ozogamicin (Besponsa®):** an antibody-drug conjugate that targets the CD22 pathway and delivers toxic drugs to cancer cells; approved for subsets of patients with advanced acute lymphoblastic leukemia (ALL)
- **Obinutuzumab (Gazyva®):** a monoclonal antibody that targets the CD20 pathway; approved for subsets of patients with CD20-positive chronic lymphocytic leukemia (CLL), including as a first-line therapy
- **Ofatumumab (Arzerra®):** a monoclonal antibody that targets the CD20 pathway; approved for subsets of patients with CD20-positive chronic lymphocytic leukemia (CLL), including as a first-line therapy
- **Rituximab (Rituxan®):** a monoclonal antibody that targets the CD20 pathway; approved for subsets of patients with chronic lymphocytic leukemia (CLL), including as a first-line therapy

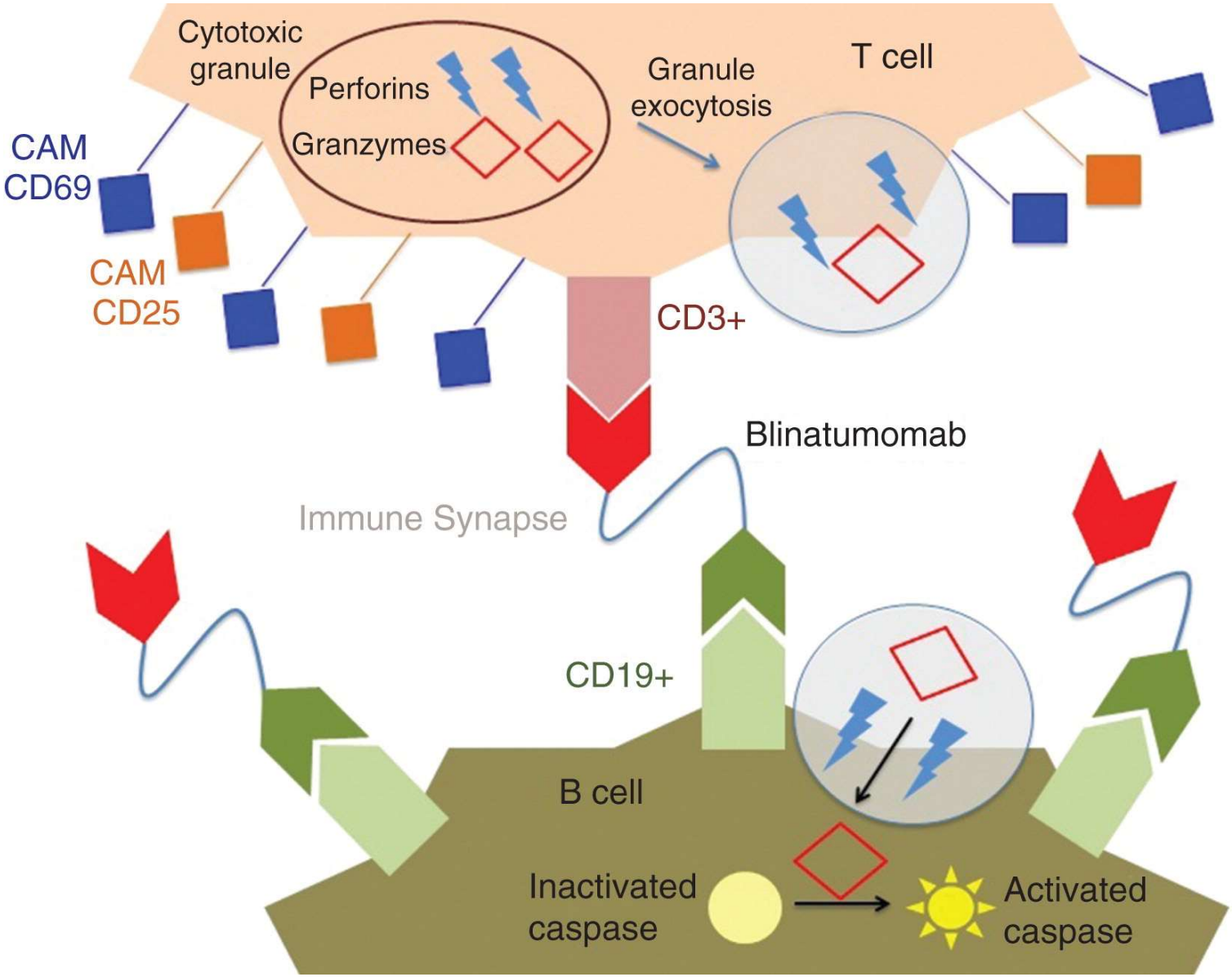
Adoptive Cell Therapy

- **Tisagenlecleucel (Kymriah®):** a CD19-targeting CAR T cell immunotherapy; approved for subsets of children and young adult patients with acute lymphoblastic leukemia (ALL)

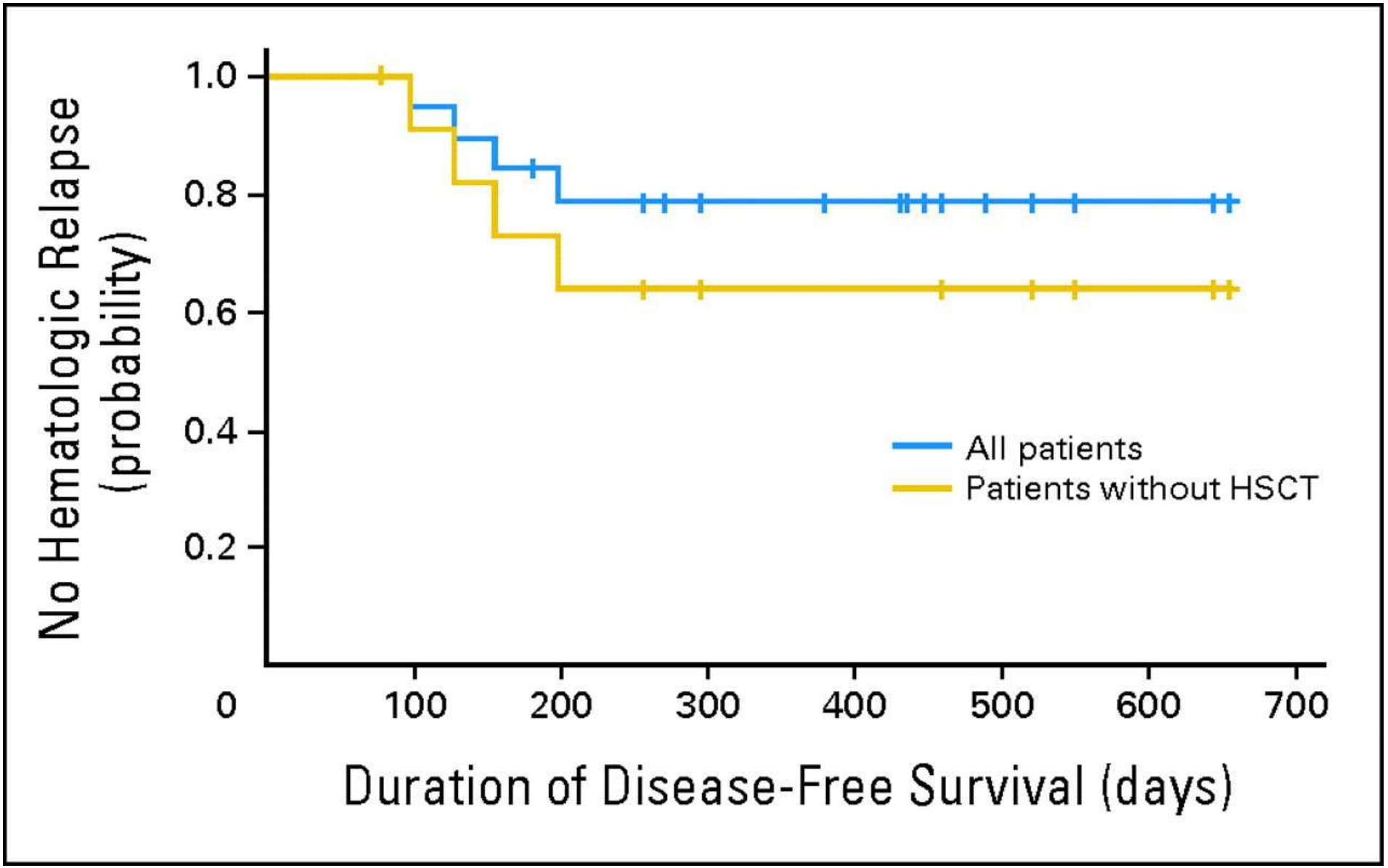
Immunomodulators

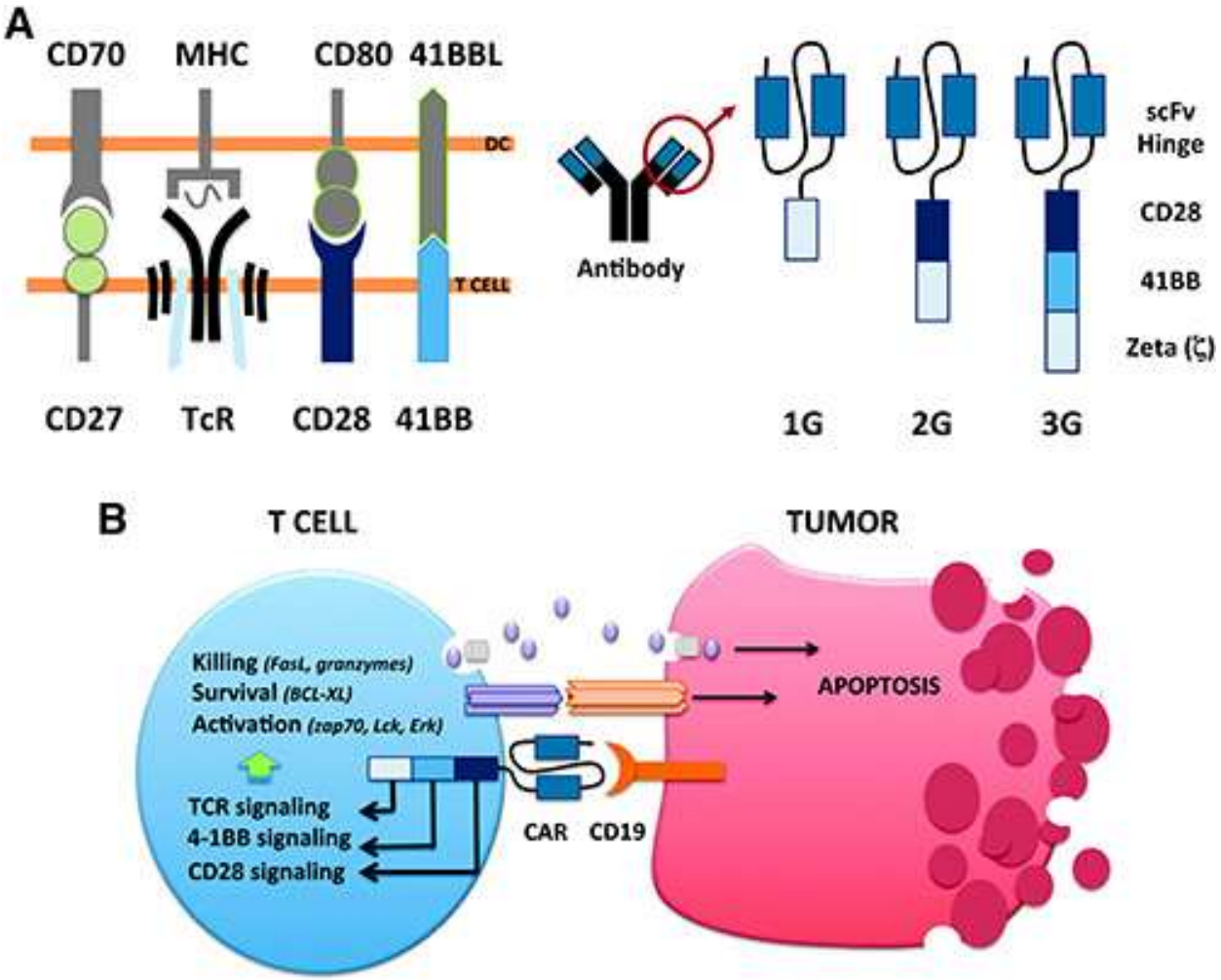
- **Interferon alfa-2a (Roferin®-A):** a cytokine that targets the IFNAR1/2 pathway; approved for subsets of patients with hairy cell leukemia and Philadelphia chromosome positive chronic myeloid leukemia (CML)
- **Interferon alfa-2b (Intron A®):** a cytokine that targets the IFNAR1/2 pathway; approved for subsets of patients with hairy cell leukemia and aggressive follicular non-Hodgkin lymphoma


CD20
Rituximab
Small Loop
Large Loop
Binding Site
B-Cell membrane
NH2
COOH
CD20
B Cell
Mechanisms of Action
ADCC
CMC
Apoptosis
Macrophage
Complement Receptor
Rituximab
C3b
FcγR
Monocyte
Natural Killer
Perforin
Cytotoxins
C1q
Complement activation
Membrane Attack Complex (MAC)
Cell Lysis
Inhibition of
p38 MAPK Signaling Pathway
Raf1 - MEK1/2 - ERK1/2 Pathway
NF-κB Pathway
Akt Signaling Pathway


Cytotoxic granule
Perforins
Granzymes
Granule exocytosis
T cell
CAM CD69
CAM CD25
CD3+
Blinatumomab
Immune Synapse
CD19+
B cell
Inactivated caspase
Activated caspase

Primary Investigator	Indication	Phase	No. of patients	Treatment regimen	Response	Overall Survival
Goebeler et al. 2016[23]	Adult R/R B-NHL	I	76	Continuous infusion, escalating doses. MTD 60μg/m^2/day given in n = 35	At MTD: ORR FL = 80% MCL = 71% DLBCL = 55% Other = 50%	Not available (Median response duration 404 days)
Viardot et al. 2016[24]	Adult R/R DLBCL	II	25	Continuous infusion with weekly dose escalation, to target 112 μg/day	ORR 43%	5.0 months
Topp et al. 2011[25]	Adult MRD positive B-ALL	II	21	Continuous infusion 15 μg/m^2/day	80% MRD response	Not available (At median follow-up 50.8 months 50% still in remission)
Gökbuget et al. 2017[28]	Adult MRD positive B-ALL	II	116	Continuous infusion 15 μg/m^2/day	78% MRD response post cycle 1, 80% MRD response overall	36.4 months
Topp et al. 2014[29]	Adult R/R B-ALL	II	36	5–30 μg/m^2/day	69% CR/CRh (88% MRD response post cycle 1)	9.8 months
Topp et al. 2015[31]	Adult R/R B-ALL	II	189	9 μg/day for first week cycle 1, 28 μg/day thereafter	43% CR/CRh (82% MRD response)	6.1 months
Martinelli et al. 2015[35]	Adult Ph-positive R/R B-ALL	II	45	9 μg/day for first week cycle 1, 28 μg/day thereafter	CR/CRh 36% (86% MRD response)	7.1 months
Kantarjian et al. 2017[33]	Adult R/R B-ALL	III	405 (B: 271, SOC 134)	9 μg/day for first week cycle 1, 28 μg/day thereafter	B: 46% CR/CRh SOC: 28% CR/CRh	B: 7.8 months SOC: 4.0 months
Von Stackelberg et al. 2016[36]	Paediatric R/R B-ALL	I/II	70 (at recommended dosage)	In phase II: 5 μg/m^2/day for first week, 15 μg/m^2/day thereafter	38.6% CR	7.5 months


No Hematologic Relapse
(probability)
1.0
0.8
0.6
0.4
0.2
0
100
200
300
400
500
600
700
All patients
Patients without HSCT
Duration of Disease-Free Survival (days)



https://www.genengnews.com/insights/car-t-cell-therapy/

Immunotherapy for Lymphoma

Targeted Antibodies

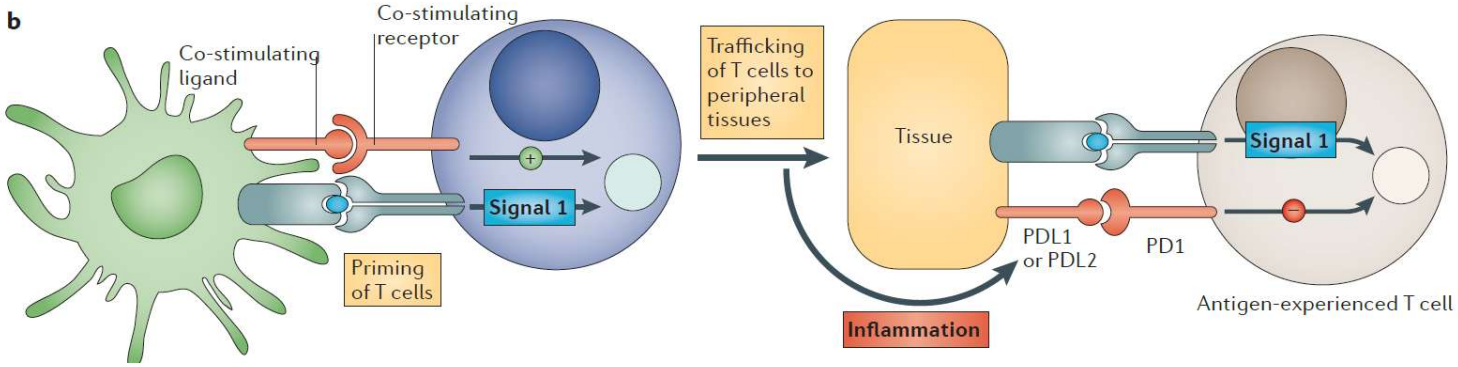
- **Brentuximab vedotin (Adcetris®):** an antibody-drug conjugate that targets the CD30 pathway and delivers toxic drugs to tumors; approved for subsets of patients with either Hodgkin or non-Hodgkin lymphoma, including as a first-line therapy
- **Ibritumomab tiuxetan (Zevalin®):** an antibody-drug conjugate that targets the CD20 pathway and delivers toxic drugs to tumors; approved for subsets of patients with non-Hodgkin lymphoma
- **Obinutuzumab (Gazyva®):** a monoclonal antibody that targets the CD20 pathway; approved for subsets of patients with non-Hodgkin lymphoma, including as a first-line therapy
- **Polatuzumab vedotin (Polivy™):** an antibody-drug conjugate that targets the CD79b pathway and delivers toxic drugs to tumors; approved for subsets of patients with non-Hodgkin lymphoma
- **Rituximab (Rituxan®):** a monoclonal antibody that targets the CD20 pathway; approved for subsets of patients with CD20-positive non-Hodgkin Lymphoma (NHL), including as a first-line therapy

Immunomodulators

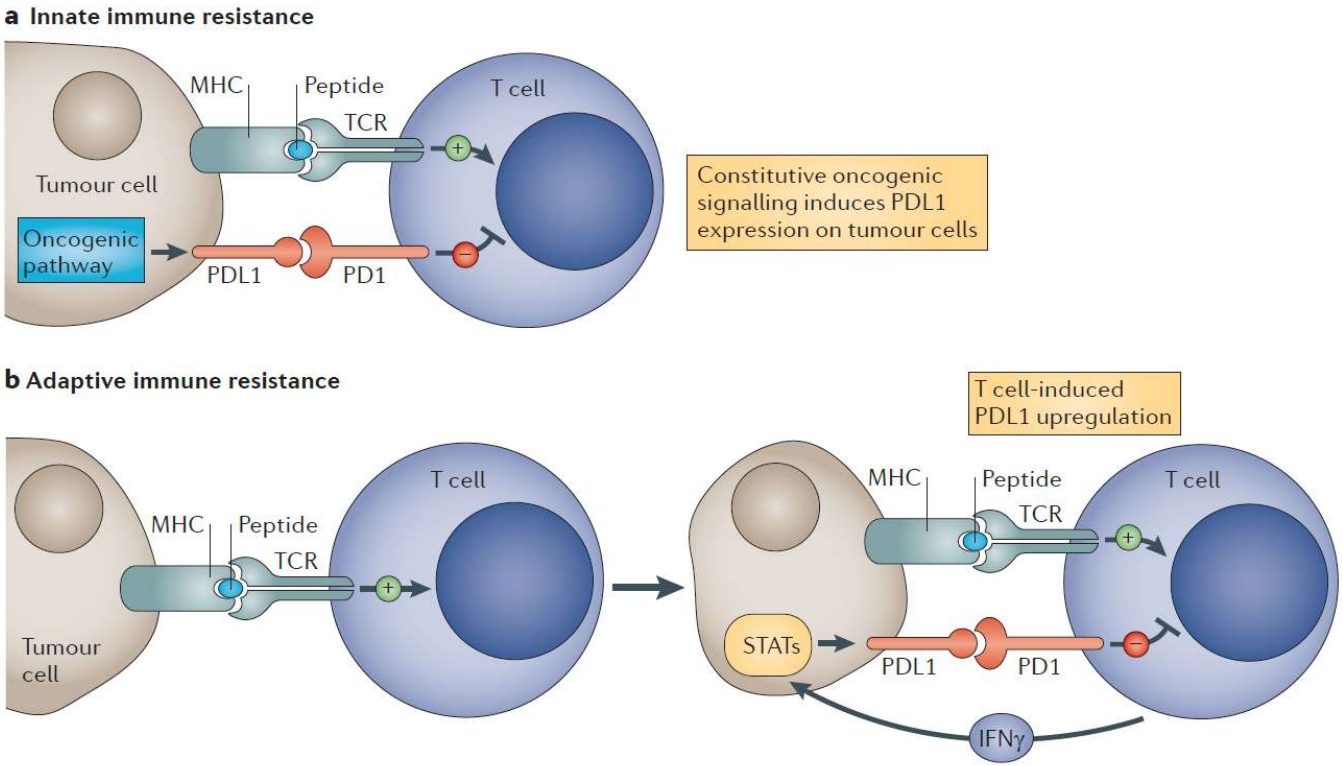
- **Nivolumab (Opdivo®):** a checkpoint inhibitor that targets the PD-1/PD-L1 pathway; approved for subsets of patients with classical Hodgkin lymphoma
- **Pembrolizumab (Keytruda®):** a checkpoint inhibitor that targets the PD-1/PD-L1 pathway; approved for subsets of patients with classical Hodgkin lymphoma and PMBCL
- **Interferon alfa-2b (Intron A®):** a cytokine that targets the IFNAR1/2 pathway; approved for subsets of patients with follicular lymphoma

Adoptive Cell Therapy

- **Axicabtagene ciloleucel (Yescarta®):** a CD19-targeting CAR T cell immunotherapy; approved for subsets of patients with non-Hodgkin lymphoma
- **Tisagenlecleucel (Kyrmriah®):** a CD19-targeting CAR T cell immunotherapy; approved for subsets of children and young adult patients with acute lymphoblastic leukemia (ALL)

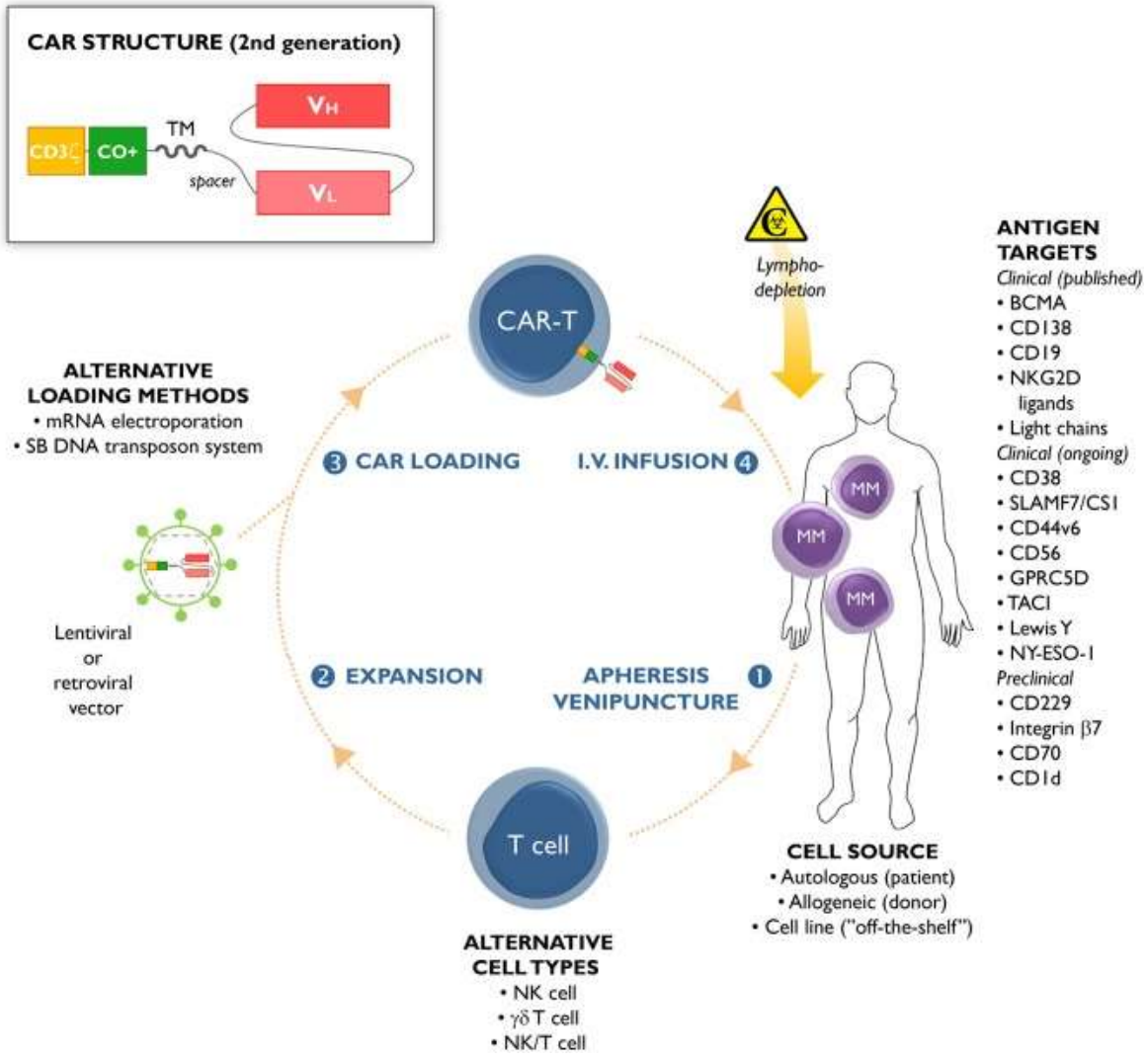


Pardoll– Nature Reviews- 2012



Pardoll– Nature Reviews- 2012

What’s Next?


CAR STRUCTURE (2nd generation)
CD3ζ
CO+
TM
spacer
VH
VL
CAR-T
T cell
Lympho-depletion
ANTIGEN TARGETS
Clinical (published)
• BCMA
• CD138
• CD19
• NKG2D ligands
• Light chains
Clinical (ongoing)
• CD38
• SLAMF7/CS1
• CD44v6
• CD56
• GPRC5D
• TACI
• Lewis Y
• NY-ESO-1
Preclinical
• CD229
• Integrin β7
• CD70
• CD1d
ALTERNATIVE LOADING METHODS
• mRNA electroporation
• SB DNA transposon system
Lentiviral or retroviral vector
3 CAR LOADING
I.V. INFUSION 4
2 EXPANSION
APHERESIS VENIPUNCTURE 1
MM
MM
MM
CELL SOURCE
• Autologous (patient)
• Allogeneic (donor)
• Cell line ("off-the-shelf")
ALTERNATIVE CELL TYPES
• NK cell
• γδ T cell
• NK/T cell

ARTICLES
https://doi.org/10.1038/s41591-019-0410-x
nature medicine

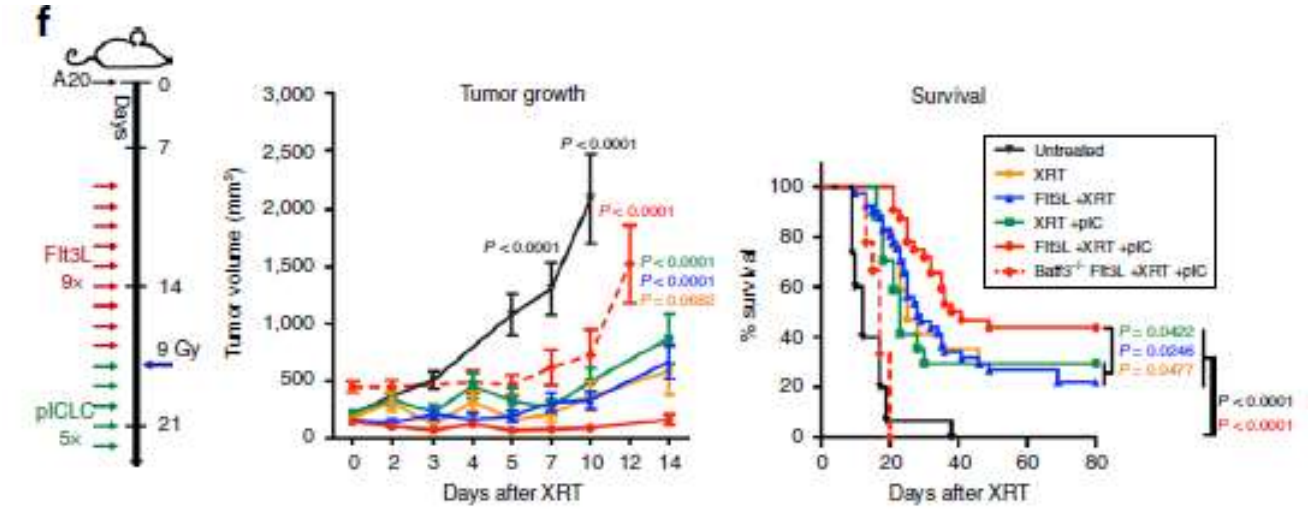
Systemic clinical tumor regressions and potentiation of PD1 blockade with in situ vaccination

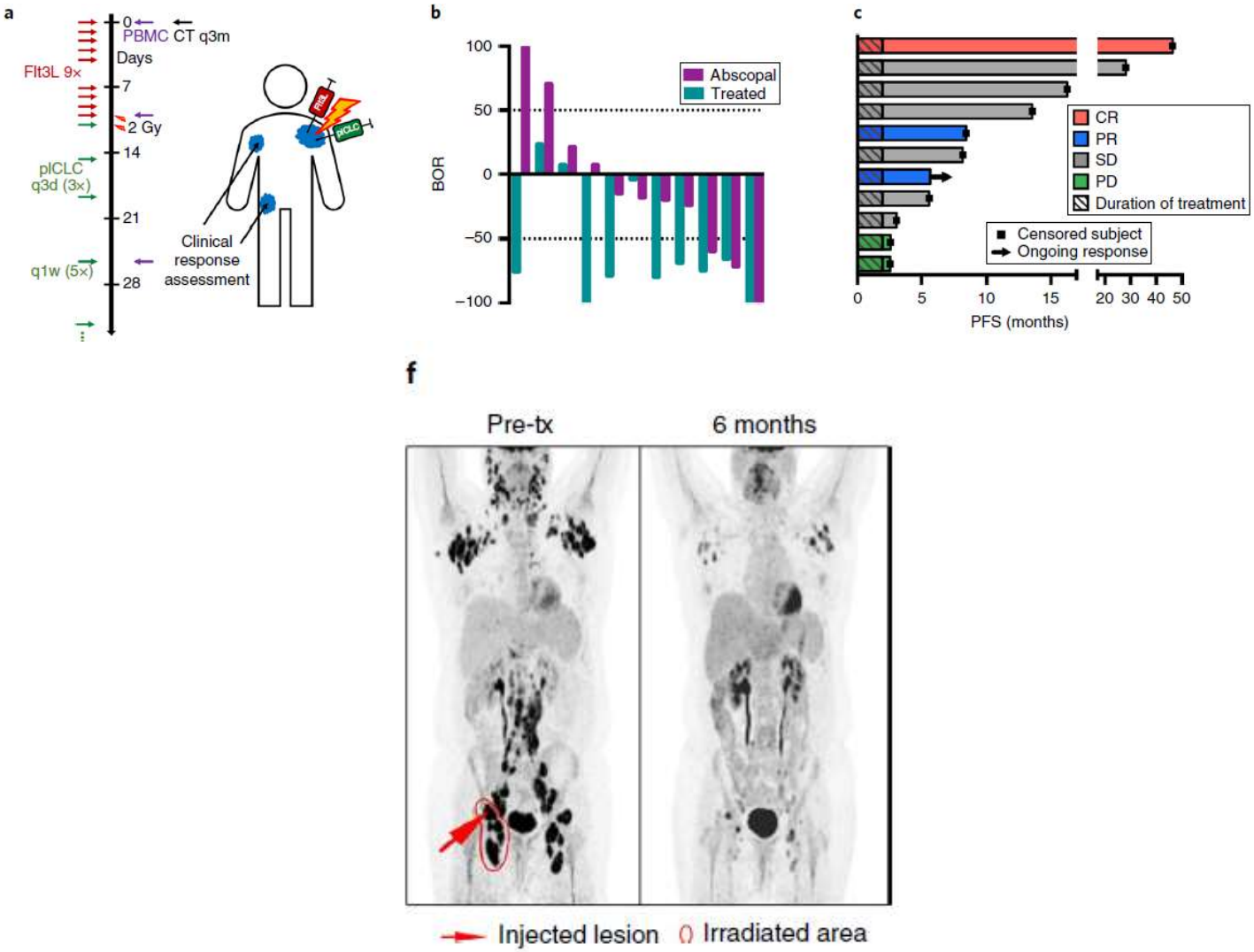
Linda Hammerich[1,2], Thomas U. Marron[1,2], Ranjan Upadhyay[1,2], Judit Svensson-Arvelund[1,2], Maxime Dhainaut[2,3], Shafinaz Hussein[4], Yougen Zhan[4], Dana Ostrowski[1], Michael Yellin[5], Henry Marsh[5], Andres M. Salazar[6], Adeeb H. Rahman[2], Brian D. Brown[2,3], Miriam Merad[2,7] and Joshua D. Brody[1,2*]

Murphy Lab Journal Club

7/17/2019

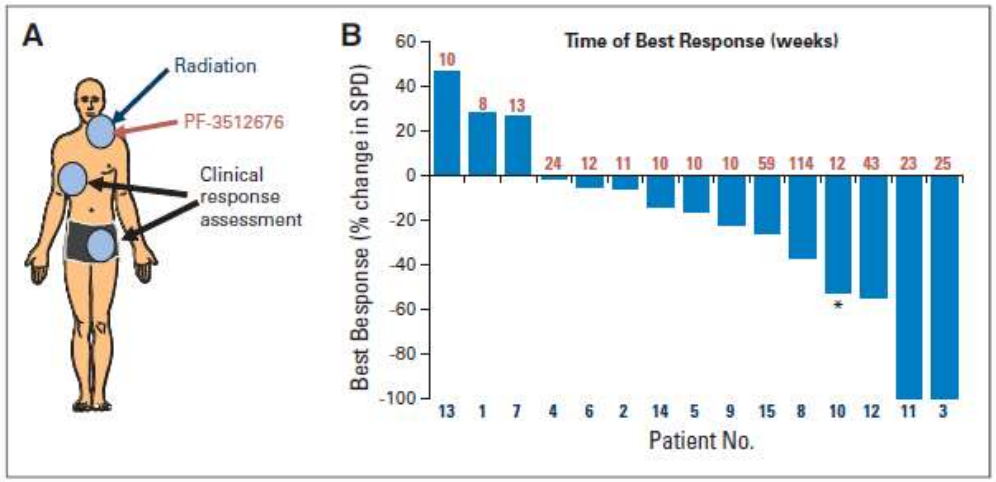
In-situ vaccination with Flt3L, RT, and pICLC

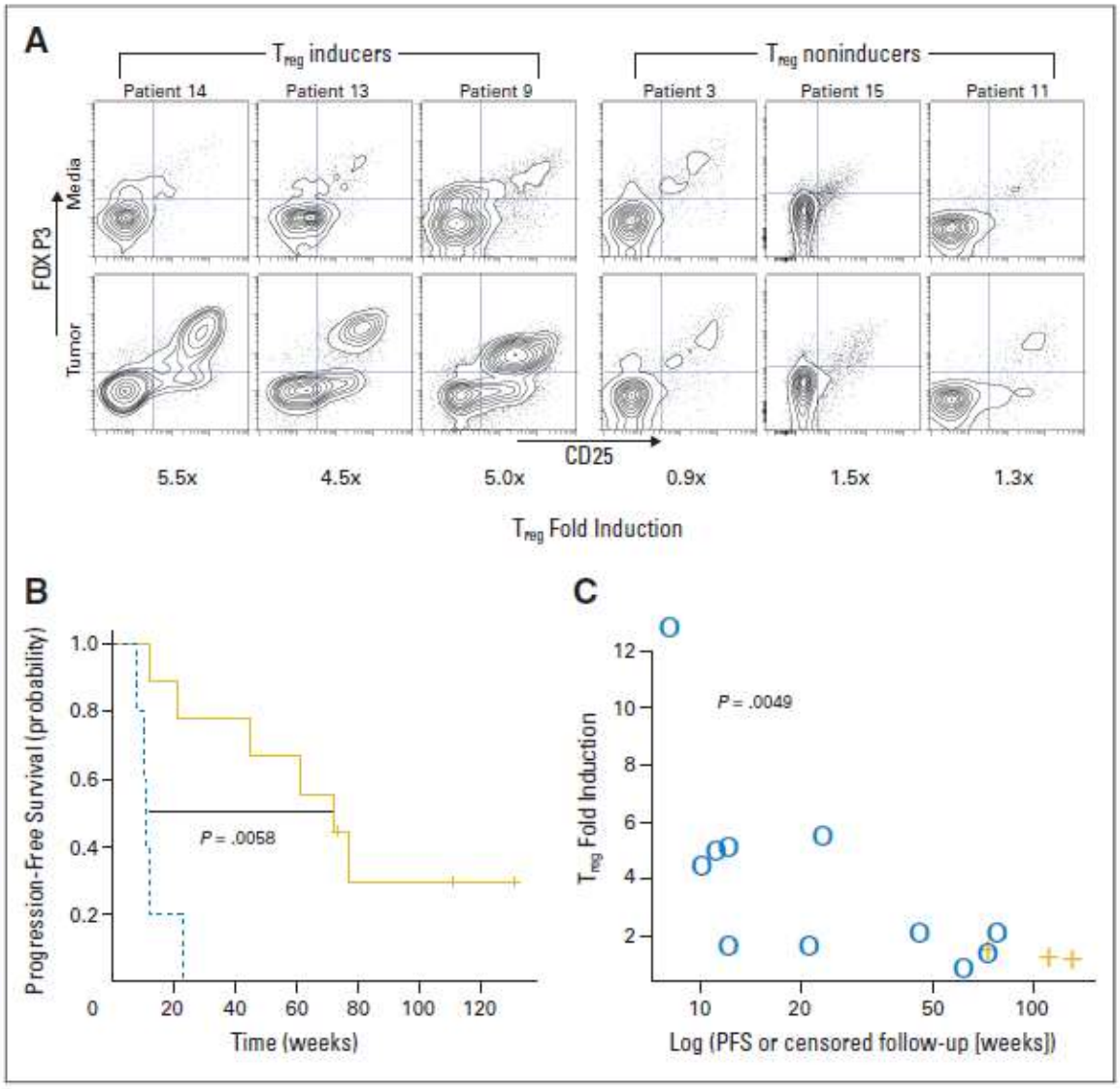



a
0
PBMC CT q3m
Days
Flt3L 9×
7
2 Gy
14
pICLC
q3d (3×)
21
q1w (5×)
28
Clinical
response
assessment
b
100
50
0
−50
−100
BOR
Abscopal
Treated
c
CR
PR
SD
PD
Duration of treatment
Censored subject
Ongoing response
0
5
10
15
20
30
40
50
PFS (months)
f
Pre-tx
6 months
Injected lesion
Irradiated area

In Situ Vaccination With a TLR9 Agonist Induces Systemic Lymphoma Regression: A Phase I/II Study

Joshua D. Brody, Weiyun Z. Ai, Debra K. Czerwinski, James A. Torchia, Mia Levy, Ranjana H. Advani, Youn H. Kim, Richard T. Hoppe, Susan J. Knox, Lewis K. Shin, Irene Wapnir, Robert J. Tibshirani, and Ronald Levy




A
Treg inducers
Treg noninducers
Patient 14
Patient 13
Patient 9
Patient 3
Patient 15
Patient 11
FOX P3
Media
Tumor
CD25
5.5x
4.5x
5.0x
0.9x
1.5x
1.3x
Treg Fold Induction
B
Progression-Free Survival (probability)
1.0
0.8
0.6
0.4
0.2
0
20
40
60
80
100
120
Time (weeks)
P = .0058
C
Treg Fold Induction
12
10
8
6
4
2
P = .0049
10
20
50
100
Log (PFS or censored follow-up [weeks])

Published OnlineFirst March 15, 2016; DOI: 10.1158/1078-0432.CCR-15-3026

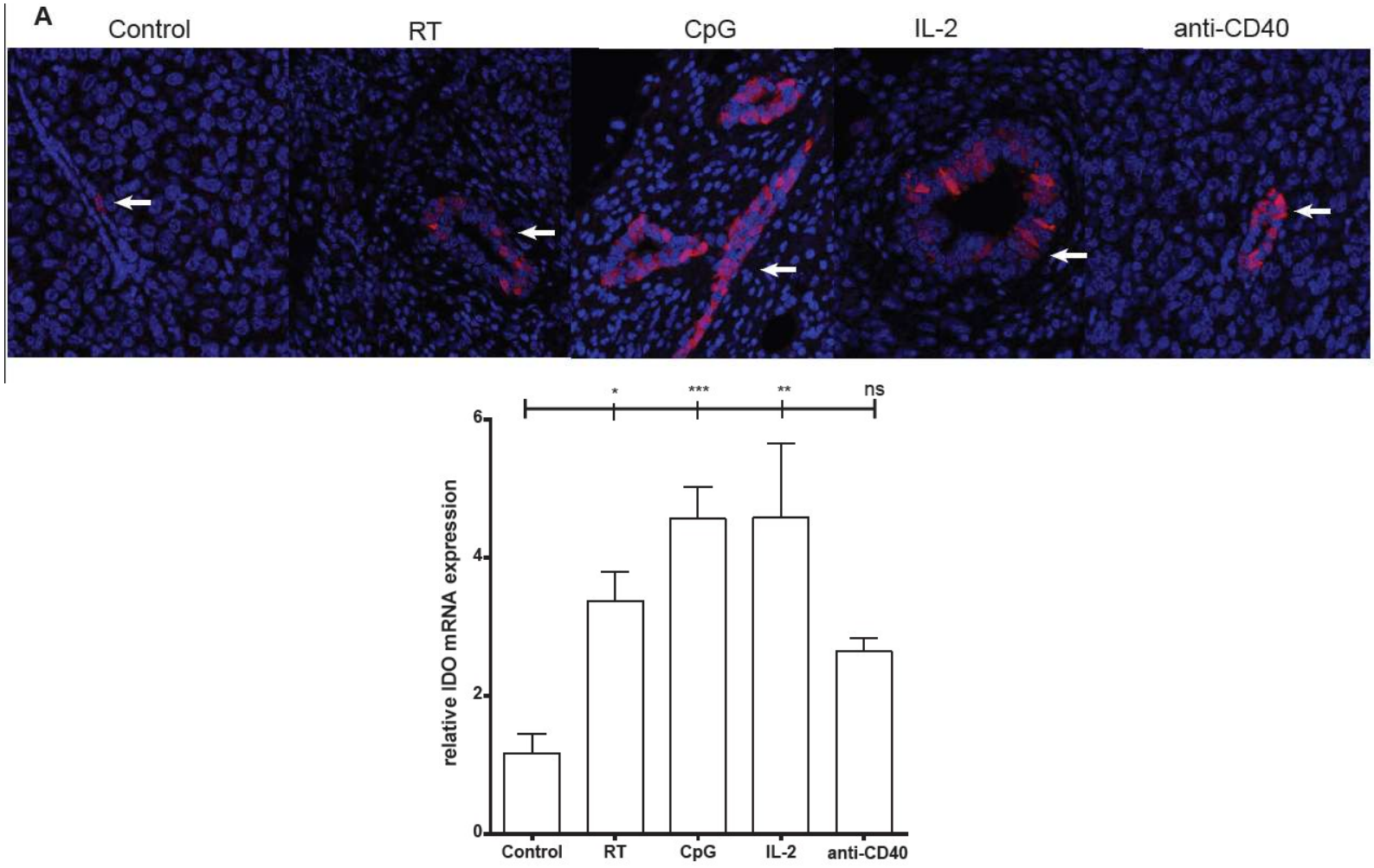
Cancer Therapy: Clinical

Clinical Cancer Research

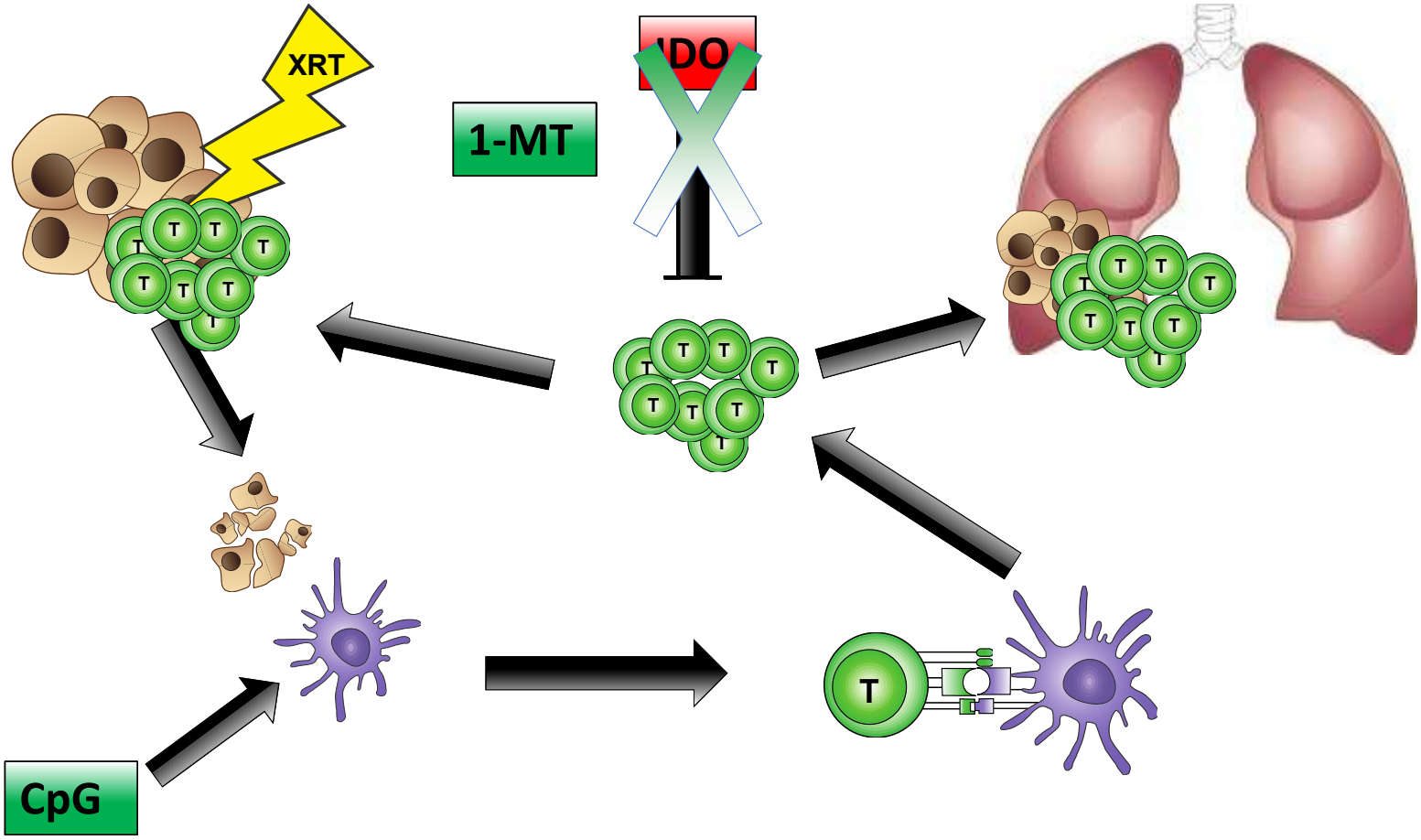
Blocking Indolamine-2,3-Dioxygenase Rebound Immune Suppression Boosts Antitumor Effects of Radio-Immunotherapy in Murine Models and Spontaneous Canine Malignancies

Arta M. Monjazeb[1], Michael S. Kent[2], Steven K. Grossenbacher[3], Christine Mall[3], Anthony E. Zamora[3], Annie Mirsoian[3], Mingyi Chen[4], Amir Kol[5], Stephen L. Shiao[6], Abhinav Reddy[1], Julian R. Perks[1], William T.N. Culp[2], Ellen E. Sparger[2], Robert J. Canter[7], Gail D. Sckisel[3], and William J. Murphy[3,8]

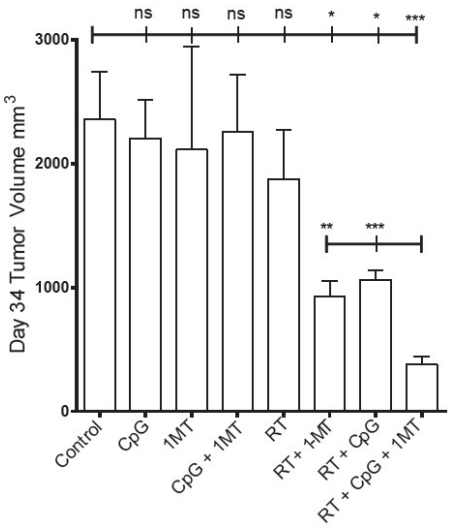
IDO Expression is Up-regulated by Inflammatory Therapies

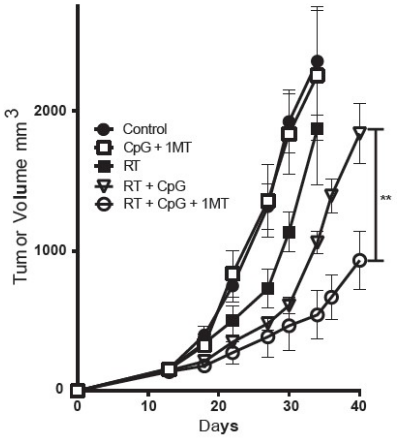


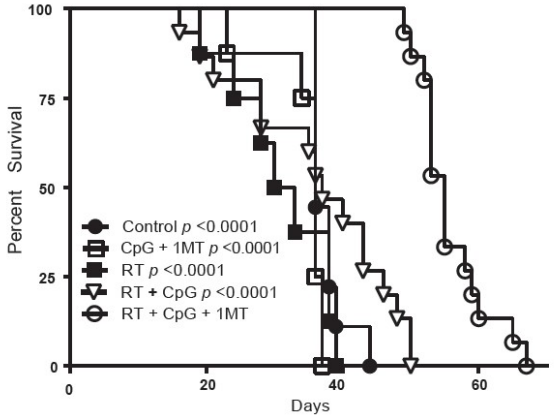
Hypothesis



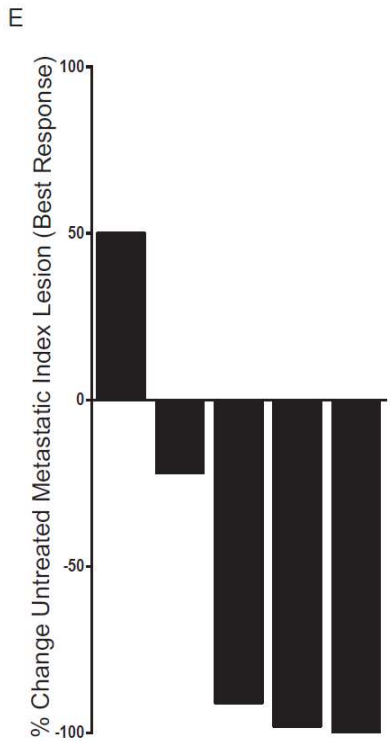
IDO Blockade Improves Anti-tumor Effects of RT + CpG

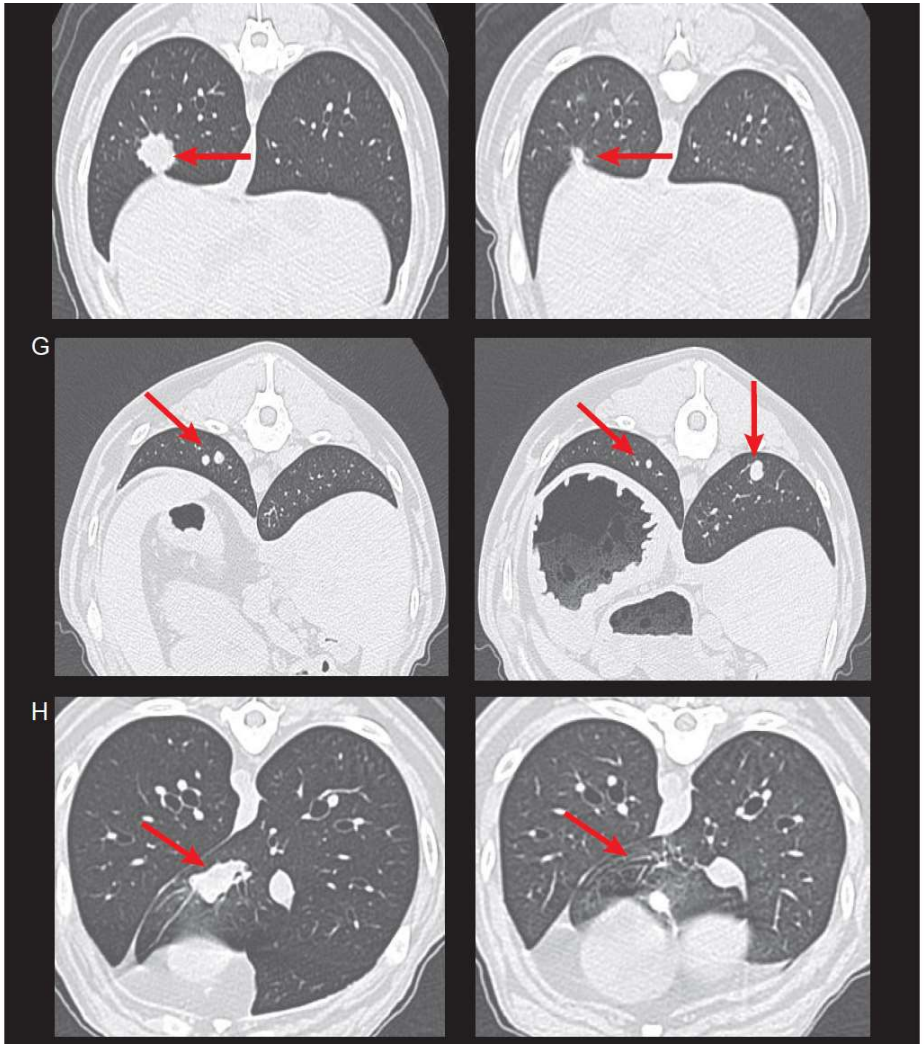




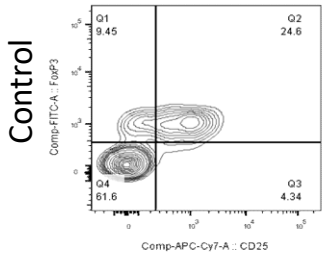


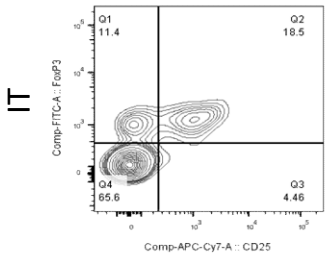
Canine Trial: Abscopal Responses

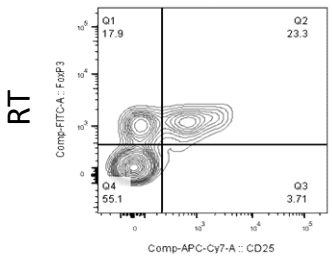


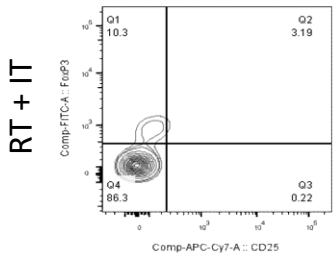


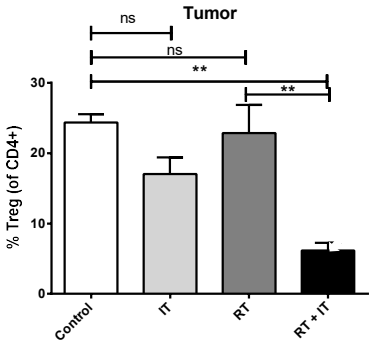
Triple Therapy Reduces Tregs

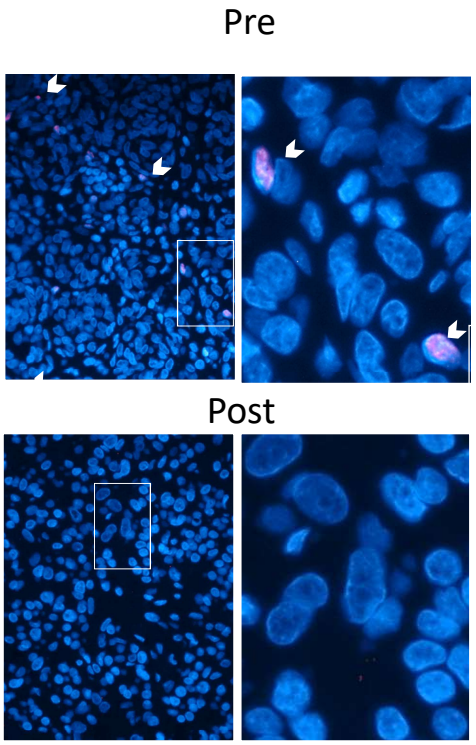


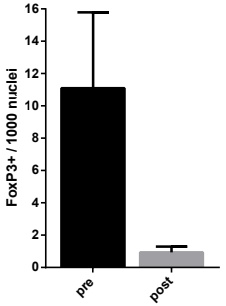




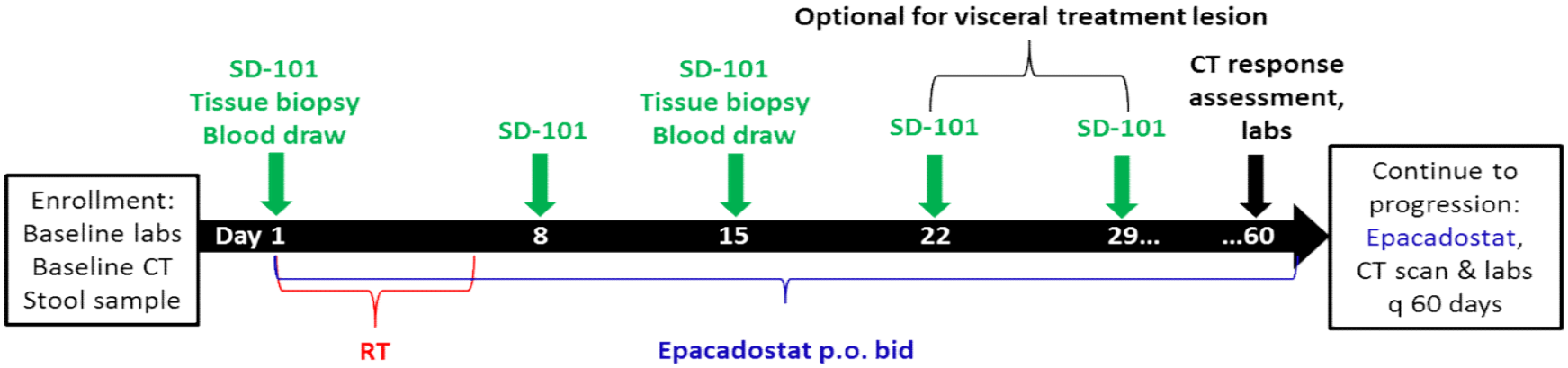








UCDCC 271



Concurrent RT (Days 1-5)

- Cohort 1 (solid tumors): (8 Gy x 3) or (4 Gy x 5)
- Cohort 2 (lymphoma): (8 Gy x 3) or (4 Gy x 5) or (2 Gy x 2)

+

Intralesional SD-101 (Day 1, 8, 15, 22, 29)

4 mg injection into RT treatment lesion

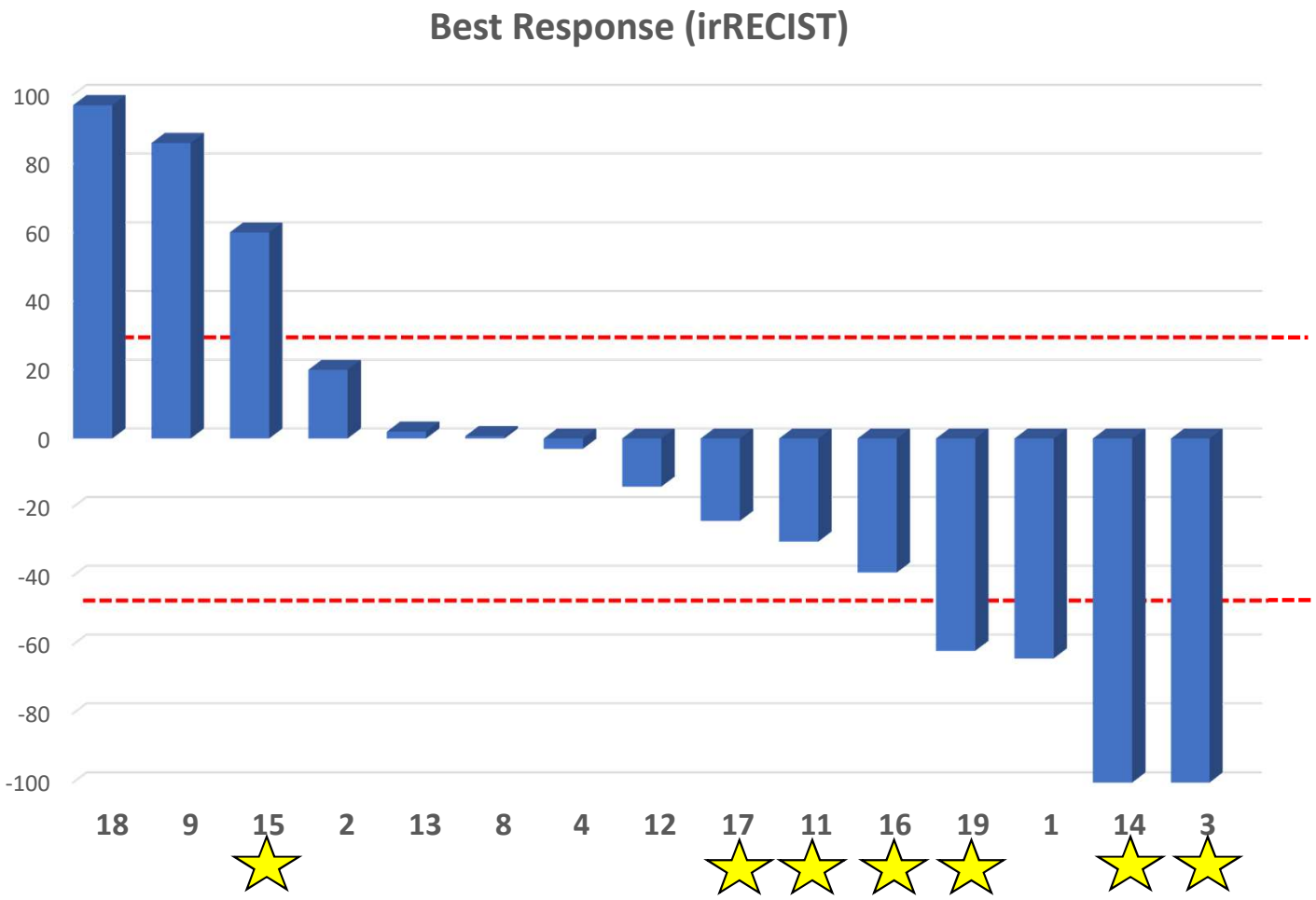
+

Epacadostat

50-300 mg PO bid

Phase II Expansion Cohorts **Simon Two-Stage Design**	
Cohort 1:	Solid tumor (16-30 patients) P0=0.05, p1=0.20, r1=1, n1=16, rTot=3, nTot=30, α=0.05, power=0.8
Cohort 2:	Lymphoma (7-14 patients) P0=0.05, p1=0.3, r1=0, n1=7, rTot=2, nTot=14, α=0.05, power=0.8

Phase I Dose Finding **3+3 Design: (3-6 patients per dose level, 6-18 patients total)**	
Dose level -3:	50 mg PO bid
Dose level -2:	100 mg PO bid
Dose level -1:	200 mg PO bid
Dose level 1:	300 mg PO bid

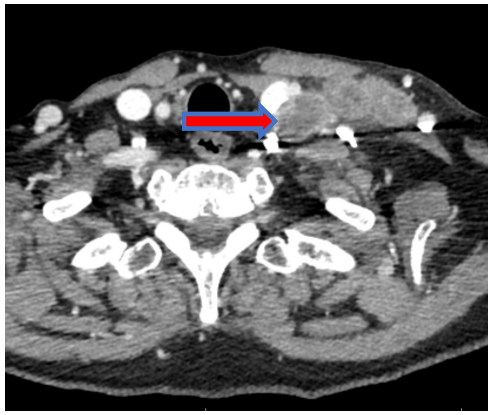


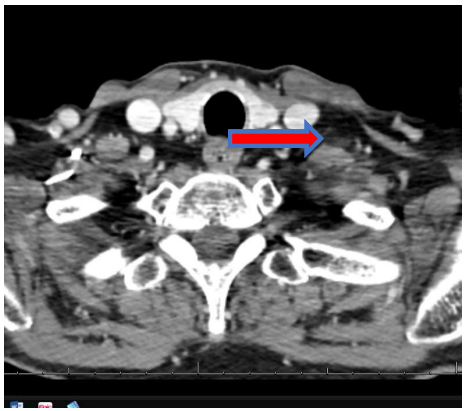
OR = 4/15 (2 CR)
SD = 8/15
PD = 3/15
DCR = 12/15

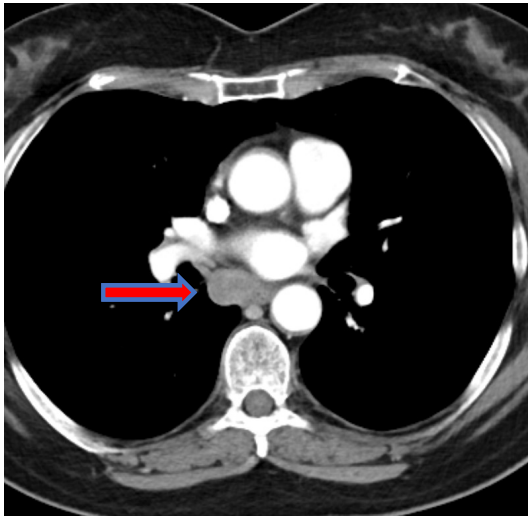
★=Failed prior C.I. (7/15)

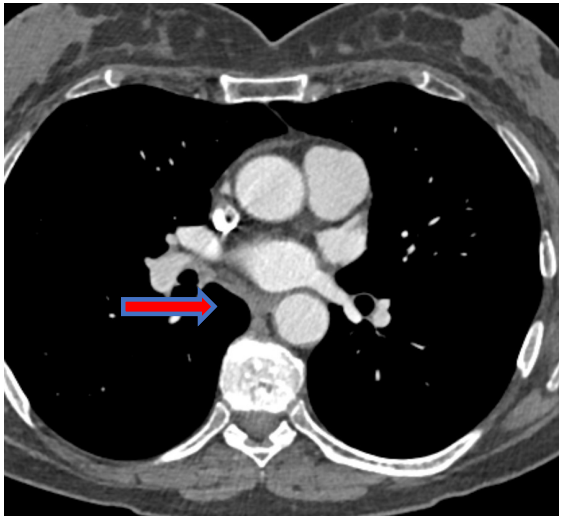
OR = 3/7 (2 CR)
SD = 3/7
PD = 1/7
DCR = 6/7

Response Pt 3









Response Pt 14