American Association for Cancer Research

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Immuno-Oncology Drug Development Workshop

October 13 & 14, 2016

Hyatt Regency on Capitol Hill

Washington, DC

American Association for Cancer Research

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Welcome

Marc Theoret, MD

Workshop Co-Chair

American Association for Cancer Research

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Session I

CONSIDERATIONS IN THE PRECLINICAL EVALUATION OF I-O PRODUCTS

Moderator: Whitney Helms, PhD

Speakers:

Kristina Howard, DVM, PhD

Alan Korman, PhD

Rodney Prell, PhD

Timothy MacLachlan, PhD, DABT

David, Clarke, PhD, DABT

Considerations in the Nonclinical Evaluation of Immuno-Oncology Products

- **Food and Drug Administration**
- 10903 New Hampshire Avenue,
- Silver Spring, Maryland 20993
- White Oak Campus, Building 22, Room 1315

- **October 13, 2016**

Regulation of Cancer Immunotherapy Products by FDA

CDER

- Monoclonal Abs
  - Ipilimumab (2011)
  - Pembrolizumab (2014)
  - Nivolumab (2014)
  - Atezolizumab (2016)
- Fusion proteins
  - Blinatumomab (2014)
- Cytokines
  - IL-2
  - INF-γ

CBER

- Genetically modified T cells
- Cancer Vaccines
  - Sipuleucel-T (2010)
- Oncolytic Vectors
  - Imlygic (2015)

- *ICH S9 Nonclinical Evaluation for Anticancer Pharmaceuticals (2010)*
- *ICH S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals plus Addendum (2012)*
- *FDA Guidance: Preclinical Assessment of Investigational Cellular and Gene Therapy Products (2013)*
- *FDA Guidance for Industr:y Immunogenicity Assessment for Therapeutic Protein Products (2014)*

Goals of a Standard Nonclinical Program

- Provide safety data to support an appropriate starting dose and to inform on clinical monitoring
  - Traditionally based on toxicology studies in healthy animals
- Provide support for the rationale and biological plausibility of the study
  - Xenograft studies and in vitro mechanism of action studies

Challenges with Immuno-oncology Products

- Species relevance
  - Differences in thresholds for immune activation
- Translating in vitro data to in vivo data
  - Data used to calculate a Minimally Anticipated Biological Effect Level (MABEL) or Pharmacological Effect Level (PEL)
- What to do with combinations

Calculating a MABEL

- There is no universal approach for determining a FIH dose based on a MABEL, regardless of indication
- Useful data inputs:
  - *In vitro* pharmacology data from target cells from human and toxicology species
  - Concentration-effect data from *in vitro* and *in vivo* studies
  - If using animal data, then provide a comparison of
    - Animal-human differences in exposure/drug distribution
    - Animal-human differences in expression level and distribution of target
    - Animal-human differences in affinity of target binding and intrinsic efficacy
    - Duration and reversibility of biologic effect
    - Dose-exposure relationship (PK/PD)

Expectations for Nonclinical Immunotherapeutic Packages

- Pharmacology of the targeted pathway
  - Is the target an agonist or antagonist of immune activity
- Assessment of Cytokine Release Potential
- **Studies using human cells that take into account multiple mechanisms of action**
- Receptor Occupancy

Points to Consider for this Session

- Are there better models that we could use for predicting/understanding safety?
- Is there an optimal way to use non-traditional data to set appropriate starting doses for these products?
- How much nonclinical data do we need to support combination therapy?
- How much can we leverage nonclinical data to make decisions about disease selection and optimal dosing?


FDA
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ADMINISTRATION

Checkpoint Inhibitor Induced Autoimmunity in a Humanized Mouse Model

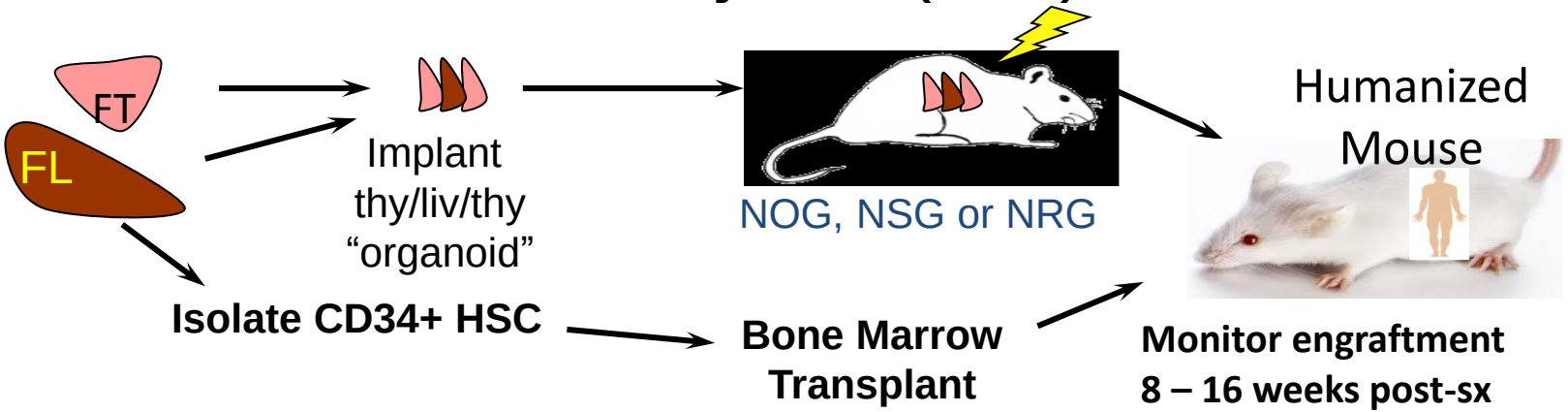
Kristina E. Howard, DVM, Ph.D.
Division of Applied Regulatory Science
Office of Translational Sciences/CDER
Food & Drug Administration

The ideas, findings, and conclusions in this presentation have not been formally disseminated by the Food and Drug Administration and should not be construed to represent any Agency determination or policy.

Outline

- Humanized mouse model system
- Study of checkpoint inhibitor nivolumab
  - Study design
  - Flow cytometric endpoints
  - Histopathology
- Conclusions

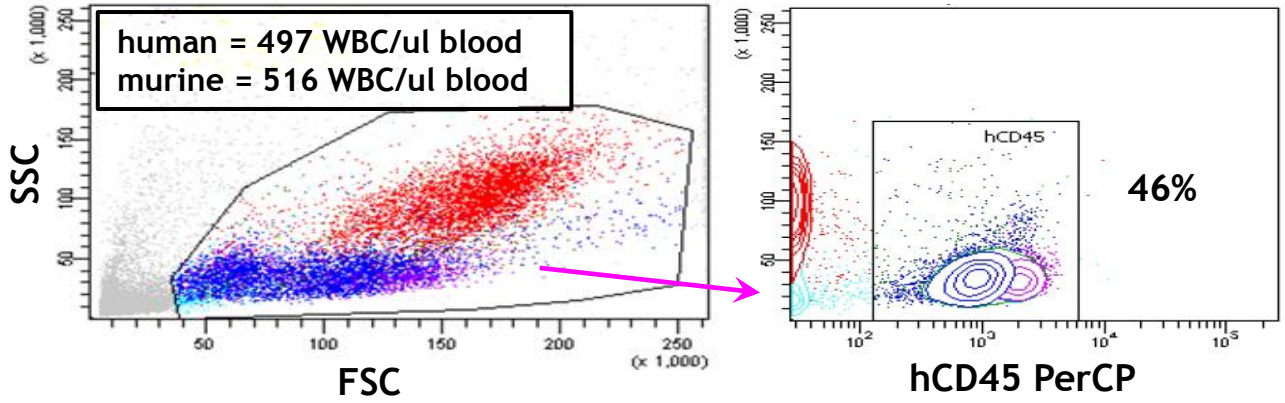
Bioengineering a human immune system:
Bone Marrow/Liver/Thymus (BLT) mouse

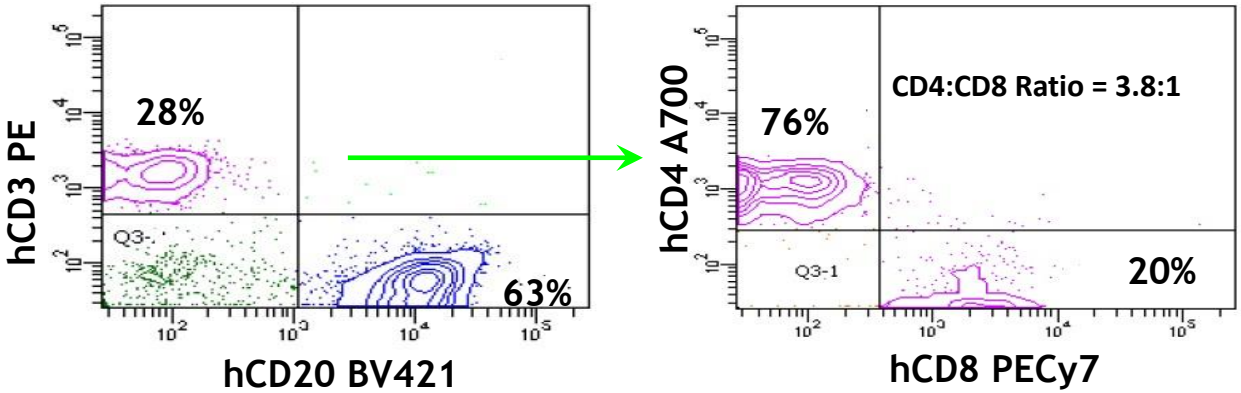


- Engraftment is monitored via flow cytometric analysis of whole blood beginning 8 weeks following surgery
- At least two sequential bleeds, 3-4 weeks apart, are needed to show increasing human leukocyte numbers prior to use in studies
- Range of humanization (for use in study) is generally accepted to be 20-25% human; however, we monitor humanization in absolute hWBC/µl blood in order to enable comparability between studies/groups.

Human leukocytes in PBMC

Approximately 12 weeks post-surgery:



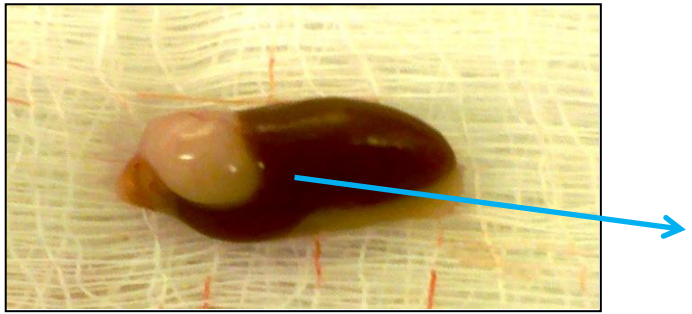


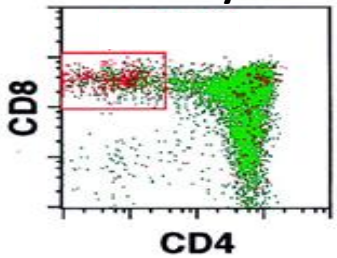
CD45: pan-WBC
CD3: All T-cells
CD20: Mature B-cells
CD4: helper T-cells
CD8: cytotoxic T-cells

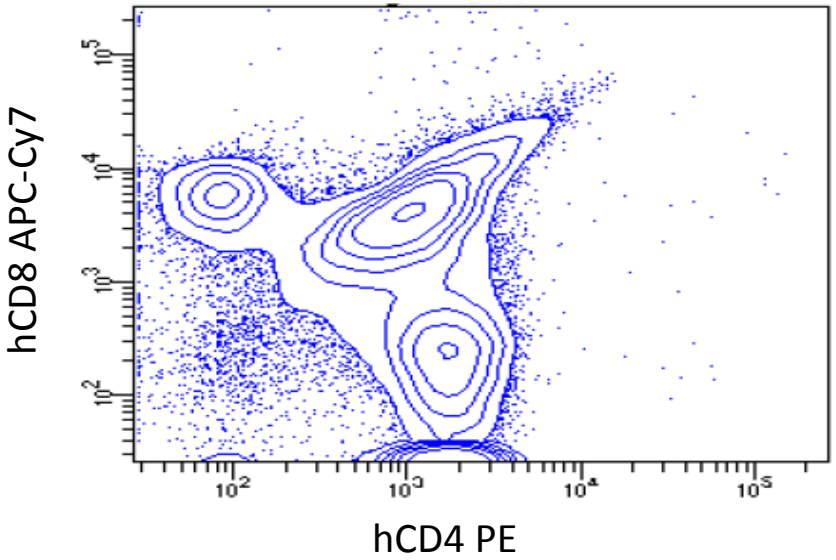
Typical range of human CD4:CD8 ratio = 1.0 – 4.0

Thymic organoid = human thymus

Analysis of organoid cell populations by flow cytometry







McFarland R D et al. PNAS 2000;97:4215-4220

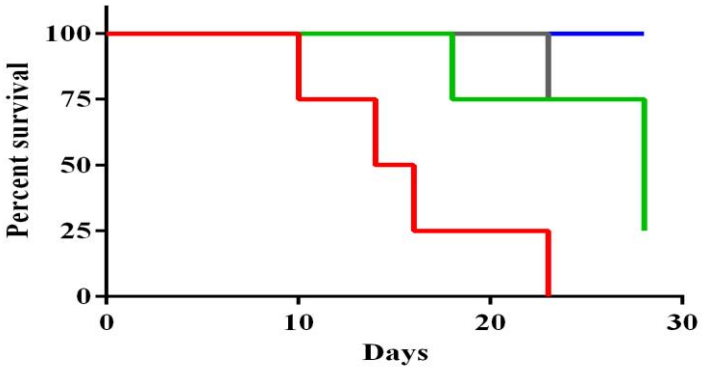
Study design

- Two pilot studies using nivolumab
  - BLT/NOG mice (n=14, 4 donors)
  - BLT/NOG-hGMCSF-hIL3 mice (n=16, 2 donors)
- Goals
  - Determine if BLT humanized mice could develop autoimmunity
  - Establish dosing range
  - Assess strain susceptibility

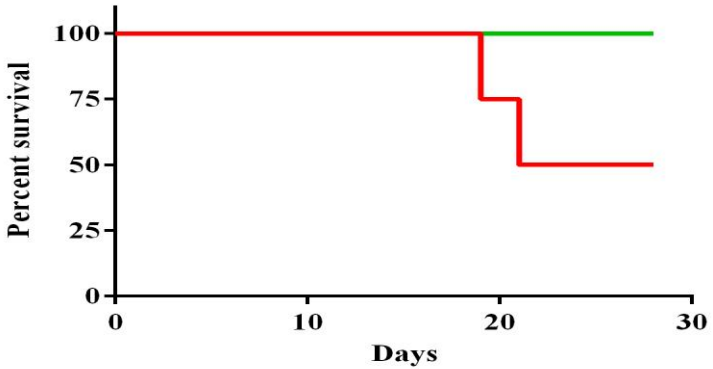
- Basic design
  - Doses selected to ensure that adverse events occurred if they were possible
  - Saline, 2.5, 5.0 & 10 mg/kg, twice weekly, IP
  - PBMC evaluated at Day -1, 14, 28 (necropsy)
  - Spleen and bone marrow evaluated at necropsy
  - All tissues evaluated via histopathology

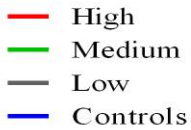
Survival Curves

NOG-BLT

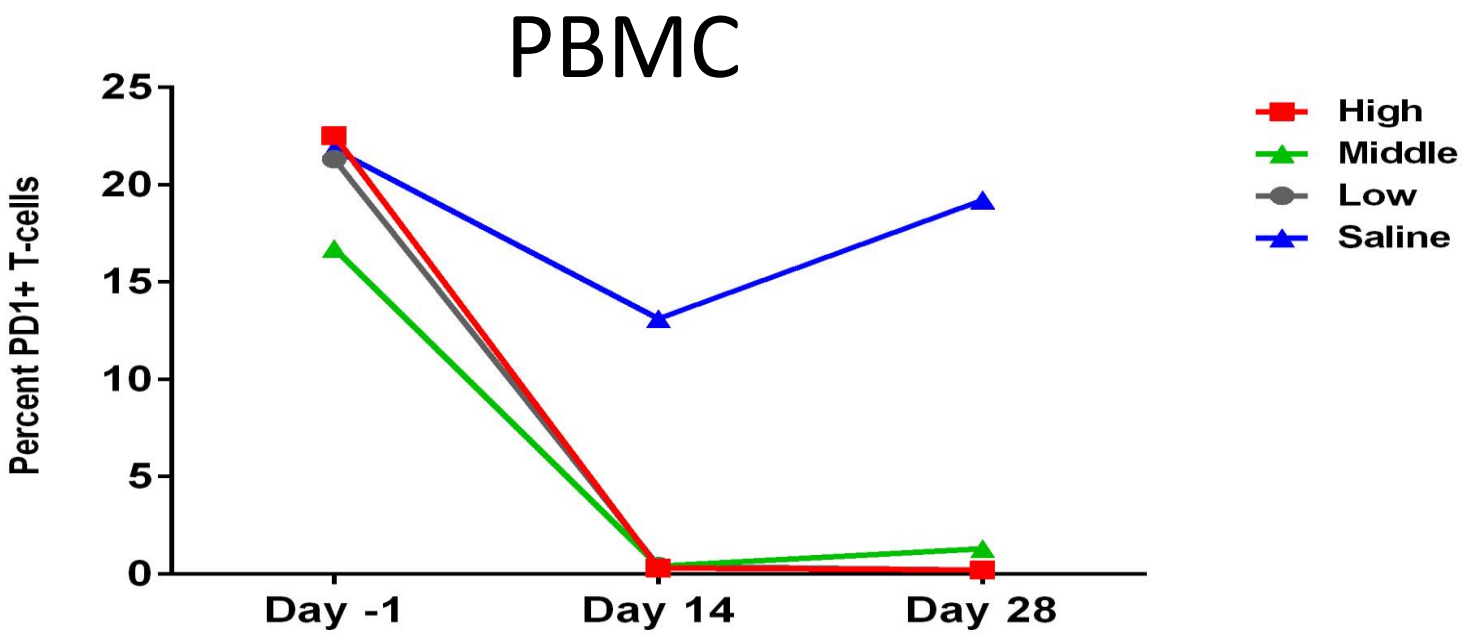


NOG/hGMCSF/hIL3-BLT



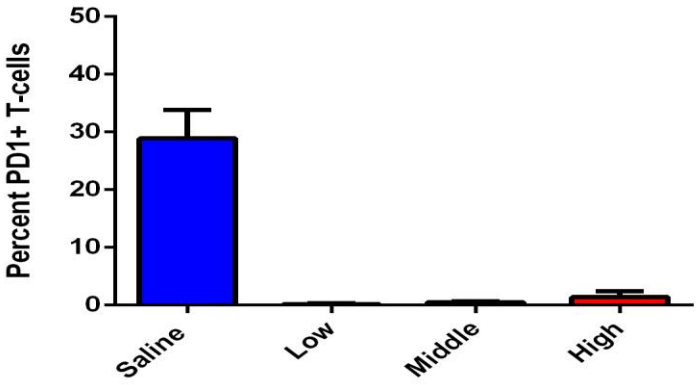


Percentage PD1+ T-cells

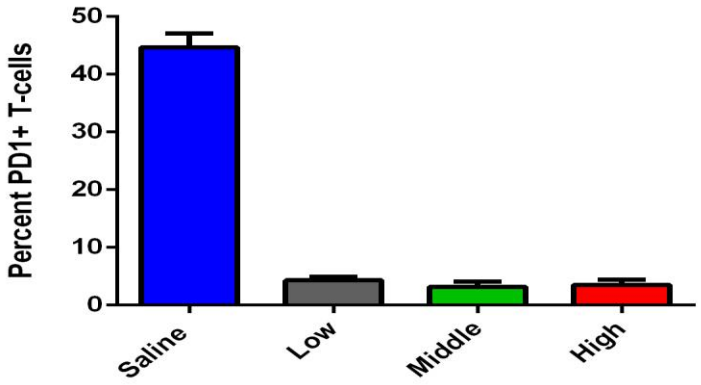


Percentage PD1+ T-cells

Spleen

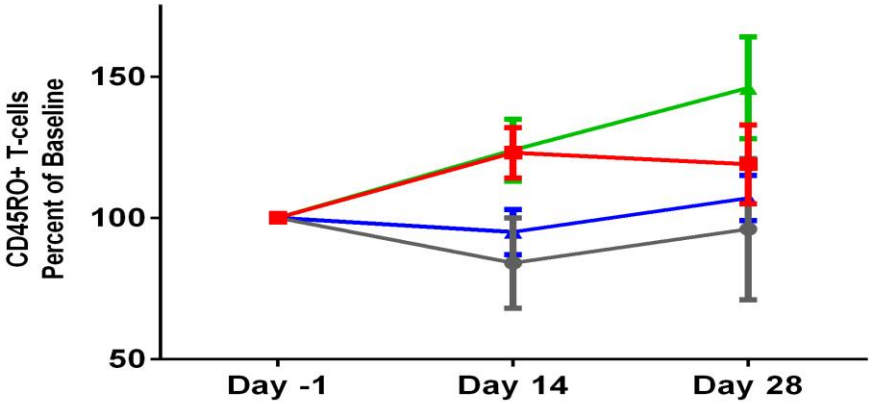


Bone Marrow

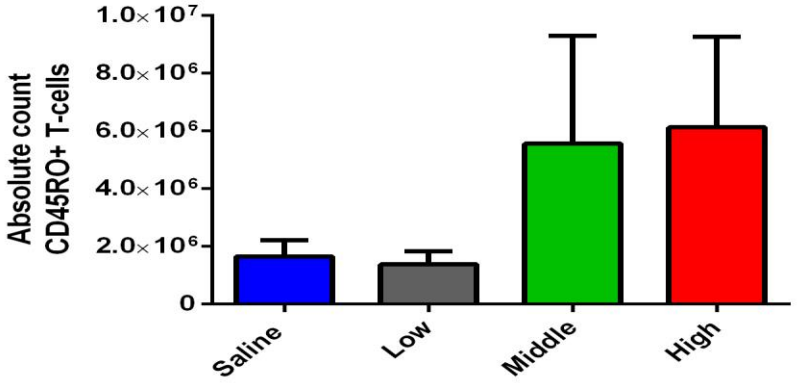


Activated T-cells

PBMC



Spleen

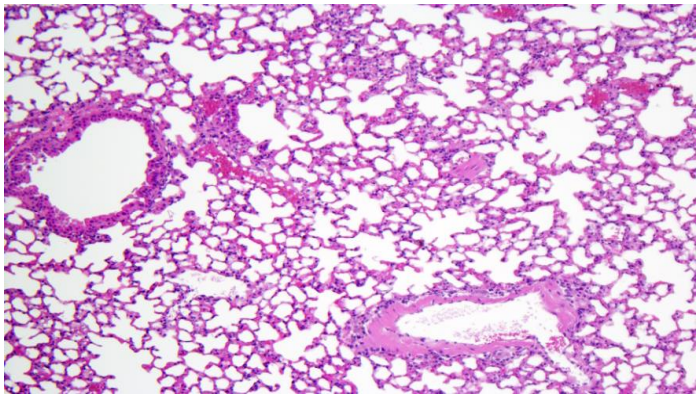


Typical adverse events observed in BLT/NOG humanized mice

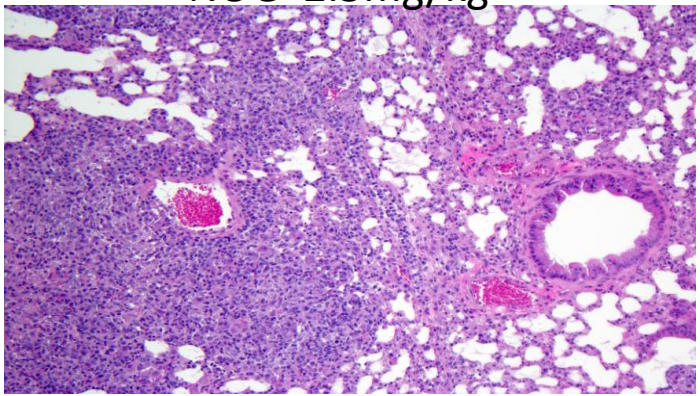
Adverse Reactions	Observed In Nivolumab Pilot
Pneumonitis	Low dose: 3/4 Medium dose: 2/4 High dose: 2/4
Hepatitis	Low dose: 3/4 Medium dose: 3/4 High dose: 4/4
Nephritis	Low dose: 1/4 Medium dose: 1/4 High dose: 2/4
Rash/Dermatitis	Low dose: 1/4 Medium dose: 3/4 High dose: 2/4
Adrenalitis	Low dose: 1/4 High dose: 1/4

Pathology: Lung

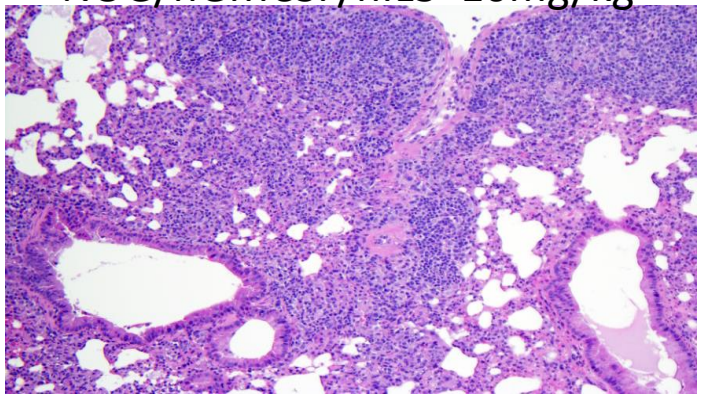
Saline control



NOG 2.5mg/kg

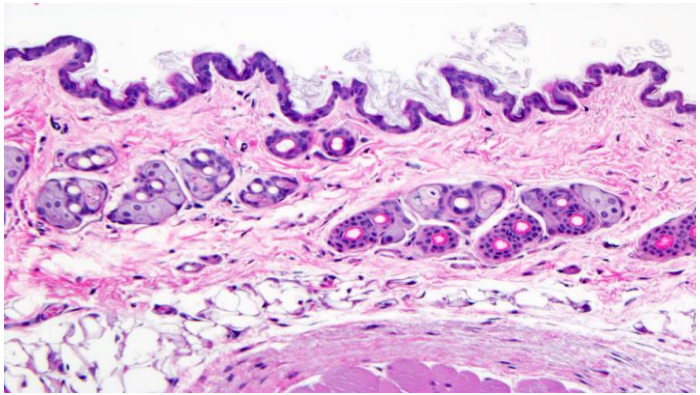


NOG/hGMCSF/hIL3 10mg/kg



Pathology: Skin

Saline control



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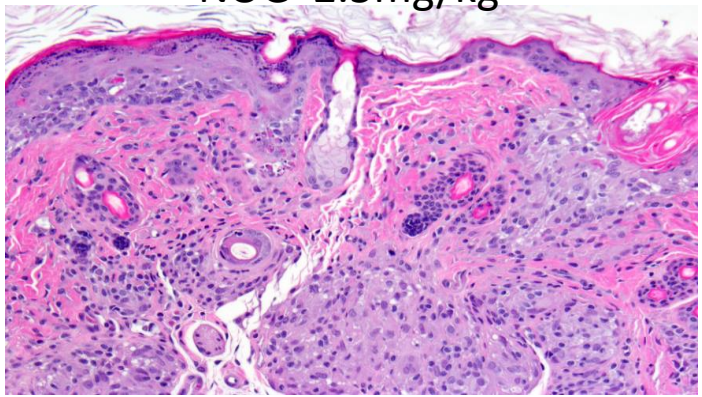
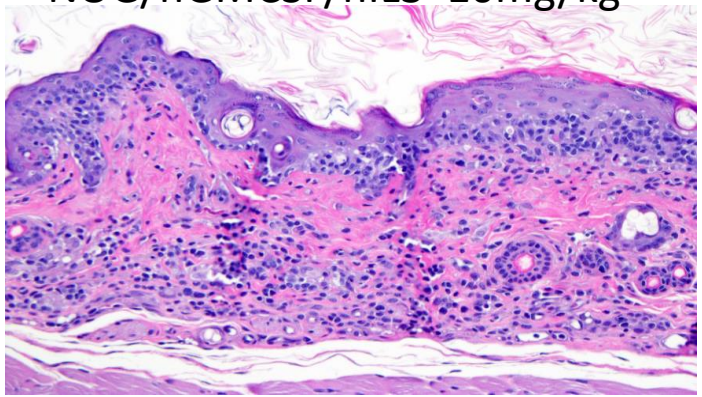
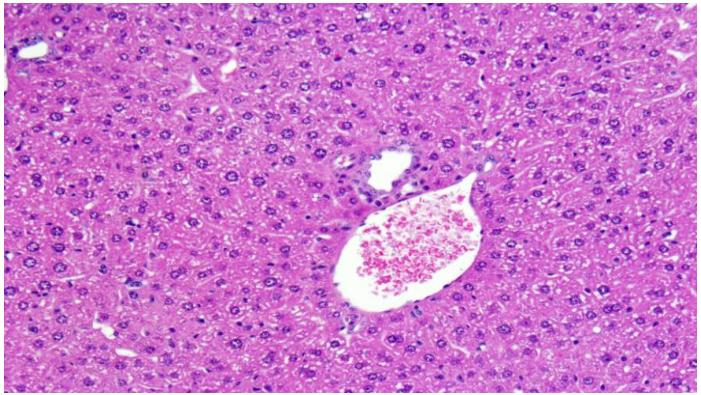


NOG/hGMCSF/hIL3 10mg/kg

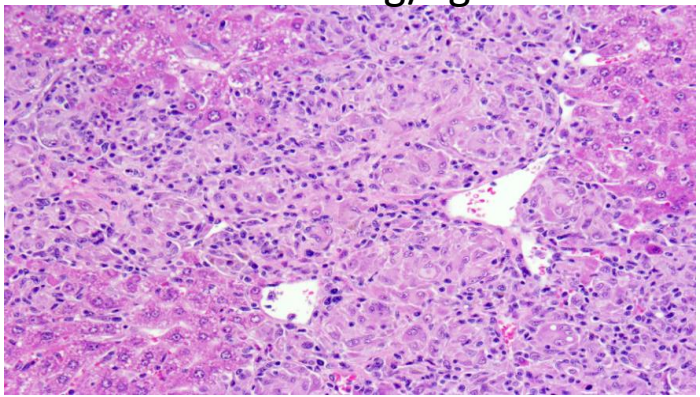


Pathology: Liver

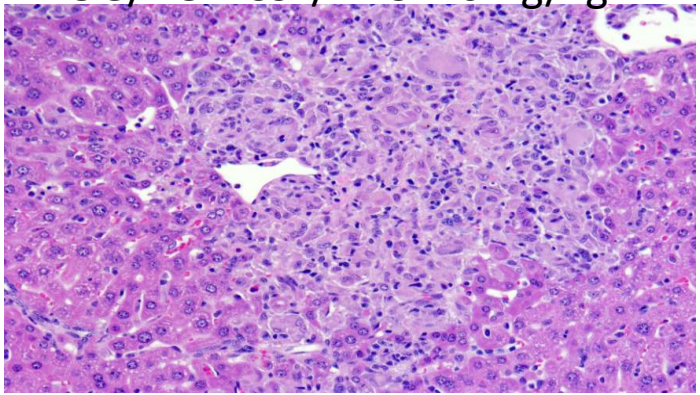
Saline control



NOG 10mg/kg

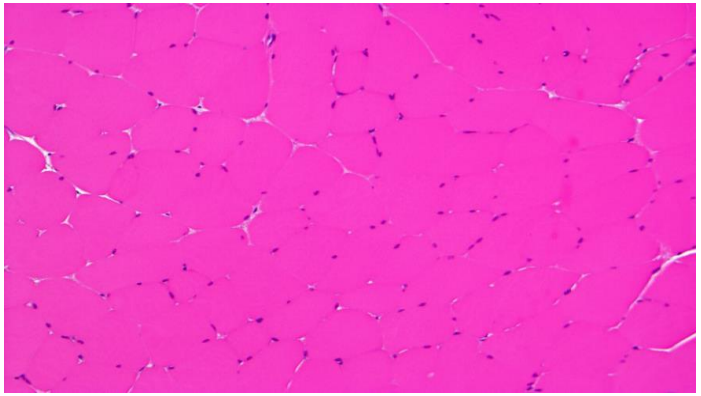


NOG/hGMCSF/hIL3 10mg/kg

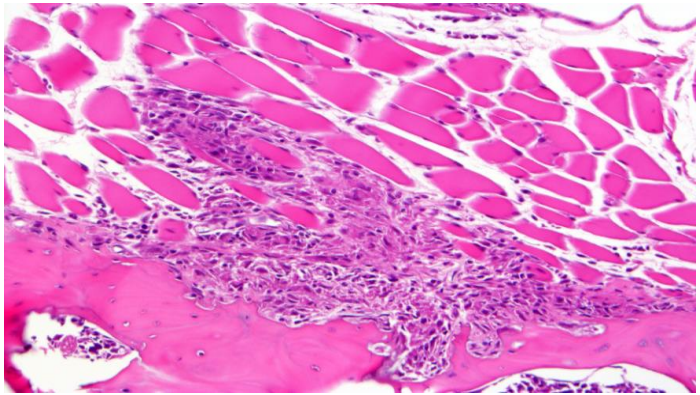


Pathology: Muscle

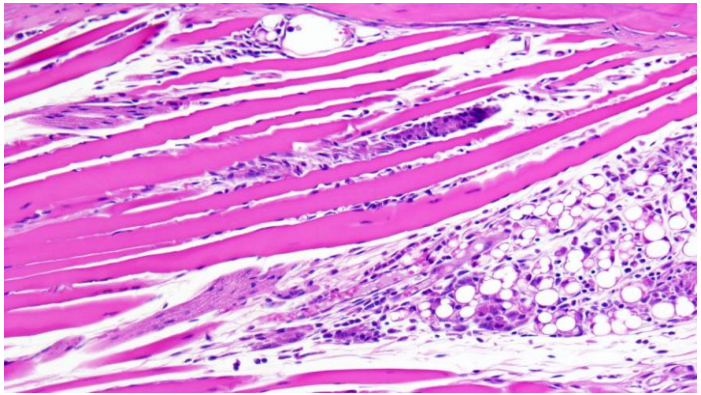
Saline control



NOG 2.5mg/kg

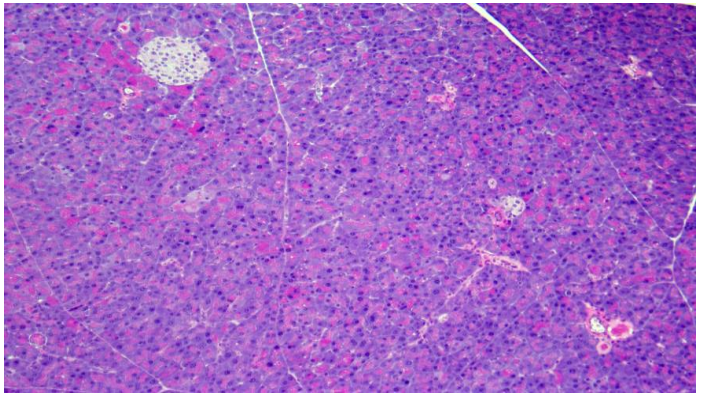


NOG/hGMCSF/hIL3 10mg/kg

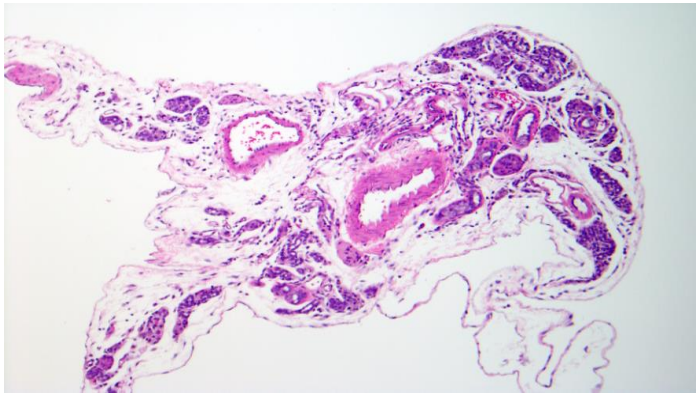


Pathology: Pancreas

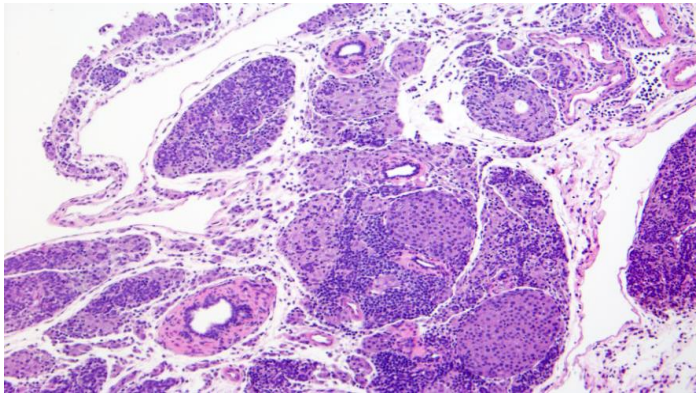
Saline control



NOG 10 mg/kg



NOG/hGMCSF/hIL3 10 mg/kg



Conclusions

- Anti-PD-1 nivolumab effectively neutralizes PD-1 on T-cells in immune humanized mice
- Mice experienced adverse events in a dose-dependent manner
- T-cells became more activated as drug was administered
- Immune humanized mice can experience profound auto-immunity in response to checkpoint inhibitor therapy

Acknowledgements

DARS/OCP/OTS/CDER

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Taconic Biosciences

Advanced Bioscience Resources

OND/CDER

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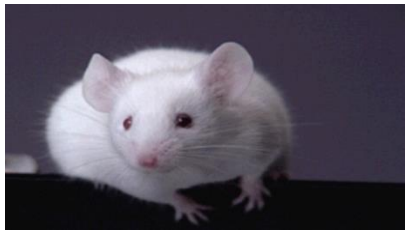
L. Peyton Myers, Ph.D.



CANCER IMMUNOTHERAPY: BEYOND NOAEL FOR FIRST IN HUMAN DOSE SELECTION

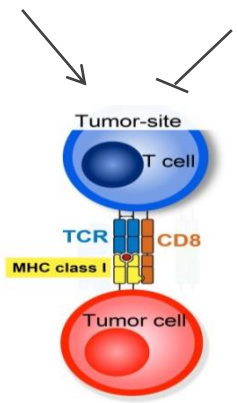
FDA-AACR: Immuno-oncology Drug Development Workshop
Washington, D.C.
October 13-14, 2016

Genentech
A Member of the Roche Group

T Cell-Based Cancer Immunotherapy Approaches

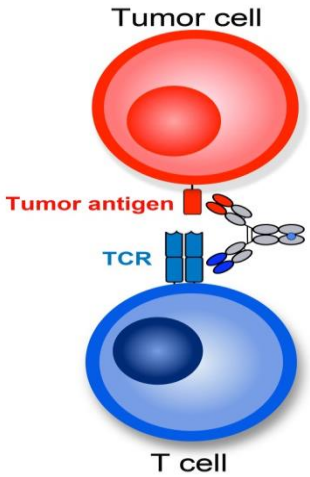
Immune Modulation

Activating Receptors	Inhibitory Receptors
CD28	CTLA-4
OX40	**PD-L1/PD-1**
CD27	TIM-3
CD137	BTLA
HVEM	B7-H4R
CD226	



- Tumor-specific T cell clones
- MHC-bound peptide antigen
- Costimulatory signals

T-Cell Recruitment



Bispecifics:
- **BiTE**
- **DART**
- **TDB**
- **TCB**

T-cell recruiting bispecifics
- Avoid need for ex-vivo T-cell manipulation
- Controlled dose and schedule

Atezolizumab (anti-PD-L1)

Nonclinical safety study designs

Mouse (pilot)

Group	MPDL3280A Dose Level (mg/kg)	Strain	No./Group Toxicity[a]	No./Group TK	No./Group Immunology
1	0 (vehicle)	C57Bl/6	8F	9F	15F
2	10	C57Bl/6	8F	9F	15F
3	50	C57Bl/6	8F	9F	15F
4	0 (vehicle)	CD-1	8F	9F	15F
5	50	CD-1	8F	9F	15F

Cyno (GLP)

Group No.	No. of Males/Females	Dose Level (mg/kg)	Route of Administration	No. Necropsied:	
				Terminal Day 60	Recovery Day 143
1	5/5	0 (vehicle)	IV/SC	3/3	2/2
2	5/5	5	IV	3/3	2/2
3	5/5	15	IV	3/3	2/2
4	5/5	50	IV	3/3	2/2
5	5/5	15	SC	3/3	2/2
6	5/5	50	SC	3/3	2/2
7	3/3	0 (vehicle)	IV	–	–
8	3/3	50	IV	–	–

- Standard endpoints
  - Body weight, clin chem, hematology, gross and microscopic pathology
  - TK/ATA
- Exploratory endpoints
  - Immunophenotyping (activation markers)
    - CD25, CD69 on CD4 and CD8 T cells
  - Serum cytokine analysis

Prell, R. et al SOT 2013.

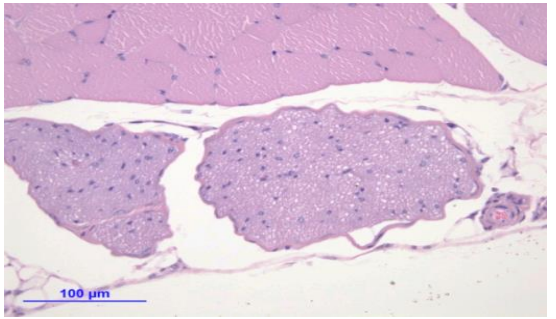
Key Results from 15-Day Pilot Toxicity Study in Mice

- TA-related findings:
  - Neuropathy of the sciatic nerve*
    - No clinical signs
    - Minimal axonal degeneration with lymphocytic infiltration
    - 10 mg/kg & 50 mg/kg groups, terminal & recovery
    - Seen in C57Bl/6, not CD-1 mice (strain-specific response)

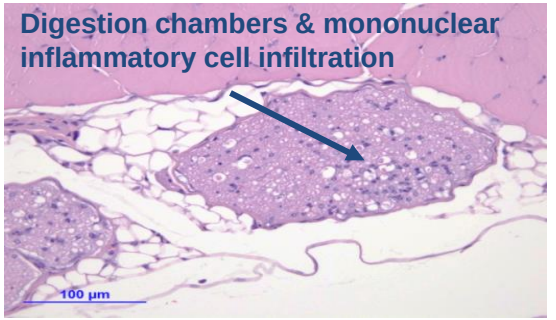
Animal ID	Dose level	Day 17	Day 43
C57Bl/6	0 (vehicle)	0	0
C57Bl/6	10	2 of 4	1 of 4
C57Bl/6	50	2 of 4	3 of 4
CD-1	0 (vehicle)	0	0
CD-1	50	0	0

* Reported in PD-1-deficient (K/O) NOD-H2$^{b/b}$ mice (Yoshida, T. et al PNAS 2008 105:3533)

Normal Sciatic Nerve



Affected Sciatic Nerve



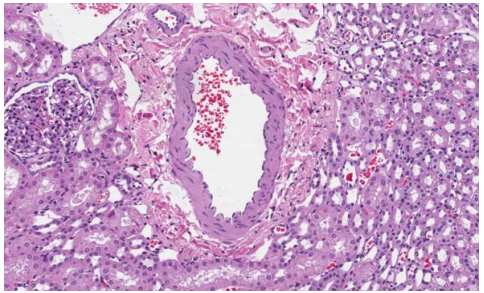
Prell, R. et al SOT 2013.

Key Findings in Cynomolgus Monkey Toxicity Study

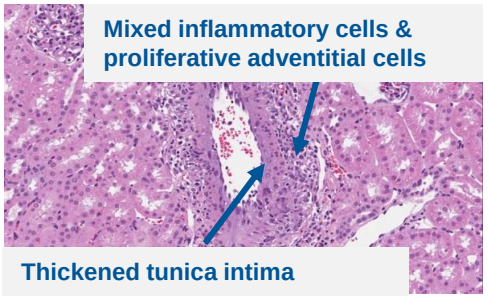
- **No apparent drug-related effect on in-life assessments**
- **Periarteritis/arteritis at terminal necropsy**
  - Mixed inflammation around and involving blood vessels (mononuclear cells)
  - Medium-sized muscular arteries in one or more organs
  - Minimal to mild overall – no evidence of thrombosis, hypoxic tissue damage
  - No control or low dose (5 mg/kg) animals with finding
  - No animals affected at recovery necropsy
  - No clinical signs, changes in clinical pathology, or autoAbs

Animal ID	Dose level	Route	Tissues affected
5005 M	15 mg/kg	SC	Heart, Liver
6002 M	50 mg/kg	SC	Kidney, Stomach, Epididymis
6003 M	50 mg/kg	SC	Kidney
4505 F	50 mg/kg	IV	Heart, Periaortic connective tissue, Tongue, Stomach, Pancreas, Cecum, Rectum, Reproductive tract

Normal Artery, Kidney



Affected Artery, Kidney (#6002)



FIH dose selection based on receptor occupancy

☒ Cytokines

No evidence of cytokine release in isolated human PBMCs

Transient increase in one high dose cyno

☒ In vivo toxicology program

NOAEL 5 mg/kg in cynomolgus monkeys

Approx 50x safety factor at proposed starting dose of 0.3 mg/kg

☑ Receptor occupancy

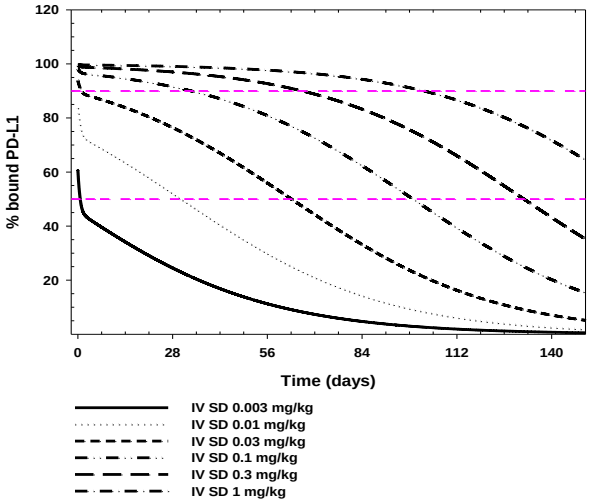
0.05 ug/mL: projected serum concentration to achieve 100% RO

RO approximately 80% at Cmax for agreed FIH dose of 0.01 mg/kg

Agreement with FDA to allow single patient cohorts up to a dose of 0.3 mg/kg

Minimize the number of patients exposed to very low dose levels

Projected Receptor Occupancy



Dose (mg/kg)	Time above 50% saturation	Time above 90% saturation
0.003 IV SD	< 1day (~12hr)	0
0.01 IV SD	~30 days	0
0.03 IV SD	~63 days	1
0.1 IV SD	~99 days	~33 days
0.3 IV SD	~132 days	~66 days
1 IV SD	> 169 days	~102 days

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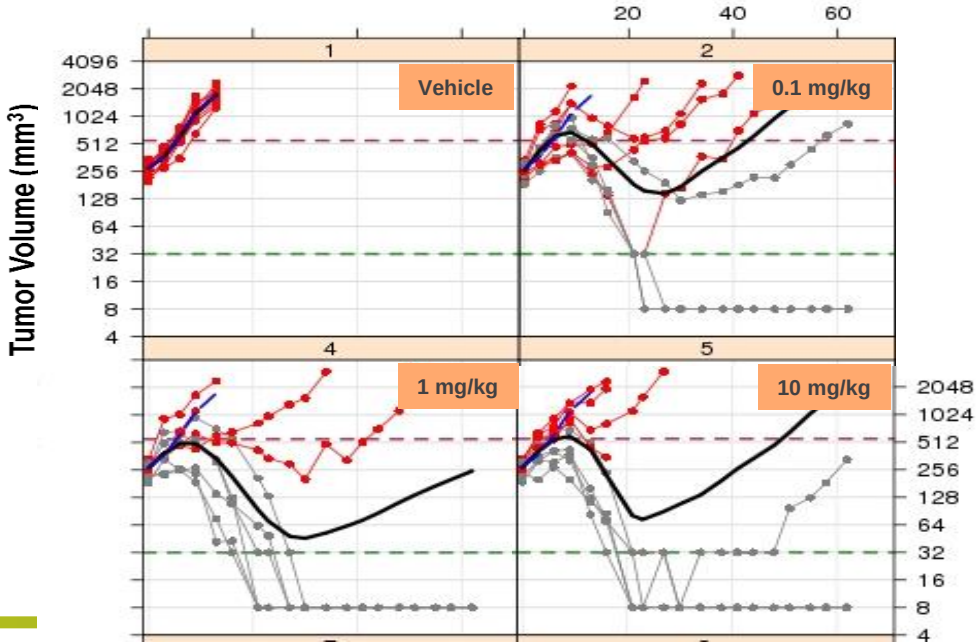
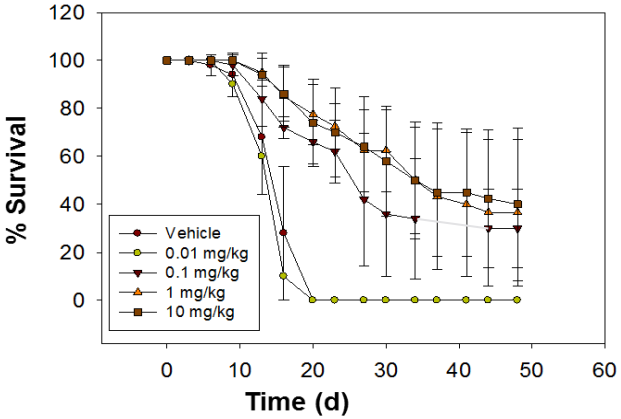
MOXR0916 (anti-OX40)

In vivo efficacy studies of PRO307205 treatment in EMT6 model show trend of dose response

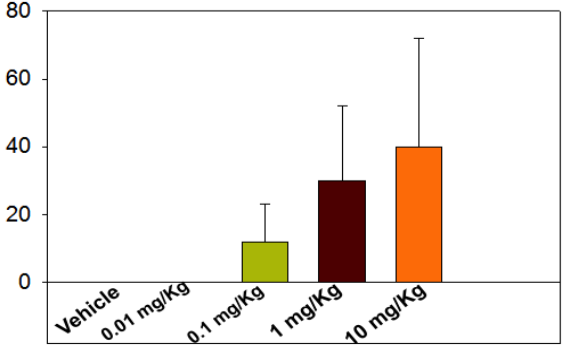
Tumor growth kinetics in individual animals from one representative efficacy study



Survival analysis

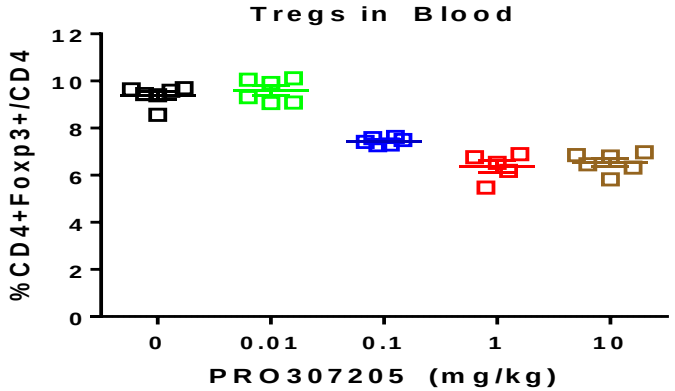


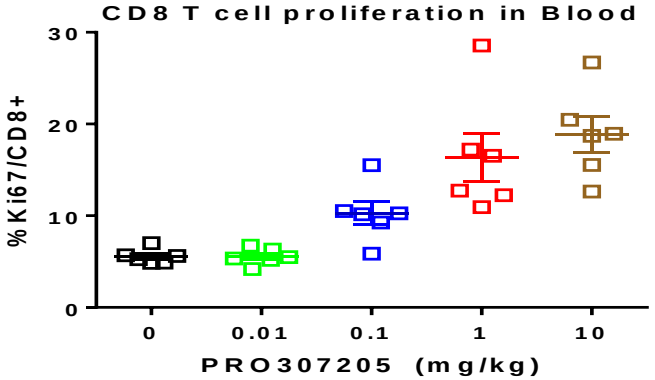
% of complete response

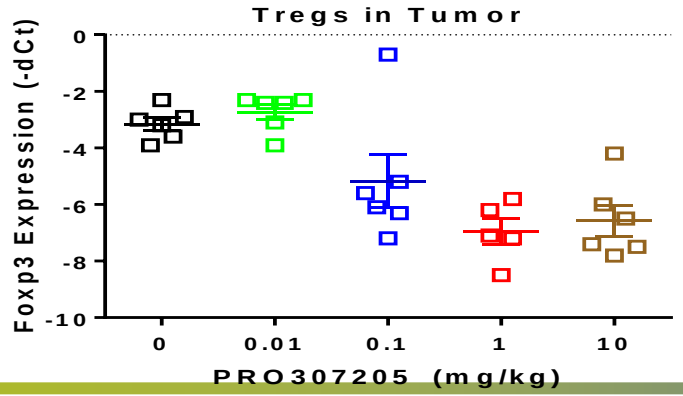


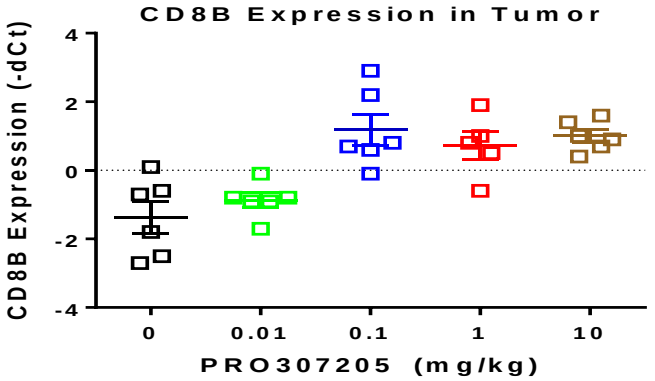
Mean±SD calculated based on 5 dose ranging efficacy studies

PRO307205 induces dose dependent MOA associated PD modulation in blood and tumors



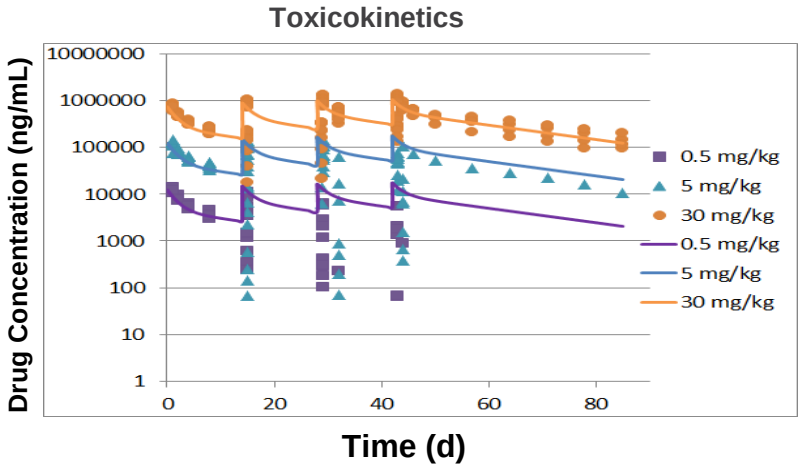


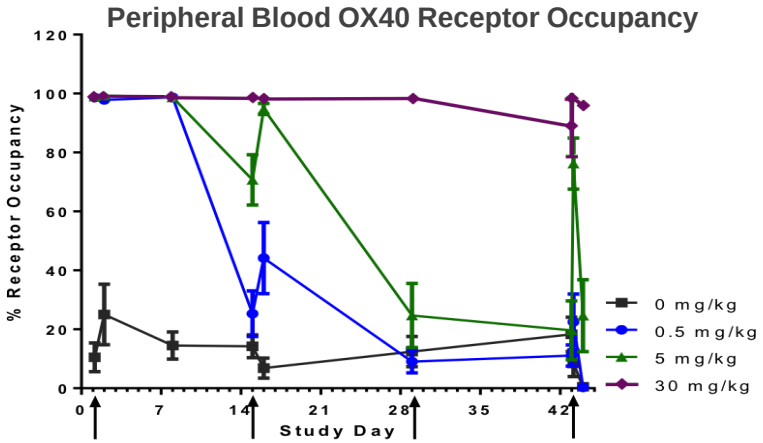




All data shown from EMT6, similar trend in PD modulation observed in multiple tumor models

MOXR0916 cynomolgus monkey PK/PD





- MOXR0916 binds human and cyno OX40 with equivalent affinity
- PK is as expected for typical IgG1 and dose proportional
  - Projected human CL = 2.5 ml/d/kg, $t_{1/2}$ ~ 3 wk
- ATAs detected in all animals in the 0.5 mg/kg and 5 mg/kg (but not 30 mg/kg) dose groups, with loss of exposure and receptor occupancy
- No significant activation or proliferation of peripheral T cells
- No significant reduction in absolute peripheral T cell counts

FIH dose selection based on minimal pharmacologically active dose (MPAD)

☒ **Cyno tox study (NOAEL approach) and in vitro cytokine release assay**

- OX40 is transiently expressed only on activated T cells
- Healthy cynos/unstimulated PBMCs will have negligible activated T cells (lack of relevant antigens)

☒ **In vitro studies of T cell proliferation and cytokine production**

- Artificially sensitive because pre-stimulation with anti-CD3 required to upregulate OX40

☒ **Receptor occupancy**

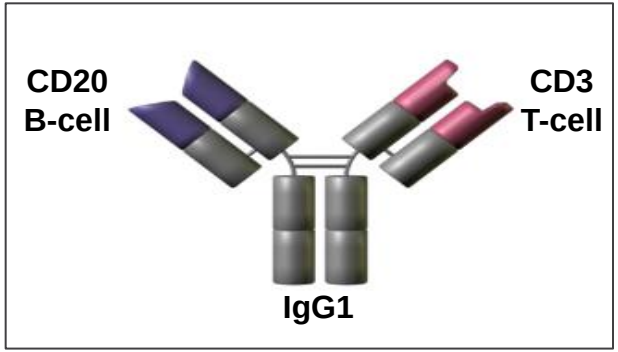
- Relationship between peripheral RO and efficacy/toxicity not established because of variability in mouse studies and lack of antigen stimulation in cynos

☑ **Anti-OX40 in mouse tumor model provides the only measurement of pharmacological activity in vivo**

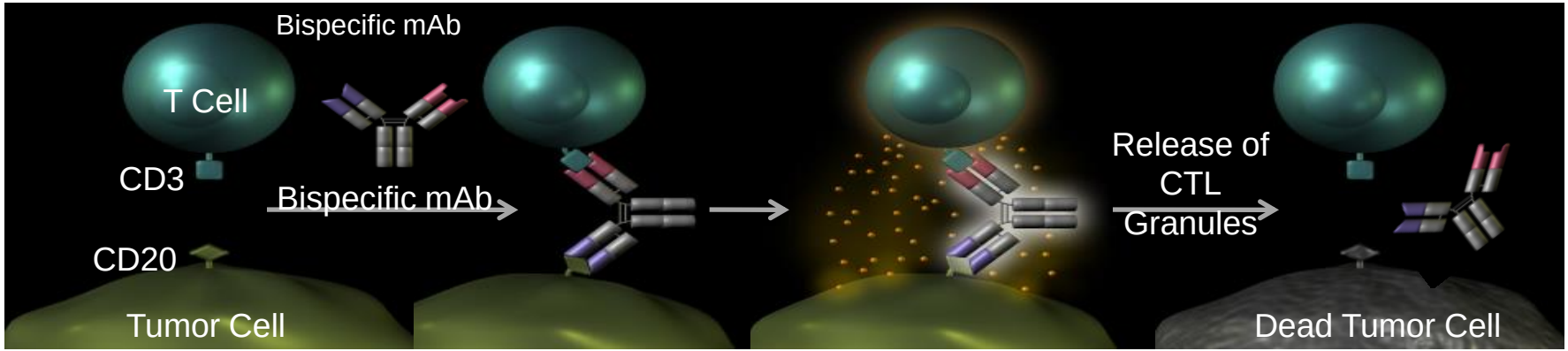
- PD effects were observed in mouse tumor model at doses ≥ 0.1 mg/kg
- 0.1 mg/kg projects to a human starting dose of 0.002 mg/kg (~200 mcg flat dose)
  - Scaling of PK: adjust for 6 fold difference in clearance
  - Adjust for 8.2 fold difference in potency

Anti-CD20/CD3 bispecific antibody

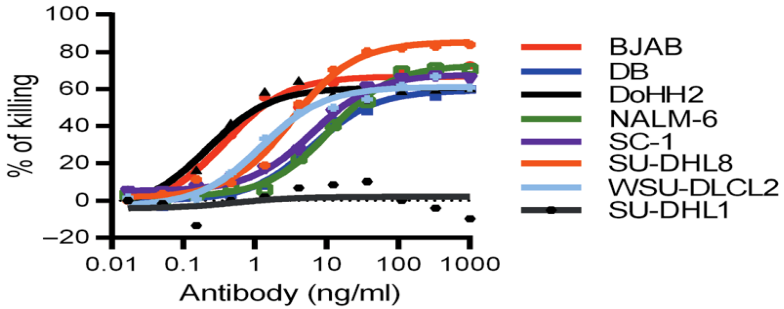
Anti-CD20/CD3 Bispecific Antibody

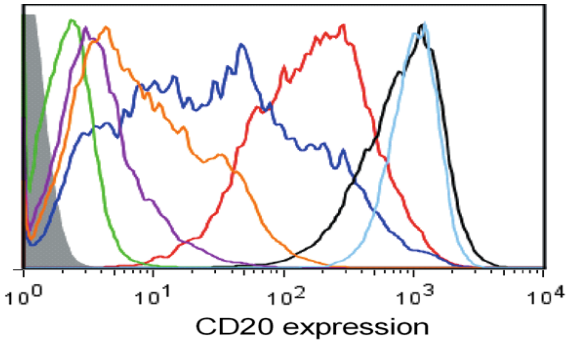


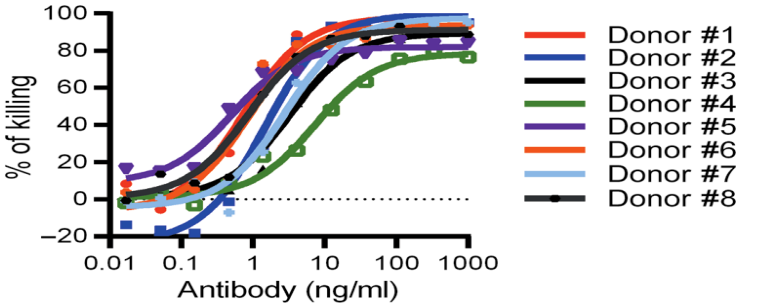
- **Produced using 'knobs in holes' technology**
  - Full length bi-specific, PK similar to conventional IgG1
  - Glycosylation mutation (N297G) eliminates ADCC function => MOA distinct from rituximab and obinutuzumab
- **aCD3 arm recruits T-cells to B-cells**
  - T-cell activation requires CD20 target engagement
  - Pre-treatment immune response to tumor not a pre-requisite
  - Active against indolent (non-dividing) and chemo-resistant cells

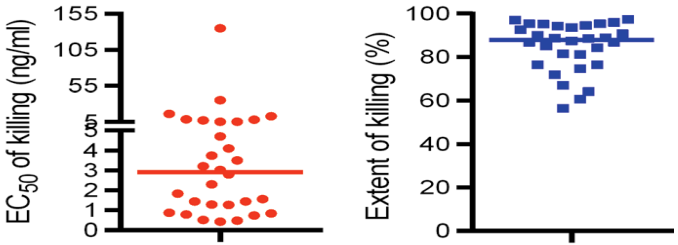


Activity of Anti-CD20/CD3 Against Human B-Cell Lymphoma Cell Lines and Healthy Donor B-Cells









Healthy donor B cell killing

Sun et al. 2015

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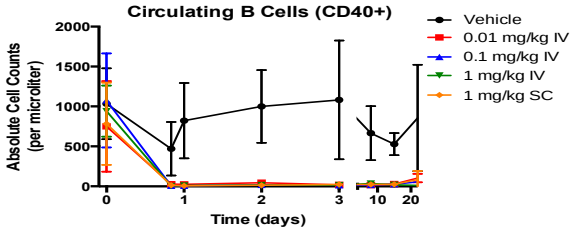
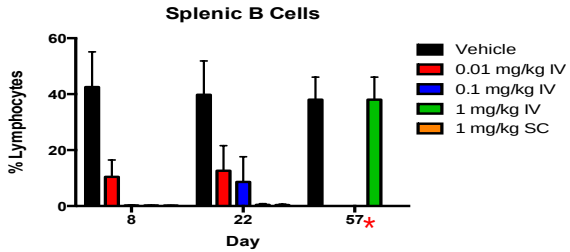
Single-dose GLP Toxicity Study in Cynomolgus Monkeys: Expected PD Effects Observed

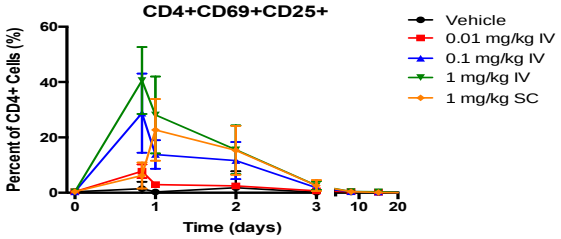
B-Cell Depletion

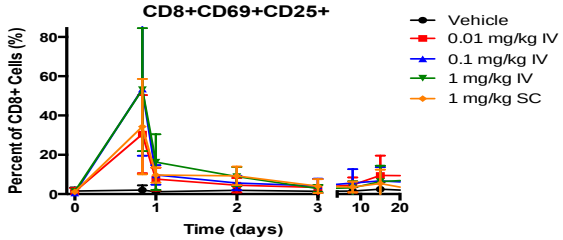




Complete or near complete tissue B cell depletion at ≥ 0.1 mg/kg @ D8 (IV = SC)

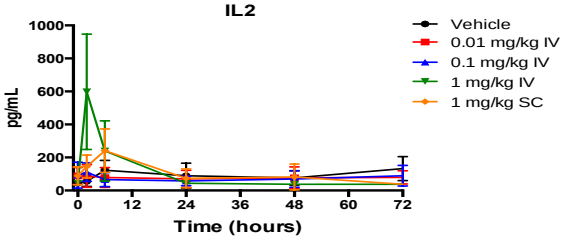
T-Cell Activation

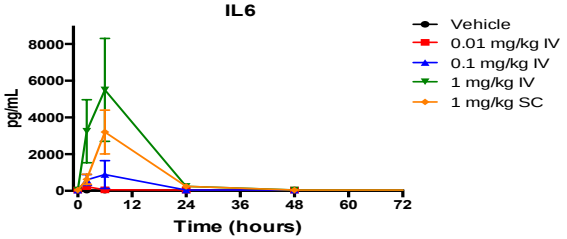




T cell activation at ≥ 0.01 mg/kg (SC<IV, slightly delayed)

Cytokine Release





Dose-dependent ↑ key cytokines at ≥ 0.01 mg/kg (SC<IV, slightly delayed)

* Only Vehicle and 1 mg/kg IV groups present at Recovery D57

FIH Dose Selection based on MABEL

- Select a dose expected to have MINIMAL biological effects
  - Predicted C_{max} that is expected to have minimal effects, e.g., the lowest of

☒ **Cyno tox study (NOAEL approach)**

☒ **Receptor occupancy**

☒ **Double transgenic mouse tumor model provides the measurement of pharmacological activity in vivo**

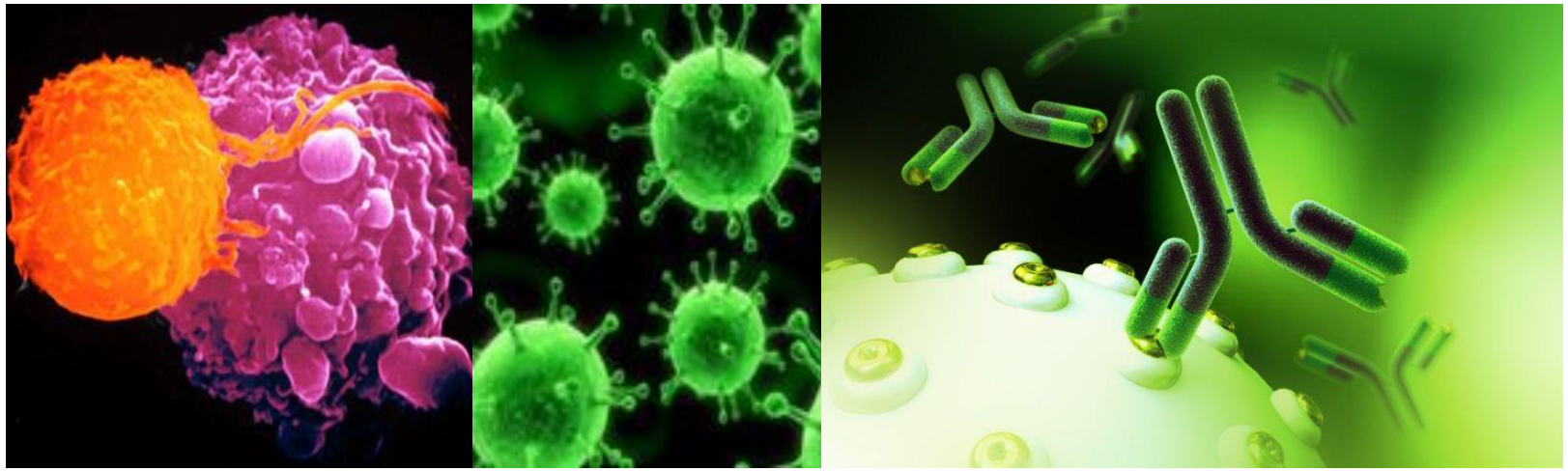
☑ **In vitro studies (EC_{20}) of T cell proliferation and/or cytokine production**

Acknowledgements

Atezolizumab Team

MOXR0916 Team

Anti-CD20/CD3 Bispecific Antibody Team



Nonclinical Safety Evaluation of T-cell Immunotherapies

Tim MacLachlan
Global Head of Biologics Safety Assessment
Executive Director, Preclinical Safety
Novartis Institutes for Biomedical Research

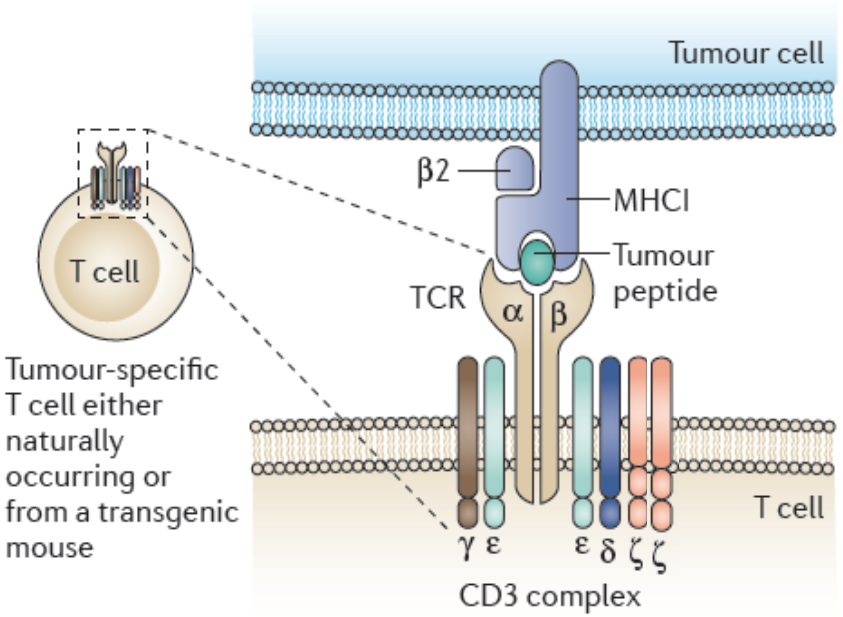
FDA/AACR Immuno-oncology Drug Development Workshop
October 13, 2016
Washington DC

NOVARTIS

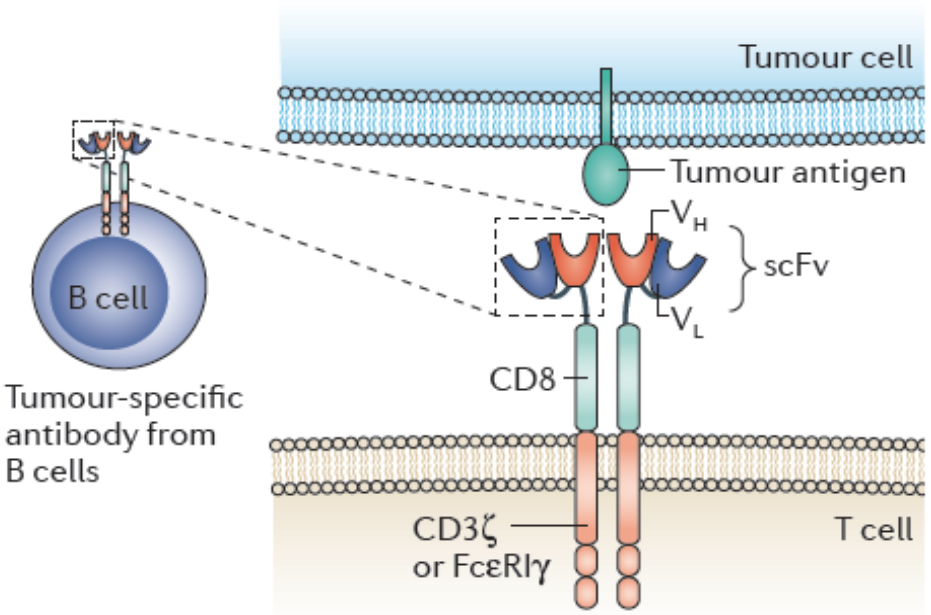
Two flavors of T-cell therapies

Overview

"TCR T-cells"



"CAR T-cells"



Nat Rev Cancer 2013;13:525

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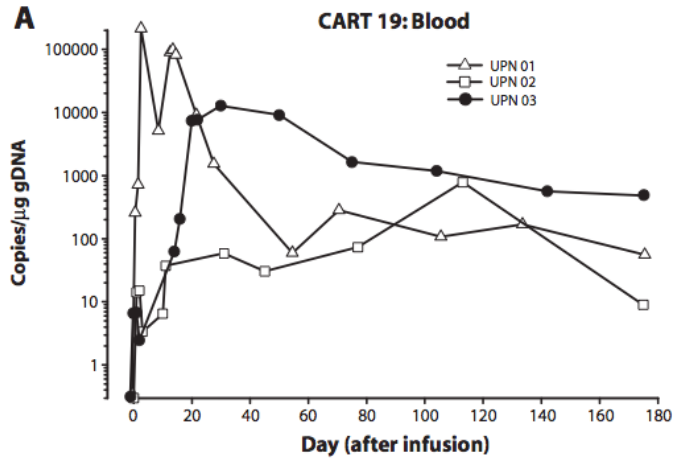
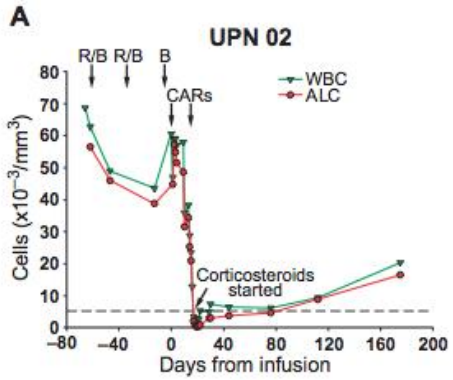
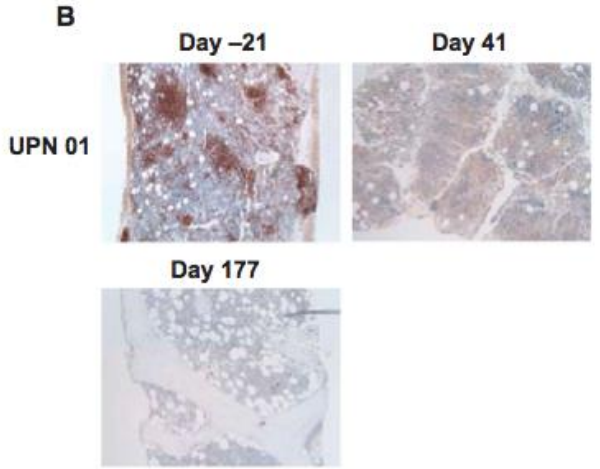
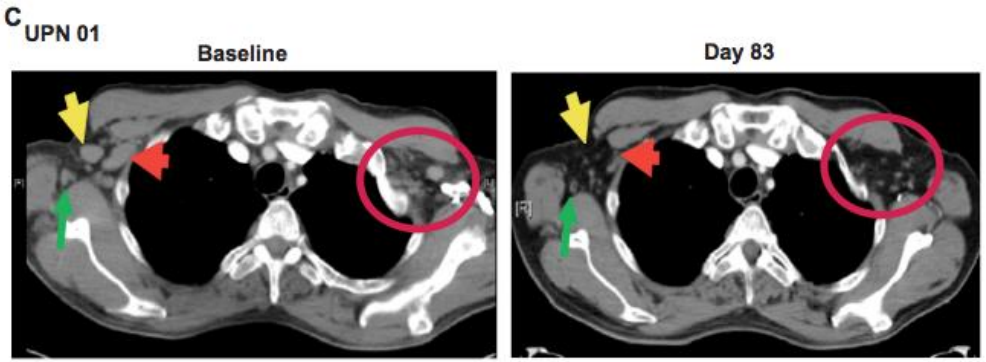
Promising activity in the clinic

"CART 19"/"CTL019" – CAR T-cell targeting CD19









Kalos et al. Sci.Trans.Med. 2011. 10(3):95

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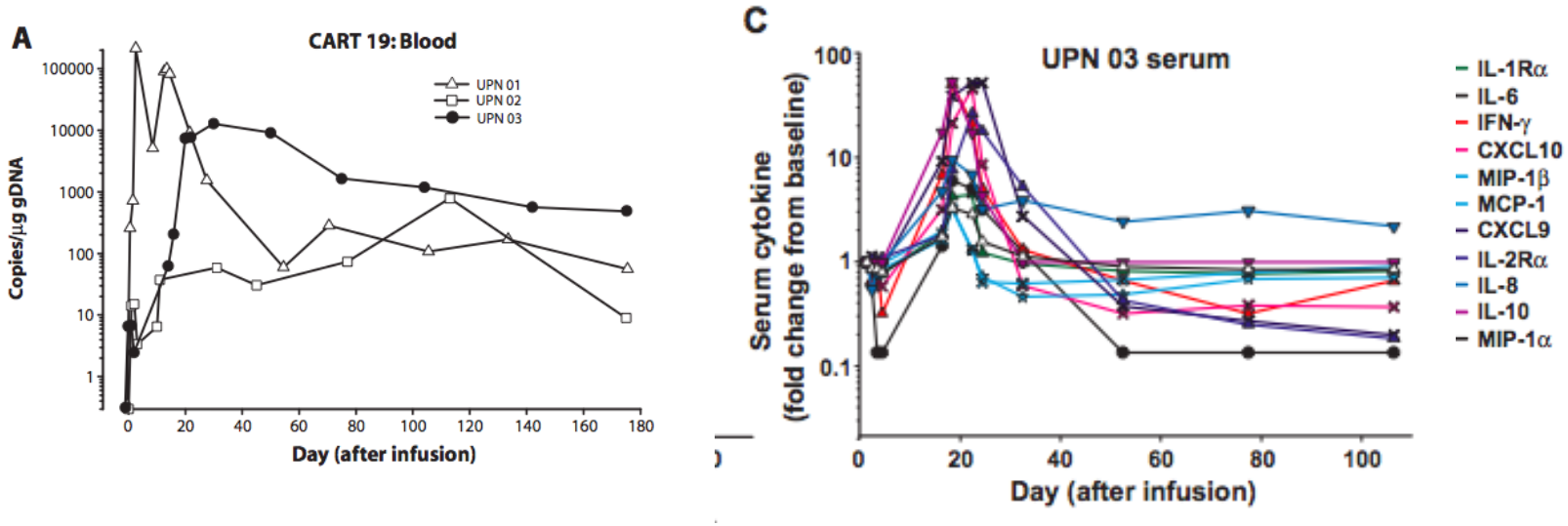
Cytokine release toxicity…

“On-target, on-tumor”

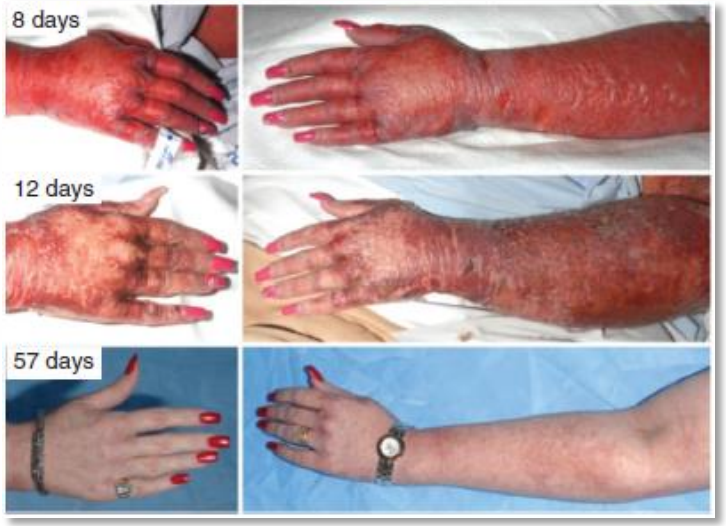


- Under control with antibodies to IL-6R and steroids

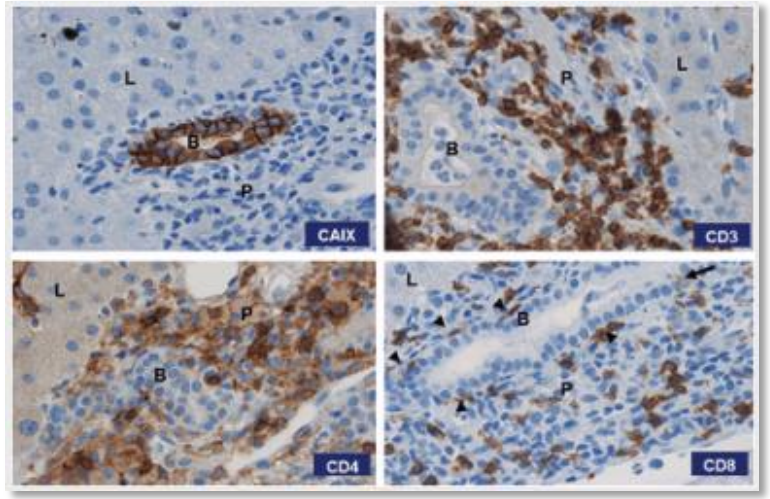
Normal tissue toxicity

“On-target, off-tumor”

MART1-TCR T-cells



CAIX-CAR T-cells



Nat Biotech 2013;31:999

- Some toxicities temporary
- Some deaths with TCR T-cells
- “Off-target, off-tumor” also possible, have been observed with TCR T-cells

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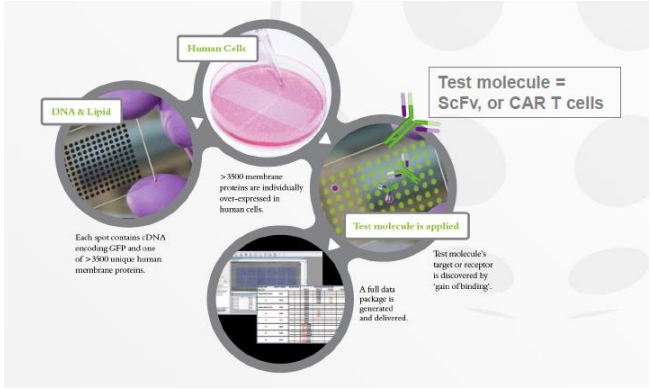
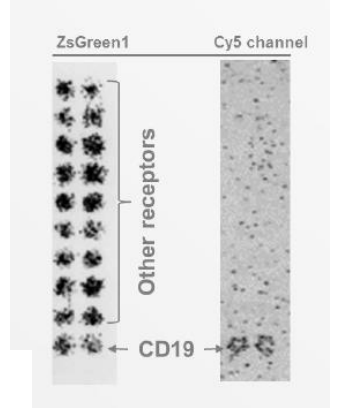
Options for nonclinical assessment

- Target distribution
  - “On target, off tumor”
    - Leveraging different methods (eg, RNASeq, RT-PCR, ISH, IHC, IP/WB, Flow cytometry
- Potential for cross reactivity –
  - “Off target, off tumor”
  - MHC peptide homology screens (TCR T-cells)
  - Chip-based protein interaction arrays, ie Retrogenix (CAR T-cells)
- Normal cell killing in culture?
- Genotoxicity?
- Graft v host?





Horvath, unpublished

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Options for nonclinical assessment

- In vivo assessment – still under development…
  - Studies in immunocompromised mice with/without tumor
    - Good for combining efficacy/safety into one study, but, would be irrelevant if not cross reactive to mouse antigen, which is often
    - Lack of host immune system contribution to effect
  - Studies in immunocompetent animals
    - Use of “surrogate” cells, various challenges with creating test article, conditioning regimens, culturing conditions, dosing

T Cells Engineered With Chimeric Antigen Receptors Targeting NKG2D Ligands Display Lethal Toxicity in Mice

Heather VanSeggelen[1], Joanne A Hammill[1], Anna Dvorkin-Gheva[1], Daniela GM Tantalo[1], Jacek M Kwiecien[2,3], Galina F Denisova[1], Brian Rabinovich[4], Yonghong Wan[1] and Jonathan L Bramson[1]

Preconditioning – 150mpk CTX
CAR-T dosing ~10e6 cells/animal

Safety of targeting ROR1 for cancer immunotherapy with chimeric antigen receptor-modified T cells in a primate model

S Carolina Berger[1*], Daniel Sommermeyer[1], Michael Hudecek[2], Michael Berger[1], Ashwini Balakrishnan[1], Paulina Paskiewicz[3], Paula Kosasih[1], Christoph Rader[4], Stanley Riddell[1]

No preconditioning
CAR-T dosing ~100e6 cells/animal

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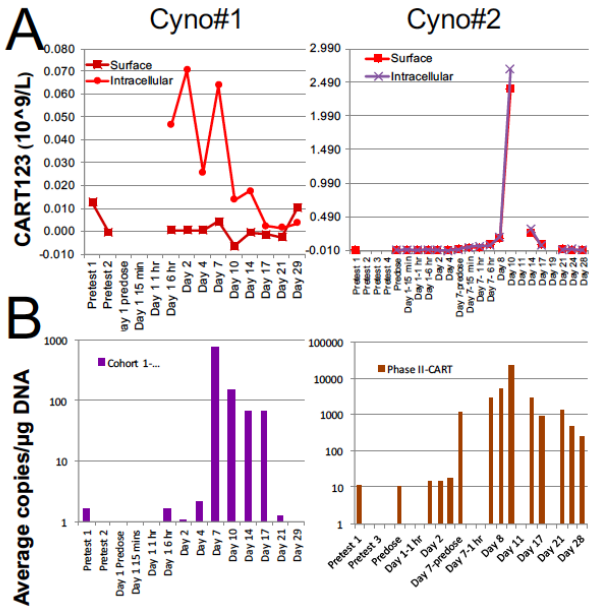
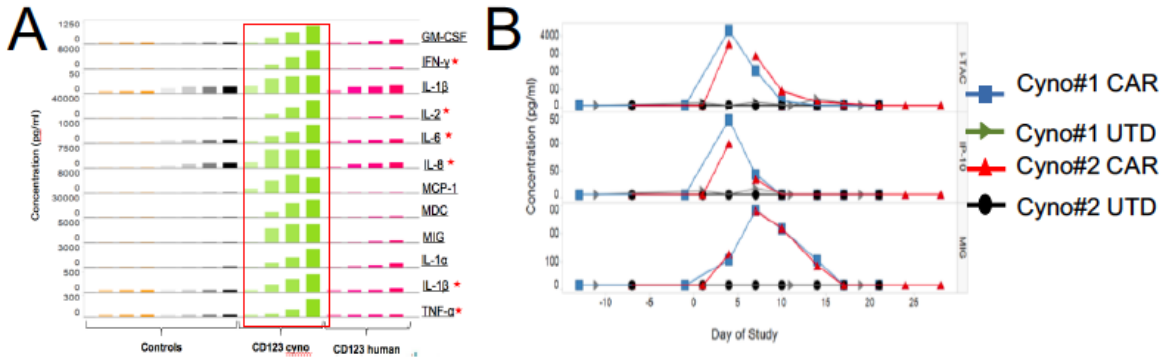
Options for nonclinical assessment

- In vivo assessment – still under development…
  - Recent developments in NHP studies –
    - Expansion of CD123 targeting CAR-Ts in vivo *(MacLachlan et al, ASGCT 2015)*

Expansion



Cytokine release in vitro and in vivo



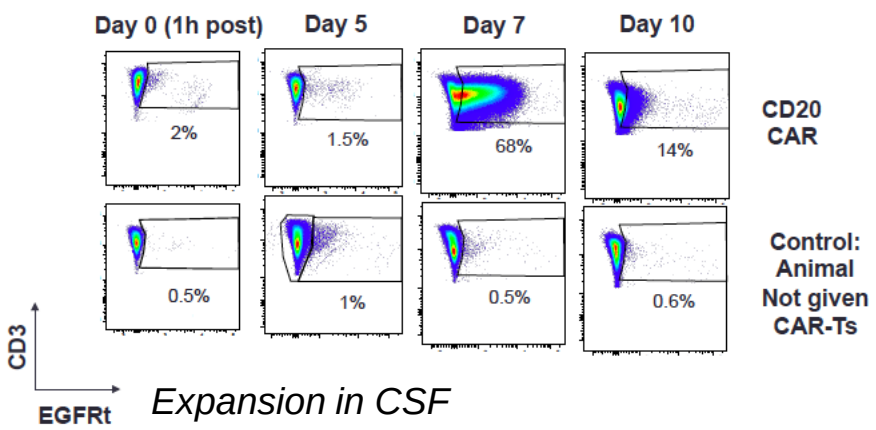
- Preconditioning 4mpk pentostatin, 60mpk CTX
- CAR-T dosing 200e6 to 800e6 cells per animal

NOVARTIS

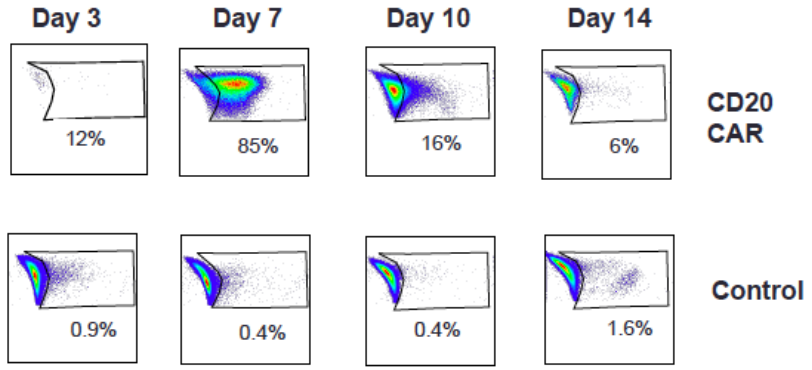
Options for nonclinical assessment

- In vivo assessment – still under development…
  - Recent developments in NHP studies –
    - Cytokine release and neurotoxicity in vivo with a CD20 targeting CAR-T *(Leslie Kean, Mike Jensen, Seattle Childrens Research Institutue; Rafael Ponce, Juno Therapeutics, unpublished)*

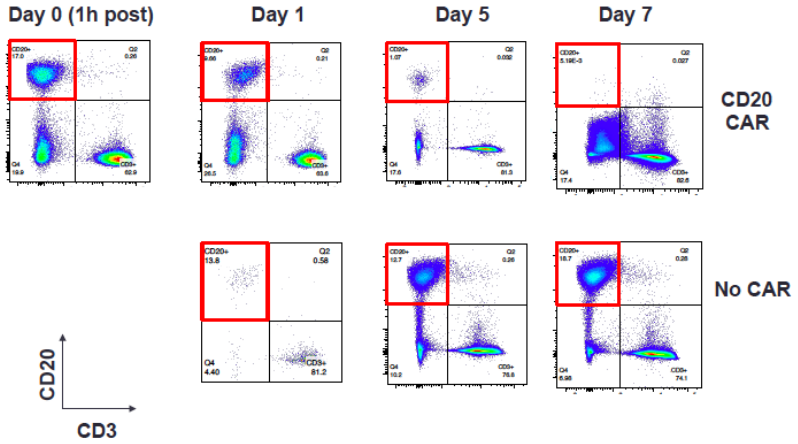
Expansion in blood



Expansion in CSF



Depletion of CD20+ cells



Preconditioning 40mpk CTX x2
CAR-T dosing ~40e6 cells/animal

Concomitant with clinical signs of tremors and balance issues

“CAR-T Consortium”

- Nascent group of nonclinical scientists focused on nonclinical safety and pharmacology evaluation of T-cell immunotherapies

- Mission – to share non-confidential information on nonclinical experience and to align on vision of a comprehensive and feasible nonclinical evaluation of T-cell immunotherapies

NOVARTIS

Summary

Opinions on appropriate nonclinical strategies

- Current view
  - ***This is an evolving field of safety science, sponsors are wading through a number of nontraditional options at this point***

  - Utilize methods that are well understood, use these data to determine clinical path (if any) and if any additional nonclinical data are needed
  - Data to include in IND/CTA submissions -
    - Target expression/localization analysis
    - Selectivity of components of CAR or full CAR-T itself

- Possible future directions for in vivo studies
  - Mouse cross reactive scFvs used in efficacy experiments with full histopathology
  - Creation of large animals CAR-Ts under optimized conditioning regimens

NOVARTIS

Summary

Opinions on appropriate nonclinical strategies

- "Human is the bioreactor"
  - Many factors play role in expansion

- Clinical dosing recommendations…
  - In the range of 5e6 to 250e6 CAR+ cells per dose
  - Trials range greatly in ped v adult, preconditioning, flat v BW, fractionating dose, etc
  - Nonclinical efficacy studies in NSG mice range between 1e6 and 10e6 CAR+ cells (eq to ~3500e6 cells in 70kg pt)
  - Some evidence that dose fractionation in clinic can mitigate cytokine release

- CAR-T "switches" to mitigate toxicity
  - Many variants in play – iCasp9, tEGFR/HER2/etc, "split" CARs, etc… no large clinical trials yet

NOVARTIS

Development of a Vaccine-Based Immunotherapy Regimen (VBIR)

David W. Clarke, PhD, DABT
Drug Safety R&D
13 Oct 2016

Pfizer WORLDWIDE RESEARCH & DEVELOPMENT

SCIENCE FOR LIFE-CHANGING IMPACT

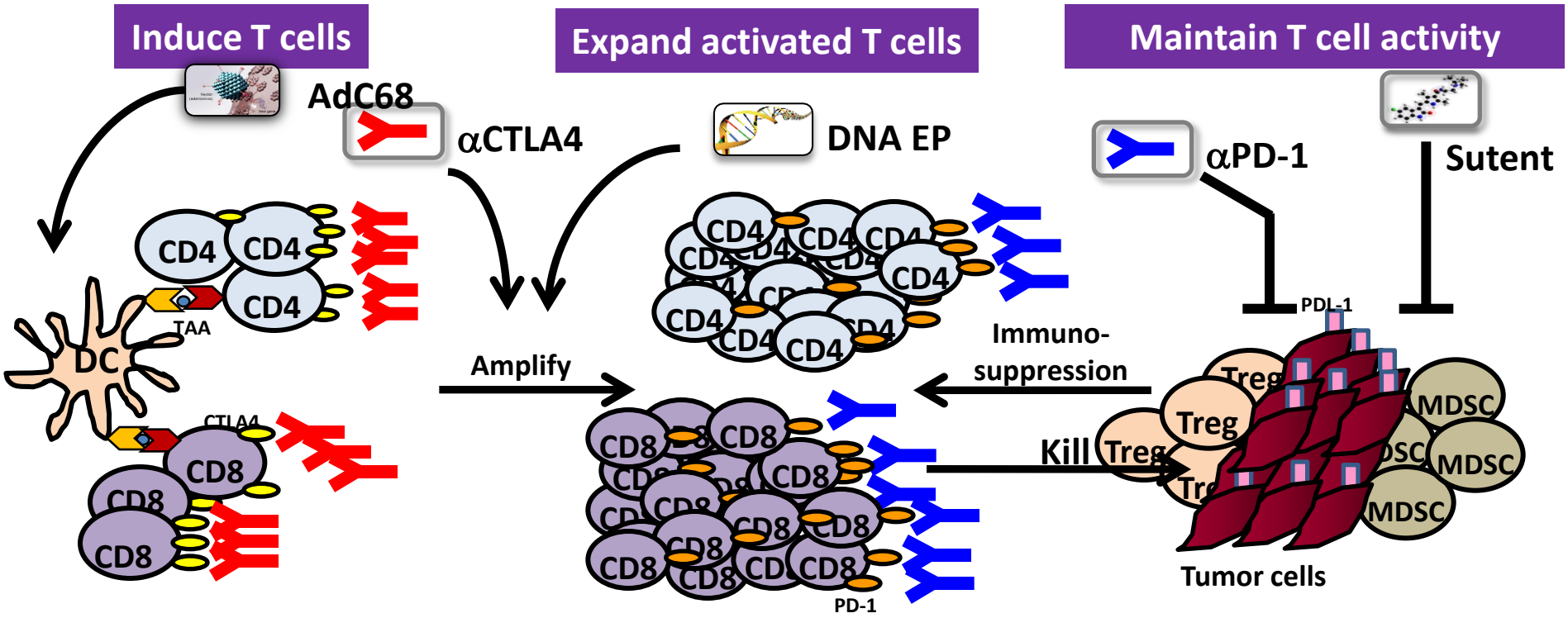
Vaccine Based Immunotherapy Objectives

Reset the immune system to generate and maintain "therapeutic levels" of tumor specific T-cells and antibodies in the majority of patients

Destroy tumor cells resulting in
- **high ORR**
- **durable responses**
- **low side effects**

Race to generate sufficient immune responses to prevent
- **tumor proliferation**
- **immune escape**

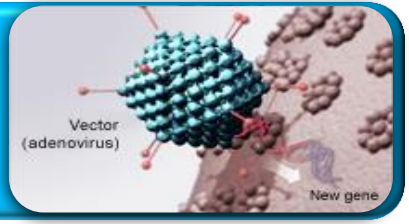
Learning from previous immunotherapy trials: application to Vaccine Based Immunotherapy Regimen (VBIR)



Antigen delivery technologies and immune modulators in VBIR to drive immune responses

Induce T cells
(break T cell tolerance to 'self')

Adenoviral vectors encoding tumor associated antigens



\+ αCTLA4

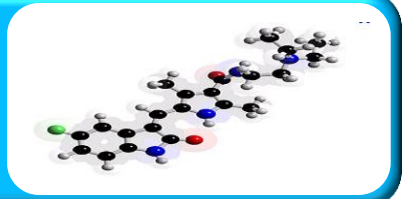
Expand T cells
to 'therapeutic' levels

DNA encoding tumor associated antigens

\+ αCTLA4

Maintain T cell activity
in the immunosuppressive tumor

Sutent



or αPD-1

- TAAs make VBIR cancer indication specific
- VBIR components clinically validated & unique to PFE

Selection of Tumor Antigens for the PrCa VBIR: Multi-antigen approach is critical

- Selection of tumor associated antigens are based on expression profile, clinical precedence and efficacy / immunogenicity in humans

Antigen	Expression in PrCa
PSA Prostate specific antigen	Expression level correlates with high Gleason score
PSCA Prostate stem cell antigen	Majority of bone mets (>90%)
PSMA Prostate specific membrane antigen	Majority of lymph node mets (>80%)

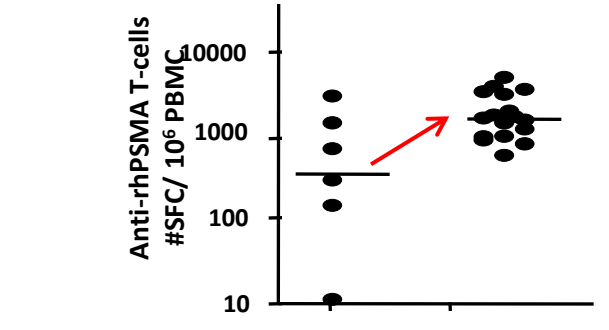
Eertwegh et al, Lancet Oncology 13: 509 (2012)
Tjoa B et al, The Prostate 40:125 (1999)
Gu et al, Oncogene 19: 1288 (2000)
Thomas-Kaskel A et al Int. J Cancer 119: 2428 (2006)
Gulley et al, Can. Imm.Imm. 59:663 (2010)
Lam et al, CCR 11:2591 (2005)
Minner et al, The Prostate 71:281 (2011)
Raica et al, Magyar U. 9:301 (1997)

Benefits of multi-antigen polyclonal tumor-specific immune response:

- Provide therapeutic benefit to a broad patient population
- Decreases risk of immune escape by the tumor

Induce: Recombinant AdV delivered rhPSMA induces robust T-cell responses

- Most tumor associated antigens are self antigens
  - immune system will not respond to them (tolerance)
- Solution: Adenoviral vectors (AdV) efficiently present poorly immunogenic tumor antigens to the immune system



AdV-rhPSMA	+	+
α-CTLA4		+

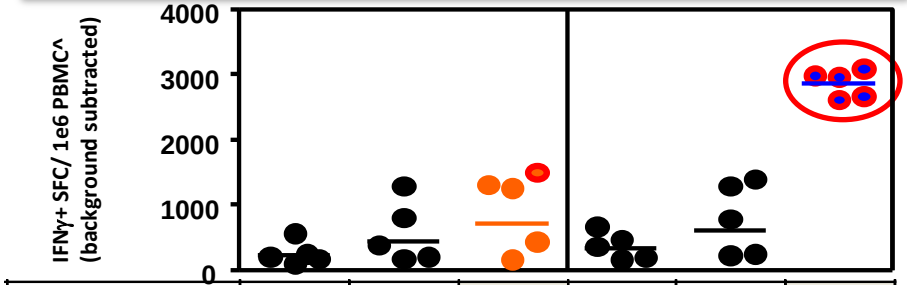
PFE Data

PFE assets

- AdV-rhPSMA
- αCTLA4 mAb

Expand: injection site and route of αCTLA4 are important for TAA specific CD4/8 T cell expansion

PSMA specific IFNγ T cell response kinetics

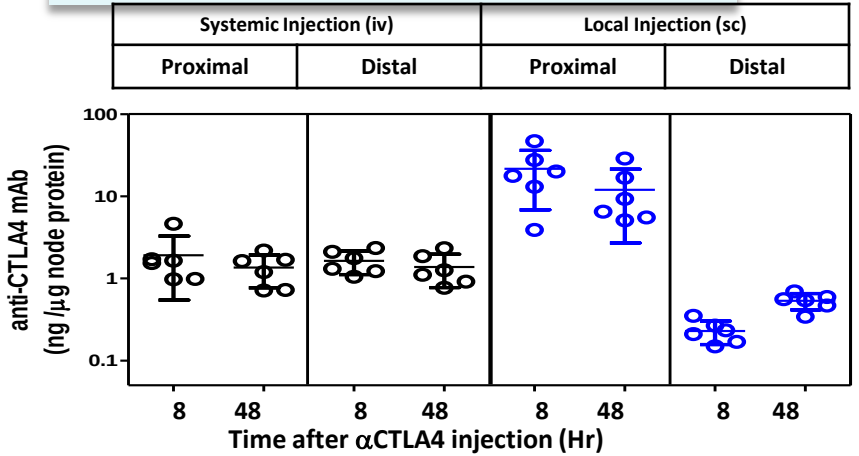


Vaccine schedule	AdV w0	DNA w8	DNA w17	AdV w0	DNA w8	DNA w17
αCTLA4 route			systemic			Local

^ 15d post vaccine IFNγ ELISPOT responses from individual animals
*Responses that exceed the upper limit of detection are outlined in red.
αCTLA4= 10 mg/kg

αCTLA4 in Lymph Nodes

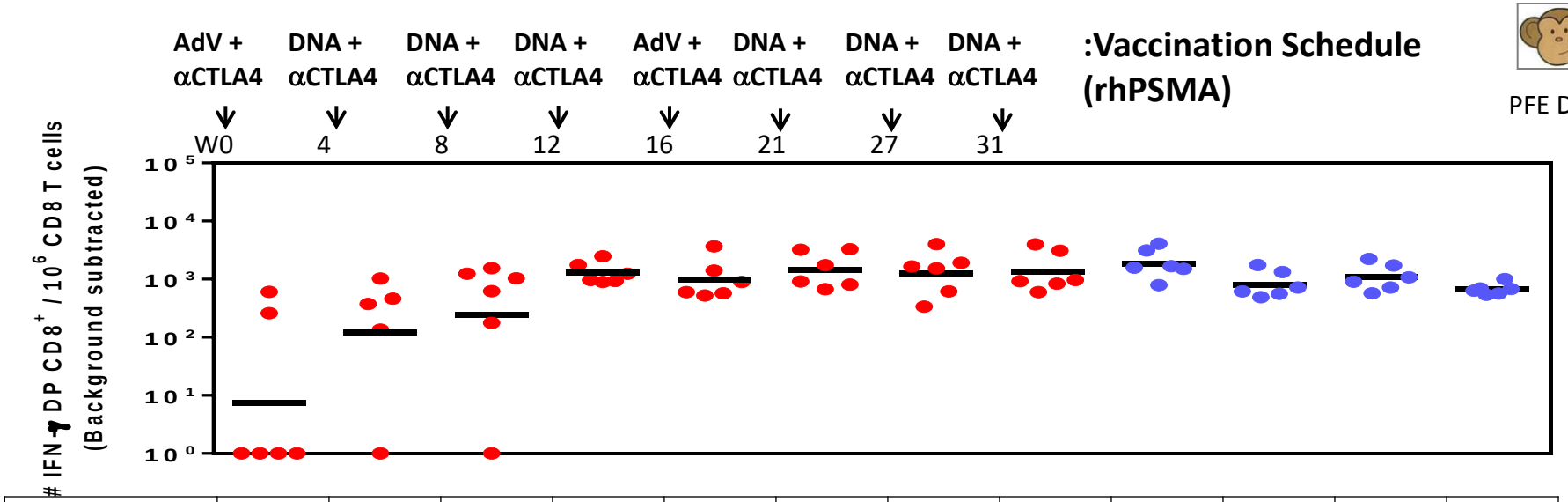
PFE Data



Proximal= Inguinal ; Distal= Axillary

- Significant improvement of IFNγ T-cell vaccine responses by local delivery of αCTLA4
- Lower clinical dose of mAb than systemic dose anticipated (10-15x fold)
- Robustly and safely achieve therapeutic levels of TAA T cells without expansion of non-specific T-cells

Expand: High levels of antigen (self) specific polyfunctional CD8 T cell titers maintained at 16wks post last vaccination



PFE Data

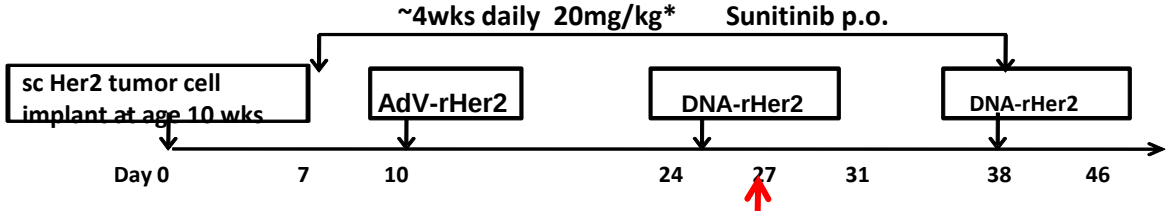
Readout, wks	2	6	10	14	18	23	29	33	35	39	43	47
Geomean	7	119	246	1276	969	1442	1260	1326	1850	809	1071	671

- Polyfunctional IFNγ (IL2+ or TNFα+) CD8 T cell titers are high but starting to decline at 16 wks post last vaccination

AdC68 : 2e11 VP; DNA= 5 mg; CTLA4= 33mg at prime and increased 50% (≤224 mg) to mitigate neutralization by ADA

Maintain: Synergistic anti-tumor efficacy by combination of Sutent and cancer vaccine

Schedule

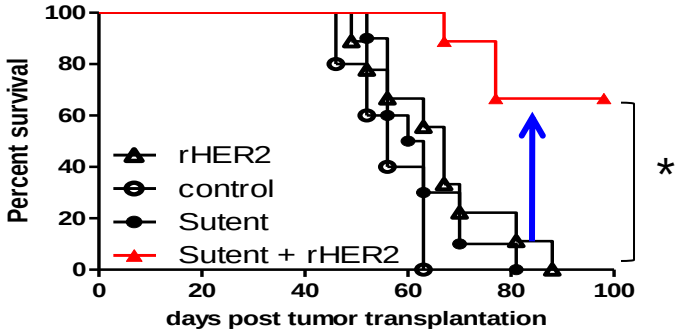


PFE Data

*low dose sunitinib

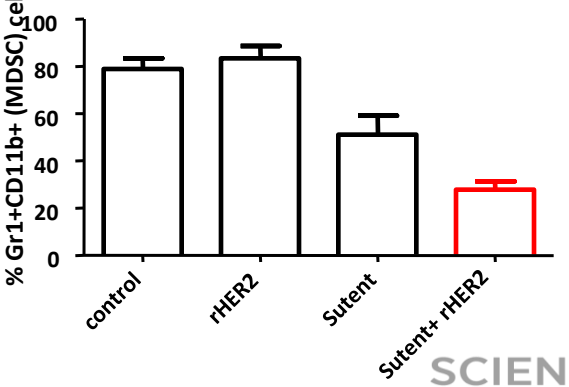
Model intentionally set-up that vaccine or Sutent as monotherapies provide limited therapeutic benefit

Synergistic effect



Mechanism of Action day 27

Reduction of circulating MDSCs



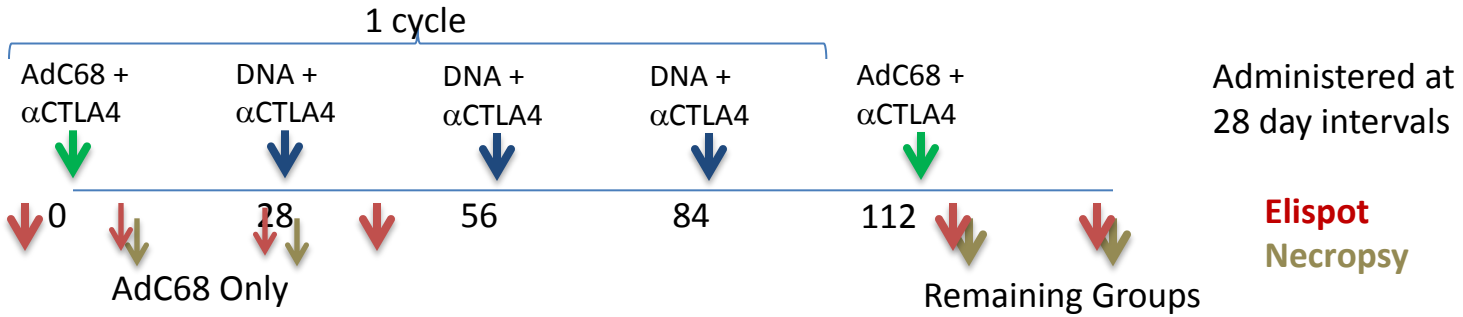
Considerations for the non-clinical development

- How to demonstrate efficacy
  - Many tumor models lack fully functioning immune system
  - Often limited homology with rodents
    - No NHP tumor models
    - Consider rodent version of vaccine for proof of concept
  - Regimen design based on immune responses
- Safety consideration with breaking tolerance of self antigen
  - Non-tumor expression
  - Preliminary safety studies using homologous antigen – AdC68 and DNA with rhesus sequence in rhesus monkeys

Nonclinical toxicology study - NHPs

- Tumor-specific antigens administered as adenovirus or plasmid DNA vector (with electroporation)
- αCTLA4 mAb – enhances expansion of vaccine-induced T cell responses
- Doses represent highest proposed clinical doses; Regimen mimicked proposed clinical regimen
- Potential to be combined with immune modulators (sutent/Anti-PD1/L1) clinically

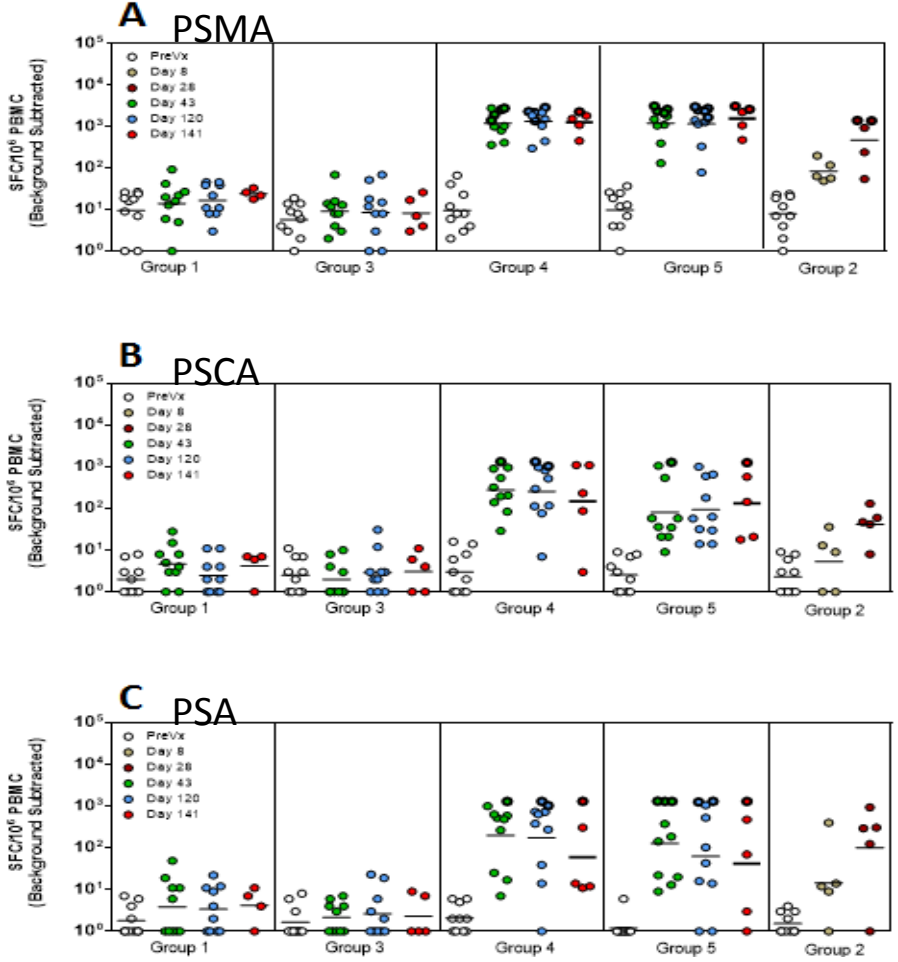
Regimen:



	Group	Necropsy	#/Necropsy
1	Control	D120 / D141	5 / 5
2	AdC68-alone – IM	D 8 / D29	5 / 5
3	αCTLA4-only (High) – SC	D120 / D141	5 / 5
4	AdC68-IM/DNA-EP + αCTLA4-SC (Low)	D120 / D141	5 / 5
5	AdC68-IM/DNA-EP + αCTLA4-SC (High)	D120 / D141	5 / 5

NonClinical toxicology study - Results

- Endpoints
  - Full in-life, clinical pathology and microscopic pathology evaluation
  - Immune Response –
    - Antigen specific T-cell titers
    - Ab response to the antigen
- Results
  - No evidence of systemic toxicity
    - Microscopic findings indicative of local irritation at injection site and immune stimulation at draining LN
    - No evidence of toxicity in any other organ
    - Robust T-cell response to all 3 antigens



Studies to evaluate AdC68 as a novel vector

- AdC68
  - Similarities to human adenovirus serotype 4 (subgroup E)
  - Cell entry mediated by CAR receptor (similar to Adv5)
  - Evaluated separately (single dose) in the repeat dose toxicity study
  - Performed a biodistribution study in a cotton rat
- Results
  - No evidence of systemic toxicity, microscopic findings indicative of local irritation at injection site and immune stimulation
  - Distribution consistent with other AdV, marked decrease in copy numbers between Day 2 and 31
  - Limited copy numbers still present at Day 90

Development of the Vaccine-Based Immunotherapy Regimen

- Followed a logical progression, demonstrating need for the various components and the dose regimen and routes
- Demonstrated robust and durable T cell response to the encoded antigens
- Nonclinical toxicity study dosed through a complete cycle
  - No evidence of systemic toxicity, effects only at the local injection site, or related to the induced immune response
  - Expected distribution and persistance for the novel adenovirus
- Potential to combine with additional immune modulators

Clinical Study

- Currently in Phase 1 - NCT02616185

- Patient populations:
  - nmCRPC, pre and post secondary hormones
  - post op, rising PSA
- Endpoints
  - Antigen specific CD4/8 T cells and pAb
  - PSA, CTCs, radiographic scans

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Sophie Bertelli

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Yolanda de Vicente
Kirsten Paulson
Jim Balun

American Association for Cancer Research

FINDING CURES TOGETHER℠

Session I Panel Discussion

CONSIDERATIONS IN THE PRECLINICAL EVALUATION OF I-O PRODUCTS

Moderator: Whitney Helms, PhD

Speakers:

Kristina Howard, DVM, PhD
Alan Korman, PhD
Rodney Prell, PhD
Timothy MacLachlan, PhD, DABT
David, Clarke, PhD, DABT

Panelists:

Danuta Herzyk, PhD
Janis Taube,MD, MSc
Allen Wensky, PhD

American Association for Cancer Research

FINDING CURES TOGETHER℠

Session IIa

Considerations for Dose-Finding

Moderator: Geoffrey Kim, MD

Speakers:

Eric Rubin, MD

David Feltquate, MD, PhD

Mark Ratain, MD

Hong Zhao, PhD

Approaches to Dose-Finding for Immuno-Oncology Agents and Combinations

Eric H. Rubin, M.D.

Merck Research Laboratories

KN-001: FIH Pembrolizumab Study

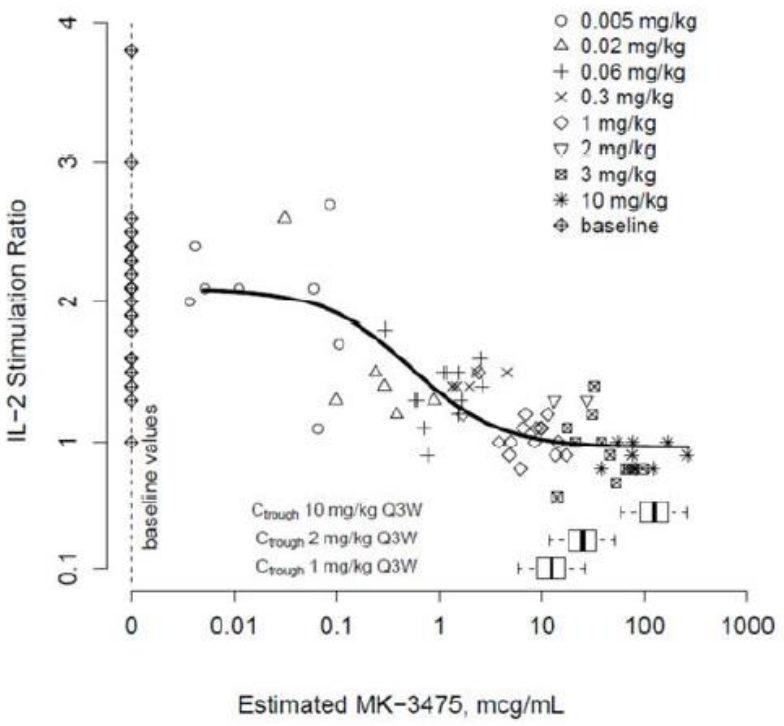
- Initial dose-finding approach included cohorts of 1 mg/kg, 2 mg/kg, and 10 mg/kg Q2W
  - No DLTs at any dose
  - Based on initial PK and 26 day half-life, dosing interval changed to Q3W
  - Intra-patient dose escalation, ex vivo IL2 assay, and translational PK-PD modeling used to select a RPTD of 2 mg/kg Q3W
  - Subsequent randomized cohorts of 2 mg/kg vs 10 mg/kg in melanoma and NSCLC confirmed similar efficacy for these doses
- Ultimately this study was expanded to 1235 patients and was used to support regulatory approvals in previously treated melanoma and NSCLC, as well as a PD-L1 IHC companion diagnostic assay

Intra-patient Dose Escalation Approach to Evaluate Pharmacodynamics

- Patients were escalated in 3 steps (at days 1, 8 and 22) from low (0.005 to 0.06 mg/kg) to high doses (2 and 10 mg/kg)
- Ex vivo IL-2 assay
  - Staphylococcal enterotoxin B induces lymphocyte IL-2 release
    - active PD-1 pathway blocks IL-2 release
    - pembrolizumab inhibition of PD-1 pathway releases this blockage
    - IL-2 stimulation is measured in presence or absence of exogenously added pembro at saturating levels
    - Stimulation ratio = $\frac{\text{[IL-2] SEB + 25µg/mL pembro}}{\text{[IL-2] SEB}}$

Ex-vivo IL2 assay

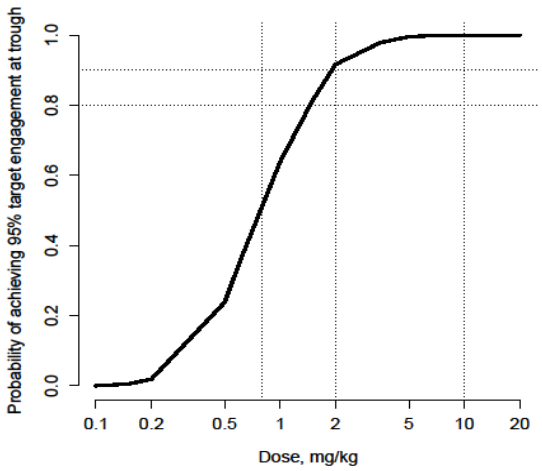
- 95-% saturation level reached at ~1 mg/kg Q3W
- Simulations showed > 95% of the effect of pembro on *ex vivo* IL-2 release achieved at C_{trough} reached with a dose regimen of ~1 mg/kg Q3W
- Therefore, 1 mg/kg Q3W is lower boundary for clinical efficacy

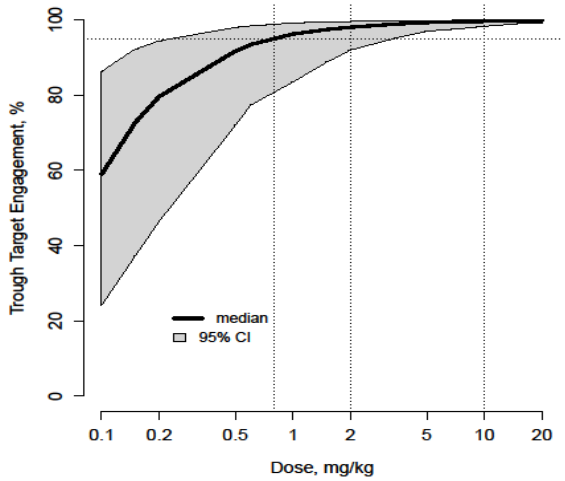


Keytruda Exposure is Associated with Complete Functional Blockade of PD-1 in the *ex vivo* IL-2 Release Assay at Doses of 1 mg/kg Q3W or Higher

Selection of Recommended Phase 2 Dose Based on Target Engagement

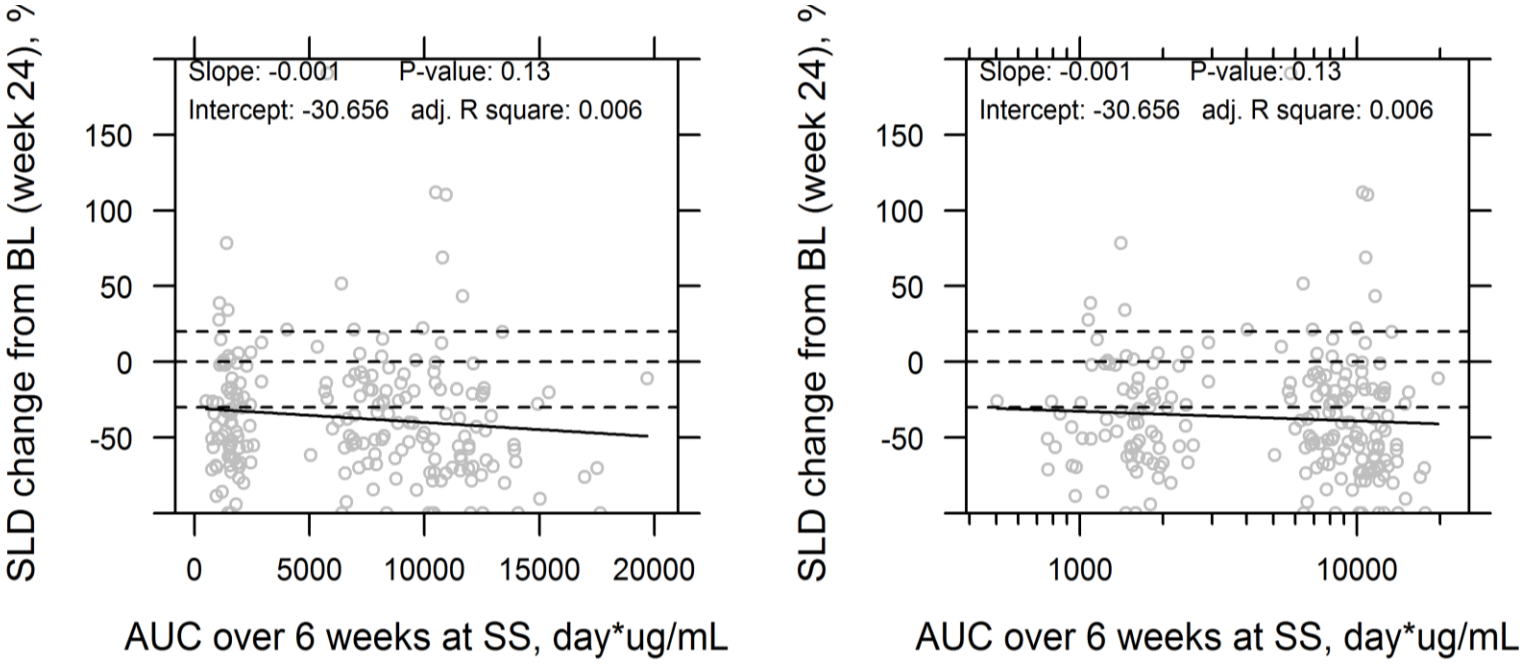
- Based on clinical PK and modeling, at 1 mg/kg Q3W, the probability of achieving full target engagement at trough is 64%
- ≥ 2 mg/kg the probability is 90% or higher
- Dose of 2 mg/kg falls likely near the plateau of the underlying exposure-response achieving near-maximal clinical efficacy
- Therefore proposed recommended phase 2 dose = 2 mg/kg Q3W





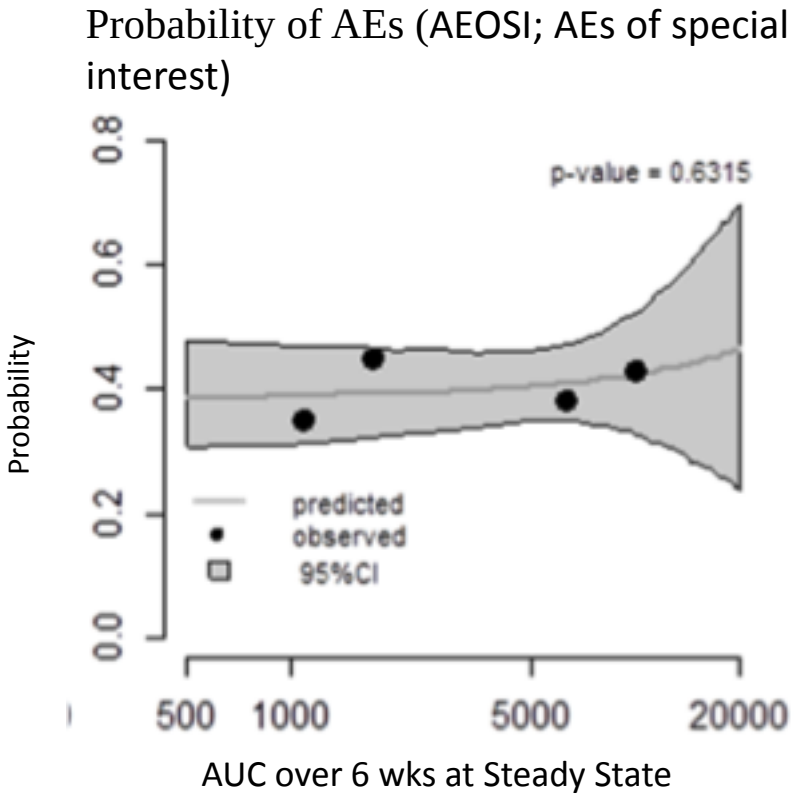
PK-PD Modeling of Tumor Size Change Guided RPTD Selection

- Exposure-**response** analysis: flat exposure-response between 2Q3, 10Q3, 10Q2
  - Key point: Tumor size change at week 24 was used for modeling as response instead of conventional RECIST criterion
    - **Change in Tumor size vs Exposure: no difference between 2Q3, 10Q3, 10Q2**



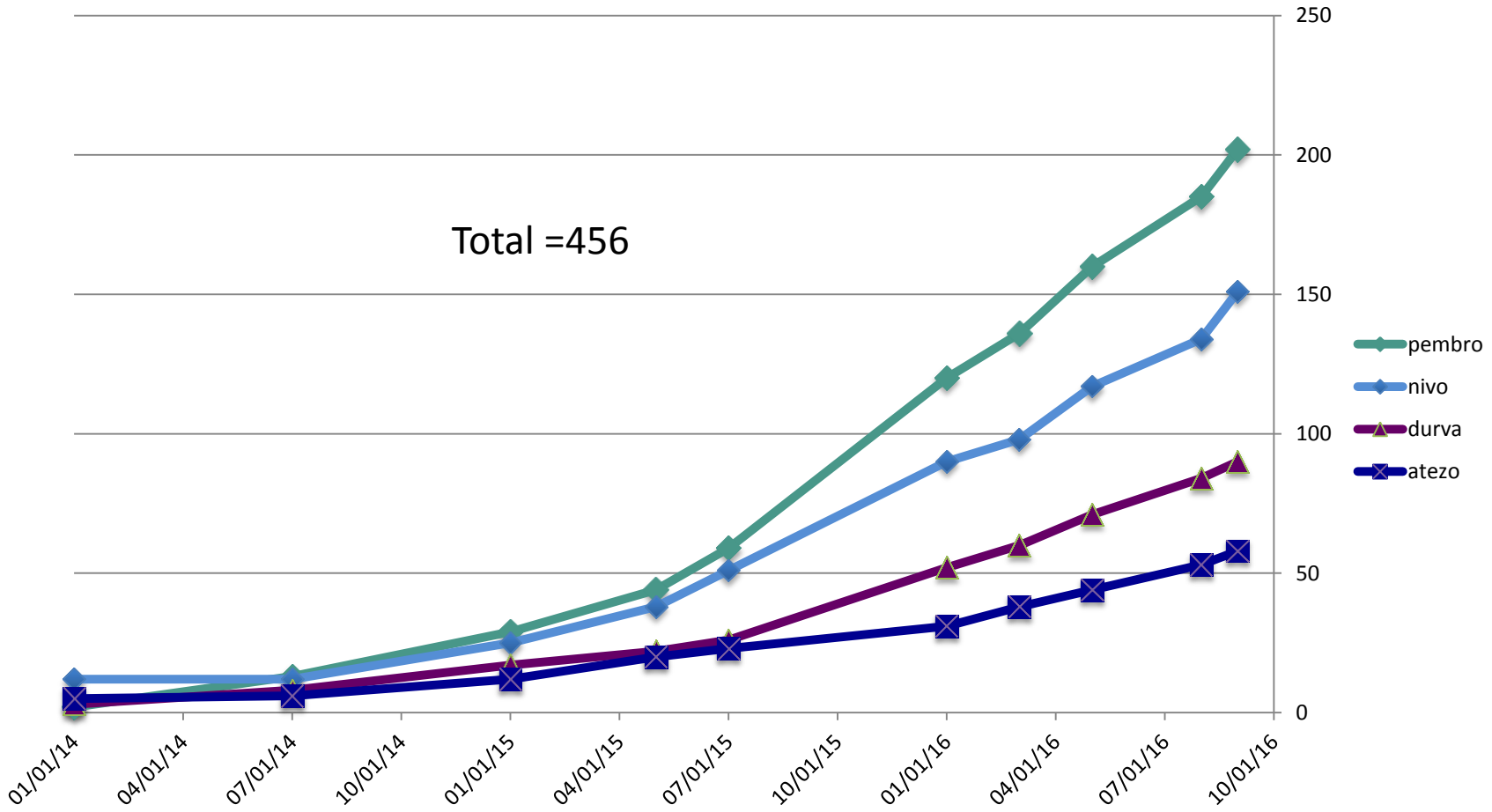
The black line shows the (log)linear regression of change from baseline vs. AUC.
Dashed reference lines indicate +20%, 0 and -30% change.

Flat Exposure-AE Relationship Supported Selection of RPTD of 2 mg/kg Q3W



Solid lines represent model estimated probability and shaded areas represent the 95% confidence intervals. P-value represents significance level of the exposure-response term when forced into the model.

Number of Combination Studies with anti-PD-1/PD-L1 Antibodies*



*Listed in clinicaltrials.gov as of 20-Sep-2016

Approach to Determination of Combination Doses

- Many pembrolizumab combination studies sponsored by a collaborating company
- Pembrolizumab dose fixed at 200 mg Q3W
- Multiple variations in approach to identification of recommended dose for the agent combined with pembrolizumab

Approach to Determination of Combination Doses

- Company A – small molecule A
  - No MTD identified yet with monotherapy administration of Drug A
  - 3+3 up and down DLT approach, “standard” DLT criteria
  - Starting dose of molecule A based on clinical safety and pharmacodynamic data, RPTD for monotherapy Drug A not yet identified
  - Maximum administered dose specified in case no MTD
    - Rationale for selection of maximum administered dose not provided
  - “The RP2D will be based on all available data including DLT data and an assessment of X-inducible genes and safety and tolerability data”
  - “The sponsor may also choose to investigate lower dose level(s) and enroll 3 or more additional patients prior to Phase 2 “
- This approach has the usual risk of selection of a non-tolerable RPTD based on the small numbers 3+3 approach

Approach to Determination of Combination Doses

- Company B – small molecule B
  - No MTD identified with monotherapy administration of Drug B
  - 6+6 up and down approach, “standard” DLT criteria
  - Starting dose of molecule B based on RPTD of monotherapy Drug B
    - One dose level -1 specified in case recommended monotherapy dose not tolerated in combination with pembro
    - No dose escalation

- Better than 3+3 but still risk in selecting a non-tolerable RPTD based on 6 patients

Approach to Determination of Combination Doses

- Company C – monoclonal antibody Drug C
  - No MTD identified yet with monotherapy administration of Drug C
  - “A Toxicity Probability Interval design with a target DLT rate of 30% will be applied to identify an MTD of Drug C in combination with pembrolizumab“
  - “standard” DLT criteria
  - Starting dose based on preclinical data and preceding monotherapy cohort data
  - Maximum administered dose specified in case no MTD
    - Rationale for selection of maximum administered dose not provided
  - “The totality of the data will be considered before deciding on the dose(s) to carry forward to Part B and the escalation schedule may be adjusted based on pharmacodynamics (PD), PK, and safety data emerging throughout the study. “

Table 1 Dose Escalation and Confirmation Rules Based on the Modified Toxicity Probability Interval Design

	Number of Subjects Treated at Current Dose											
Number of Toxicities	3	4	5	6	7	8	9	10	11	12	13	14
0	E	E	E	E	E	E	E	E	E	E	E	E
1	S	S	S	E	E	E	E	E	E	E	E	E
2	D	S	S	S	S	S	S	S	E	E	E	E
3	DU	DU	D	S	S	S	S	S	S	S	S	S
4		DU	DU	DU	D	D	S	S	S	S	S	S
5			DU	DU	DU	DU	DU	D	S	S	S	S
6				DU	DU	DU	DU	DU	DU	D	S	S
7					DU	DU	DU	DU	DU	DU	DU	D
8						DU	DU	DU	DU	DU	DU	DU
9							DU	DU	DU	DU	DU	DU
10								DU	DU	DU	DU	DU
11									DU	DU	DU	DU
12										DU	DU	DU
13											DU	DU
14												DU

E = Escalate to the next higher dose
S = Stay at the current dose
D = De-escalate to the next lower dose
DU = The current dose is unacceptably toxic
Target toxicity rate ↘ 30%
Flat non-informative prior Beta (1,1) is used as a prior and ε1=ε2=0.05{03TFYL}, {03RRDF}, {03FL3C}

Yuan Ji, Ping Liu, Yisheng Li and B. Nebiyou Bekele
A modified toxicity probability interval method for dose-finding trials
Clin Trials, October 2010

DLT Criteria in Combination Studies

- Combination of Drug A with an approved dose + an experimental agent Drug B
- What about severe toxicities that are attributed to Drug A?
  - "After all, every drug has side effects and sometimes they are severe"
  - Should these NOT be counted as DLTs?
    - Could affect dose-finding if a patient uniquely susceptible to severe toxicity from Drug A is enrolled by chance

DLT Criteria in Combination Studies

- What about severe toxicities that are attributed to Drug A?
  - On the other hand, other than an infusion reaction that occurs immediately after Drug A, can we really be sure that an observed DLT originates only from Drug A?
  - NO! Toxicities that are well-known for Drug A may still be enhanced (more frequent and/or severe) with co-administration of Drug B

DLT Criteria in Combination Studies

- What about severe toxicities that are attributed to Drug A?
  - This is another reason to avoid small numbers and the 3+3 approach
  - Adaptive approaches such as Toxicity Probability Interval can account for “chance” enrollment of susceptible patients and provide greater confidence that the identified RPTD for the combination is tolerable
    - Typical approach: dose-finding stops once 14 patients are enrolled at a given dose meeting or below the targeted calculated DLT probability rate
    - DLT probability rate can be adjusted based on expected rates for each drug administered as monotherapy, but is generally below 35%

Acknowledgements

- Dinesh DeAlwis
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- Peter Kang
- Andreas Lindauer
- Alise Reicin
- Stefan Rossenu
- Jeff Sachs
- Melissa Tice

Challenges in IO-IO Combination Dose Finding: A Case Study of Ipilimumab/Nivolumab in NSCLC

David Feltquate MD PhD

Head of Early Clinical Development, Oncology

Bristol-Myers Squibb

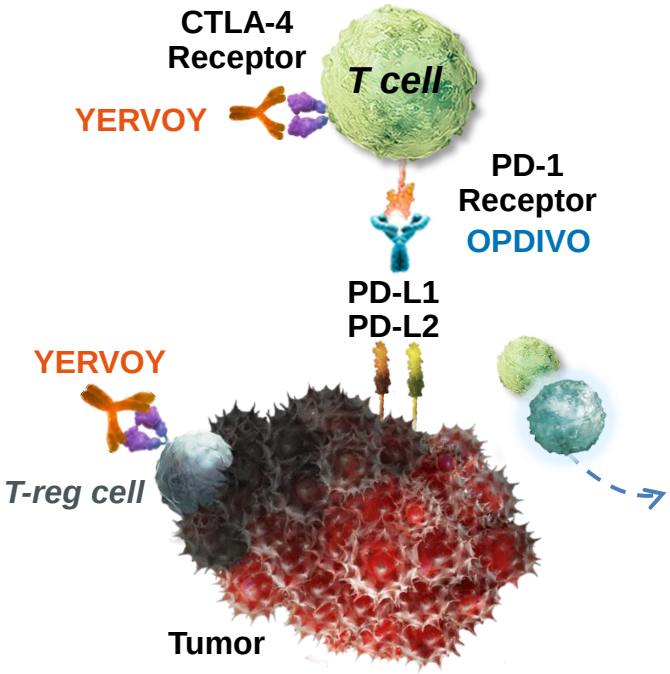
Scientific Rationale for Combining nivolumab (anti-PD-1) and ipilimumab (anti-CTLA4)

Complementary MoAs that work together to maximize anti-tumor immunologic responses

YERVOY™ (ipilimumab)
Injection for intravenous infusion

YERVOY blocks CTLA-4 to:

- **Help stimulate T-cell activation and proliferation**
- **Deplete T-reg cells and reverse immune-suppression**
  - **Efficacy of CTLA-4 Ab in mouse tumor models dependent on Fc receptor binding Ab isotype**



OPDIVO™ (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

OPDIVO blocks PD-1 to:

- **Help stimulate T-cell activation and proliferation**
- **Reactivate quiescent T-cells within the tumor**

Memory T cell

Some activated T cells become memory cells that can support subsequent immune responses by recognizing the tumor antigen

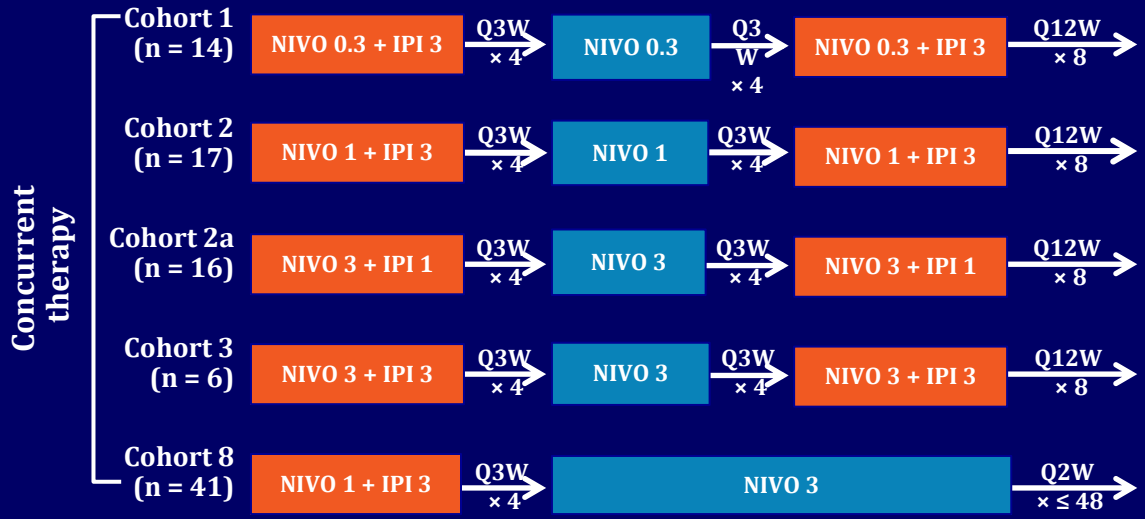
Selby, M. *et al*., Cancer Imm Res 2013

Background

- **Ipilimumab and Nivolumab (Ipi/Nivo) is the first IO-IO Combination approved to treat cancer (Melanoma)**

- **Safety and Efficacy first evaluated in a Phase 1b study (CA209-004)**
  - **Ipilimumab, 3mg/kg Q3wk x 4 (approved dose/schedule)**
    - **Ipi was core component of regimen**
    - **Various Nivo doses added to Ipi core**

Melanoma Phase 1b Study Design (CA209-004) to evaluate the Ipi/Nivo Combination



- Cohorts enrolled sequentially
- Cohort 2a added after Cohort 3
- Original cohorts used maintenance combination

All dose units are mg/kg.
IPI, ipilimumab; NIVO, nivolumab; Q2W, every 2 weeks; Q3W, every 3 weeks; Q12W, every 12 weeks.

1. Adapted from Kluger HM, et al. Presented at SMR 2014.
2. Wolchok JD, et al. *N Engl J Med* 2013;369:122-133.

Select Data for I3/N1 and I1/N3 cohorts from Phase 1b MEL Study

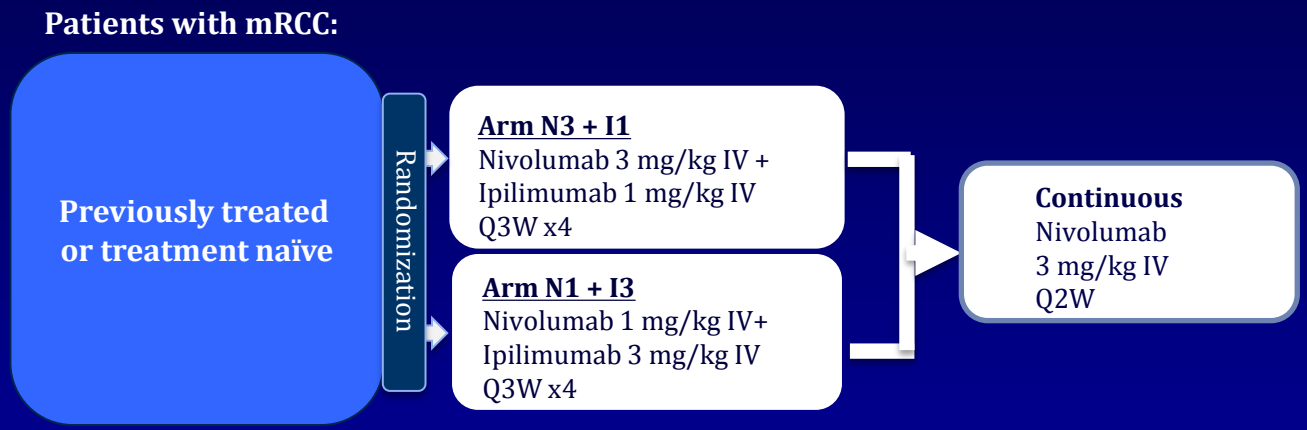
Patients with an event	I3/N1 (Cohort 2) (n=17)		I1/N3 (Cohort 2a) (n=16)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Treatment-related AEs, %	100	65	81	44
Treatment-related AEs leading to discontinuation, %	24		19	

	I3/N1 (Cohort 2) (n=17)	I1/N3 (Cohort 2a) (n=16)
ORR	47	50

- Small sample size in initial Phase 1b
- Most events leading to discontinuation occurred during the first 4 cycles
- ORR similar between subjects who remained on treatment or discontinued

1. Wolchok et al. *N Engl J Med* 2013;369:122-133.
2. Larkin et al. *N Engl J Med* 2015;373:23-34.
3. Kluger et al. Presented at SMR 2014. Adapted from Postow M, et al. Presented at Melanoma Bridge 2015.

CA209-016: RCC Phase Ib study design (N + I cohort)



Select Data for I3/N1 and I1/N3 cohorts from Phase 1b RCC Study

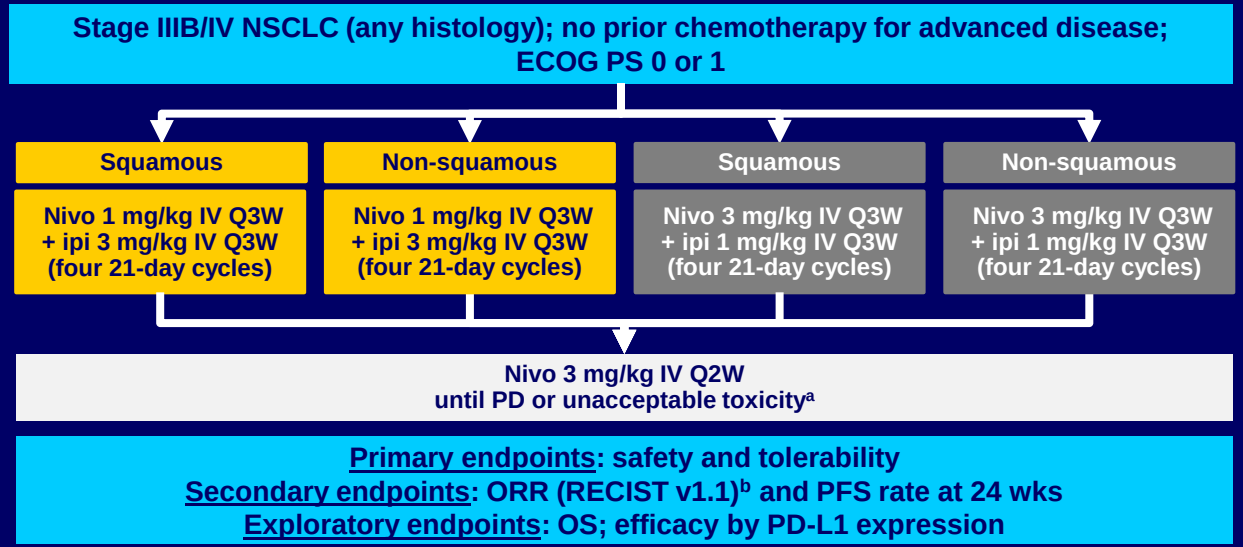
Patients with an event	I3/N1 (n=47)		I1/N3 (n=47)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Treatment-related AEs, %	94	64	83	34
Treatment-related AEs leading to discontinuation, %	26		9.5	

	I3/N1 (n=47)	I1/N3 (n=47)
ORR	40	38

- Randomized cohorts with larger sample size
- Ipi 1/Nivo 3 similar anti-tumor activity but safer profile than Ipi 3/Nivo 1

Hammers et al, 2014 ESMO.

Initial Ipi/Nivo cohorts for NSCLC evaluated in a Phase 1b Study (CA209-012)



Adapted from Antonia SN, et al. Presented at CMSTO_3272. .

Select Data for I/N and N cohorts from Phase 1b NSCLC Study

Patients with an event	I3/N1 (n=24)		I1/N3 (n=25)		N3 (n=52)		I1/N1 (n=31)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Treatment-related AEs, %	92	58	84	49	71	19	52	15
Treatment-related AEs leading to discontinuation (DC), %	38		32		10		6	

	I3/N1 (n=24)	I1/N3 (n=25)	N3 (n=52)	I1/N1 (n=31)
ORR, %	13	20	23	16

- Majority of AEs leading to DC occurred after 1 or 2 treatments
- Deaths (2) observed
- Lower anti-tumor activity than Nivo mono possibly due to early DC
- Additional cohort of Ipi 1/Nivo 1 added later

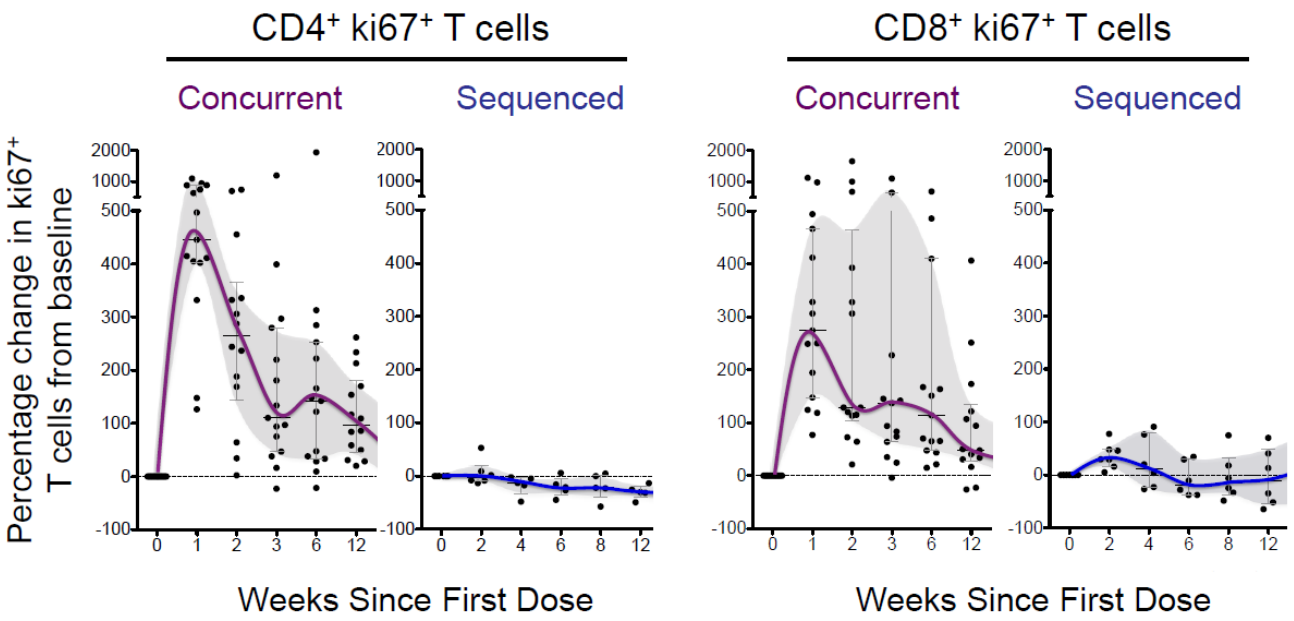
Adapted from Rizvi NA, et al. Presentation at WCLC. 2015.
Adapted from Hellmann MD, et al. Presentation at ASCO. 2016_3001.

It is feasible to give a starting dose of N3/I1

N1+I3 N=24	N3+I1 N=25
G3 diarrhea (C1)	G2 dyspnea/G3 pneumonitis (C1)
G2 pneumonitis/G3 rash (C1)	G3 ulcerative colitis/G5 TEN (C1)***
G3 AST/ALT (C1)	G3 Guillain-Barre (C1)
G3 diarrhea/G3 vomiting (C1)	G3 pleural effusion (C1)***
G3 polyarthritis, G3 pneumonitis (C1)	G2 pneumonitis (C2)
G2 tongue hyperkeratosis(C1)	G3 colitis (C2)
G4 AST/ALT (C2)	G3 gastroparesis/G3 colitis (C2)
G3 colitis/G5 resp failure (C2)	G2 infusion reaction (C3)***
G3 nephritis (C2)	G3 fatigue/G3 adrenal insufficiency (C7)
G3 hyperthyroid (C3)	
G3 pneumonia (C4)	

***Cases that may not be reflective of dose-related toxicities

Increased frequency of activated **(ki67⁺)** CD4⁺ and CD8⁺ T cells with concurrent nivolumab + ipilimumab

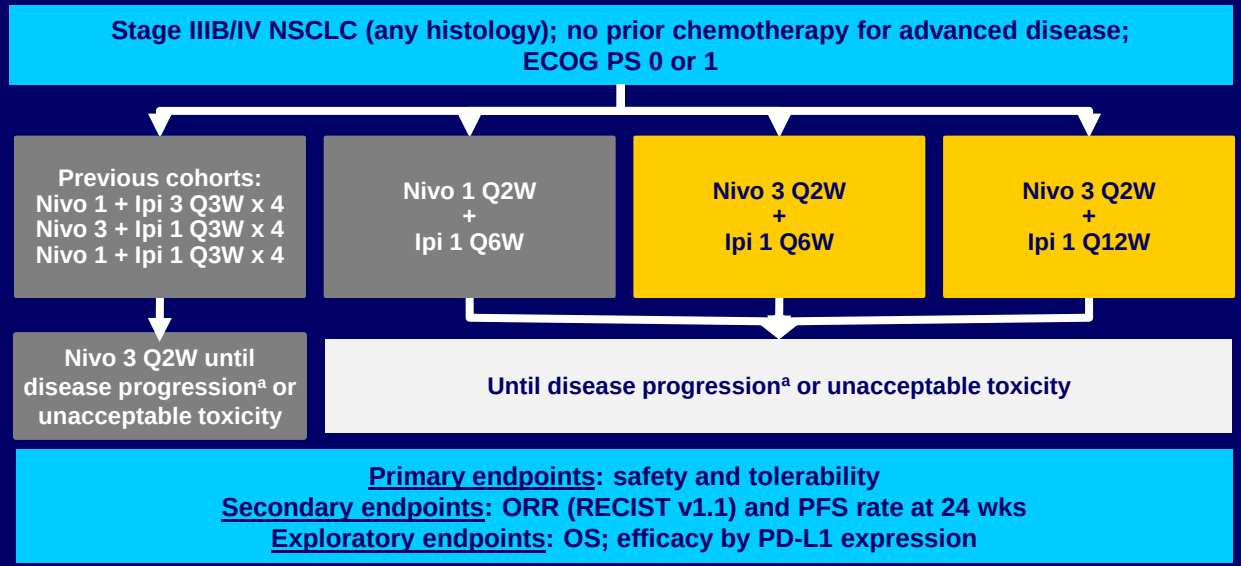


Key Insights Inform 2nd Generation NSCLC Ipi/Nivo Regimen

- Original schedule based on ipilimumab as the core compound (MEL)
- In NSCLC, nivo mono clearly active; no data on activity of Ipi mono
- Initial concurrent treatment important for pharmacodynamic effects
- Concurrent Nivo/Ipi feasible (1/1)
- Initial dose of Nivo 3/Ipi 1 is sufficiently tolerable to evaluate

- Question: How much and how often to give Ipi with Nivo 3 Q2wk?

2nd generation Ipi/Nivo cohorts evaluated in a Phase 1b Study (CA209-012)



Adapted from Hellmann MD, et al. Presentation at ASCO. 2016_3001.

2nd Generation Ipi/Nivo Combo is much more tolerable with greater clinical activity than the original schedule

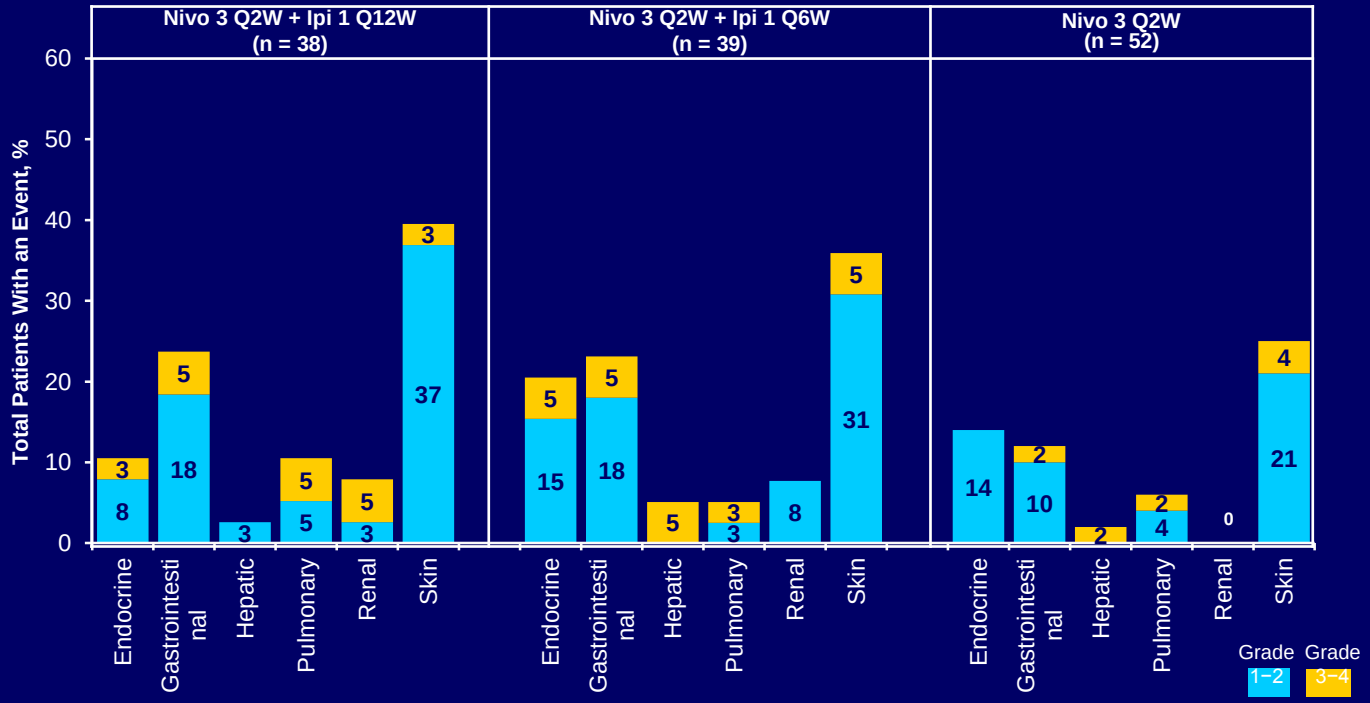
	Nivo 3 Q2W + Ipi 1 Q12W (n=38)		Nivo 3 Q2W + Ipi 1 Q6W (n=39)		Nivo 3 Q2W (n=52)	
	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4
Treatment-related AEs, %	82	37	72	33	71	19
Treatment-related AEs leading to discontinuation, %	11	5	13	8	10	10

	Nivo 3 Q2W + Ipi 1 Q12W (n=38)	Nivo 3 Q2W + Ipi 1 Q6W (n=39)	Nivo 3 Q2W (n=52)
All-Comers, ORR, %	47	39	23
PD-L1+ (>1%), ORR, %	57	57	28

2nd Generation Ipi/Nivo Combination has a safety profile very similar to Nivo monotherapy with an approximate doubling of ORR

[a]Antonia SJ, et al. Presentation at CMSTO 2014; Adapted from Hellmann MD, et al. Presentation at ASCO. 2016_3001

Treatment-related select AEs observed with 2nd Generation Ipi/Nivo and Nivo monotherapy



Adapted from Hellmann MD, et al. Presentation at ASCO. 2016_3001.

Summary and Conclusions

- Combinations of IO-IO agents such as Ipi/Nivo are feasible to administer
- Evaluation of different dose/schedules of IO-IO combinations benefit from larger sample sizes and randomized evaluation
- Systematic evaluation of dose/schedule for IO-IO combinations by tumor type may be needed as optimal/maximal effects may vary by tumor type

Randomized dose-escalation and dose-ranging trial designs

Mark J. Ratain, M.D.

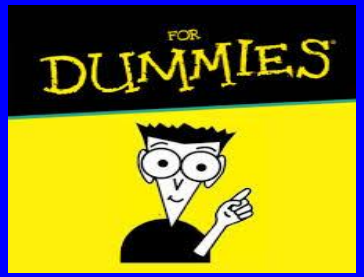
University of Chicago

FDA-AACR Immuno-Oncology Workshop

Washington, DC

October 13, 2016

Historical Oncology Clinical Development Plan (more is better)



- **Phase 1**
  - Escalate in cohorts of 3-6 patients to the highest dose that results in less than 33% incidence of dose-limiting toxicity
  - Treat 6 patients at final ("recommended phase II") dose
- **Phase 2**
  - Treat a sufficient number of patients at a single dose to either prove the drug is inactive or to estimate the Response Rate to the desired level of precision

Proposed Immuno-Oncology Combinations Clinical Development Plan

- **Phase 1**
  - **Randomized dose-escalation**
  - **A subset of each dose cohort is randomized to monotherapy**
- **Phase 2**
  - **Randomized dose-ranging (appropriate for monotherapy as well)**


PRECLINICAL
PHASE I
PHASE II
PHASE III
PHASE IV
• Lab & animal studies
• Safety study
• 20-80 people
• Safety study
• Identify side effects
• Measure effectiveness
• 100-300 people
• Measure effectiveness
• Monitor side effects
• 1,000-3,000 people
• Monitor long-term side effects

Traditional View of Design of Oncology Combinations (B + W)

1. Fix B, escalate W
2. Fix W, escalate B
3. Fix W/B ratio
4. Escalate B &W

1. Compare B+W (at “RPTD”) to B alone
2. Test activity of B+W in disease resistant to B

Compare B+W to TBD

Clin Cancer Res; 16(21) November 1, 2010

Cancer Therapy: Clinical

Clinical Cancer Research

Analysis of the Yield of Phase II Combination Therapy Trials in Medical Oncology

Michael L. Maitland[1,2,3], Christine Hudoba[4], Kelly L. Snider[5], and Mark J. Ratain[1,2,3]

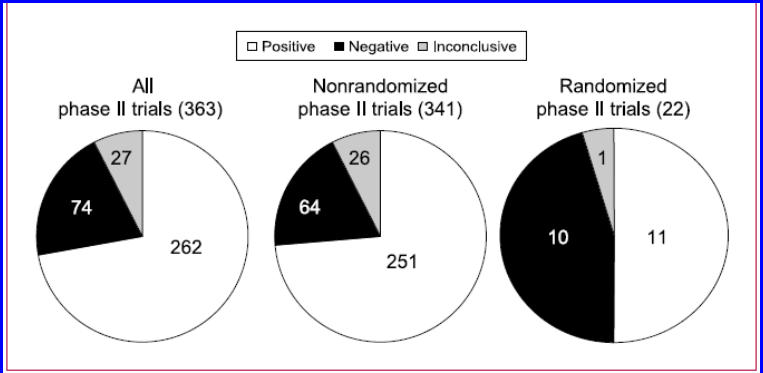


Table 1. Combination phase III trials leading to new acceptable standard of care treatment

First Author	Journal of publication	Year	Disease	Combination
Comella	Ann Oncol	2005	Colorectal	OXAFAFU
Eichhorst	Blood	2006	CLL	Fludarabine + cyclophosphamide
Falcone	J Clin Oncol	2007	Colorectal	FOLFOXIRI
Flinn	J Clin Oncol	2007	CLL	Fludarabine + cyclophosphamide
Habermann	J Clin Oncol	2006	Lymphoma (diffuse large B-cell)	R-CHOP
Hitt	J Clin Oncol	2005	Head and neck	Paclitaxel + cisplatin + fluorouracil
Long	J Clin Oncol	2005	Cervix	Cisplatin + topotecan
Petrylak	New Engl J Med	2004	Prostate	Docetaxel + estramustine
Rifkin	Cancer	2006	Multiple myeloma	Pegylated liposomal doxorubicin + vincristine + dexamethasone
Rothenberg	J Clin Oncol	2003	Colorectal	FOLFOX4

The positive predictive "contributory" value for Phase 2 trials published in 2001-2002 was 0.038, and enrolled >16,000 subjects.

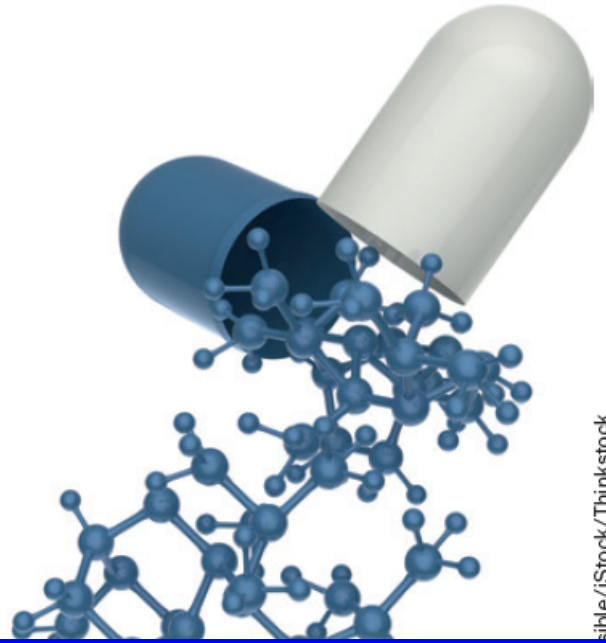
TARGETED THERAPIES

Redefining the primary objective of phase I oncology trials

Mark J. Ratain

Cytotoxic agents are conventionally dosed on the basis of the maximum tolerated dose defined in phase I trials. A study assessing adverse events in over 2,000 patients treated with molecularly targeted agents suggests a need to redefine criteria for dosing of molecularly targeted agents, which should be based on randomized, dose-ranging phase II trials.

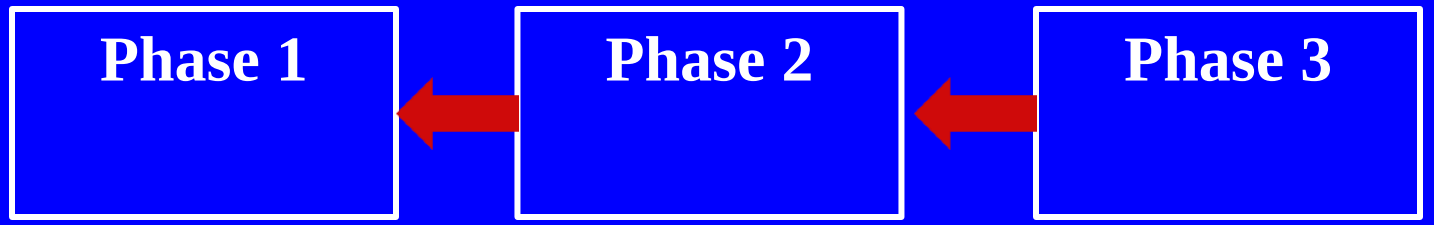
Ratain, M. J. *Nat. Rev. Clin. Oncol.* **11**, 503–504 (2014); published online 5 August 2014; corrected online 9 September 2014; doi:10.1038/nrclinonc.2014.135



ible/iStock/Thinkstock

Take home message: The optimal dose cannot be ascertained in Phase 1, and the objective should be to define a range of Phase 2 doses.

Proposed View of Design of Oncology Combinations (B + W)



Randomized dose-escalation trial to define arms for Phase 2

Randomized dose-ranging trial to define optimal experimental arm(s) appropriate for Phase 3

Define control arm for Phase 3 (if no plan for Phase 3, don't bother with Phase 1)

Nanda *et al. SpringerPlus* (2016) 5:947
DOI 10.1186/s40064-016-2457-1

SpringerPlus

RESEARCH Open Access

A randomized phase I trial of nanoparticle albumin-bound paclitaxel with or without mifepristone for advanced breast cancer

Rita Nanda[1,6*], Erica M. Stringer-Reasor[1], Poornima Saha[1], Masha Kocherginsky[2], Jean Gibson[1], Bernadette Libao[1], Philip C. Hoffman[1], Elias Obeid[1], Douglas E. Merkel[3], Galina Khramtsova[1], Maxwell Skor[1], Thomas Krausz[4], Ronald N. Cohen[5], Mark J. Ratain[1], Gini F. Fleming[1] and Suzanne D. Conzen[1]

The nab-paclitaxel starting dose was 100 mg/m^2 (dose level 1), with the plan to de-escalate to 80 mg/m^2 (dose level −1) and 60 mg/m^2 (dose level −2) for subsequent dose levels as needed.

A novel randomized phase I design was utilized, although the mifepristone dose escalation was to follow the traditional '3 + 3' design with up to four dose cohorts (300, 600, 900, and 1200 mg) to determine the maximally tolerated dose (MTD). The starting dose of mifepristone was 300 mg. Toxicity was assessed weekly during the first

Patients were randomized to nab-paclitaxel plus mifepristone versus nab-paclitaxel plus placebo treatment during the first cycle of each dose level in a 3:2 ratio (with a planned minimum of five patients per dose level).

Table 2 Dose limiting toxicities in patients randomized to mifepristone for cycle 1

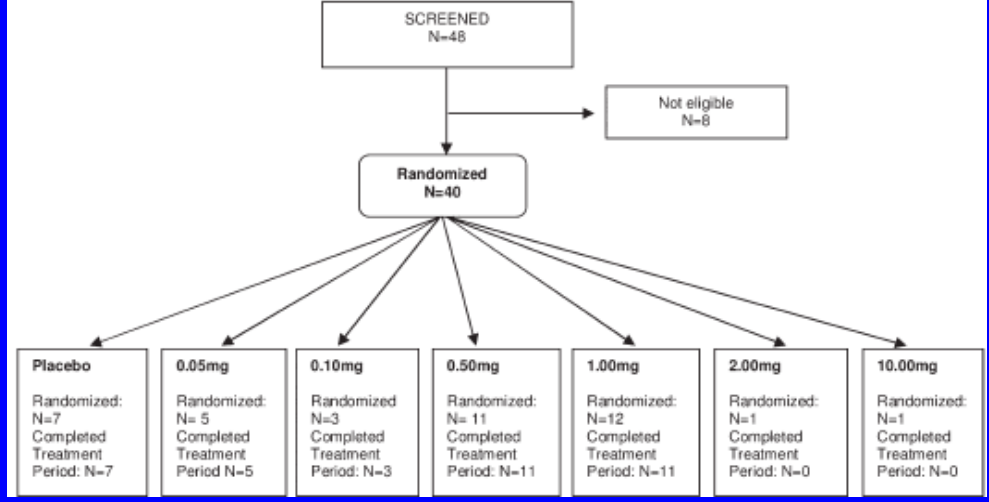
Patient	DLT	Type of DLT
Dose level 1: nab-paclitaxel 100 mg/m^2 + mifepristone 300 mg		
2-M	Y	Neutropenia
4-M	Y	Neutropenia
Dose Level −1: nab-paclitaxel 80 mg/m^2 + mifepristone 300 mg		
5-M	Y	Neutropenia
6-M	N	None
9-M	Y	Neutropenia

ORIGINAL ARTICLE

Inflamm Bowel Dis • Volume 16, Number 10, October 2010

Phase I, Double-blind, Randomized, Placebo-controlled, Dose-escalation Study of NI-0401 (a Fully Human Anti-CD3 Monoclonal Antibody) in Patients with Moderate to Severe Active Crohn's Disease

C. Janneke van der Woude, MD, Pieter Stokkers, MD,† Ad A. van Bodegraven, MD,‡ Gert Van Assche, MD,§ Zbigniew Hebzda, MD,¶ Leszek Paradowski, MD,‖ Geert D'Haens, MD,** Subrata Ghosh, MD,†† Brian Feagan, MD,‡‡ Paul Rutgeerts, MD,§ Gerard Dijkstra, MD,§§ Dirk J. de Jong, MD,¶¶ Bas Oldenburg, MD,*** Mahdi Farhan, MD,††† Tristan Richard, PhD,††† Yann Dean, PhD,††† and Daniel W. Hommes, MD,‡‡‡ on behalf of the Initiative on Crohn's and Colitis (ICC), The Netherlands*



Concomitant use of oral corticosteroids (≤20 g daily prednisone or equivalent) or 5-aminosalicylate (5-ASA) agents (at a stable dose for at least 2 weeks prior study day 1 [SD1] visit), thiopurines, or methotrexate (both at a stable dose for at least 8 weeks prior to SD1 visit) was permitted provided that treatment remained stable at least until week 6 of the study period. Patients who had received anti-

Conclusions: NI-0401 was tolerated at doses ≤1 mg with manageable side effects. NI-0401 induced a dose-dependent modulation of the TCR-CD3 complex. No significant improvement of CDAI was observed but 1 mg NI-0401 demonstrated an improvement in CDEIS.

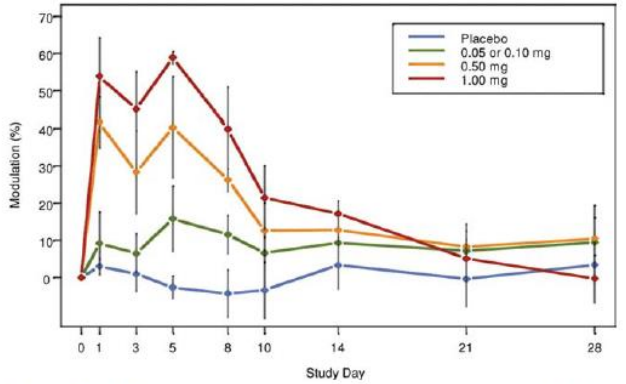


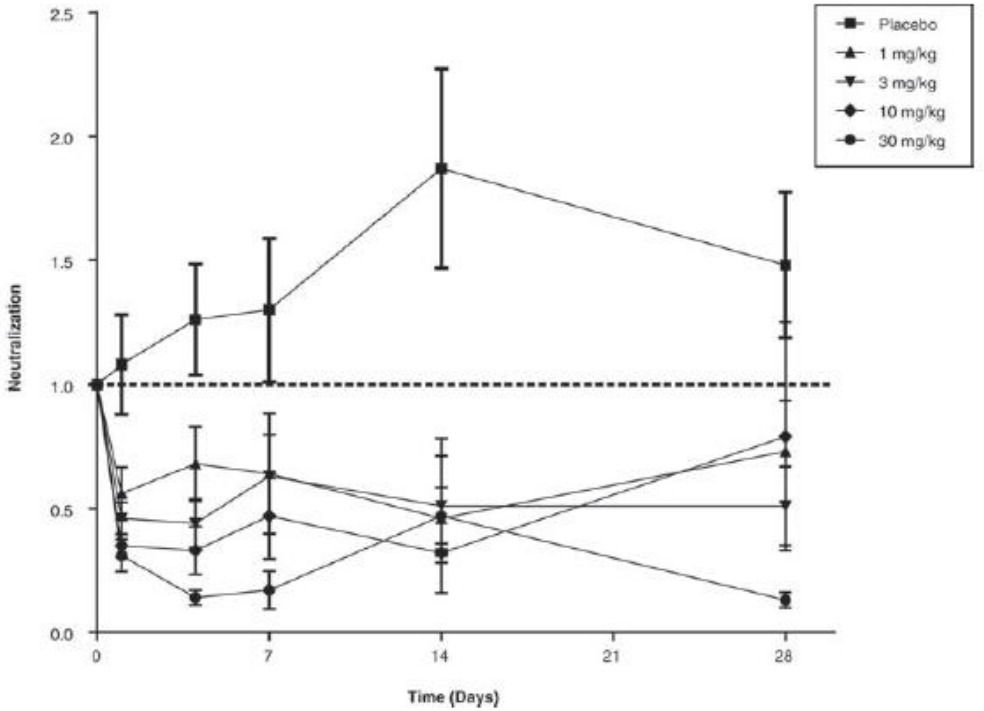
FIGURE 2. Mean CD3 modulation by dose group. Both the magnitude and duration of CD3 modulation increased in a dose-related manner (error bars on data points represent the standard error of the mean).

Safety profile and clinical activity of sifalimumab, a fully human anti-interferon α monoclonal antibody, in systemic lupus erythematosus: a phase I, multicentre, double-blind randomised study

Joan T Merrill,[1] Daniel J Wallace,[2] Michelle Petri,[3] Kyriakos A Kirou,[4] Yihong Yao,[5] Wendy I White,[5] Gabriel Robbie,[5] Robert Levin,[6] Seth M Berney,[7] Vishala Chindalore,[8] Nancy Olsen,[9,10] Laura Richman,[5] Chenxiong Le,[5] Bahija Jallal,[5] Barbara White[5,11]; for the Lupus Interferon Skin Activity (LISA) Study Investigators

Ann Rheum Dis 2011;**70**:1905–1913. doi:10.1136/ard.2010.144485

Adults aged ≥18 years who met four or more of the 11 revised American College of Rheumatology classification criteria for SLE[43 44] were randomised 2:1 to receive one intravenous dose of sifalimumab (0.3, 1, 3, 10 or 30 mg/kg) or placebo, in ascending dose, blinded cohorts. In each cohort, six to eight subjects received sifalimumab and three to four received placebo on study day 0.



ARD Online First, published on March 23, 2016 as 10.1136/annrheumdis-2015-208562

OPEN ACCESS

EXTENDED REPORT

Sifalimumab, an anti-interferon-α monoclonal antibody, in moderate to severe systemic lupus erythematosus: a randomised, double-blind, placebo-controlled study

Munther Khamashta,[1] Joan T Merrill,[2] Victoria P Werth,[3,4] Richard Furie,[5] Kenneth Kalunian,[6] Gabor G Illei,[7] Jorn Drappa,[7] Liangwei Wang,[8] Warren Greth,[7] on behalf of the CD1067 study investigators

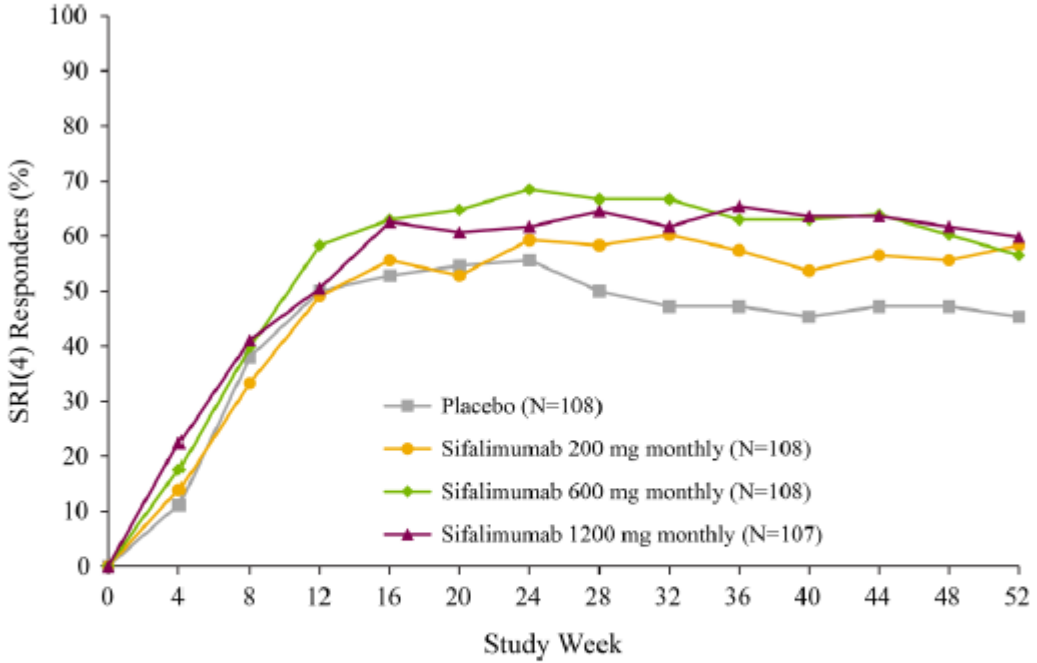


Figure 1 Primary end point: patients achieving a SRI(4) at week 52 (mITT population). Treatment was administered on days 1, 15 and 29, and then every 28 days thereafter. mITT, modified intention-to-treat; SRI(4), systemic lupus erythematosus responder index.

Double-Blind, Placebo-Controlled, Dose-Escalation Study to Evaluate the Pharmacologic Effect of CP-690,550 in Patients With Psoriasis

Mary G. Boy[1], Cunshan Wang[2], Bethanie E. Wilkinson[2], Vincent Fung-Sing Chow[2,4], Alan T. Clucas[2], James G. Krueger[3], Anderson S. Gaweco[2,4], Samuel H. Zwillich[2], Paul S. Changelian[2,4] and Gary Chan[2]

Journal of Investigative Dermatology(2009) **129,** 2299–2302; doi:10.1038/jid.2009.25; published online 19 February 2009

	Placebo (*n*=13)	5 mg b.i.d. (*n*=5)	10 mg b.i.d. (*n*=5)	20 mg b.i.d. (*n*=9)	30 mg b.i.d. (*n*=9)	60 mg q.d. (*n*=9)	50 mg b.i.d. (*n*=8)
LSM (%)	−11.5	−27.5	−47.0	−53.0	−51.7	−42.8	−71.8
SE (%)	6.9	11.1	11.1	8.2	8.2	8.2	8.7
P - value*	N/A	0.225	0.0088	0.0003	0.0005	0.0052	<0.0001

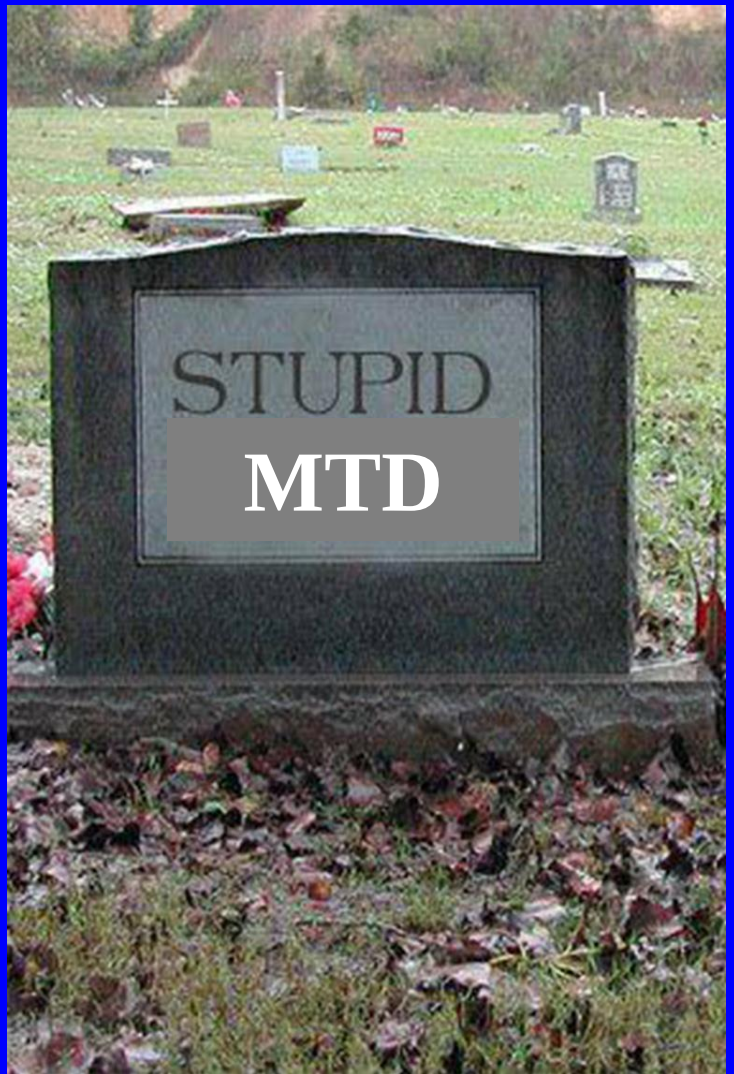
In this phase 1, randomized, dose escalation, double-blind study, each of the six CP-690,550 dosage cohorts (oral administration of 5, 10, 20, 30, and 50 mg two times-daily (b.i.d.) and 60 mg once-daily (q.d.)) had a concurrent, parallel, placebo control. Cohorts were conducted sequentially except for the 60 mg q.d. and 50 mg b.i.d. cohorts, which were conducted concurrently. Patients received treat-

Randomized dose-escalation studies

- Used frequently outside of oncology, either as monotherapy or in combination
- Ideally includes “0 dose” group, pooled across active dose levels
  - Can crossover to active dose after evaluation for primary toxicity or biomarker endpoint
- Aim to identify range of doses for randomized dose-ranging Phase 2

Randomized dose-ranging trials

- The norm outside of oncology!
- The concept of counting dose-limiting toxicities should constrain the dose, but not define the dose.


STUPID
MTD


STUPID
MTD
I'M WITH
STUPID
BSA

Randomized POC studies for combinations

- Need clear hypothesis that is testable and if disproven should lead to discontinuation of the combination's development
- Need biomarker assay that is suitable for serial sampling in patients (e.g., blood-based biomarkers)
- Design trial to compare effect of combination versus monotherapy for biomarker

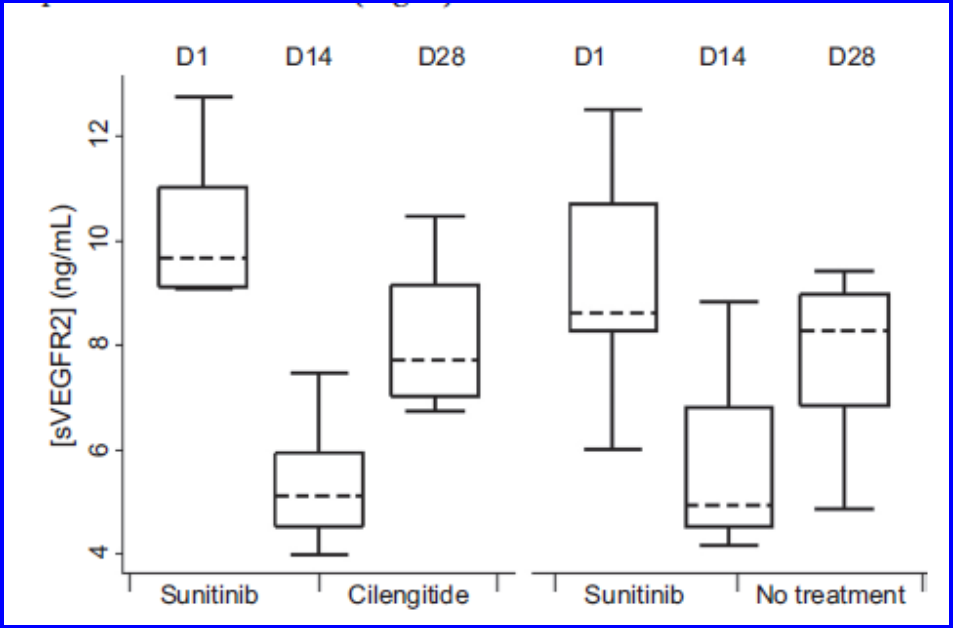
Clin Cancer Res; 21(22) November 15, 2015

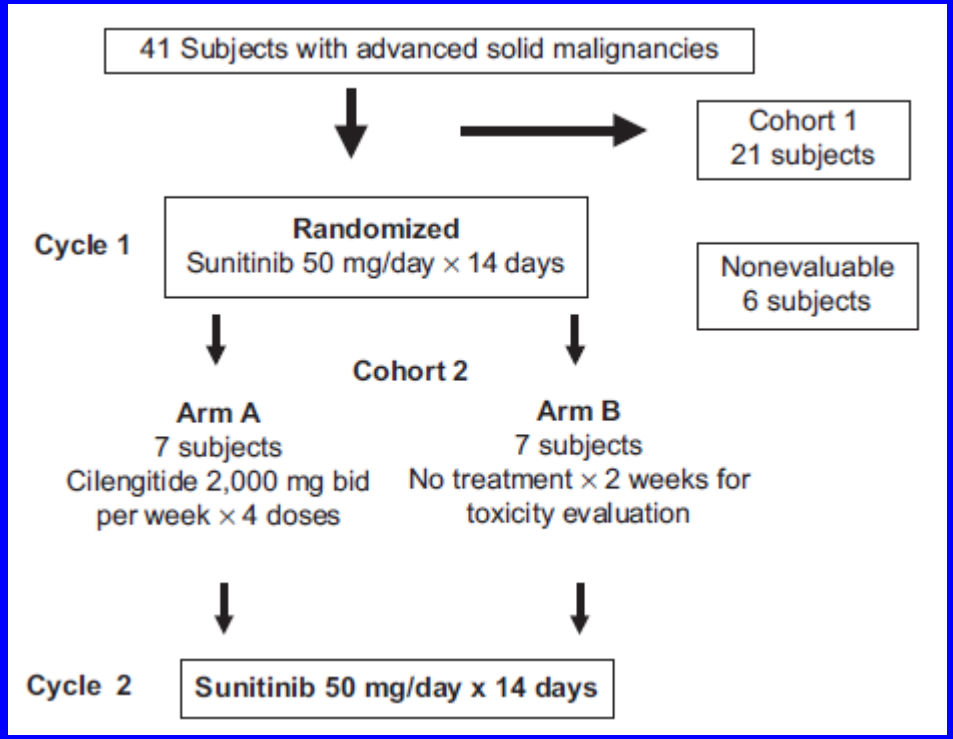
Personalized Medicine and Imaging

Clinical Cancer Research

Serum C-Telopeptide Collagen Crosslinks and Plasma Soluble VEGFR2 as Pharmacodynamic Biomarkers in a Trial of Sequentially Administered Sunitinib and Cilengitide

Peter H. O'Donnell[1,2,3], Sanja Karovic[1], Theodore G. Karrison[3,4], Linda Janisch[1], Matthew R. Levine[1], Pamela J. Harris[5], Blase N. Polite[1,3], Ezra E.W. Cohen[1,3], Gini F. Fleming[1,2,3], Mark J. Ratain[1,2,3], and Michael L. Maitland[1,2,3]





- **Serum biomarker was primary endpoint**
- **Clear evidence <u>against</u> POC**

In conclusion, combination development is difficult

- And particularly difficult for IO combinations
  - Significant efficacy without regression
  - Delay in manifestation of efficacy in many patients
- Randomized trials are necessary throughout the development of IO combinations

FDA-AACR Workshop:
Immuno-Oncology Drug Development

Session IIA: Considerations for dose-finding

Regulatory Considerations
- Optimizing Dose Selection for Immuno-Oncology Products

October 13, 2016

Hong Zhao, Ph.D.
Office of Clinical Pharmacology
OTS, CDER, FDA

DISCLAIMER

The views of this presentation represent my personal perspectives and do not reflect the official position of the United States Food and Drug Administration.

Presentation Outline

- Importance of dose selection
- Factors to be considered
- Recommendations
- Communication with FDA
- Take home messages

FDA's Mission

- FDA is responsible for **protecting the public health by assuring the safety, efficacy and security** of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.

- FDA is responsible for **advancing the public health by helping to speed innovations that make medicines more effective, safer, and more affordable** and by helping the public get the accurate, science-based information they need to use medicines and foods to maintain and improve their health.

Importance of Dose Selection

Innovative and Efficient Drug Development

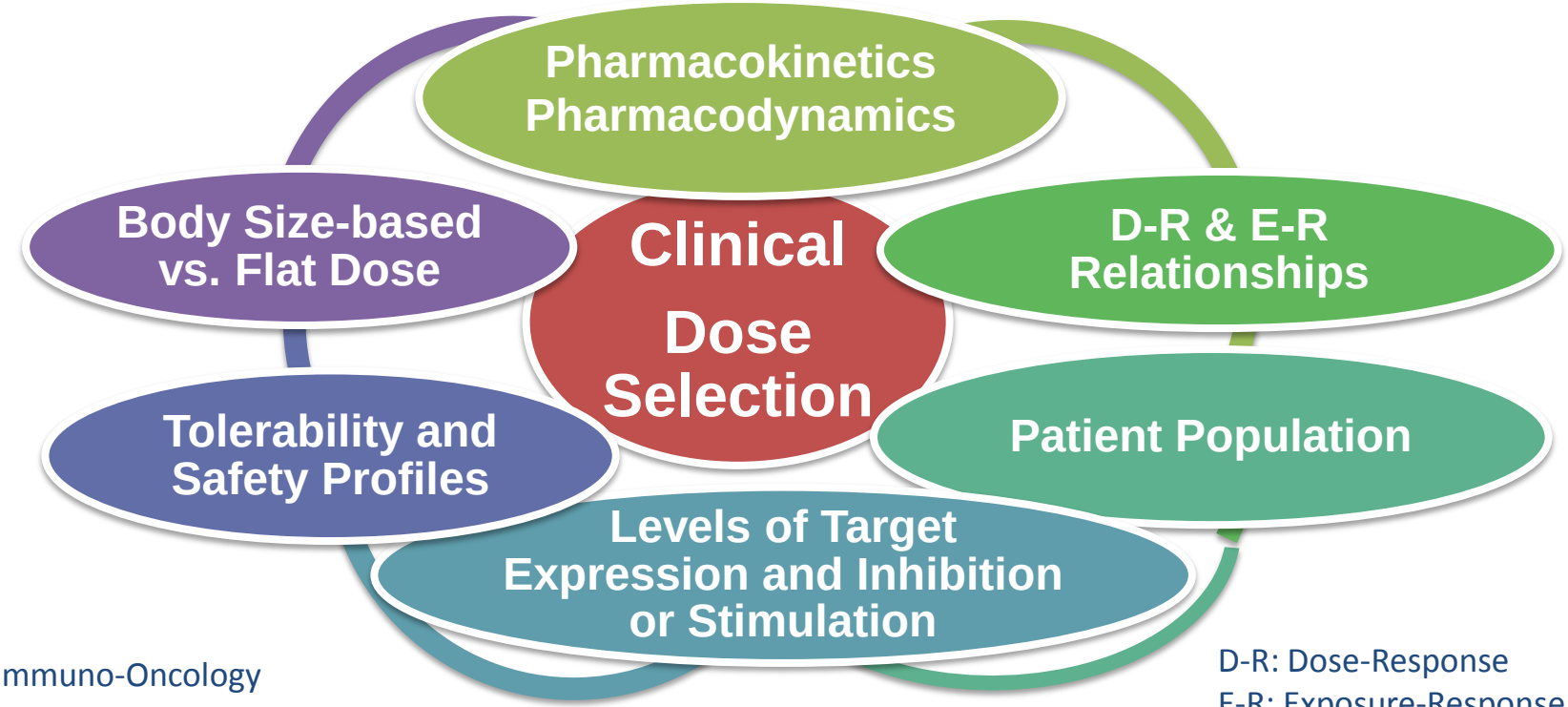
Give the right drug
at the right dose
to the right patient
at the right time

Maximize efficacy
Minimize toxicity

Increase the success
rate of drug development

Slide adapted from Dr. Ruby Leong's talk at 2014 AAPS/NBC

Factors to be Considered in Clinical Dose Selection for I-O Products



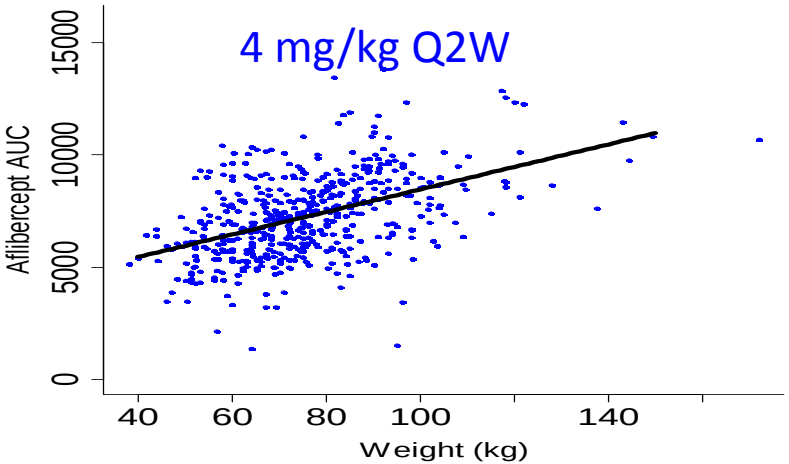
I-O: Immuno-Oncology

D-R: Dose-Response
E-R: Exposure-Response

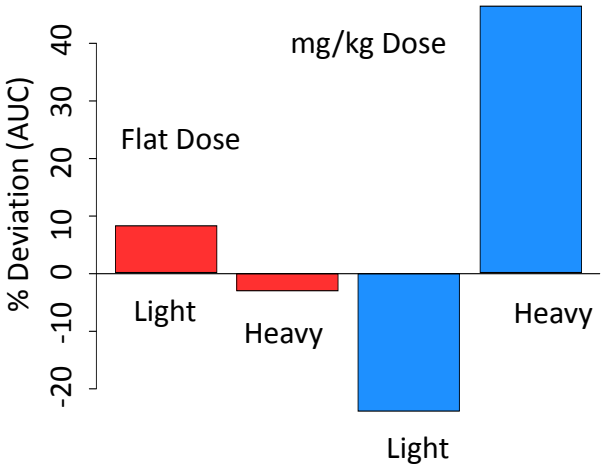
- **Body Size-based Dose or Flat Dose?**
  - **Exposure-Response Considerations**

Body Size-based vs Flat Dose

Aflibercept: Lighter patients had lower exposure



Drug Clearance is not related to BW



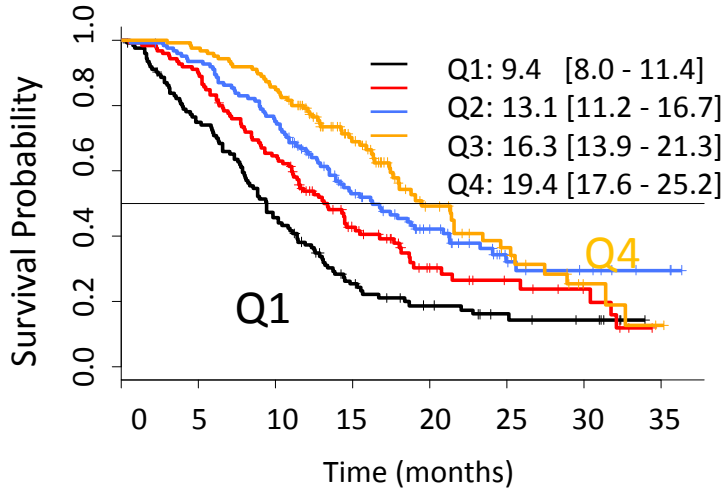
Deviation of exposure from median BW

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/125418Orig1s000ClinPharmR.pdf

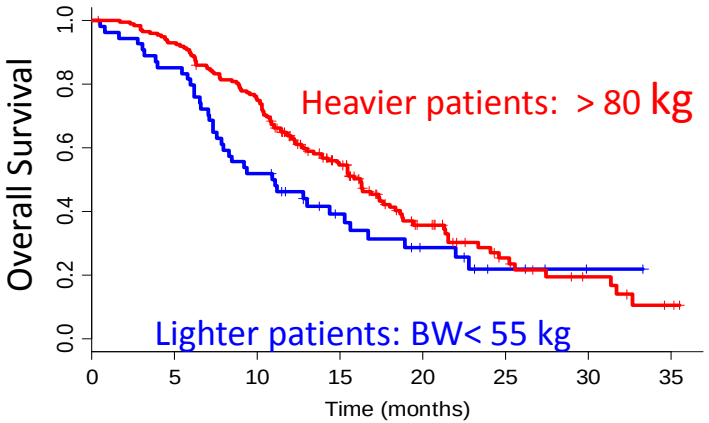
Possibility of Improving Survival Benefit in Patients with Lighter Body Weight

(Aflibercept)

E-R relationship for Overall Survival (OS)



Lighter patients had less OS benefit



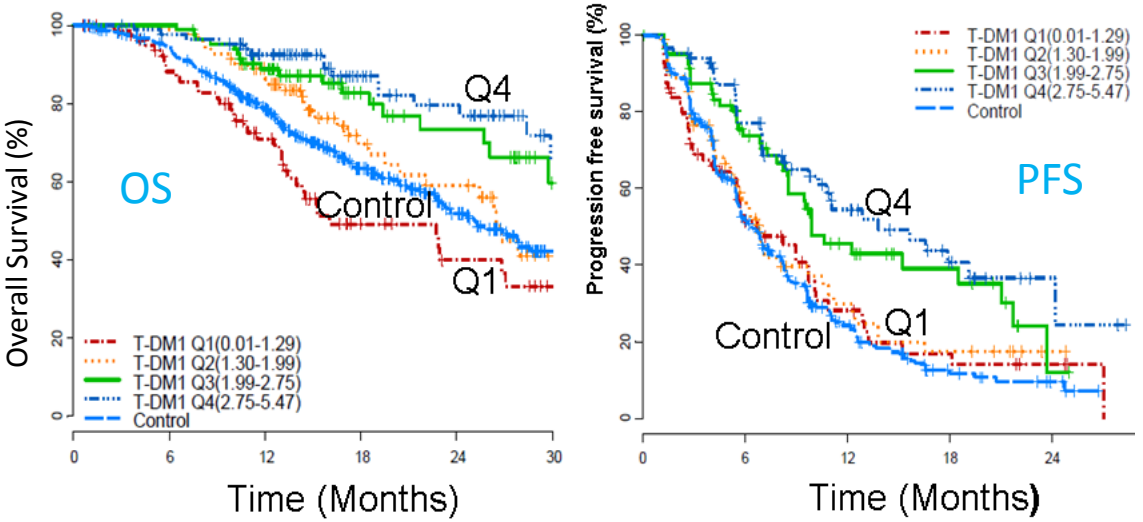
MTD was not reached.

How much of this difference is due to poor dosing?

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/125418Orig1s000ClinPharmR.pdf

Increase Efficacy with Increasing Exposure

(T-DM1: 3.6 mg/kg Q3W, MTD)



Exposure metric: Day 21 trough concentration

Control: Lapatinib + Capecitabine

PFS: Progression-free survival

Wang J. et al., CPT Jan. 2014 Epub
http://www.nature.com/clpt/journal/vaop/naam/abs/clpt201424a.html

Possibility of Improving Survival Benefit in Patients with Low Exposure (T-DM1)

Multivariate Cox-Regression Analysis after adjusting for covariates:
ECOG, number of disease sites, prior anthracycline use, prior trastuzumab, visceral disease, measurable disease, HER2 shed antigen and tumor burden.

Comparison	HR (95% CI)*	P-value
TDM-1 Q1 vs. Control	0.97 (0.65, 1.46)	0.89
TDM-1 Q2 vs. Control	0.68 (0.44, 1.05)	0.080
TDM-1 Q3 vs. Control	0.40 (0.22, 0.72)	0.0024
TDM-1 Q4 vs. Control	0.35 (0.20, 0.63)	0.0005

Patients with low exposure (Q1) had no survival benefit compared to control.
E-R relationship for safety was not identified at 3.6 mg/kg Q3W dosing regimen.

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/125427Orig1s000Approv.pdf

ECOG: Eastern Cooperative Oncology Group

- **One Dosing Regimen Fits All Cancer Types?**
  - **Exposure-Response Considerations**

Effect of Disease on Exposure

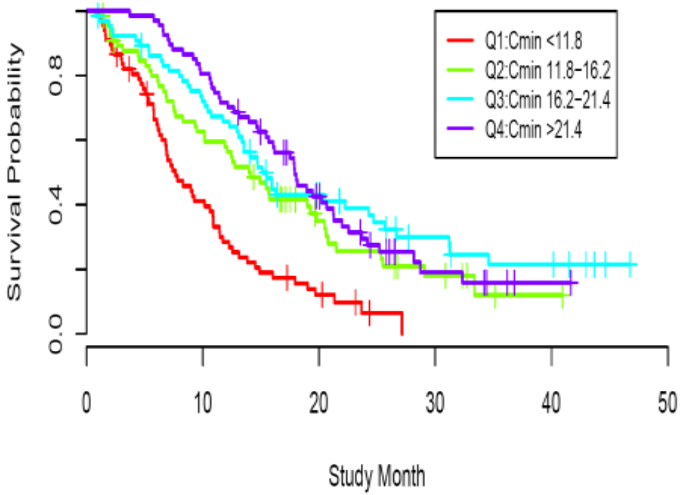
Trastuzumab: Advanced Gastric Cancer (AGC) vs. Breast Cancer (BC)
Same dose regimen (8 mg/kg initial and 6 mg/kg Q3W)

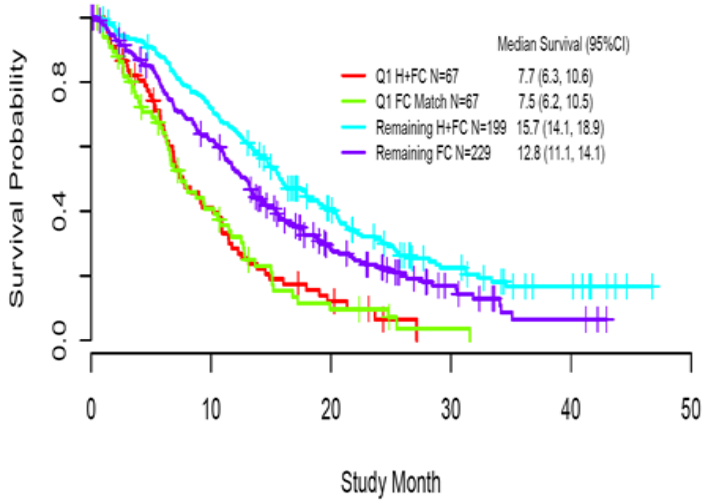
Population PK analysis

- Higher clearance and 24-63% lower Cmin at steady-state in AGC than in BC
- Covariates: Gender and race do not lead to clinically relevant changes in AUC, Cmax or Cmin at steady-state, body weight effect could not be excluded

*Jun Yang: J Clin Pharmacol published online 1 May 2012*http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/103792s5250ltr.pdf

Possibility of Improving Survival Benefit in Patients with Low Exposure





Combination of E-R and case-control analysis identified the subgroup who is not benefiting from trastuzumab treatment under the current regimen.

Jun Yang: J Clin Pharmacol published online 1 May 2012
http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/103792s5250ltr.pdf

Effect of Disease on Exposure

Ramucirumab:

- Gastric cancer (8 mg/kg Q2W alone or in combination with weekly paclitaxel)
- Colorectal cancer (8 mg/kg Q2W prior to FOLFIRI)
- NSCLC (10 mg/kg + Docetaxel Q3W)

- Gastric cancer patients with lower exposure is not benefiting from ramucirumab under the current dosing regimen

Ramucirumab Supplement BLA Approval Letter:
http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2014/125477Orig1s002ltr.pdf

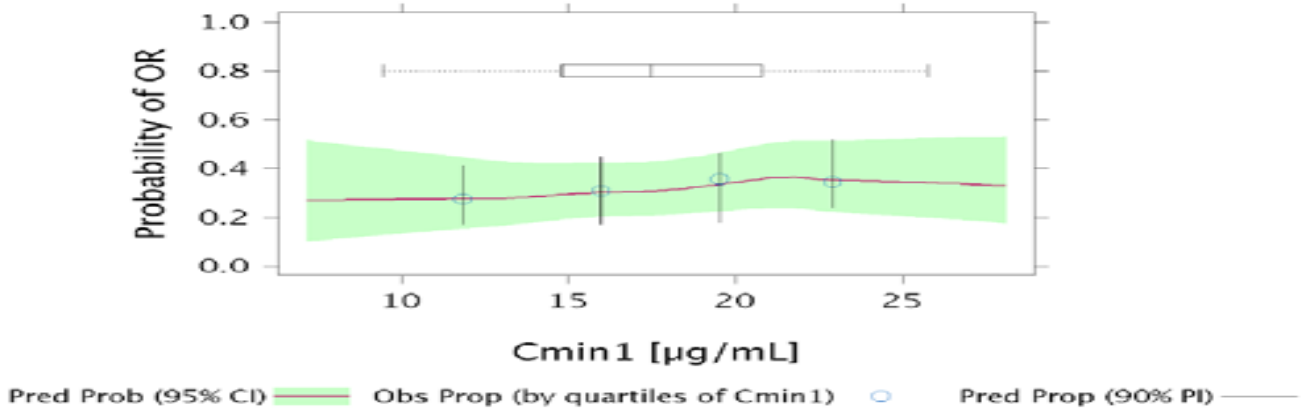
Optimizing Dose Selection

Dose-Response & Exposure-Response

Nivolumab: Flat D-R at 0.1-10 mg/kg, Q2W

Dose (mg/kg)	0.1	0.3	1	3	10	0verall
Melanoma ORR	35.3 (14.2, 61.7) N=17	27.8 (9.7, 53.5) N=18	31.4 (16.9, 49.3) N=35	41.2 (18.4, 67.1) N=17	20.0 (5.7, 43.7) N=20	30.8 (22.3, 40.5) N=107

Flat E-R for ORR at exposures from 3 mg/kg Q2W dose



http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/125554Orig1s000ClinPharmR.pdf

- **Dose Finding for Immuno-Oncology (I-O) Combination Therapies**

Considerations in I-O Combination

- Using combinations of drugs directed at multiple therapeutic targets to
  - improve treatment response
  - minimize development of resistance or
  - minimize adverse events
- Plausible biologic rationale for combination use
- Nonclinical models demonstrating improved clinical outcome (additive or synergistic)
- Optimal with known effective dose for each monotherapy
- Optimal with known D-R & E-R relationships for efficacy of each product
- Optimal with known D-R & E-R relationships for safety of each product
- Safety or efficacy profiles may be tumor-specific
- Safety or efficacy profiles may be different for different dose combinations

FDA Guidance for Industry: Co-development of two or more new investigational drugs for use in combination
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM236669.pdf

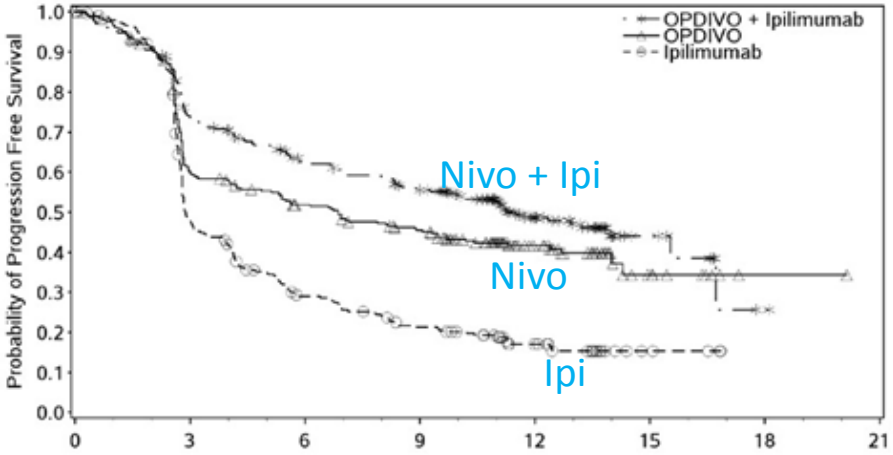
Dose Finding for I-O Combination

- Nivolumab + Ipilimumab combination
  - both are active in metastatic melanoma
  - PD-1 and CTLA-4 are non-redundant immune checkpoints in T-cell differentiation and function
  - Anti-tumor synergy demonstrated in animal models
  - Known D-R & E-R relationships for efficacy of each product
  - Known D-R & E-R relationships for safety of each product
- Nivolumab + Ipilimumab dose finding
  - Nivo 0.3 mg/kg + Ipi 1 mg/kg
  - Nivo 1 mg/kg + Ipi 3 mg/kg
  - Nivo 3 mg/kg + Ipi 1 mg/kg
  - Nivo 3 mg/kg + Ipi 3 mg/kg

Longer PFS in the Nivolumab+Ipilimumab Arm

Progression-free Survival: Unrespectable or Metastatic Melanoma

Dosing Regimen
Nivo + Ipi:
Nivo 1 mg/kg
+ Ipi 3mg/kg
Q3W for 4 doses
followed by
Nivo 3 mg/kg Q2W



Number of Subjects at Risk							
OPDIVO + Ipilimumab							
314	219	173	151	65	11	1	0
OPDIVO							
316	177	147	124	50	9	1	0
Ipilimumab							
315	137	77	54	24	4	0	0

Dosing regimen
Nivo:
3 mg/kg Q2W
Ipi:
3 mg/kg Q3W for 4 doses followed by placebo Q2W

Dose Finding for I-O Combination

- Concurrent administration or sequential dosing?
- Same E-R relationship for efficacy/safety in combination as in monotherapy or sensitizing/potentiating?
- Same E-R relationship for efficacy/safety across tumor types or tumor specific?
- PK/PD modeling and simulation to guide dose selection and optimize combination treatment

Regulatory Recommendations

- Identify the optimal systemic exposures of the immuno-oncology products in the **general patient population**
- Assess the effects of the following factors on systemic exposures of the immuno-oncology products
  - ✓intrinsic factors (e.g. age, sex, body weight, organ impairment, disease, immunogenicity) and
  - ✓extrinsic factors (e.g., concomitant drugs) on systemic exposure of the I-O products

Regulatory Recommendations

- Before commencing trials to support registration, optimize the dosing regimen
  - Conduct **adequate** dose exploration
  - Investigate **more than one dose level/dosing schedule** for activity and safety
  - Collect sparse PK data in clinical trials
  - Explore relationship between body size and clearance of the I-O products
  - Explore D-R and E-R relationships for activity/efficacy and safety

- After completing registration trials
  - Conduct analyses to confirm E-R relationship supporting the recommended dose/dosing regimen

Communication with FDA

- Shared public health goal of early availability of safe, effective, and high-quality drugs to the American public
- Provides valuable scientific and regulatory advice, resulting in more efficient and robust development programs
- Helps sponsors define adequate evidence of effectiveness, safety, and product quality
- Enhanced communication, enhancing regulatory science and expediting drug development
- FDA draft guidance (2015): Best Practices for Communication between FDA and IND Sponsors During Drug Development: Guidance for Industry and Review Staff

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM475586.pdf

Communication with FDA

Clinical dose finding and selection for future clinical trials

- Early & frequent communication with FDA
  - Request meeting with FDA in early stage of drug development
  - Consult FDA as needed throughout the development process
- Milestone meetings: **Pre-IND**, **EOP1**, **EOP2**, **pre-BLA**

  Discipline-specific Type C meetings
- **Pre-BLA** meeting: Discuss what constitutes a complete application

Take Home Messages

- Use of **optimal biological dose/dosing regi**men
- Better utilization of **target interaction and biomarker** data for dose selection
- **Adequate dose ranging** and **use of more than one dose level or dosing schedule** in clinical trial(s) to assess drug activity/efficacy and safety
- **Collect PK** data in **all** clinical trials
- Use of **dose-response and exposure-response** analyses to help dose selection
- **Dose individualization** for specific populations
- **Early engagement** with the regulatory agency on dose selection
- **Address the 'dose question' pre-marketing rather than post-marketing**

Acknowledgments

- Dr. Atiqur Rahman
- Dr. Lei Zhang
- Dr. Issam Zineh
- Clinical pharmacology review teams
- Pharmacometrics review teams


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Session IIa Panel Discussion

Considerations for Dose-Finding

Moderator: Geoffrey Kim, MD

Speakers:

Eric Rubin, MD

David Feltquate, MD, PhD

Mark Ratain, MD

Hong Zhao, PhD

Panelists:

Stephanie Goff, MD

MedImmune

A member of the AstraZeneca Group

Pathophysiology of Immune Mediated AEs

David Berman MD, PhD

SVP, Head of Oncology

MedImmune

Theoretical framework for immune mediated AEs

Drug-related + inflammatory in nature + alternative causes are excluded

Select I-O mechanisms	Central Tolerance Thymus	Peripheral Tolerance Lymph node	Peripheral Tolerance Tissue	Immune mediated AE
CD3 bispecific	bypass			On-target, off-tumor[a]
Anti CTLA4		bypass		Multiple organ[b]
Anti PD-1/L1			bypass	Multiple organ; < CTLA4[c]
Cancer vaccine; oncolytic virus				None to Rare [d]

a: blinatumimab USPI; b: ipilimumab USPI; c: nivolumab USPI, pembrolizumab USPI, atezolizumab USPI; d: Sipuleucel-T USPI, Talimogene laherparepvec USPI

CTLA-4 is key regulator of T cell tolerance

Deletion of CTLA-4 in mice leads to massive lympho-proliferation

- Massive lympho-proliferation in multiple organs
- Death by Week 3

Blockade of CTLA-4 in mice does not lead to prominent immune pathology

- No pre-clinical models validated

Blockade of CTLA-4 in patients leads to immune mediated AEs

- Multiple organs may be involved
- Most common sites: enterocolitis, dermatitis, hepatitis and endocrinopathies
- May range from mild to fatal

Waterhouse, P.,et al Science 1995; Tivol, E. A., et al Immunity 1995; Ipilimumab USPI; Ribas A et al JCO 2013

Enterocolitis overlaps but distinct from IBD and GVHD

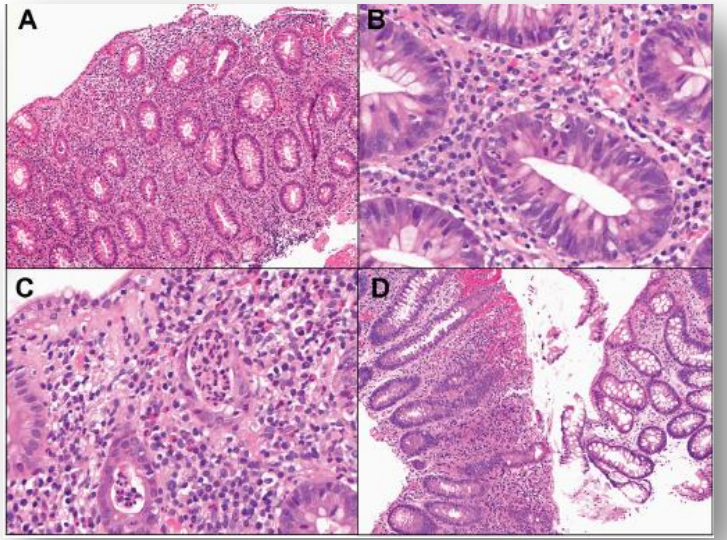
Prospective study to prevent and identify biomarkers of ipilimumab induced enterocolitis

Endoscopic biopsies while on ipilimumab (Week 1-2)

- Up to 1/4 had inflammation
- Predominantly left colon; mixed inflammatory pattern
- No association with subsequent Grade ≥ 2 enterocolitis

Histology overlaps, but distinct from IBD and GVHD

- Similar to UC, but left colon > rectum, no diffuse ulceration
- No consistent hallmarks of CD
- Distinct from GVHD



Ulcerative colitis (UC): diffuse transmural inflammation with ulceration extends continuously from rectum proximally
Crohn's disease (CD): granulomas and transmural, chronic inflammation
Graft vs host disease (GVHD): sparse inflammation with crypt epithelial apoptosis)

Berman D et al Cancer Immunity 2010

No Association Between Humoral Response to Enteric Flora and Enterocolitis

Ipilimumab induces non-specific fluctuations in humoral responses

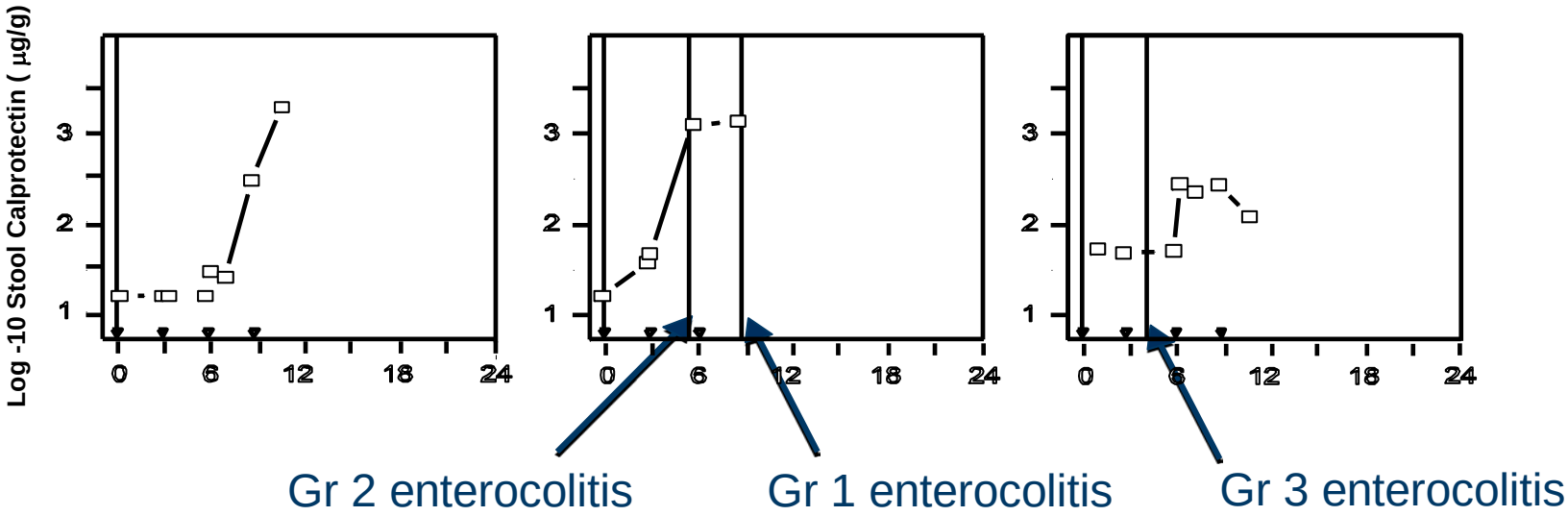
	Number of Patients Positive, by Worst Grade Enterocolitis*					
Enterocolitis*	Anti-I2	Anti-ASCA IgA	Anti-ASCA IgG	Anti-CBir	Anti-OmpC	Anti-pANCA
	← Crohn's disease →					Ulcerative colitis
Any Grade (N=115)	**18**	**17**	**18**	**20**	**42**	**20**
None (n=61)	13	11	13	15	21	10
Grade ≥ 2 (n=42)	3	4	2	4	17	9

*Twelve patients had worst Grade 1 (not included in table)
I2: fragment of bacterial DNA associated with P. Fluorescens; ASCA: anti-S. cerevisia antibody; pANCA: perinuclear staining anti-neutrophil cytoplasmic antibody; Ompc: E. coli outer membrane porin; CBir: bacterial flagellin CBir

Berman D et al Cancer Immunity 2010

Fecal calprotectin not specific for enterocolitis

Neutrophil-derived biomarker of inflammatory bowel disease activity

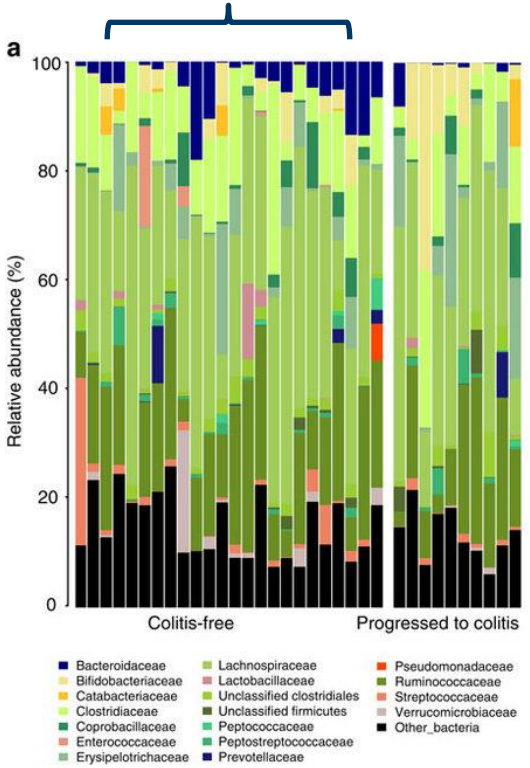


Berman D et al Cancer Immunity 2010

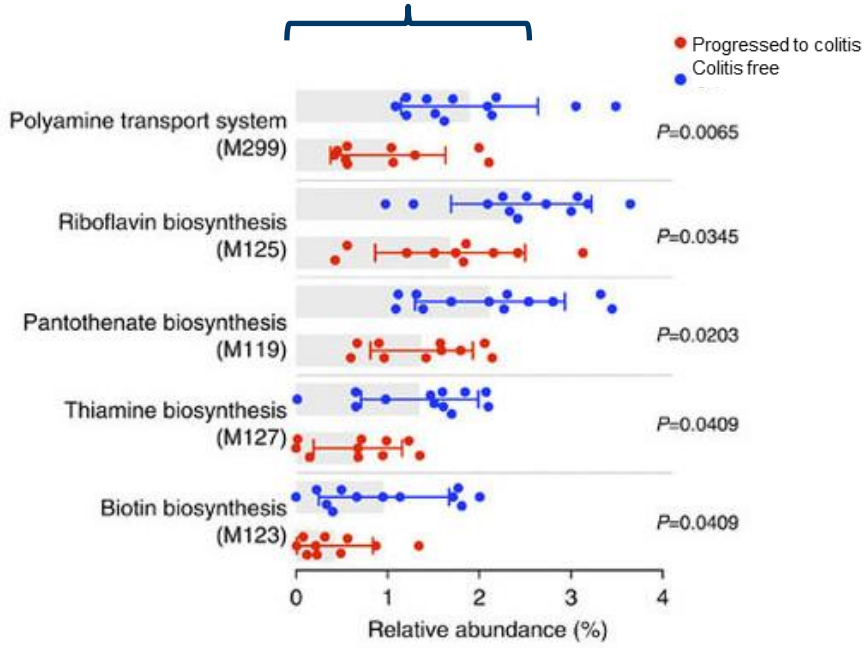
Microbiota may influence sensitivity to enterocolitis

Fecal microbiota contributes may have immune modulatory role

Increased Bacteroidetes phylum correlated with resistance to enterocolitis



Paucity of microbial polyamine transport and B vitamin biosynthesis associated with higher risk



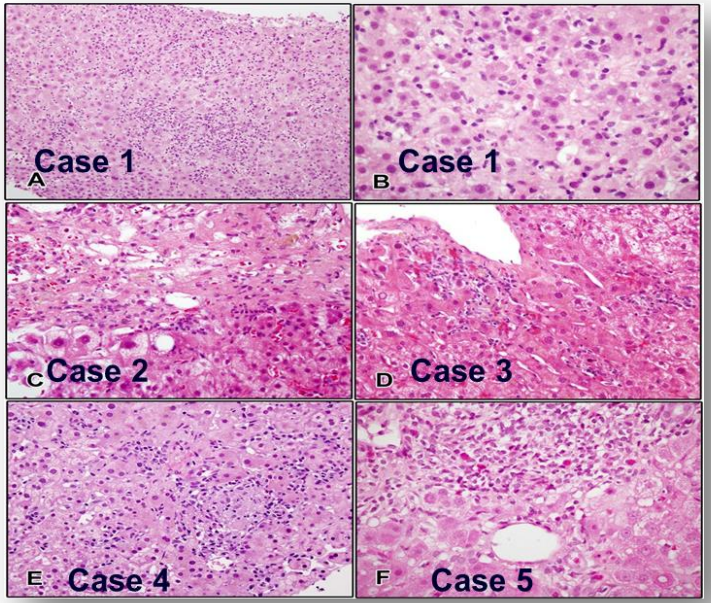
Dubin et al Nature Communication 2015

Hepatitis is inflammatory but pathology is non-specific

Case series of 5 patients with severe hepatitis

Histology overlaps with acute viral hepatitis or autoimmune hepatitis

- Portal inflammation, necrosis, plasma cells, eosinophils
- No association identified w/autoimmune serology
- Requires clinicopathologic correlation

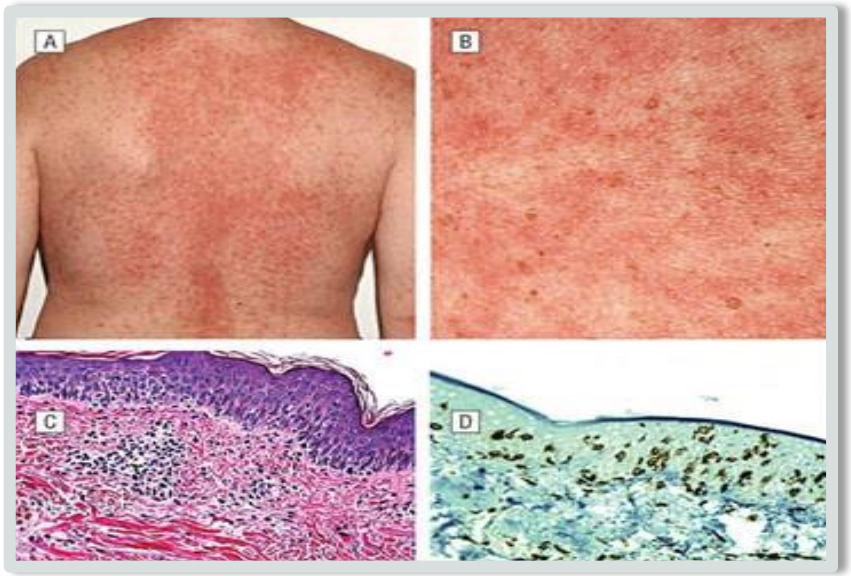


Kleiner D and Berman D. Dig Dis Sci 2012

Dermatitis distinct from GVHD and autoimmune skin diseases

NCI case series of 63 patients, 8 of whom developed dermatitis

Similar to maculopapular drug reaction, requires clinicopathologic confirmation



Predominantly T cell by occasional eosinophil

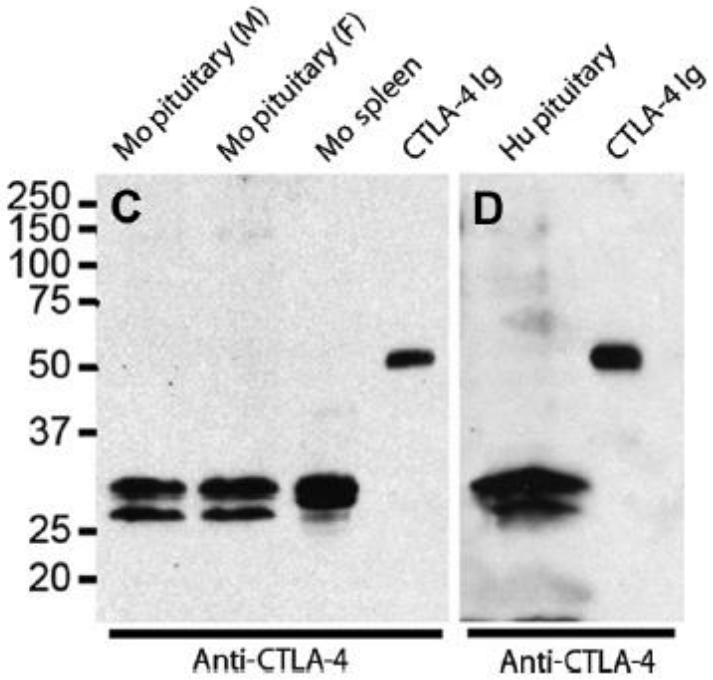
Heavy CD8 T cell component

Jaber et al. Arch Dermatol 2006

Hypophysitis may be due to CTLA4 expression in pituitary

Ipilimumab binding to CTLA-4 may fix complement, leading to inflammation

Western blot: CTLA-4 expression



Iwama et al. Sci Trans Medicine 2014; 6 (230

Original CTLA4 imAE guidance serves as basis for PD-1/L1

More work needed on pathophysiology

Management	Pathophysiology	Future work
Close monitoring	Inflammatory in nature	Need biomarkers to predict
Rule out alternative etiology	Overlaps but distinct from classic autoimmunity & GVHD	Dissociate toxicity from efficacy?
Drug interruption or discontinuation	Unlike autoimmune disease, usually reversible	Intersection of biology with autoimmune research
Corticosteroids	MOA for some rare imAE not known	Pathophysiology of imAE from other IO mechanisms

Adverse Events in Immuno-Oncology: Academic Perspective

FDA-AACR Workshop: Immuno-Oncology Drug Development

Washington, DC

October 13-14, 2016

Major Consideration for Safety/Toxicity of I-O Agents

- AEs by type of I-O Agent
- Etiology/Mechanism
- Management and effect on efficacy outcomes
- Nursing Staff and Education of Ancillary Medical Personnel
- Patient Education - Role in Safety
- Patient Selection and Prior Conditions -
- Phase 1 drug development, DLT period, DLT definitions and MTD
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- Biomarkers
- Experimental approaches to prevention and treatment
- Cost
- Risk/Benefit

Types of adverse events from immune therapy

- Hypersensitivity reaction to agent
- From direct or induced cytokine effects (IL-2 or interferon-like effects, cell transfer) **(not irAEs)**
  - Similar to infection/sepsis
  - Direct toxic effect on cells
  - Induced mediators (NO) and vascular effects
  - Central (CNS) effects
  - Innate immunity (NK cells)
  - Rarely auto-immune (T cell mediated)
  - Usually resolve within days to weeks without steroids
  - Life threatening Sx from cell transfer may require anti-cytokines or steroids (or kill switch)
- Inflammatory/autoimmune –
  - Generally from blockade of immune checkpoints
  - Likely T cell mediated and likely progressive and prolonged symptoms without steroids or secondary immune suppression
  - Certain events possibly mediated by auto-antibody
  - Generally less common and very mild cytokine related symptoms
- Idiosyncratic, tissue cross-reactive, immune-complex, etc
  - Liver toxicity from co-stimulatory agents?

Adverse Events from Immune Checkpoint Inhibitors or Co-Stimulator

- Generally do not induce cytokine like effects
- Autoimmunity can affect any organ system
  - But skin, GI, liver, and endocrine organs most common
- Incidence/severity anti-CTLA-4 > PD-1/PD-L1 antagonists> co-stimulatory agents
  - Exception was anti-CD28
  - Cytokine effects of anti-CD3
- Dose-relationship for anti-CTLA-4; not evident for active range of anti-PD-1/PD-L1
- Re-challenge with same agent often (but not always) leads to recurrent toxicity
- High grade AE to one class does not preclude safe administration of the other class (example anti-CTLA-4 → anti-PD-1)
- Vast majority of events (except endocrine) completely reversible over time
  - Steroids can be discontinued after adequate period for complete resolution
- Treatment of AE with immune suppressive agents does not appear to markedly affect outcome (for immune checkpoint inhibitors)
  - Induce lymphocyte resistance to steroids?

With greater experience, rare but very severe/life-threatening/fatal events

- Systemic inflammatory syndromes
- Enteritis/bowel perforation
- DKA/IDDM
- Debilitating arthralgias
- CNS (ascending or multi-focal motor neuropathy), leptomeningeal, neurologic (Myasthenia)
- Optic neuritis, uveitis: (visual changes/loss) (immediate evaluation by ophthalmologist)
- Pneumonitis
- Myositis and Myocarditis
- Stevens-Johnson Syndrome
- Nephritis
- Hematologic (cytopenias)

Mechanisms of Immune Checkpoint Blockade Toxicity or Co-Stimulatory Agents

- Mostly unknown
- May be epitope dependent (4-1BB)
- Cross-reactivity of Ab with normal tissue
- Activation of prior subclinical auto-immunity (recognition of self-Ag)
  - Prior genetic predisposition
  - Epitope spread
  - Cross-reactivity of tumor and normal tissue Ag
  - Increased effector cell function (Th1, Th2, Th17, other)
  - Reduced Treg function
- Cytokines may play role in pathology
- Role of antibody-dependent toxicity (serologic responses)
- Role of microbiome

General Principles for AE management (Immune Checkpoints)

- Established algorithms are applicable and useful for Ipilimumab like toxicity
- Prophylactic steroids likely reduce clinical benefit
- Supportive care for symptoms; +/-
- High dose steroids may be effective for severe events or events with potential morbid consequences if progressive (solumedrol 1 gm IV daily)
- Low threshold to admit to hospital for diagnosis or management
- Although new Sx are almost always drug-related, must rule out other causes (infection, tumor progression)
- High alert for common severe events:
  - GI (including enteritis like Sx with minimal diarrhea)
  - Increase in LFTs
  - Hypophysitis and adrenal insufficiency (+/- hypothyroidism) (check for vague symptoms and fatigue)
  - Hypothyroidism
- High alert for unusual but potentially severe and morbid events

General Principles for AE management

- **Strongly and repeatedly encourage patients and significant others to report symptoms immediately by phone**
- Once patients start to feel sick, require frequent monitoring in clinic and intermittent calls from **nursing staff**, even if initiation of steroids is delayed
  - Systemic inflammatory syndromes may evolve to other irAEs
  - Serial or concurrent irAEs are not uncommon
- Consider prophylactic Bactrim if on dual immune suppressives or after 4-6 weeks on steroids
- On the lookout for opportunistic infections after prolonged steroids + minus anti-TNF or mycophenolate (ie, CMV colitis)
- Re-assure patients that their AEs will likely resolve over time (except endocrinopathies)

The main questions in AE management

- When to start steroids?
- Low, moderate or high, IV or PO, inpatient or outpatient?
- How long for ‘induction’, how long to taper?
- When to add a second agent like mycophenolate or remicade?
- Steroid-sparing approach (start with secondary immune suppressive)?
- When to add more invasive or additional diagnostic tests (colonoscopy, biopsy, bronchoscopy, LP)?
- How often to monitor in clinic?
- When and if to re-challenge (restart combination or single agent anti-PD-1)?
- Novel approaches – non-absorbed signaling inhibitors, anti-cytokines
- Effects on efficacy outcomes?

Education of Patients and Ancillary Medical Personnel, Critical Role of Nursing

- Patient education, medic-alert bracelets (hypophysitis), EHR alerts
- Robust nursing staff involvement and proactive communication with patient
- Education of covering physicians and staff
- Inpatient attendings
- Sub-specialty consultants
- ER personnel
- Primary care and other physicians (local oncologist, other specialists for non-oncology problems)
- → Develop dedicated multi-disciplinary management teams within major centers

Patient Selection and Prior Conditions

- Major organ dysfunction (lung, renal, cardiac)
- Prior brain mets – induced inflammation
- Performance status
- Prior autoimmunity
  - Risk for same or different organ system?
- Compliance, distance from center, support network
- Viral hepatitis
- Prior allo transplant
- Prior autoimmune toxicity from I-O drug

- No known predictive biomarker (serology, microbiome, etc)
- Biomarker for monitoring and ‘early detection’
  - CAR-T Toxicity - predictive algorithms for severe toxicity

Drug development, DLT period, DLT definitions and MTD

- Mostly impacts combination development
- Most AEs (despite severity) are reversible/managed with steroids
- High incidence of severe (gr 3-4) but reversible AEs is acceptable if potential benefit is high
  - Duration for ‘acceptable’ requires definition
  - Could be as high as 50%
- Must define unacceptable events (true DLTs)
  - Irreversible with morbidity, excessive duration
  - Certain toxicities may be DLTs despite reversibility (cardiac, neuro) because of clinical consequences/morbidity/excessive demands on patients and care system, potential for severe morbidity/mortality with inadequate management
- DLT period must be limited for rapid drug development
- Dose/schedule relationships poorly defined – flexibility to increase dose despite high rate of ‘acceptable; severe events (may not yield more ‘unacceptable events’)
- Will need larger cohort sizes because of selection and random occurrence
- Difficult to detect late and rare events
  - Flexible adjustment of dose levels if late toxicities are observed

Re-challenge and sequential therapies

- Re-challenge with same agent often but not always produces same or different irAE
  - Consider risk-benefit; chance for benefit is reasonable, toxicities likely manageable
- Antibodies have long half-lives – may interact with new therapies
  - However delay of new therapies not justified in setting of progressing cancer
- Severe toxicity from one agent should not preclude trial or treatment with different agent in same ‘class’ – data from anti-PD-1 following anti-CTLA-4

Novel Future Biomarkers

- Genetic markers - predisposition
- Serologic or other evidence of clinical or subclinical prior autoimmunity
- Serial measurements of serum/plasma cytokines/inflammatory markers
- Screen for tumor/host antigen similarities (CAR-T and TCR cell therapies)

Experimental approaches to prevention and treatment

- Drug delivery specific to tumor microenvironment
- Alteration of dose/schedule
- Non-absorbable immune suppressive agents for colitis
- Anti-cytokines developed for autoimmune disease
  - Need for coordinated trials

Major Consideration for Safety/Toxicity of I-O Agents

- AEs by type of I-O Agent
- Etiology/Mechanism
- Management and effect on efficacy outcomes
- Nursing Staff and Education of Ancillary Medical Personnel
- Patient Education - Role in Safety
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- Experimental approaches to prevention and treatment
- *Cost*
- Risk/Benefit

Conclusions

- Different pattern of toxicity and implications for treatment depending on agent
- Very little science guiding prediction of toxicity and methods of management
- Management of toxicity requires substantial interactions between patients and medical staff
- Training and communication for ancillary physicians is important for optimal patient management
- Re-consider definitions of DLT and phase 1 trial designs – murky dose-response relationships, reversibility of events with steroids and other agents
- Important to assess/add substantial cost of managing toxicity for future resource allocation

Unique Aspects of Immune-mediated Adverse Events: A Regulatory Perspective

Diko Kazandjian, MD

FDA/OHOP/DOP2

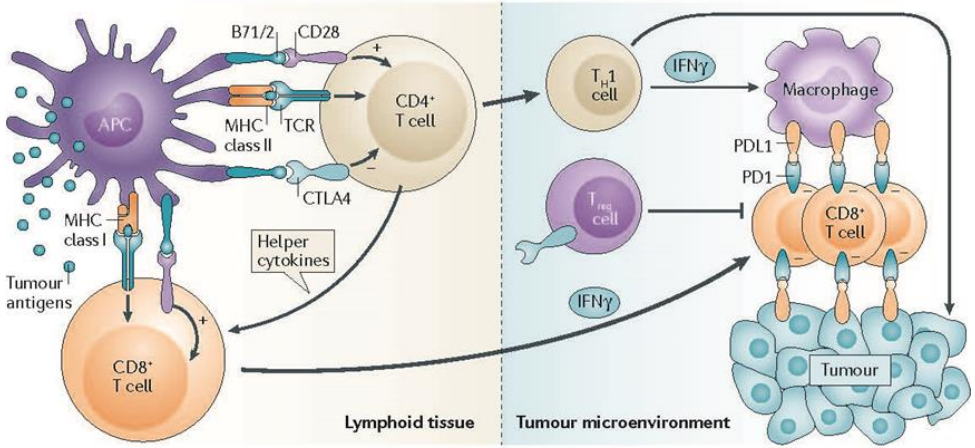
Immune system

- In normal conditions, activation of signaling pathways balance activation and inhibition of the immune system
- Cancer cells contain aberrations compared to normal cells which can signal T-cell mediated anti-cancer immunity which is one of the primary defense mechanisms of the body against neoplasia
- Important pathways have been identified, beginning with CTLA-4 then PD-1 followed by others
- Identification of these pathways have led drug development to focus on overcoming cancer cells' ability to evade the immune system
- Drugs focus on
  - Inhibiting inhibitory pathways
  - Activating stimulatory pathways

Balancing checkpoint inhibitors

- Activation of the immune system with drugs requires a balance between anti-tumor effect and unwanted consequence of auto-immunity
- Immunotherapies present a distinct repertoire of toxicity due to auto-immunity
- irAEs can virtually involve any organ
- Frequency, duration, and onset vary between different classes of IO's

CTLA-4 and PD-1/L1 inhibitors



Topalian et al, 2016

- CTLA-4 and PD-1 pathways are involved in different subsets of immune cells
- Leads to different characteristics in both efficacy and irAEs
  - Safety: PD-1 inhibition leads to activation of more restricted repertoire of T-cells
  - Efficacy: time to response observed to be sooner with PD-1 inhibitors; reactivation of TILs in metastasis

irAEs

PD-1

- Pneumonitis
- Colitis
- Dermatitis
- Hepatitis
- Nephritis
- Endocrinopathies: Hypophysitis, Thyroid, Adrenal, DM
- Encephalitis
- Other, neurologic, rheumatologic, cardiac

CTLA-4

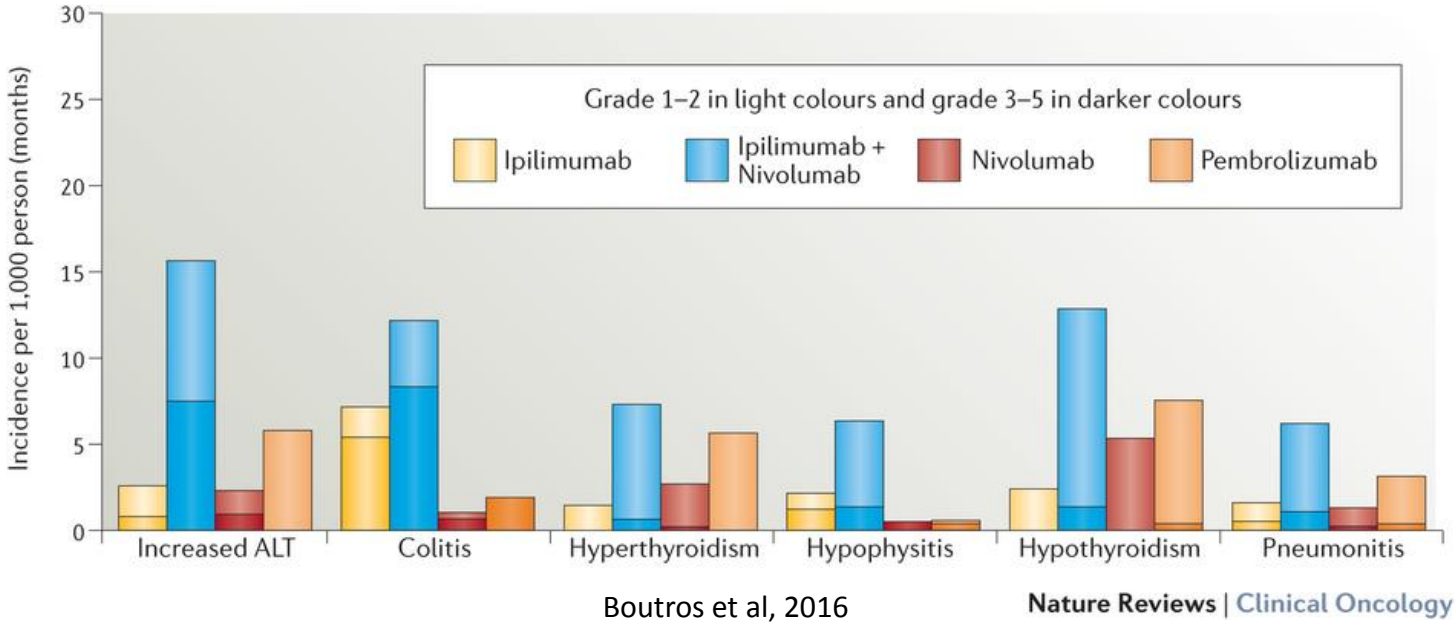
- Pneumonitis
- Colitis
- Dermatitis
- Hepatitis
- Nephritis
- Endocrinopathies
- Ophthalmologic
- Other

irAE differences

- Common irAEs are similar across drugs
- Frequency and severity may differ
- Differences are partly due to the disease indication
- However, differences are likely more a factor of patient characteristics than tumor type
  - Pneumonitis: lung cancer: smoking Hx, radiation; Hodgkin's: bleomycin

irAE differences

- With evolving data, evident that anti-PD-1's lead to fewer AEs than anti-CTLA-4 therapy; combination leads to additive effect



Boutros et al, 2016

Lessons learned

- Characterization of toxicity in early registrational studies with anti CTLA-4 and PD-1 challenging for FDA review
  - Unclear how patients were classified as having irAEs
  - Inconsistent documentation and evidence across centers and investigators
- FDA early on requested sponsors develop case definitions for irAEs for correct characterization and description prospectively to avoid issues with quality of data collected

Lessons learned

- With more recent PD-1/PD-L1 therapies developed, sponsors have also more proactively at the onset developed case definitions and educated study sites
- Case definitions for irAE evolved to
  - Exclude AEs with clear alternative non-immune etiology
  - Expand list of AE terms potentially qualifying as irAE
  - Capturing irAEs up to 100 days after last dose
  - Modification of template CRFs to capture laboratory and pathology data, timing of event, and comorbidities
  - Requirement for administration of immune-modulating therapy (except for endocrinopathies)

CRF example

CONCOMITANT IMMUNE MODULATING MEDICATIONS

Medication *(Use generic name whenever possible; use brand name for combination product)*

Date Started
DD-MMM-YYYY

Date Stopped
DD-MMM-YYYY

Use *(If AE, record event on appropriate NSAE/SAE form)*
Select from list

Total Daily Dose

Dose Unit

Frequency
Select from list

Route of Administration
Select from list

Medication *(Use generic name whenever possible; use brand name for combination product)*

Date Started
DD-MMM-YYYY

Date Stopped
DD-MMM-YYYY

Use *(If AE, record event on appropriate NSAE/SAE form)*
Select from list

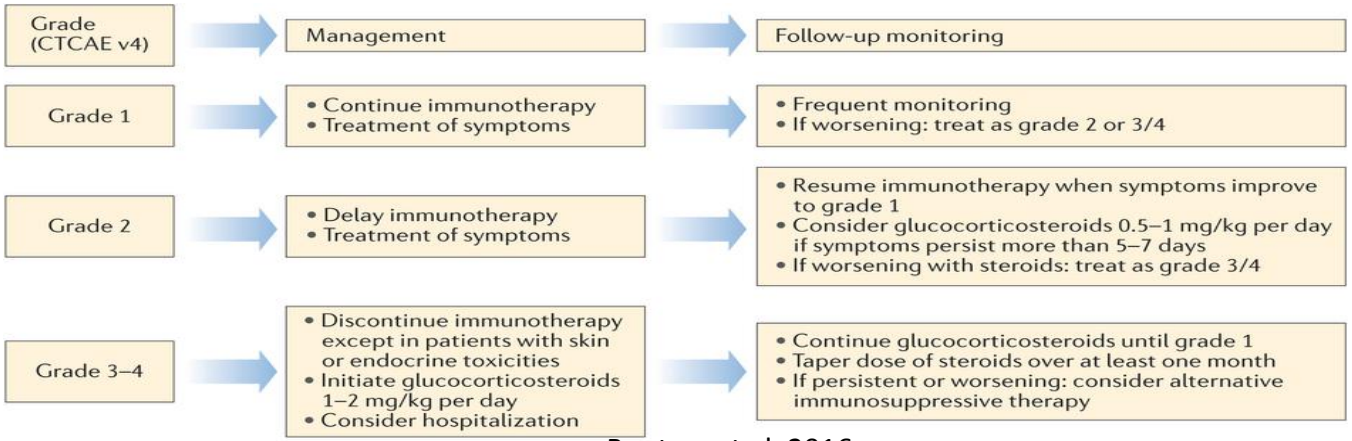
Total Daily Dose

Dose Unit

Frequency
Select from list

Route of Administration
Select from list

Lessons learned: management



Boutros et al, 2016

Nature Reviews | Clinical Oncology

- With introduction of ipilimumab and new toxicities, immune mediated in nature, creation of REMS
- Successful in educating community, not only for ipi, but the basis for management guidelines for anti-PD-1's
- Currently, many centers comfortable in managing irAEs which is done empirically

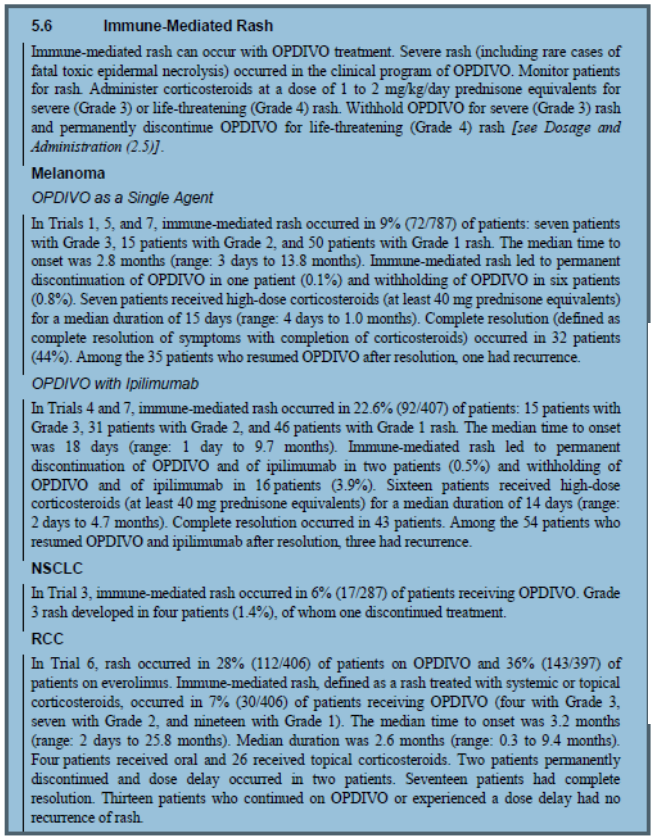
Considerations

- Various irAEs have been histologically studied to describe the pathophysiology
- However, at a patient level, most irAEs are presumed and for practical reasons are rarely biopsy proven
- Raises questions of true frequencies observed in clinical trials
  - In trials, is all pneumonitis immune-mediated?
  - Are AEs termed pneumonia truly a microbial process?
  - Are these an outcome of therapy or consequence of patient history or prior treatment with other agents?

Considerations

- As PD-1/L1 inhibitors are approved in more diseases, combinations, and indications the safety database grows
- Drug labels also expand further incorporating more clinical trial data
- In regard to irAEs and incorporation of pooled safety data, the label potentially “overloads” the prescriber with data for each disease separately
  - For irAEs is there truly a reason to believe that significant differences exist across diseases?

Case example



5.6 Immune-Mediated Rash

Immune-mediated rash can occur with OPDIVO treatment. Severe rash (including rare cases of fatal toxic epidermal necrolysis) occurred in the clinical program of OPDIVO. Monitor patients for rash. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for severe (Grade 3) or life-threatening (Grade 4) rash. Withhold OPDIVO for severe (Grade 3) rash and permanently discontinue OPDIVO for life-threatening (Grade 4) rash *[see Dosage and Administration (2.5)]*.

Melanoma

OPDIVO as a Single Agent

In Trials 1, 5, and 7, immune-mediated rash occurred in 9% (72/787) of patients: seven patients with Grade 3, 15 patients with Grade 2, and 50 patients with Grade 1 rash. The median time to onset was 2.8 months (range: 3 days to 13.8 months). Immune-mediated rash led to permanent discontinuation of OPDIVO in one patient (0.1%) and withholding of OPDIVO in six patients (0.8%). Seven patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 15 days (range: 4 days to 1.0 months). Complete resolution (defined as complete resolution of symptoms with completion of corticosteroids) occurred in 32 patients (44%). Among the 35 patients who resumed OPDIVO after resolution, one had recurrence.

OPDIVO with Ipilimumab

In Trials 4 and 7, immune-mediated rash occurred in 22.6% (92/407) of patients: 15 patients with Grade 3, 31 patients with Grade 2, and 46 patients with Grade 1 rash. The median time to onset was 18 days (range: 1 day to 9.7 months). Immune-mediated rash led to permanent discontinuation of OPDIVO and of ipilimumab in two patients (0.5%) and withholding of OPDIVO and of ipilimumab in 16 patients (3.9%). Sixteen patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 14 days (range: 2 days to 4.7 months). Complete resolution occurred in 43 patients. Among the 54 patients who resumed OPDIVO and ipilimumab after resolution, three had recurrence.

NSCLC

In Trial 3, immune-mediated rash occurred in 6% (17/287) of patients receiving OPDIVO. Grade 3 rash developed in four patients (1.4%), of whom one discontinued treatment.

RCC

In Trial 6, rash occurred in 28% (112/406) of patients on OPDIVO and 36% (143/397) of patients on everolimus. Immune-mediated rash, defined as a rash treated with systemic or topical corticosteroids, occurred in 7% (30/406) of patients receiving OPDIVO (four with Grade 3, seven with Grade 2, and nineteen with Grade 1). The median time to onset was 3.2 months (range: 2 days to 25.8 months). Median duration was 2.6 months (range: 0.3 to 9.4 months). Four patients received oral and 26 received topical corticosteroids. Two patients permanently discontinued and dose delay occurred in two patients. Seventeen patients had complete resolution. Thirteen patients who continued on OPDIVO or experienced a dose delay had no recurrence of rash.

5.6 Immune-Mediated Skin Adverse Reactions

OPDIVO can cause immune-mediated rash, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some cases with fatal outcome. For symptoms or signs of SJS or TEN, withhold OPDIVO and refer the patient for specialized care for assessment and treatment. If SJS or TEN is confirmed, permanently discontinue OPDIVO *[see Dosage and Administration (2.5)]*.

For immune-mediated rash, administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by a corticosteroid taper for severe (Grade 3) or life-threatening (Grade 4) rash. Withhold OPDIVO for severe (Grade 3) rash and permanently discontinue OPDIVO for life-threatening (Grade 4) rash.

OPDIVO as a Single Agent

In patients receiving OPDIVO as a single agent, immune-mediated rash occurred in 9% (171/1994) of patients; the median time to onset was 2.8 months (range: <1 day to 25.8 months). Immune-mediated rash led to permanent discontinuation of OPDIVO in 0.3% and withholding of OPDIVO in 0.8% of patients. Approximately 16% of patients with rash received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 12 days (range: 1 days to 8.9 months) and 85% received topical corticosteroids. Complete resolution occurred in 48% of patients. Recurrence of rash occurred in 1.4% of patients who resumed OPDIVO after resolution of rash.

OPDIVO with Ipilimumab

In patients receiving OPDIVO with ipilimumab, immune-mediated rash occurred in 22.6% (92/407) of patients; the median time to onset was 18 days (range: 1 day to 9.7 months). Immune-mediated rash led to permanent discontinuation or withholding of OPDIVO with ipilimumab in 0.5% and 3.9% of patients, respectively. Approximately 17% of patients with rash received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 14 days (range: 2 days to 4.7 months). Complete resolution occurred in 47% of patients. Approximately 6% of patients who resumed OPDIVO and ipilimumab after resolution had recurrence of rash.

5.7 Immune-Mediated Encephalitis

ODPIVO can cause immune-mediated encephalitis with no clear alternate etiology. Evaluation of patients with neurologic symptoms may include, but not be limited to, consultation with a neurologist, brain MRI, and lumbar puncture.

Withhold OPDIVO in patients with new-onset moderate to severe neurologic signs or symptoms and evaluate to rule out infectious or other causes of moderate to severe neurologic deterioration. If other etiologies are ruled out, administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for patients with immune-mediated encephalitis, followed by corticosteroid taper. Permanently discontinue OPDIVO for immune-mediated encephalitis *[see Dosage and Administration (2.5)]*.

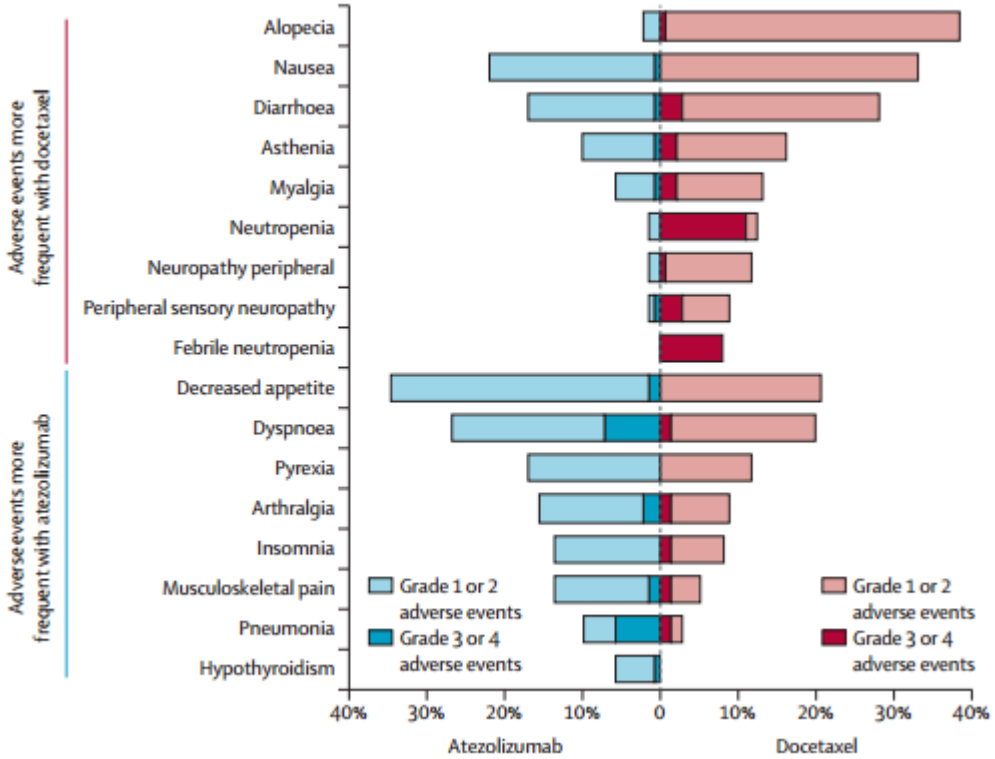
- As of 9/30/2016 the nivolumab label was 59 pages long
- Warnings and precautions section included separate analysis of nivo monotherapy for melanoma, NSCLC, RCC, cHL, and nivo/ipi combination for melanoma making the section 14 pages long
- The sponsor with FDA guidance condensed the section to 7 pages

Future Considerations

- Consistency across drug labels important to aid prescribers
  - As agents are approved for more indications, prevent the label from becoming a "data dump"
  - Maintain meaningful brevity and consistency (ie Warnings and Precautions)
  - Management guidelines of irAEs should be consistent across labels
- AE management guidelines should be meaningful to prescribers as further knowledge is gained
  - For example, lack of validated hormone monitoring guidelines at baseline for endocrinopathies; "Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders"
- Case definitions describing irAEs should also be consistent across IO's
  - Role of academics and sponsors to standardize definitions

Future Considerations

Atezolizumab versus docetaxel NSCLC (POPLAR)



Fehrenacher et al., 2016

- Potential approaches to meaningful representation of safety data

Moving forward

- Science evolving and recognition by field of potential synergistic benefit of combination immunotherapy regimens
- Some novel immuno-therapies observed not to have monotherapy efficacy but presumed synergy with anti-PD-1's
  - Push by the community to limit monotherapy trials leading to a lack of isolating drug effect in term of efficacy
  - However, also potentially challenging in being able to isolate and describe a given drug's safety profile
- Challenges include describing AEs for combinations with other non-IO drug types
  - For example, pneumonitis in anti PD-1/TKI combinations
- Although knowledge of the safely profiles of IO's quickly expanding, imperative to continue pharmacovigilance for new safety signals
  - Immune-mediated encephalitis; Steven Johnson's Syndrome

In Conclusion

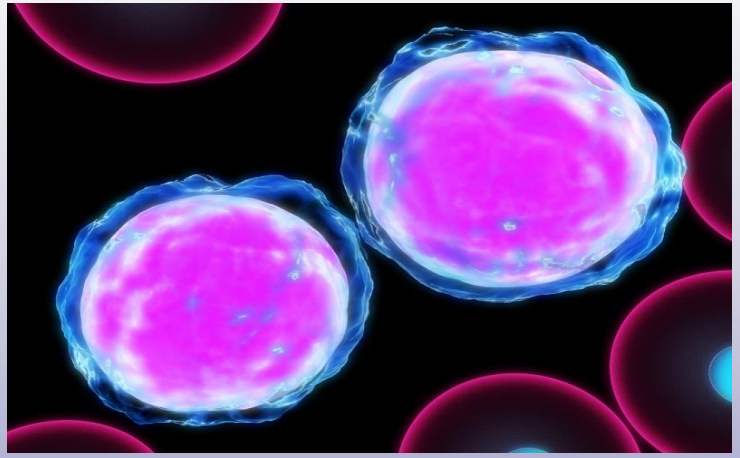
- The advent of checkpoint inhibitors have marked a paradigm shift in treatment options for many cancer types, directly translating to patients living longer
- As excitement grows with further development in the field, it will be crucial to consistently and scientifically collect safety data and educate the community with validated management guidelines
- Will be imperative to ensure that quality safety data is collected in a prospective manner on clinical trials and not as an after thought
- In addition, shared community data will be important in identifying biomarkers which can potentially predict immune-mediated toxicity
- Collaboration between all sponsors and investigators in scientific findings crucial

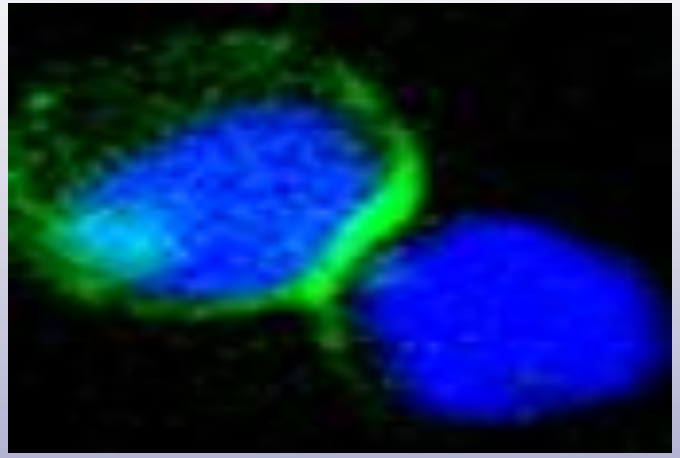
Thank you

Acknowledgements

- Drs. Blumenthal, Hazarika, Theoret, Keegan, and Pazdur for their guidance

Complications of CAR T Cell Therapy





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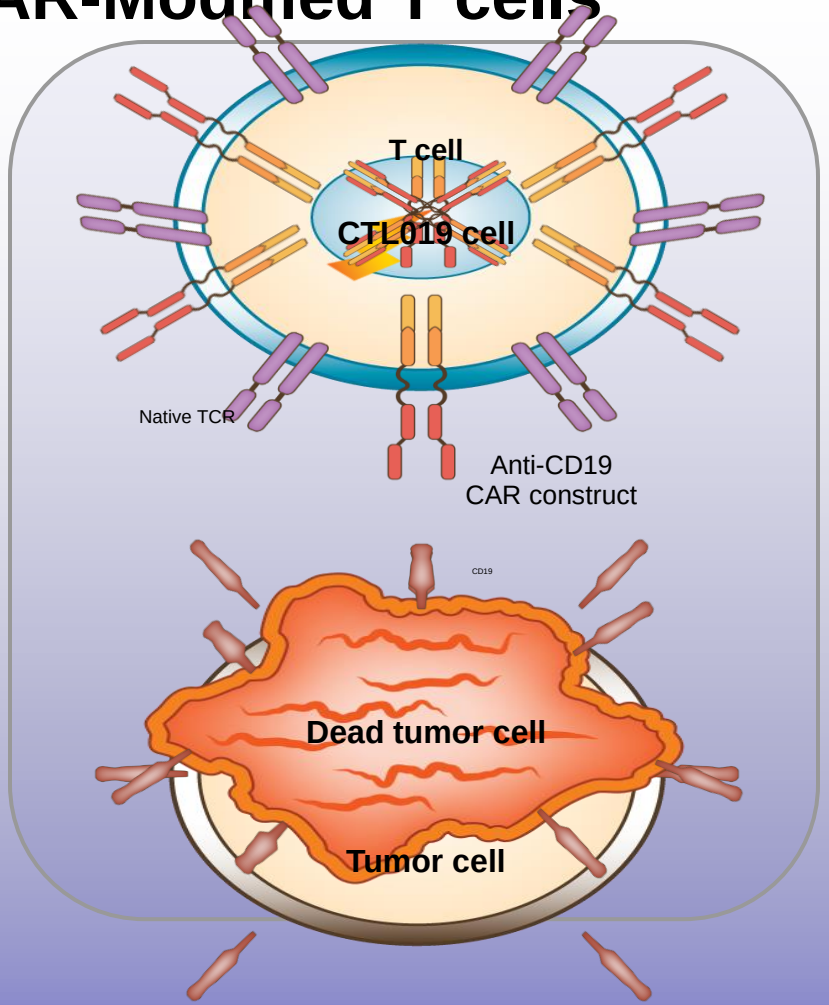
Disclosure Information

David L Porter

- Speaker and members of study team have financial interest due to potential upstream IP and patents and licensure to Novartis
- COI managed in accordance with University of Pennsylvania policy and oversight
- Funding support for trials: ACGT, LLS, NCI, Novartis
- Member, ABIM Hematology Board exam writing committee.
- Please note that some of the studies reported in this presentation were published as an abstract and/or presented at a conference. These data and conclusions should be considered to be preliminary until published in a peer-reviewed journal.

Targeting CD19+ CLL with CAR-Modified T cells

- Gene transfer (lentiviral vector) to stably express CAR on T cells confers novel antigen specificity
- CAR modified T cells can now recognize and kill CD19+ cells

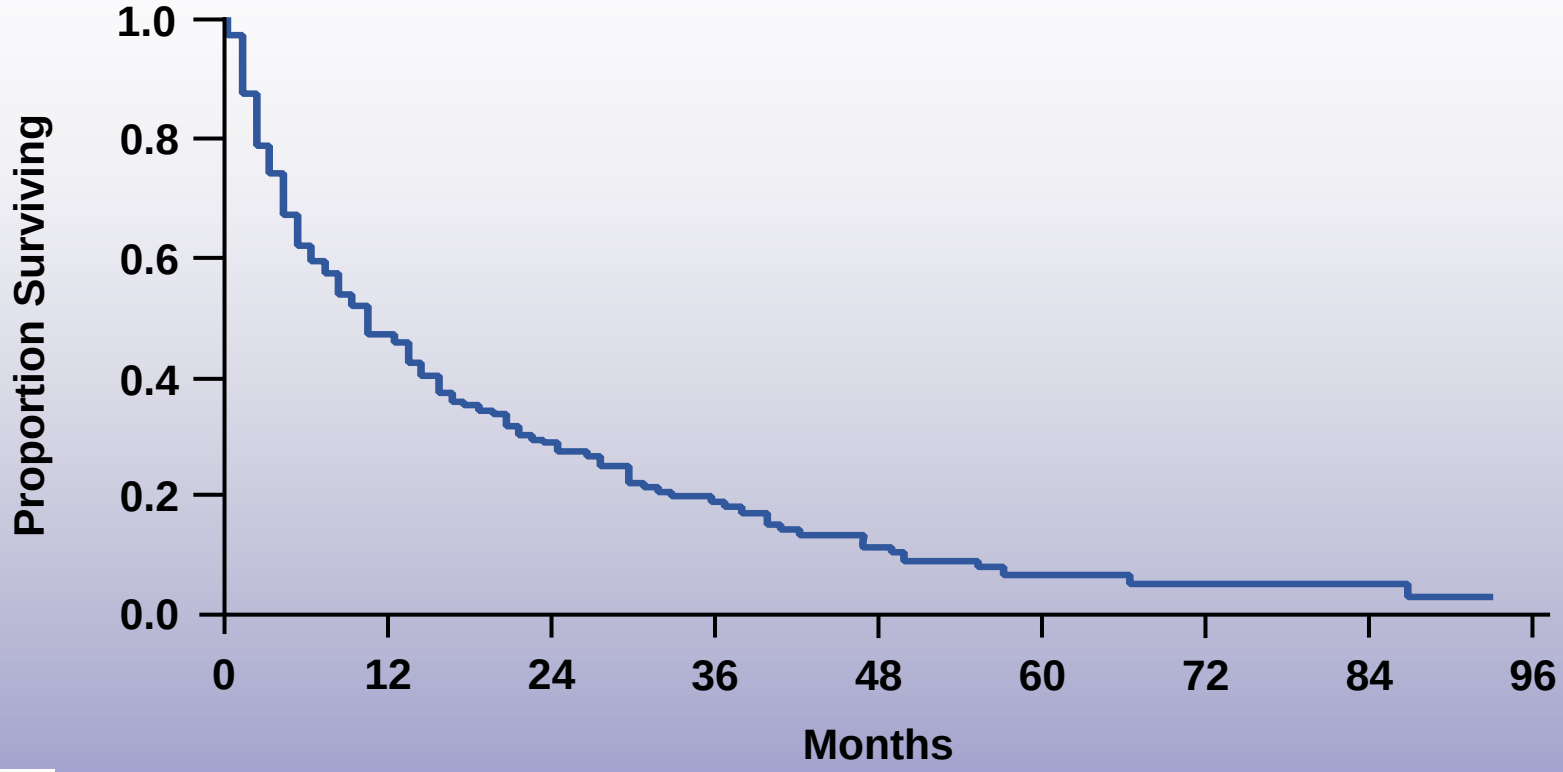


CARs Meet Leukemia

262 CTL019 Recipients

- CLL:
  - 52 adults
- ALL:
  - 115 (kids and adult)
- NHL:
  - 36 adults
- MM
  - 12 adults
- Other CARs
  - 47

Median OS of fludarabine-refractory CLL is 10 months



Brown J R Hematology 2011;2011:110-118, from Keating et al, 2002 Leuk Lymphoma 43:1755–1762 ©2011 by American Society of Hematology

CLL: Overall Response to CTL019

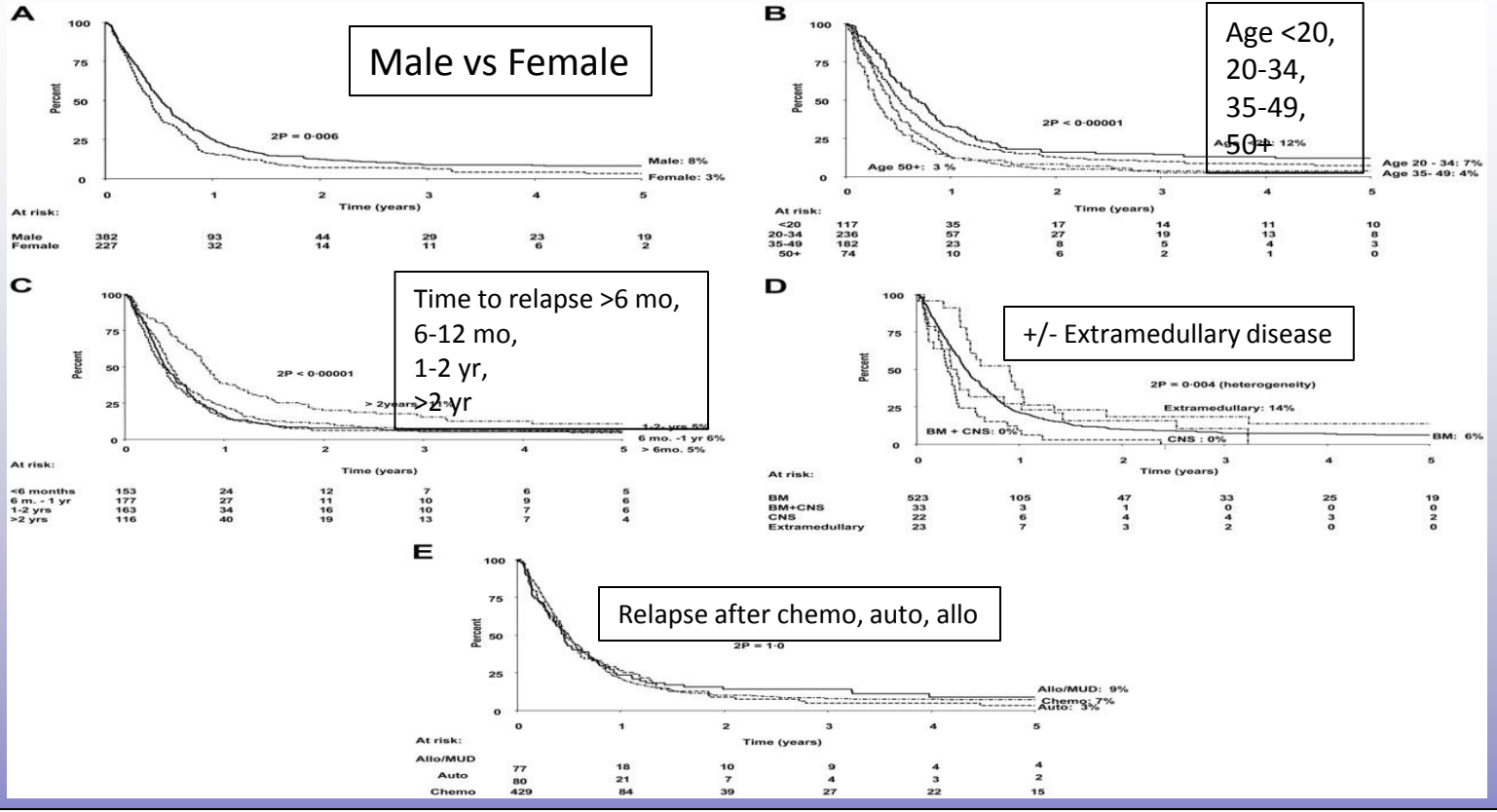
Response	N	%
Complete Response	11/43	26%
Partial Response	10/43	23%
Overall Response	21/43	49%

unpublished

ALL: Rationale for Novel Therapies

- Prognosis for relapsed or refractory ALL poor
- Median survival < 1yr
- 3 yr survival <25%
- Allogeneic SCT for refractory ALL largely ineffective
- There is a desperate need for newer, more effective therapies for advanced and high risk ALL.

Outcomes for Adults with 1st Relapse ALL



Fielding A K et al. Blood 2007;109:944-950. ECOG 2993

ALL: Overall Response to CTL019

Response	N=30	%
Complete Response	27/30	90%
No response	3/30	10%
Not evaluable (extramedullary dz (1) and short f/u (4)	5	

Maude SL, Frey N. et al. N Engl J Med 2014;371:1507-1517.

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Abramson Cancer Center

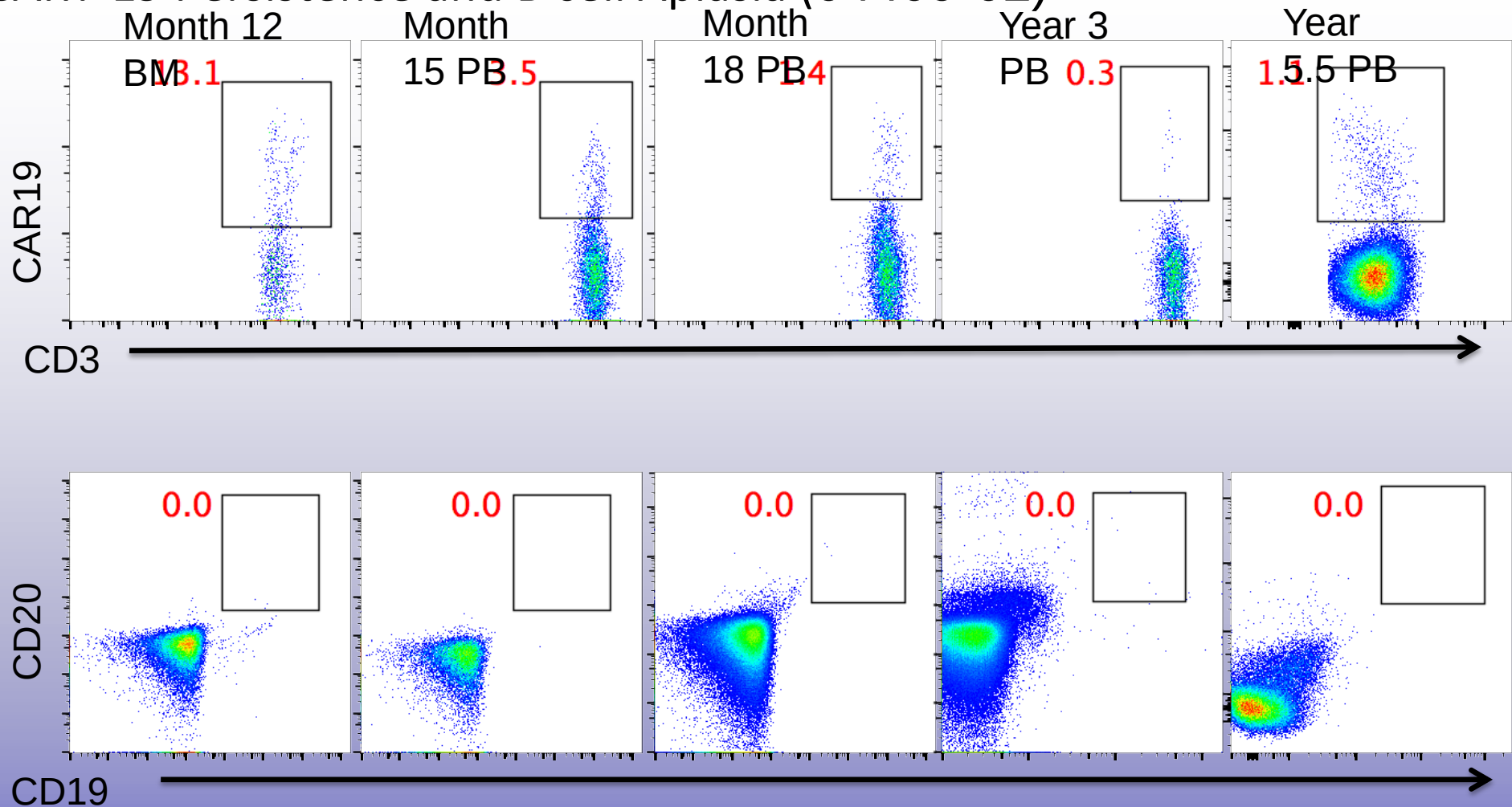
CAR T cells have dramatic activity in relapsed and refractory ALL: ASCO 2016 (n=205)

Study	Construct	N	CR	Session
Seattle (Turtle, 102)	CD3z 4-1BB	34	94%	Sat D1 (8:00-9:30a)
Penn (Frey 7002)	CD3z 4-1BB	30	72%	Sat Arie Crown 3:00-6:00)
MSK (Park, 7003)	CD3z CD28	46	78%	Sat Arie Crown (3:00-6:00)
Seattle Children's (Gardner, 3048)	CD3z 4-1BB	36	91%	Sun A (8-11am) posters
Penn (Maude 3011)	CD3z 4-1BB	59	93%	Mon D2 (4:30-6:00)

Toxicity: CTL019

- No significant acute infusional toxicity
- Hepatotoxicity, renal toxicity (reversible, grade 3)
- Tumor lysis syndrome
  - Reversible and manageable
- B cell aplasia and hypogammaglobulinemia in responding patients (toxicity or efficacy?)
  - Supported with intravenous immunoglobulin (IVIG)
  - No excessive or frequent infections
- Neurological toxicity
- Cytokine Release Syndrome (CRS)

CART-19 Persistence and B cell Aplasia (04409-02)

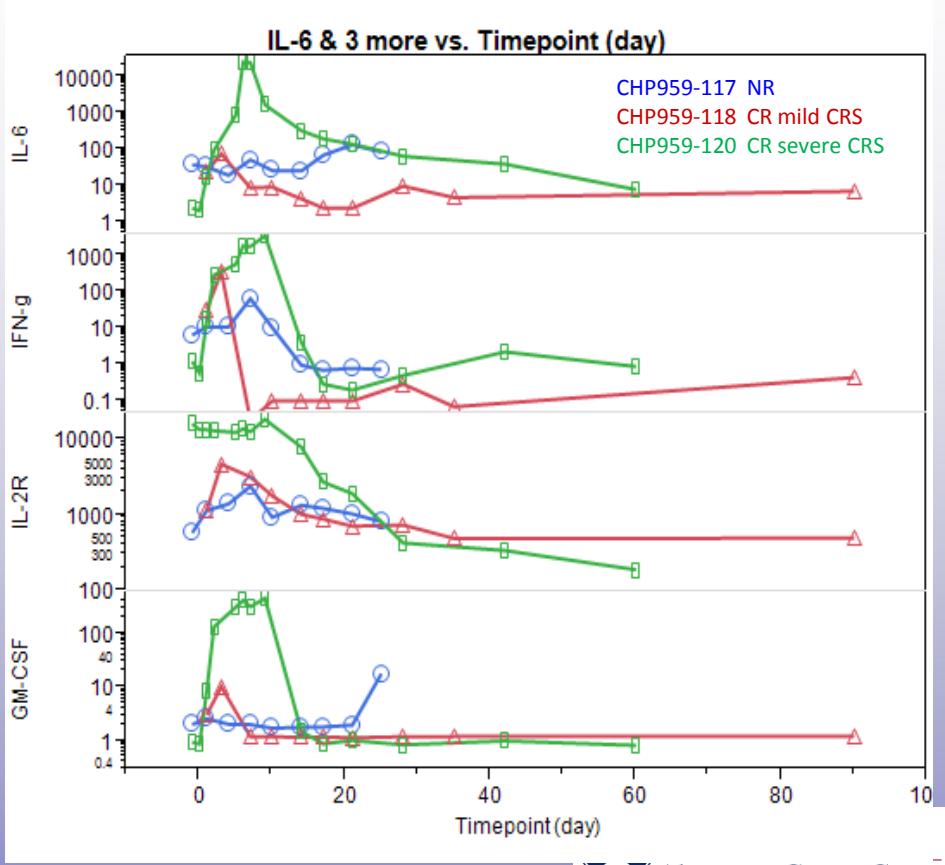


CRS after CAR T Cells (CTL019)

- Almost all responding patients developed a CRS
  - Onset 1-14 days after infusion
  - Duration 1-10+ days
- Coincident with CAR T cell activation and expansion
- Begins with escalating fevers (101-105)
- Myalgias, nausea, fatigue, anorexia
- Capillary leak, hypoxia and hypotension
- Similarities MAS/HLH

CRS after CAR T Cells (CTL019)

- Responding patients have massive elevations in IL6
- Modest elevation of IFN-g, TNF-a
- Mild increases in IL-2
- Cytokine profile correlates with response
- Biochemical changes similar to HLH/MAS (marked increases in ferritin, CRP)



IL-6 mediates CTL019 Associated CRS

- Tocilizumab
  - IL-6 receptor antagonist
  - Blocks IL-6 mediated effects
- CRS rapidly reversed with tocilizumab when needed
  - Tocilizumab administered on day 2 to 18
  - Will early treatment for CRS abrogate response?
- CRS associated with HLH/MAS
  - Hemophagocytosis, ferritin >500,000, hemolysis, DIC, altered mental status

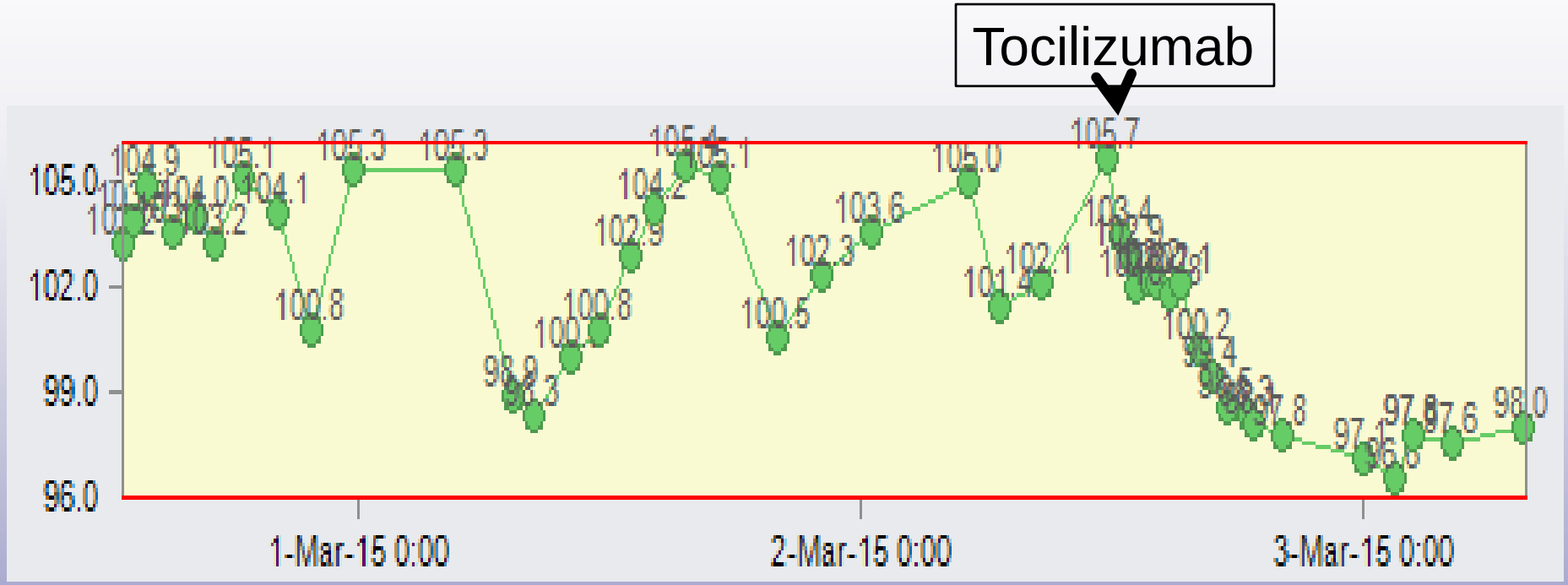
Blood. 2014;124(2):188-195


How I Treat

Current concepts in the diagnosis and management of cytokine release syndrome

Daniel W. Lee,[1] Rebecca Gardner,[2] David L. Porter,[3] Chrystal U. Louis,[4] Nabil Ahmed,[4] Michael Jensen,[2] Stephan A. Grupp,[3,5] and Crystal L. Mackall[1]

Temperature Response to Tocilizumab 21413-32



CRS with CART19 Therapy

Ref	Program/ CAR	Population	Response	CRS
Acute Lymphoblastic Leukemia				
Maude et al. NEJM 2014	PENN 4-1BB	N=30(ALL) Peds&Adults	CR=90%	100% CRS 27% Severe
Davila et al. SciTrMed 2014	MSK CD28	N=16 (ALL) Adults	CR=88%	43% Severe
Lee et al. Lancet 2015	NCI CD28	N=21 (ALL) Peds&AYA	CR=67% Intent to Treat	76% CRS 28% Severe
Non-Hodgkins Lymphoma & Chronic Lymphocytic Leukemia				
Kochenderfer JCO 2015	NCI CD28	N=15 (NHL/CLL)	CR=53% PR=27%	27% Severe
Porter et al. ASH 2014	PENN 4-1BB	N=14(CLL)	CR=29% PR=29%	42% Severe

Cytokine Release Syndrome after CAR T Cells

- Novel toxicity seen with CAR T cell therapy
- How to describe and report it?
- CTCAE inadequate and inappropriate
  - CTCAE4: Linked to infusion of IP

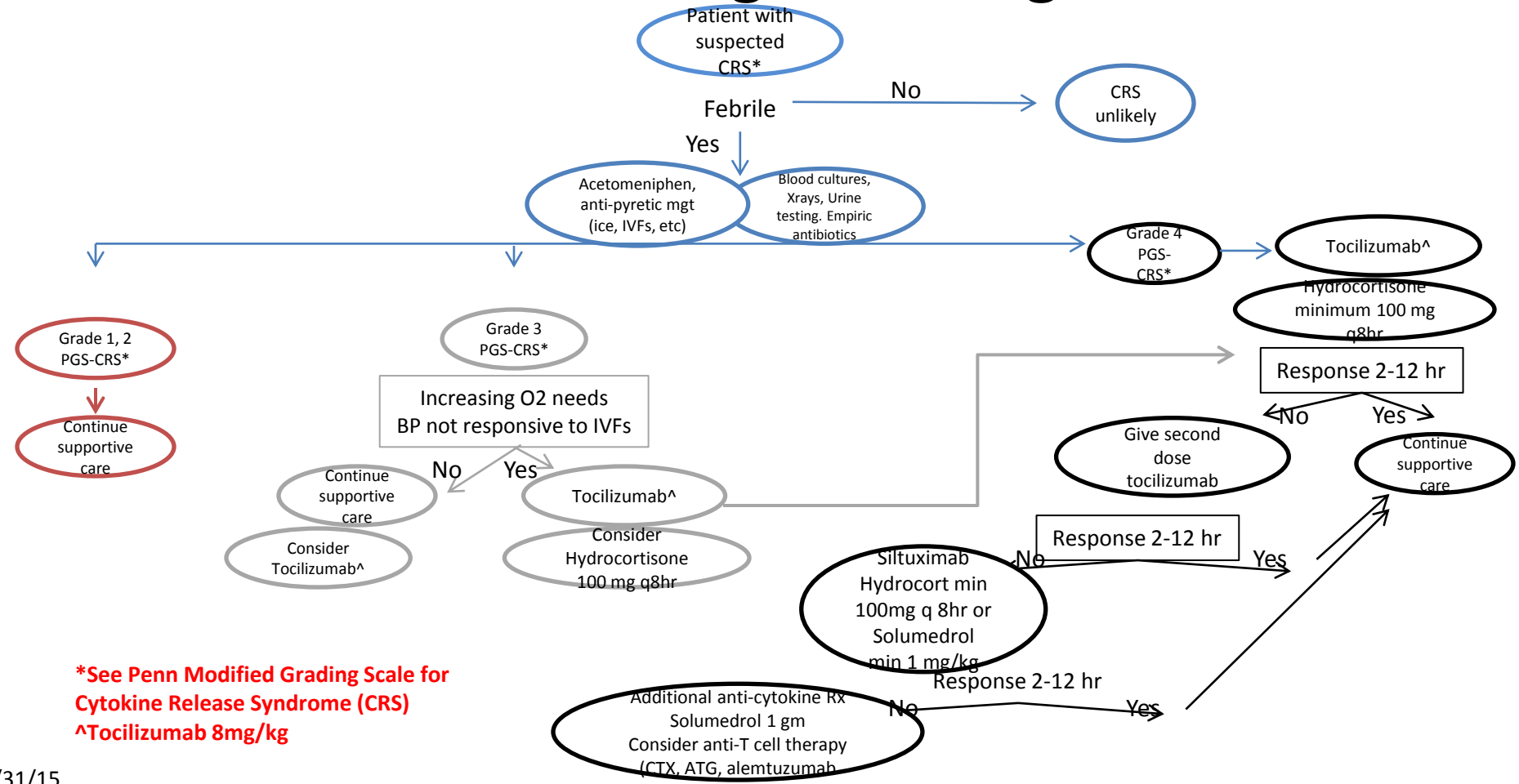
Gr 1	Gr 2	Gr 3	Gr 4
Mild; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for <=24 hrs	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening consequences; pressor or ventilatory support indicated

Penn Grading System for CTL019 - associated CRS[1]

Grade 1	Grade 2	Grade 3	Grade 4
Mild reaction: Treated with supportive care such as anti-pyretics, anti-emetics	**Moderate reaction :** Requiring intravenous therapies or parenteral nutrition; some signs of organ dysfunction (i.e. grade 2 creatinine or grade 3 LFTs) related to CRS and not attributable to any other condition. Hospitalization for management of CRS related symptoms including fevers with associated neutropenia.	**More severe reaction:** Hospitalization required for management of symptoms related to organ dysfunction including grade 4 LFTs or grade 3 creatinine related to CRS and not attributable to any other conditions; this excludes management of fever or myalgias. Includes hypotension treated with intravenous fluids or low-dose pressors, coagulopathy requiring FFP or cryoprecipitate, and hypoxia requiring supplemental oxygen (nasal cannula oxygen, high flow oxygen, CPAP or BiPAP). Patients admitted for management of suspected infection due to fevers and/or neutropenia may have grade 2 CRS.	**Life-threatening complications** such as hypotension requiring “high dose pressors”, hypoxia requiring mechanical ventilation.

1. Porter et al. Sci Trans Med 2015.

CTL019 CRS Management Algorithm



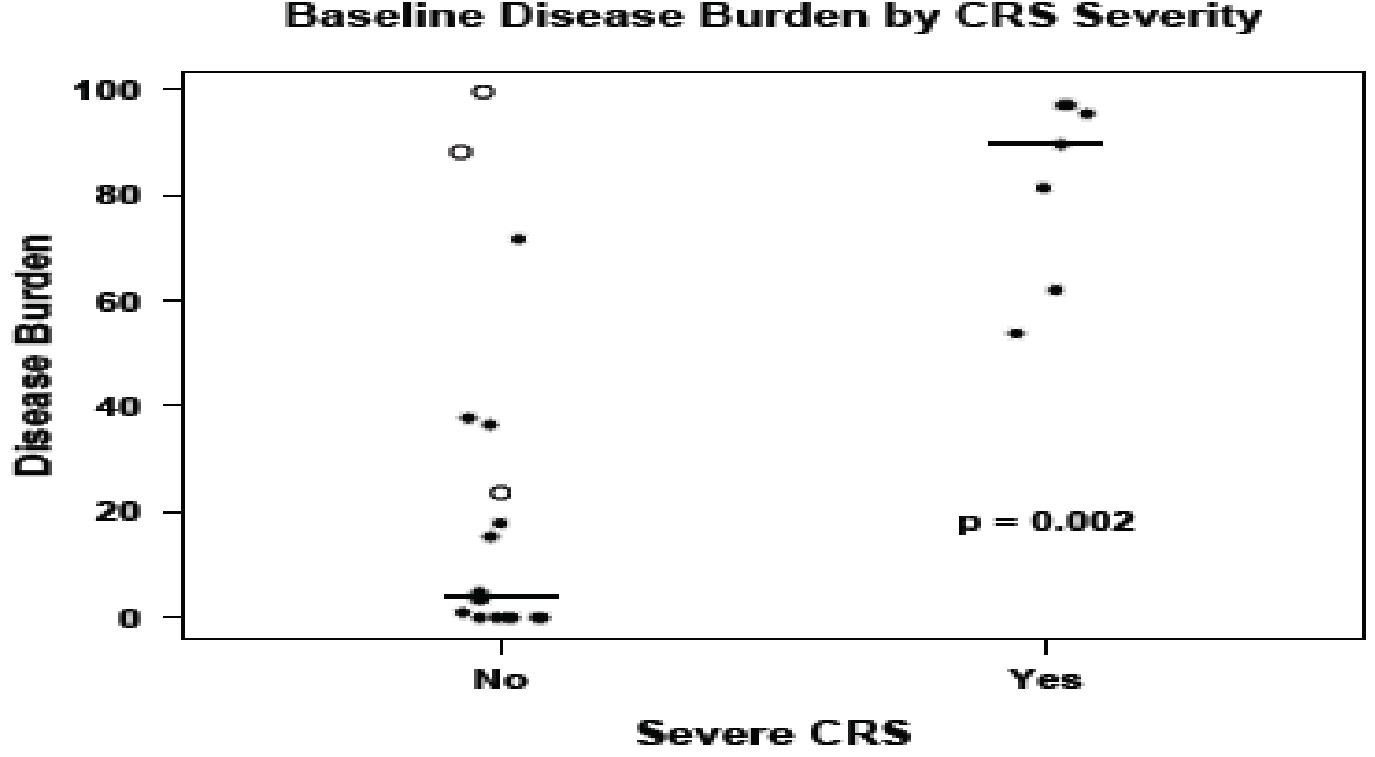
***See Penn Modified Grading Scale for Cytokine Release Syndrome (CRS)**
^Tocilizumab 8mg/kg

CRS: Predictors of severity

- Disease characteristics
  - Underlying disease (ALL>CLL/NHL)
  - Disease burden (ALL)
- Treatment characteristics
  - Infused dose
  - Product composition and other characteristics
  - LD chemotherapy
- Correlates with severe course:
  - Early changes in cytokines and CRP
  - Early onset symptoms
  - Concurrent infections

[1]Frey et al. ASH 2014
[2]Maude et al. NEJM 2014
[3]Davila et al. SciTranMed 2014
[4]Lee et al. TheLancet 2015

Severity of CRS and disease burden



Maude, et al. Submitted

Severe CRS: Poor Outcomes with Concurrent Infection [1]

- Single High Dose Infusion of 5.0×10^8
- Concurrent Sepsis
- Other factors (Age, Prior Tx, **Disease Burden**) similar to entire cohort
- TRM: 3 of 81+ patients

Age	Prior Allo	Anticytokine Therapy	Days of Anticytokine Therapy	Concurrent ID Illness	Outcome
63	N	tocilizumab x2 corticosteroids	Days 2,3	YES: Influenza B	Death-Day 5
56	Y	tocilizumab x3 etanercept x2 corticosteroids	Days 3,5,11,14	YES: Pseudomonas	Death-Day 16
32	N	tocilizumab x2 siltuximab corticosteroids	Days 3,4,5,14	YES: Stenotrophomonas	Death-Day 16

[1]Frey et al. ASH 2014, ASCO 2016

Perelman School of Medicine
University of Pennsylvania

Neurologic Toxicity

- Independent of Delirium of Fever
- Incidence 20-45%
- Presentation variable
  - Encephalopathy, aphasia, seizure
  - Many with onset after CRS resolution
- Resolution to baseline in all cases
- Mechanism of Toxicity Unclear
  - T cell vs Cytokine Mediated??
  - CAR T cells are seen in the CSF[1-4]

1Maude et al. NEJM 2014
2Davila et al. SciTranMed 2014
3Lee et al. TheLancet 2015
4Kochendorfet al. JCO 2015

Neuro Toxicity of CART19 Therapy

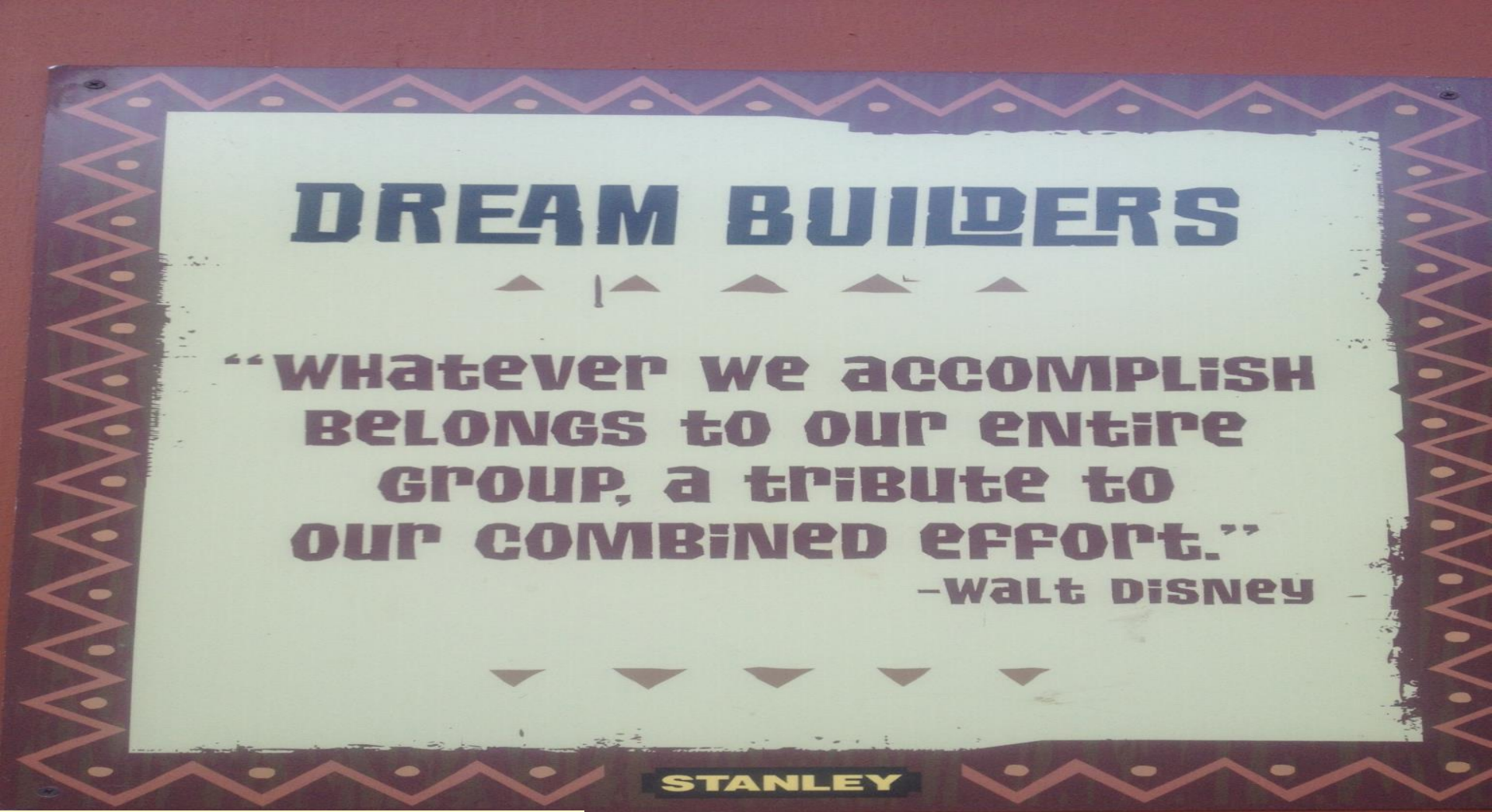
Ref	Program/ CAR	Population	Response	CRS	Neuro Toxicity
Acute Lymphoblastic Leukemia					
Maude et al. NEJM 2014	PENN 4-1BB	N=30(ALL) Peds&Adults	CR=90%	100% CRS 27% Severe	43% Total Encephalopathy Aphasia Seizure (1)
Davila et al. SciTrMed 2014	MSK CD28	N=16 (ALL) Adults	CR=88%	43% Severe	25% Gr3-4 Encephalopathy Seizure
Lee et al. Lancet 2015	NCI CD28	N=21 (ALL) Peds&AYA	CR=67% Intent to Treat	76% CRS 28% Severe	29% Total hallucinations Dysphasia encephalopathy
Non-Hodgkins Lymphoma & Chronic Lymphocytic Leukemia					
Kochenderfer JCO 2015	NCI CD28	N=15 (NHL/CLL)	CR=53% PR=27%	27% Severe	40% Total Encephalopathy Aphasia R facial par Monoclonus Ataxia
Porter et al. ASH 2014	PENN 4-1BB	N=14(CLL)	CR=29% PR=29%	42% Severe	NR

Summary: CTL019

- CTL019 dose and schedule correlate with toxicity and response
- A fractionated dosing scheme allows for
  - Real time intra-patient dose modification in response to toxicity
  - Maintenance of high response rates
- Concurrent sepsis and CRS confers a poor outcome
- Future studies will determine optimal approach to minimize toxicity while maintaining the high efficacy in CAR T cell therapy
  - Fractionated dosing
  - Inverse dosing based on disease burden
  - Timing of anti-cytokine directed therapy (prophylactic, pre-emptive, empiric)

Summary: CTL019

- CAR T cells are dramatically effective for relapsed/refractory ALL, CLL, NHL.
- They are a “living drug”.
  - Undergo massive in vivo expansion (1000 – 10,000X)
  - Persist for long periods (> 6 yrs in some cases)
    - Persisting cells remain functional
- Associated with unique toxicities including
  - Neurologic abnormalities (etiology uncertain, typically resolves spontaneously)
  - CRS (managed with supportive care and anti-cytokine therapy)
  - B cell aplasia (managed with IVIG)
- CRS requires novel grading scale to be able to report, grade and treat pts consistently
  - There is not unified acceptance of a novel grading scale.
- CAR T cell therapy is here to stay with trials expanding to other B cell malignancies and solid tumors.



Near entrance to Fantasy Land, Magic Kingdom, Disney World 2013

Colleagues and Collaborators (too many to list)

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Novartis

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ACGT ALLIANCE FOR CANCER GENE THERAPY
National grants for cancer research

Adaptive TcR, Inc

LEUKEMIA & LYMPHOMA SOCIETY®
fighting blood cancers

Novartis

CAR T-Cell Toxicities - A Regulatory Perspective

Ke Liu, MD, PhD
Chief, Oncology Branch
Division of Clinical Evaluation, Pharmacology and Toxicology
Office of Cellular, Tissue and Gene Therapies
Center for Biologics Evaluation and Research

FDA-AACR: Immuno-oncology Drug Development Workshop
October 13, 2016

Disclosures

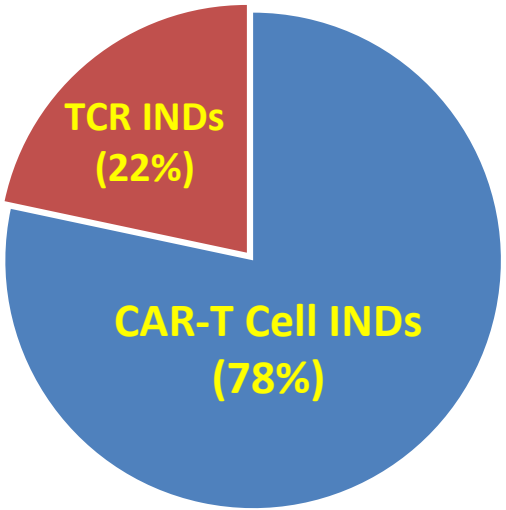
I have no financial relationships to disclose.

I will not discuss off-label use of products.

Outline

- CAR T-cell INDs under review
- Toxicities
- CBER Initiatives

TCR and CAR-T cell Products under Review

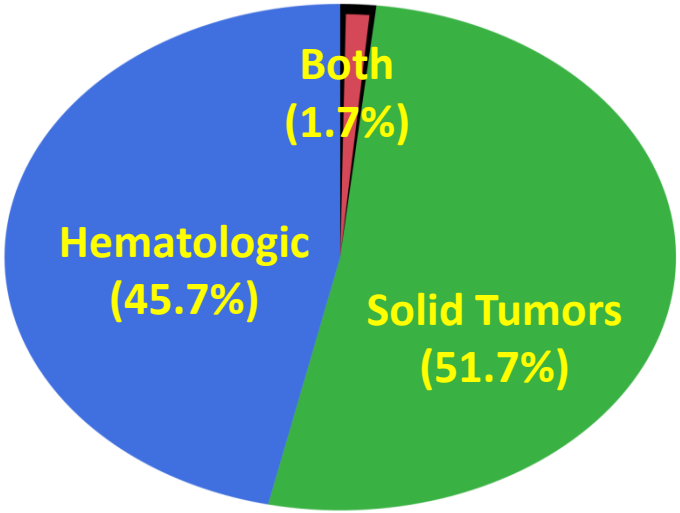


A total of ~120 TCR / CAR-T Cell INDs regulated by OCTGT/CBER

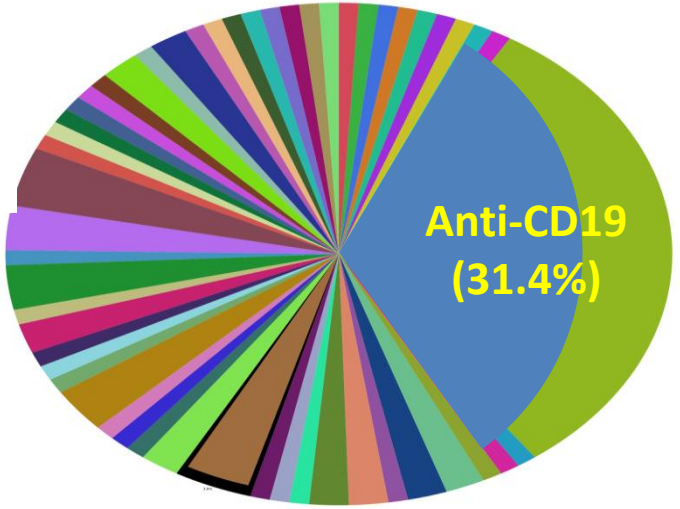
As of August 2016

TCR and CAR-T cell Products under Review

TCR / CAR-T Cell INDs for Cancer Therapy



CAR–T Cell INDs



As of August 2016

Regulatory Considerations

Toxicities – 1

- Infusion reactions
- Cytokine release syndrome
  - Specify criteria used (CTCAE not sufficient)
  - Importance of monitoring cytokine levels
- Neurotoxicity
  - Type
  - Evaluations
    - Baseline
    - During Toxicity
    - End of treatment
- Other (cytopenias, cardiac)
- Optimal management for toxicities
  - Consideration for specific algorithms

Regulatory Considerations

Toxicities – 2

- On-target / off-tumor effects
- Off-target effects
- Long-Term safety concerns
  - Persistence of CAR T-cells
  - B-cell aplasia with antiCD19 CAR T-cells
  - Potential for second malignancy
- Optimal management for toxicities
  - Short-term vs. long-term

CBER Initiatives

- CRS assessment and grading criteria in collaboration with NIH OBA RAC

- CAR-T Safety Database Pilot Project

CAR-T Safety Database Pilot Project

Objectives

- Perform cross-study / cross-IND analysis of CAR-T data
- Develop risk mitigation strategies

CAR-T Safety Database Pilot Project

- Clinical Safety Database
  - CDISC – SDTM format for data submission

- Chemistry Manufacturing and Controls (CMC)
  - Information from INDs
  - Additional inquiries to the sponsors

CAR-T Safety Database Pilot Project

Task areas

1. **Data Standardization**: Define a standard structure for collecting and storing CAR-T cell data in a format that supports cross-study/cross-IND analysis.

2. **Data Collection**: Collect CAR-T cell data from sponsors in a machine-readable format for database input.

3. **Data Management:** Develop tools for processing sponsor-submitted data, validating data, and loading data into the CAR-T cell database.

4. **Data Analysis / Modeling:** Create data analysis and reporting tools. Develop statistical models for predicting safety trends

Conclusion

- CAR-T cell therapy: innovative, personalized and promising
- Unique challenges in the toxicity management
  - Mechanism
  - Short-term and long-term monitoring and follow-up
- Opportunities:
  - Collective efforts from all stakeholders
  - Engage with regulatory agencies early and often

CAR-T Safety Database Pilot Project Team

- OCTGT
  - Kristin Baird, MD
  - Robert Sokolic, MD
  - Maura O'Leary, MD
  - Bindu George, MD
  - Wilson Bryan, MD
  - Kim Schultz, PhD
  - Denise Gavin, PhD
  - Xiaobin Lu, PhD
- OBE
  - John Scott, PhD

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- ENGILITY
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- Robert Sokolic, MD
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Open Position

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Regulatory Questions:

- Contact the Regulatory Management Staff in OCTGT: at CBEROCTGTRMS@fda.hhs.gov
  or Lori.Tull@fda.hhs.gov
  or by calling (301) 827-6536

- OCTGT Learn Webinar Series:
  http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm

A Global Picture of Immuno-Oncology Adverse Events

FDA-AACR Workshop: Immuno-Oncology Drug Development

Washington, DC

October 13-14, 2016

Elad Sharon, MD, MPH
Cancer Therapy Evaluation Program
National Cancer Institute

Financial Disclosures

- Nothing to disclose

Overview of Drug Development in Immuno-Oncology

- Imagination of the industry has been captured by immuno-oncology, particularly PD1/PDL1 agents
- Other molecules including alternative checkpoint inhibitors (TIM3, LAG3, IDO, etc.), adoptive cell transfer strategies, vaccines, cytokines, and combinations of therapies are receiving invigorated interest as the field searches for the “next big thing”
- How to deal with challenging adverse events and not miss opportunities for further development of innovative and efficacious therapies?

Oncology

And then there were five

Doctors are trying—with some success—to recruit the immune system to help with the war on cancer

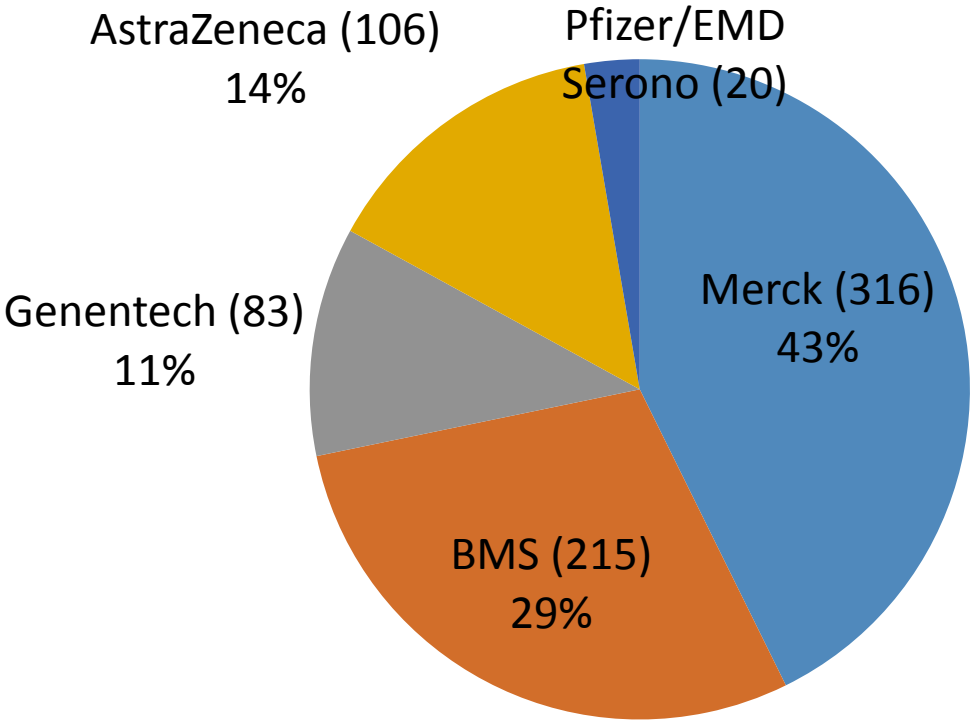
American Association for Cancer Research

The Economist PRINT EDITION, June 6, 2015

The Immunotherapy Revolution is Now

- Oncology is in the midst of a revolution in the treatment of metastatic patients, with patients in other settings (adjuvant, neoadjuvant) soon to follow
- The broad potential of PD1/PDL1 inhibitors across a wide variety of tumor types has not yet been seen in the era of targeted therapy
  - Given breadth of activity, testing widely is likely warranted and can have tremendous positive benefits for patients
- One key to developing a proper disease strategy involves the close monitoring of adverse events to determine in what context immunotherapy can be incorporated safely without compromising the benefit of existing therapeutic modalities

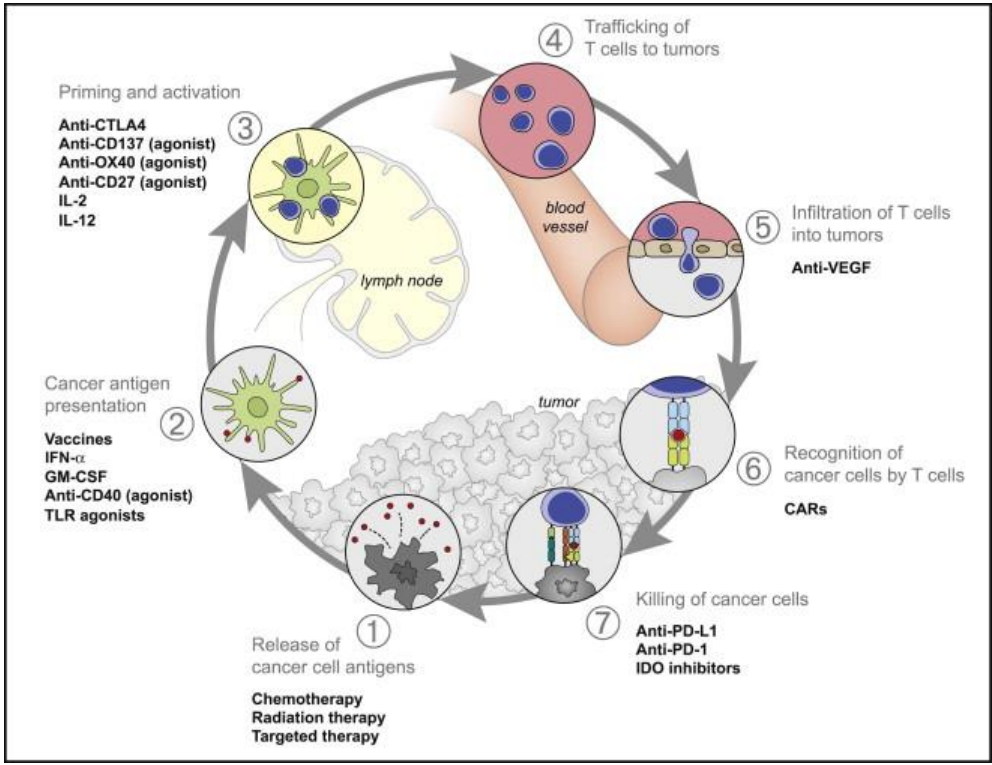
There are 728 open trials with the five leading PD1/PDL1 agents



Source: ClinicalTrials.gov, accessed 10/11/2016

T Cells Have been the Final Common Pathway

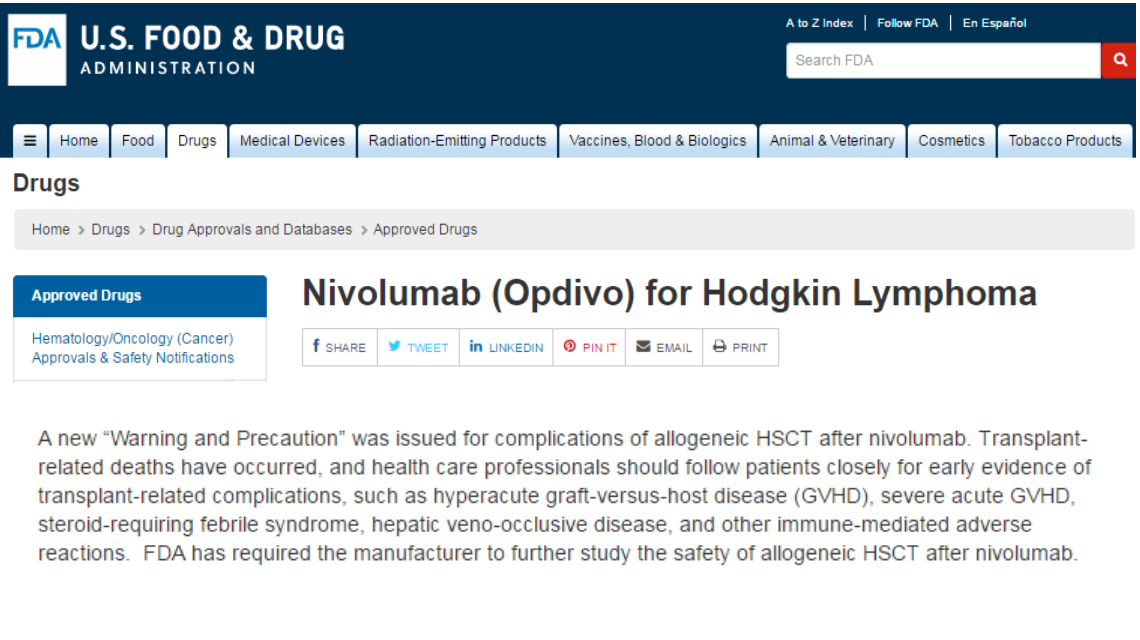
- Although specifics of therapies may be different, final common pathway of most successful immunotherapies under development is the cytotoxic T cell
  - NK cell and other therapies may have relevance, but no proven benefit to date
  - Mediation of adverse events has also been presumably due to T cell-mediated effects
  - Adverse events are largely due to an “on-target” effect

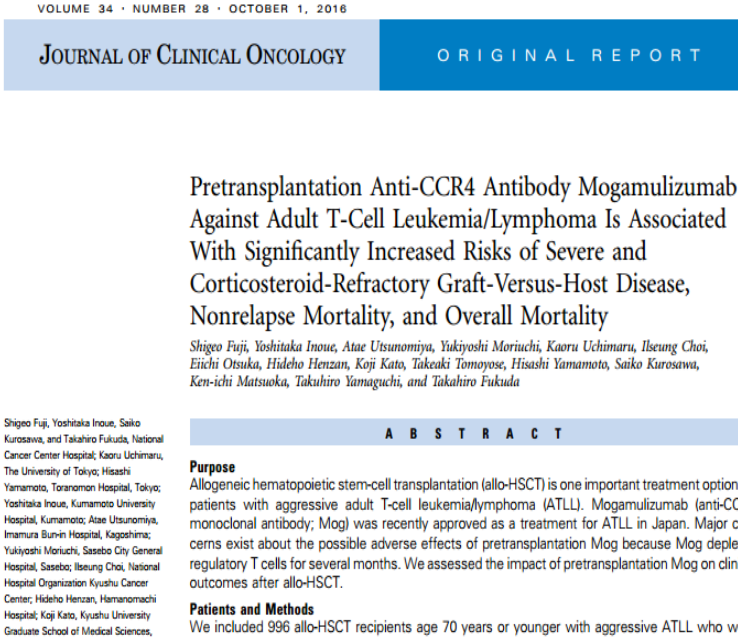


Chen and Mellman. *Immunity.* 2013

Examples: Hematologic Disease and GVHD

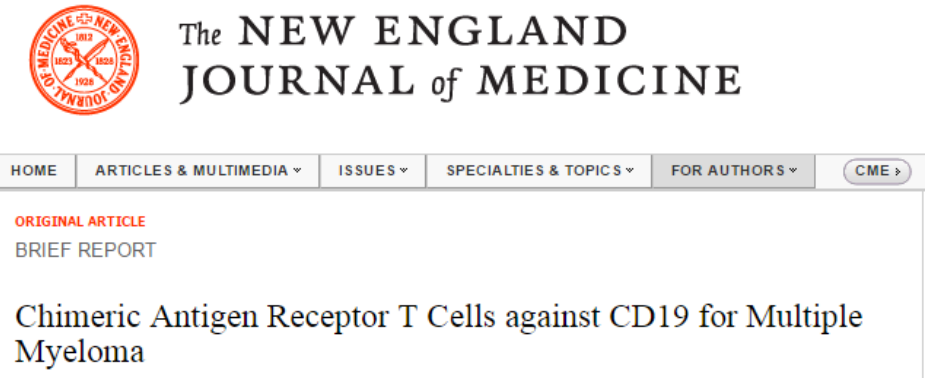
- Certain diseases or disease settings need significant risk-benefit analysis
  - Nivolumab for Hodgkin Lymphoma
  - Mogamulizumab (agent targeting CCR4 and approved in Japan for ATLL, PTCL, CTCL)





How to Predict Adverse Events: Step One: Look at similar agents

- Cross-fertilization of adverse event knowledge is as important as in any other domain of science
  - An adverse event with one PD1/PDL1 agent should be closely monitored in evaluations of other similar agents
  - A CD19-CD3 bispecific antibody with certain toxicities can inform the development of a CD19 CAR and vice versa



"…We previously treated a patient who had multiple myeloma with a CTL019 dose of 5×10^8cells on day 2 after autologous stem-cell transplantation, according to a single-patient, compassionate-use protocol. The patient had a very good partial response complicated by **severe cytokine release syndrome** and **neurotoxic effects** that were attributed to CTL019; these toxic effects were associated with a robust in vivo CTL019 expansion."

Contraindications

BLINCYTO® is contraindicated in patients with a known hypersensitivity to blinatumomab or to any component of the product formulation.

Warnings and Precautions

- Cytokine Release Syndrome (CRS): Life-threatening or fatal CRS occurred in patients receiving BLINCYTO®. Infusion reactions have occurred and may be clinically indistinguishable from manifestations of CRS. Closely monitor patients for signs and symptoms of serious events such as pyrexia, headache, nausea, asthenia, hypotension, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), increased total bilirubin (TBILI), disseminated intravascular coagulation (DIC), capillary leak syndrome (CLS), and hemophagocytic lymphohistiocytosis / macrophage activation syndrome (HLH/MAS). Interrupt or discontinue BLINCYTO® as outlined in the Prescribing Information (PI).
- Neurological Toxicities: Approximately 50% of patients receiving BLINCYTO® in clinical trials experienced neurological toxicities. Severe, life-threatening, or fatal neurological toxicities occurred in approximately 15% of patients, including encephalopathy, convulsions, speech disorders, disturbances in consciousness, confusion and disorientation, and coordination and balance disorders. The median time to onset of any neurological toxicity was 7 days. Monitor patients for signs or symptoms and interrupt or discontinue BLINCYTO® as outlined in the PI.
- Infections: Approximately 25% of patients receiving BLINCYTO® experienced serious infections, some of which were life-threatening or fatal. Administer prophylactic antibiotics and employ surveillance testing as appropriate during treatment. Monitor patients for signs or symptoms of infection and treat appropriately, including interruption or discontinuation of BLINCYTO® as needed.
- Tumor Lysis Syndrome (TLS): Life-threatening or fatal TLS has been observed. Preventive measures, including pretreatment nontoxic cytoreduction and on treatment hydration, should be used during BLINCYTO® treatment. Monitor patients for signs and symptoms of TLS and interrupt or discontinue BLINCYTO® as needed to manage these events.
- Neutropenia and Febrile Neutropenia, including life-threatening cases, have been observed. Monitor appropriate laboratory parameters during BLINCYTO® infusion and interrupt BLINCYTO® if prolonged neutropenia occurs.
- Effects on Ability to Drive and Use Machines: Due to the possibility of neurological events, including seizures, patients receiving BLINCYTO® are at risk for loss of consciousness, and should be advised against driving and engaging in hazardous occupations or activities such as operating heavy or potentially dangerous machinery while BLINCYTO® is being administered.

Preservation of dose intensity of one agent may increase adverse events of another

- Ipilimumab now FDA-approved in three strategies for melanoma:
  - Metastatic melanoma at a dose of 3 mg/kg
  - Adjuvant resected melanoma at a dose of 10 mg/kg
  - Combination with nivolumab 1 mg/kg with ipilimumab 3 mg/kg (combination for 4 doses, followed by nivolumab 3 mg/kg)
- Phase 1 trial and most BMS efforts focus on dosing strategy of **nivolumab at 3 mg/kg** with **ipilimumab at 1 mg/kg** (or similar flat dosing strategy)
- Prior therapy may affect the toxicity of the newer agent
  - Melanoma patients coming off of PD1 therapy and receiving ipilimumab at 3 mg/kg as salvage
  - Adjuvant melanoma patients who receive 10 mg/kg of ipilimumab and experience metastasis on therapy may be treated with PD1

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ORIGINAL ARTICLE

Prolonged Survival in Stage III Melanoma with Ipilimumab Adjuvant Therapy

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ABSTRACT

BACKGROUND

On the basis of data from a phase 2 trial that compared the checkpoint inhibitor ipilimumab at doses of 0.3 mg, 3 mg, and 10 mg per kilogram of body weight in patients with advanced melanoma, this phase 3 trial evaluated ipilimumab at a dose of 10 mg per kilogram in patients who had undergone complete resection of stage III melanoma.

METHODS

After patients had undergone complete resection of stage III cutaneous melanoma, we randomly assigned them to receive ipilimumab at a dose of 10 mg per kilogram (475 patients) or placebo (476) every 3 weeks for four doses, then every 3 months for up to 3 years or until disease recurrence or an unacceptable level of toxic effects occurred. Recurrence-free survival was the primary end point. Secondary end points included overall survival, distant metastasis–free survival, and safety.

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So, you've had an AE: Now what?

- After an immune-related AE, can patients be re-treated with the same agent?
  - An immune-related toxicity is often different in character from a corresponding non-immune-related toxicity
  - What is the risk of recurrence of the toxicity?
  - How soon can retreatment be considered?
  - Why doesn't dose de-escalation or reduction in treatment intensity or total exposure work?
    - There has been little work on there is no guidance on package insert of approved agents for re-treatment

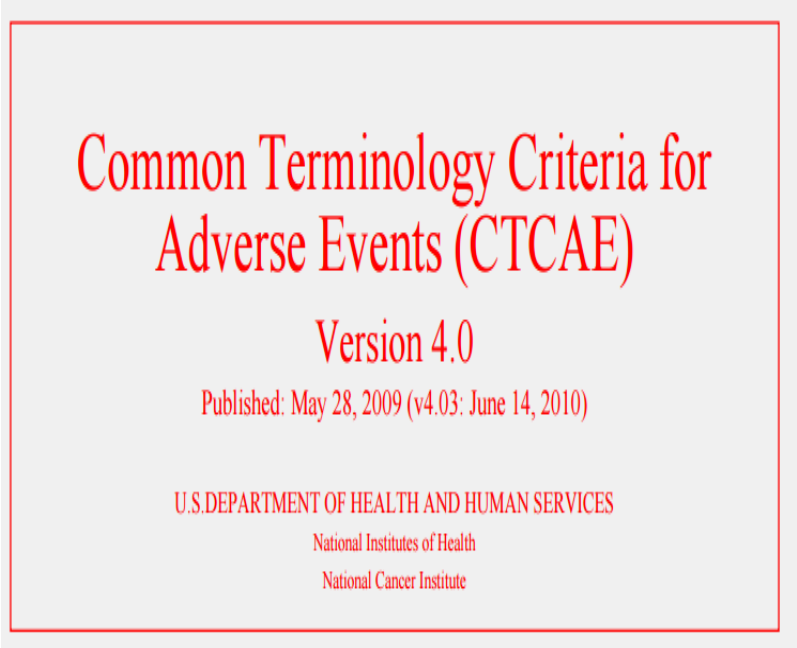
- Risk mitigation strategies should be tested with the intent of helping patients obtain access to beneficial therapies, even after an AE
  - Can patients be retreated on steroids or with other agents as risk mitigation?

The human as a knockout animal model

- Immune-related AEs may have relevance for the study of autoimmune disease
- Treatment and management of an adverse event induced by PD1/PDL1 inhibitors can teach us something about the corresponding autoimmune disorder and vice versa?
- Samples (blood, tissue, etc.) from adverse events on trial should be shared to examine commonalities between patients who exhibit the adverse event in question
  - Trial patients often have extensive workups and blood samples collected
  - Analysis of severe AE should take priority over a planned analysis of other correlative assays on trial
  - NCI trials may be available, but are industry sponsors willing to share samples from patients on trial who experience significant adverse events?
  - Consents for sharing of samples be made explicit at the outset of a trial, with opt-outs offered for patients

NCI CTCAE Terms can be updated for the era of immunotherapy

- CTCAE is a global standard for academic and industry sponsors
- If an immune-based agent is causing an adverse event, it's likely to be immune-mediated
  - New terms are added to CTCAE with each new version
  - Immunotherapy community needs new terms to describe events that are only going to become more common over time
  - "Diarrhea" is over-reported on PD1/PDL1 trials; "colitis" is likely under-reported
  - Would including "autoimmune colitis" as a term be helpful?



Eligibility Criteria should be more rational

- Too many patients are being needlessly excluded from clinical trials without evidence
  - HIV-positive patients are almost uniformly excluded from industry trials
  - Even when data are included in the product label, sponsors have been reluctant to liberalize criteria for eligibility for patients with renal and hepatic dysfunction
- Field is slow to change: templates (copy/paste) are to blame for lack of innovative thinking
- Making trials more accessible to real world patients would make them more relevant for physicians and patients

Options for the Future

- Anticipate AEs based on similar mechanisms of action or similar targets
- Consider real world use of therapies in approvals and instituting guidelines
- Update CTCAE terms for new era of immunotherapy
- Develop large, publicly accessible mechanism for analysis of adverse events with samples from patients enrolled on trials (or in community)
  - Such an initiative could be developed for each separate AE, drawing on expertise from the corresponding autoimmune disease experts (myositis, IBD, etc.)
  - Asking patients from the outset to share their samples if they experience an AE
- Experiment with different risk mitigation strategies
- Obtain real world evidence can inform analysis of specific AEs in large databases
  - Loosen eligibility on trials to better approximate real world cancer patients

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Session IIb Panel Discussion

Evaluation of Immune-Mediated Adverse Events

Moderator: Jedd Wolchok, MD, PhD

Speakers:

David Berman, MD, PhD

Mario Sznol, MD

Diko Kazandjian, MD

David Porter, MD

Ke Liu, PhD

Elad Sharon, MD, MPH

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Day 1 Summarizing Remarks

Jedd Wolchok, MD, PhD
Workshop Co-Chair