Interleukin-12 (IL-12) KOL Roundtable

NASDAQ: PDSB | April 21, 2023

PDS Biotechnology

Precision Designed Science For Immunotherapy

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Disclaimer

- PDS Biotech is hosting this roundtable
- Each panelist is speaking at the request of PDS Biotech
- Information presented is consistent with FDA guidelines

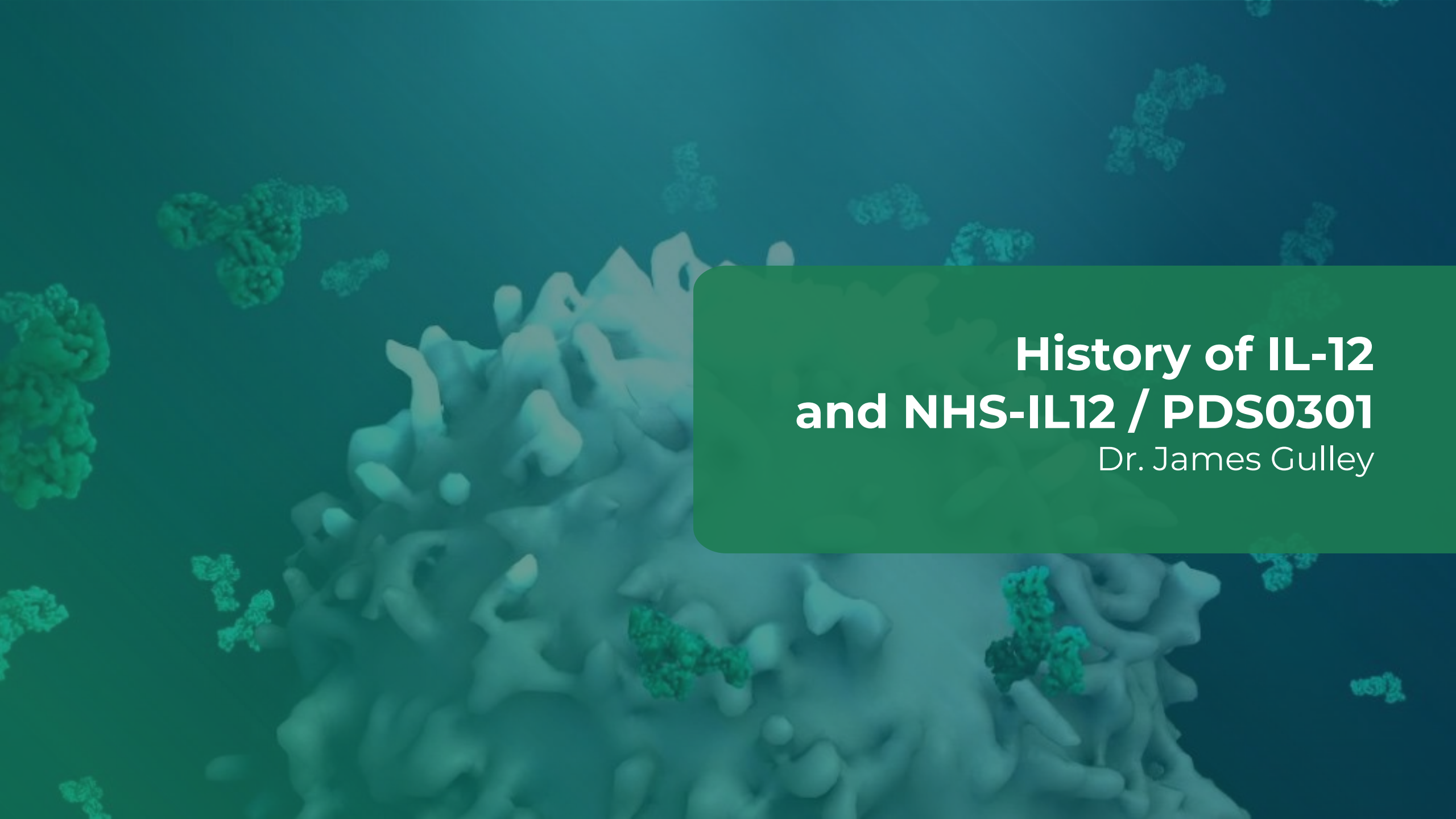
Introducing our Panel

Dr. James Gulley
Co-Director of the Center for
Immuno-Oncology
National Cancer Institute

Dr. Jeffrey Schlom
Co-Director of the Center for
Immuno-Oncology
National Cancer Institute

Today's Agenda

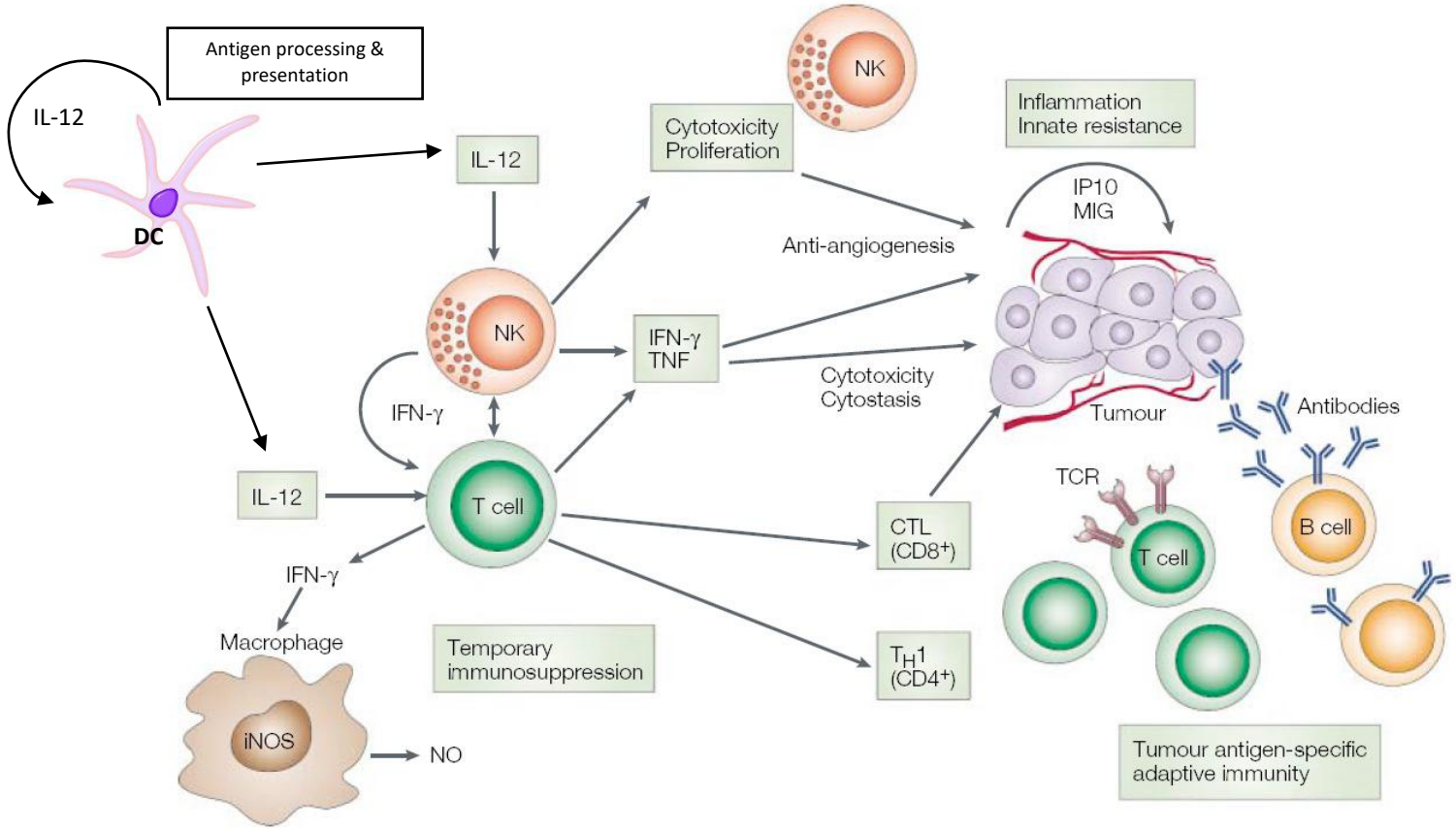
Welcome and Introductions	Dr. Lauren V. Wood
History of IL-12 and NHS-IL12/PDS0301	Dr. James Gulley
Preclinical and Mechanistic Studies of NHS-IL12/PDS0301	Dr. Jeffrey Schlom
Clinical Studies of NHS-IL12/PDS0301	Dr. James Gulley
Panel Discussion	Moderated by Dr. Lauren V. Wood
Closing Remarks	Dr. Lauren V. Wood



History of IL-12 and NHS-IL12 / PDS0301

Dr. James Gulley

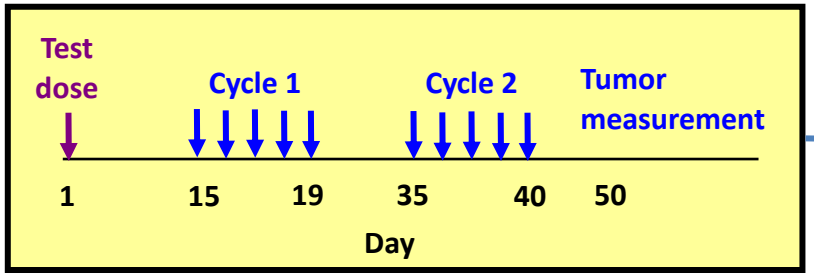
Subsequent investigations elucidate the mechanisms of IL-12 anti-tumor activity



Modified from Trinchieri G, *Nature Reviews Immunology* 2003

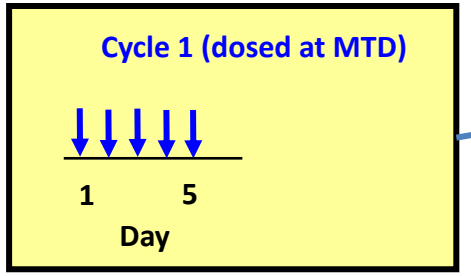
1994: Early clinical development of IL-12

Schema of Phase 1:



500 ng/kg defined as the MTD

Schema of Phase 2:



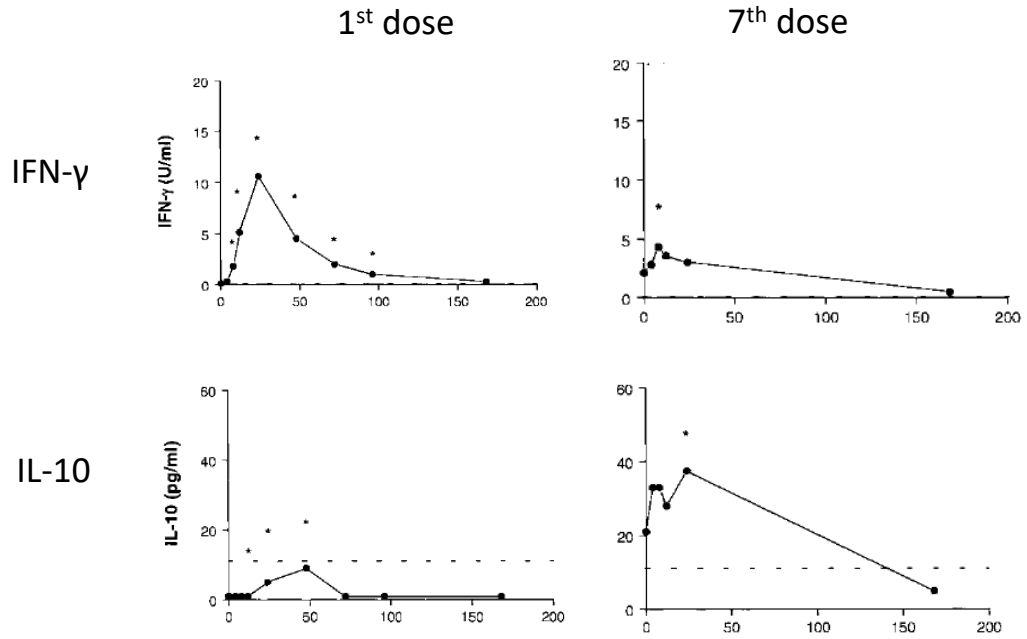
Severe toxicity in all patients; two patient deaths; trial stopped –

Explanation: Mouse and monkey data show that the 'test dose' in the phase one trial reduced the toxicity of subsequent daily administrations – clinical trials allowed to resume…

Source: Leonard J *et al, Blood* 1997, Atkins M *et al, Clin Ca Res* 1997

IL-12 de-sensitization in patients is associated with counter-induction of IL-10

- The first dose of IL-12 increases production of Th1 cytokines such as IFN-γ and TNF-α
- Frequent, repeated dosing was associated with declining IFN-γ and TNF-α levels, and a persistent elevation of the Th2 cytokine, IL-10
  - IL-10 is a negative regulator of IL-12 activity
  - Repeated administration also increased serum levels of soluble IFN-γ receptor



Source: Portielje J, *Clin Can Res* 2003

After well over a decade in the clinic, recombinant IL-12 has failed due to limited efficacy and toxicity

Selected Phase I

Tumors	Route of administration	Patients (*n*)	Objective response	Immune modulation	Angiogenesis-related effects	Refs.
Non – Hodgkin's lymphoma and Hodgkin's lymphoma †	i.v. or s.c.	42	21% ‡	↑ Circulating $CD8^+$ T cells	↓ sVEGF and sbFGF in 37% of patients	(69)
Cutaneous T cell lymphoma*	s.c. or intralesionally	10	56%	↑ $CD8^+$ and/or $TIA\text{-}1^+$ T cells in skin biopsy from regressing lesions	ND	(59)
Melanoma, renal cell carcinoma*	i.v.	28	3%	Induction of IFN-γ, IL-15 and IL-18, maintained in patients with tumor regression or prolonged disease stabilization	ND	(60)
Phase 2						
Cervical carcinoma †	i.v.	34	3%	↑ Lymphoproliferative responses to HPV 16 E4, E6 and E7 peptides	ND	(65)
Renal cell carcinoma †	s.c.	30	7%	↑ sIFN-γ, IL-10 and neopterin, maintained in cycle 2	ND	(61)

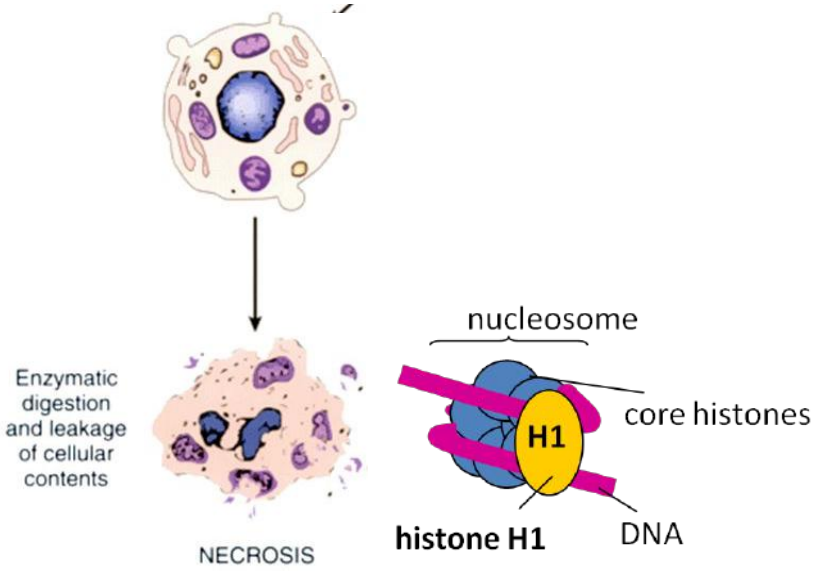
- Limited efficacy observed in RCC and melanoma
- Promising activity against lymphomas
- Immunomodulatory effects clearly demonstrated
- Toxicities problematic, tolerability improved with s.c. delivery
- **Frequent, repeated dosing causes a de-sensitization effect that limits efficacy…**

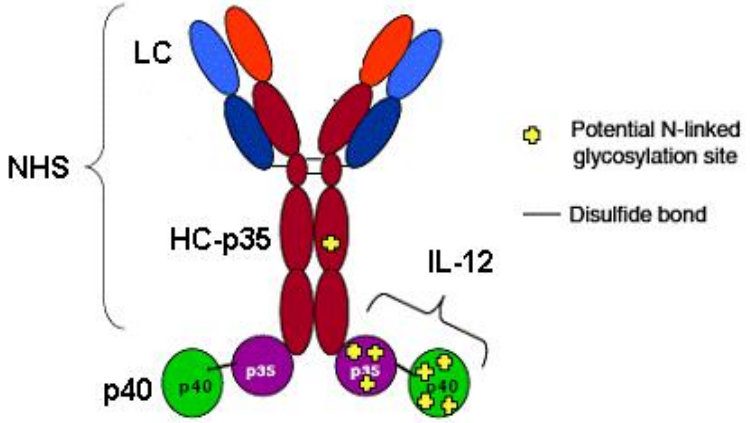
Re-thinking IL-12 immunotherapy

- A strategy for success with NHS-IL12 (PDS0301):
  - NHS-IL12 targets IL-12 delivery to the tumor, increasing exposure at the tumor site while reducing systemic exposure
  - Further improved tolerability due to the reduced potency of NHS-IL12
  - NHS-IL12 is a large macromolecule (~250 kDa) with a longer PK than rIL-12, providing efficacious exposure with a single s.c. dose, eliminating the need for frequent dosing
  - Administration by s.c. route will promote lymphatic absorption of the large NHS-IL12 molecule, promoting IL-12 effects at draining lymph nodes prior to systemic distribution
  - Monitor the IL-10/IFN-γ axis to guide the establishment of optimal dose schedules in the clinic

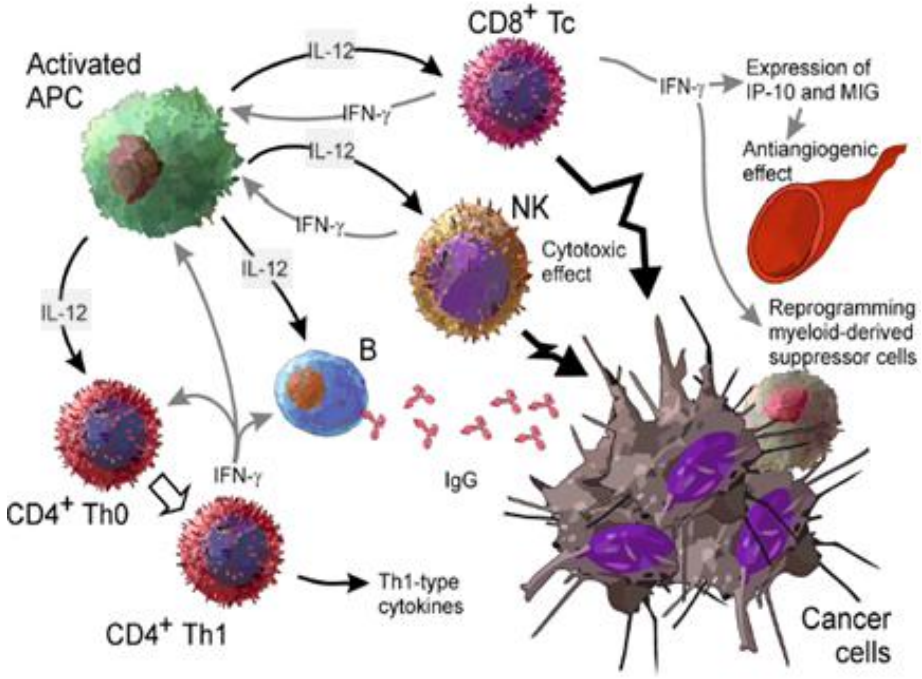
NHS-IL12 - Molecule Overview

- Molecule Composition
  - M9241 (NHS-IL12) is an immuno-cytokine comprised of two IL-12 heterodimers each fused to one of the H-chains of the IgG NHS76 (fully human) antibody
  - It is a complex molecule with several glycosylation sites
  - IL-12 has been genetically modified to eliminate a proteolytic cleavage site (p40 clipping resistant)
  - The junction region between the IL-12 and NHS76 has been de-immunized.
- Molecule Characteristics
  - NHS76 targets regions of tumor necrosis where cell membrane integrity has been lost and DNA has become exposed.
  - It has affinity for both single- and double-stranded DNA
  - Tolerability is further increased by administering NHS-IL12 by the s.c. route of administration to achieve a slow, sustained release into the bloodstream and enhance lymphatic absorption
  - No ADCC or CDC activity in vitro





MOA: Innate & Adaptive Immunity Driving Force

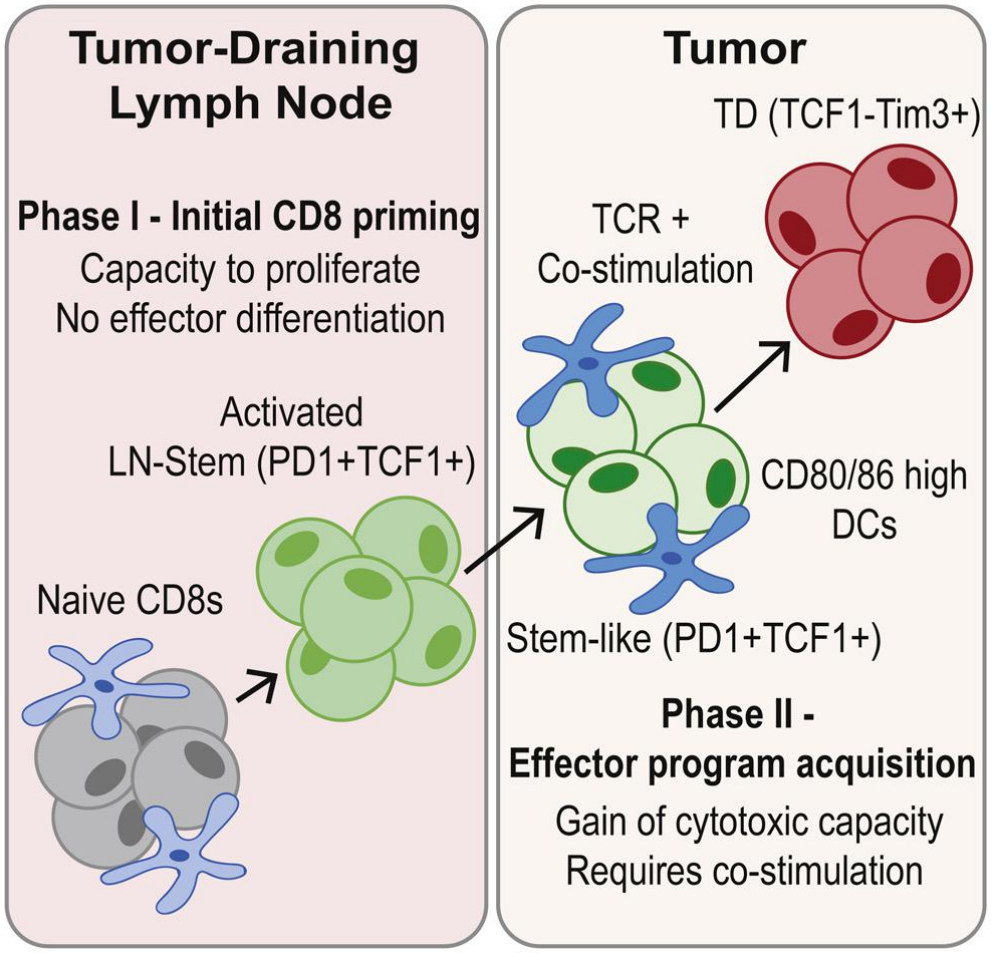


- Distinct Mechanisms for IL-12 as a Tumor Targeting Therapy
- Induces differentiation of naïve CD4+ T-cells to the Th1 phenotype
- Increases the proliferation and lytic capacity of CD8+ cytotoxic T cells and NK cells
- Promotes IFN-γ production via NK & T-cells
  - Increases the production of IP-10 (interferon-inducible protein 10) and MIG (monokine induced by interferon gamma) which then mediates an anti-angiogenic effect
  - Enhances antigen-presentation through paracrine upregulation of MHC class I and II expression

Source: Lasek et al 2014

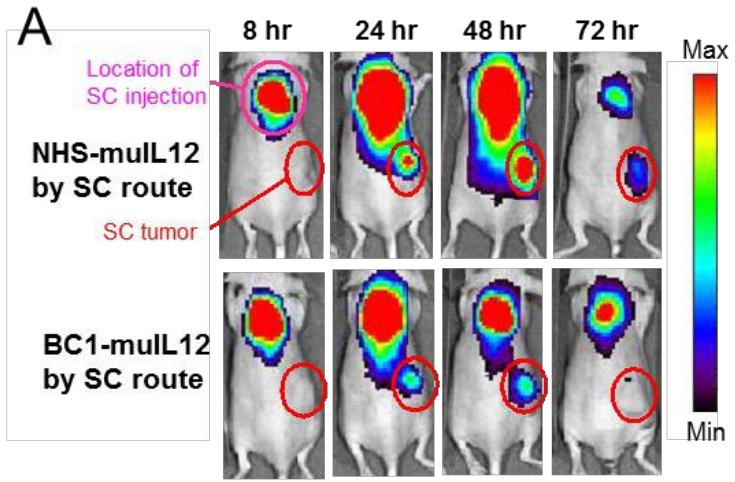
Effector programing of CD8+ T-cells dependent on APC in TME

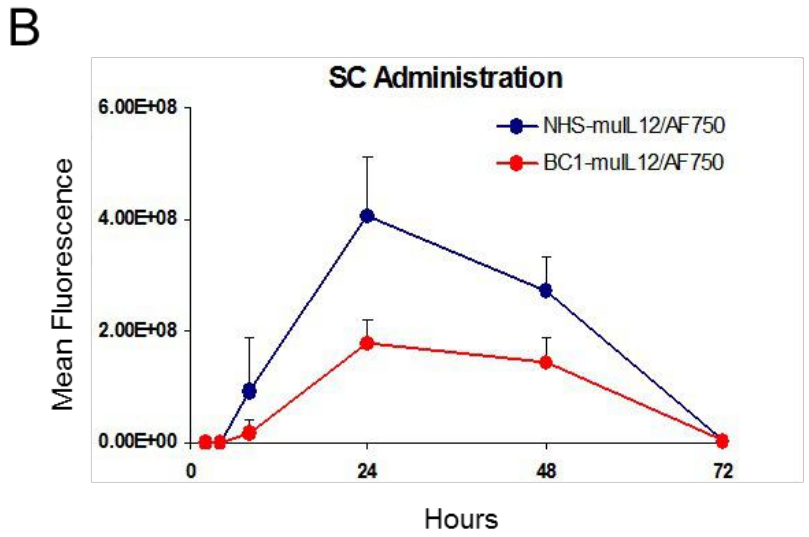
- CD8+ T cells in tumor-draining lymph nodes maintain a TCF1+ stem-like program
- Tumor-specific CD8+ T cells migrate to the tumor in the stem-like state
- CD8+ T cells only acquire the canonical effector program within the tumor
- Effector program acquisition requires co-stimulation in the tumor microenvironment



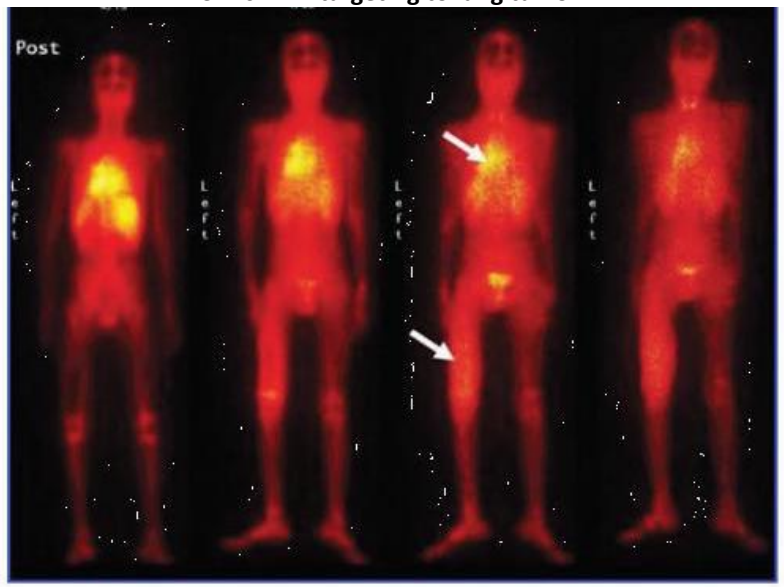
Source: Prokhnevska…Kissick et al. CD8+ T cell activation in cancer comprises an initial activation phase in lymph nodes followed by effector differentiation within the tumor. *Immunity* Dec 2022

Kinetic Analysis of Tumor Localization Following s.c. Administration of AF750-labeled NHS-muIL12 and BC1-muIL12

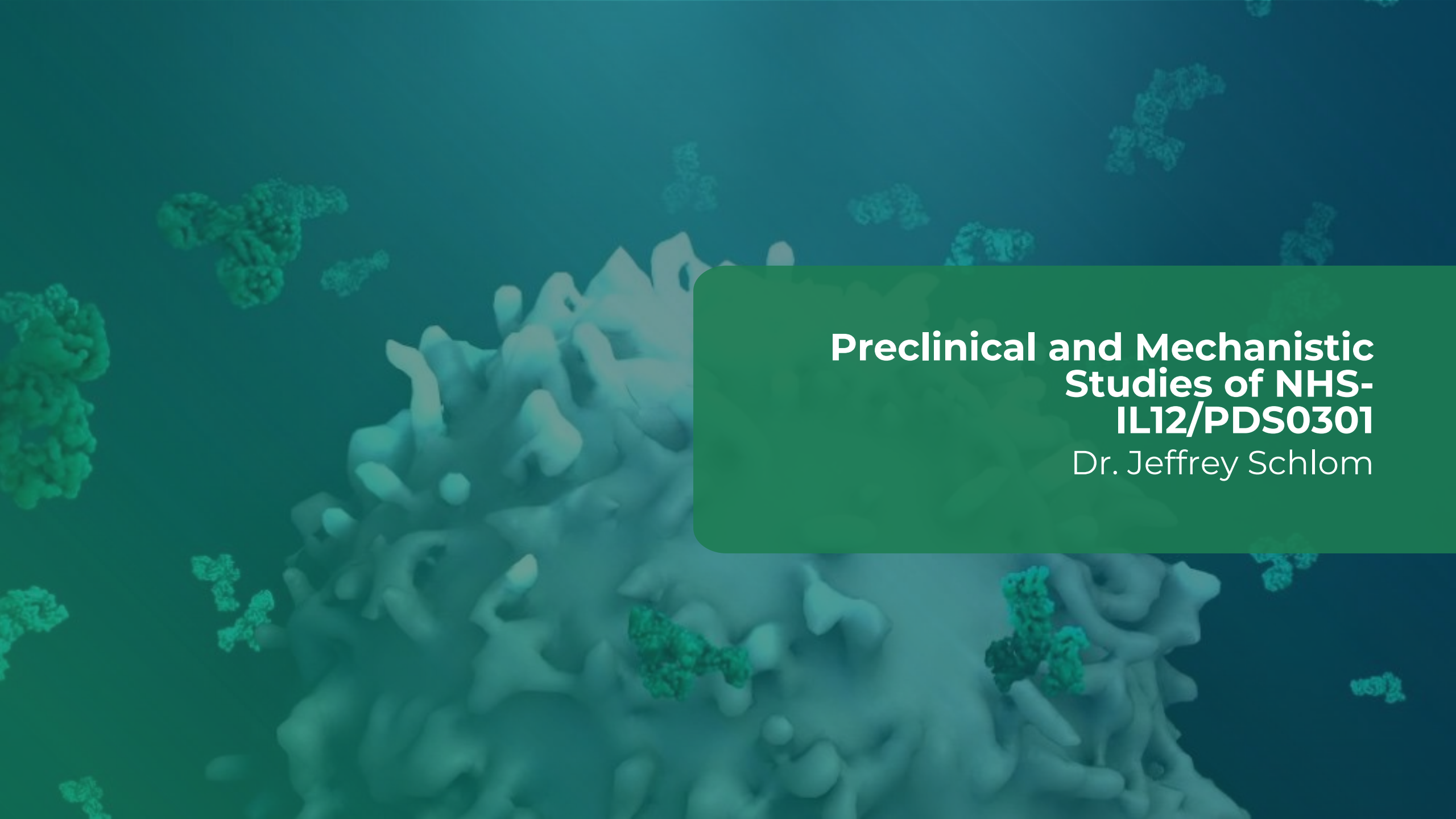




131I-chTNT targeting to lung tumor



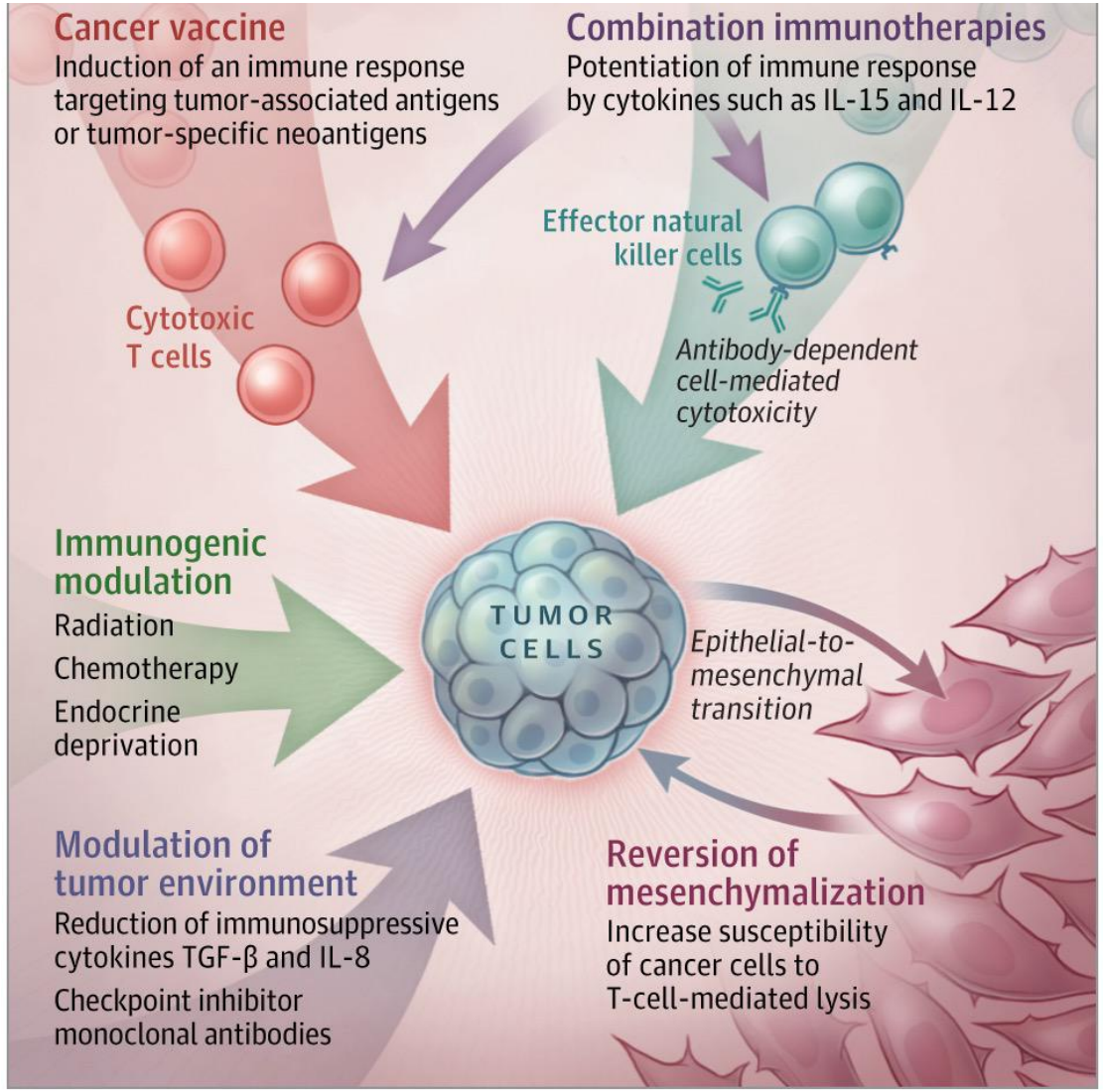
- chTNT is a mouse/human chimeric Ab
- ^{131}I-chTNT is a targeted radiotherapeutic
- Image at right shows biodistribution of ^{131}I-chTNT in a patient with lung cancer.
- ^{131}I-chTNT is licensed in China for advanced lung cancer treatment
- **NHS-76 is a fully human 2nd generation TNT antibody**



Preclinical and Mechanistic Studies of NHS-IL12/PDS0301

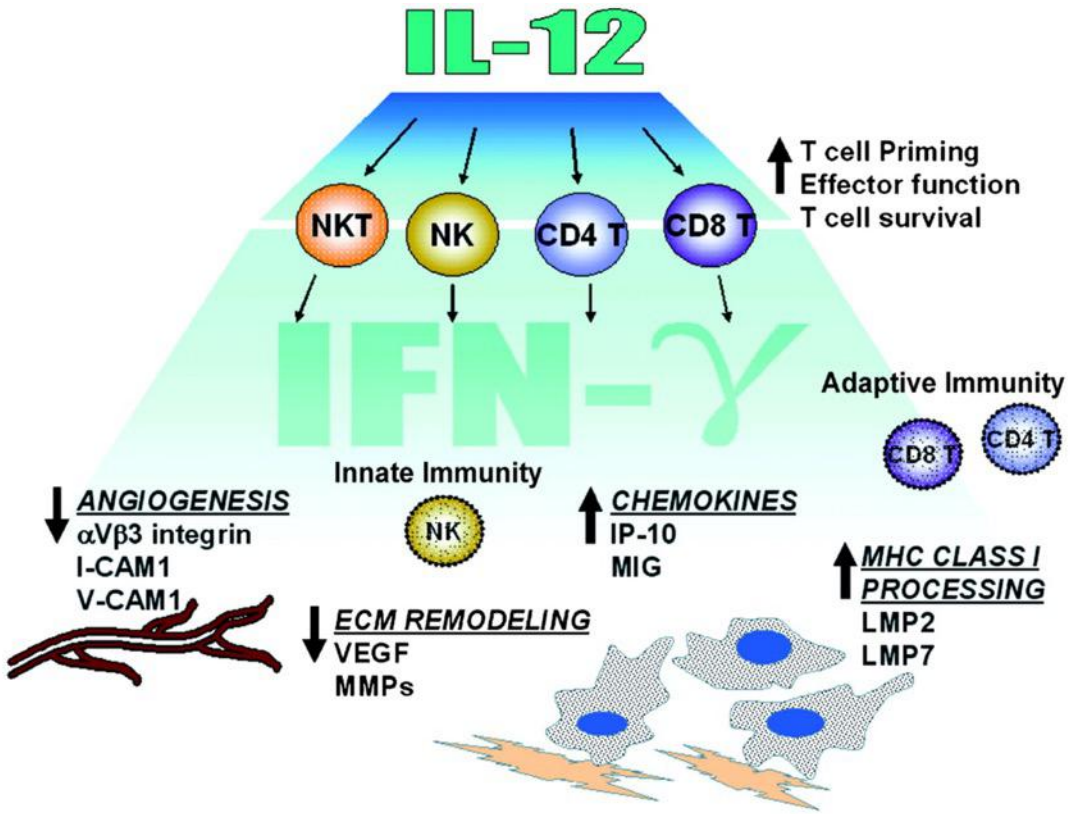
Dr. Jeffrey Schlom

Components of Effective Cancer Immunotherapy



Source: Schlom and Gulley. JAMA, 2018

Exploiting Immunotherapy Combinations With NHS-IL12/PDS0301



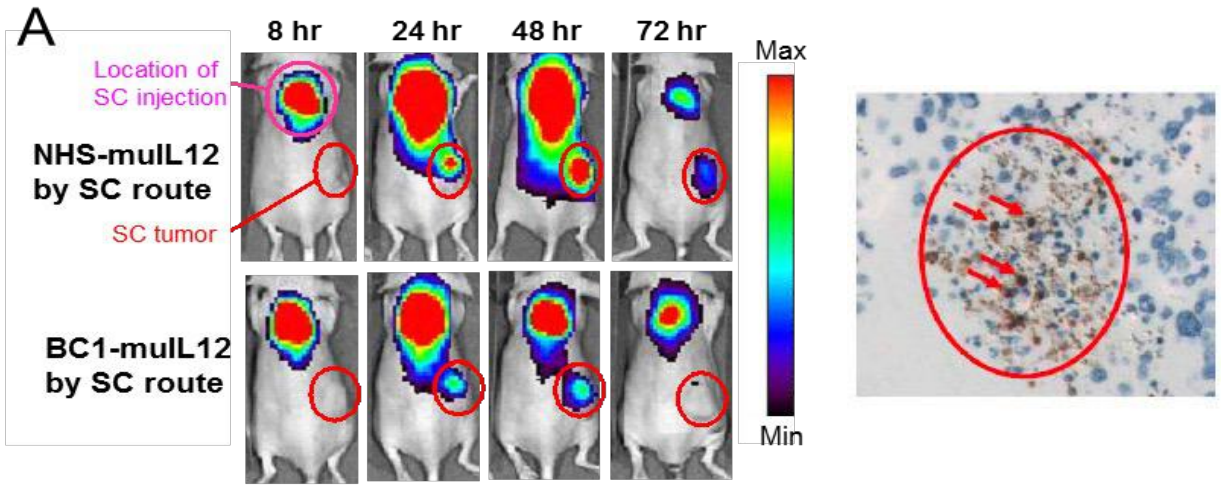
Potential of IL-12 as an anti-cancer therapy:

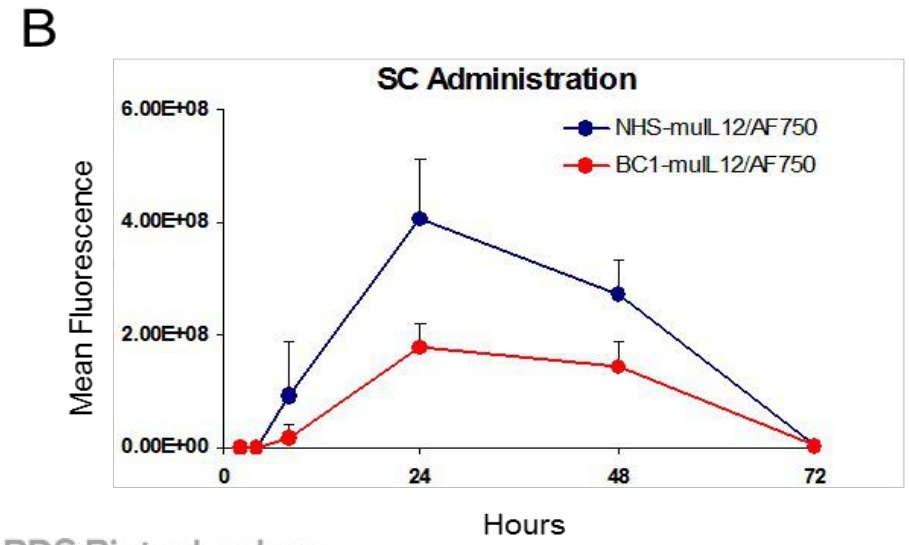
- Bridges host innate and adaptive immunity
- Produced by activated APCs (macrophages, DCS, neutrophils, B cells)
  - ❖ Drives Th1 differentiation of helper T cells
  - ❖ Promotes IFN-γ production via NK & T cells
  - ❖ Increases proliferation and lytic capacity of NK, NKT, and $CD8^+$ T cells
  - ❖ Stimulates further IL-12 production in DCs & enhances antigen presentation
  - ❖ Upregulates IP-10/CXCL10 & MIG/CXCL9
    - mediate an anti-angiogenic effect
    - drive infiltration of $CD8^+$ T cells

Clinically, recombinant human IL-12 has a narrow therapeutic index and its systemic administration can result in significant toxicity

Image: Del Vecchio, et al. Cancer Res, 2020

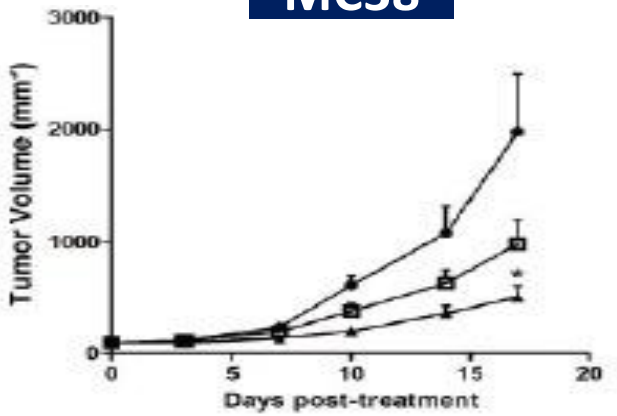
Tumor Localization Kinetics of AF750-labeled NHS-muIL12 and BC1-muIL12 (sc)



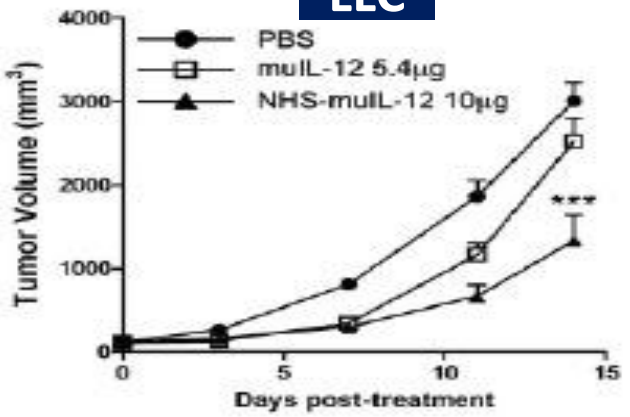


Antitumor Effect of NHS-muIL12 vs. muIL12 (sc)

MC38



LLC



Fallon…Schlom, Greiner. Oncotarget, 2014; Greiner…Schlom. Immunotargets Ther., 2021

The Combination of PDS0101, NHS-IL12 and Bintrafusp alfa Reduced Tumor Volume and Increased T-cell Clonality in TC-1–bearing Mice

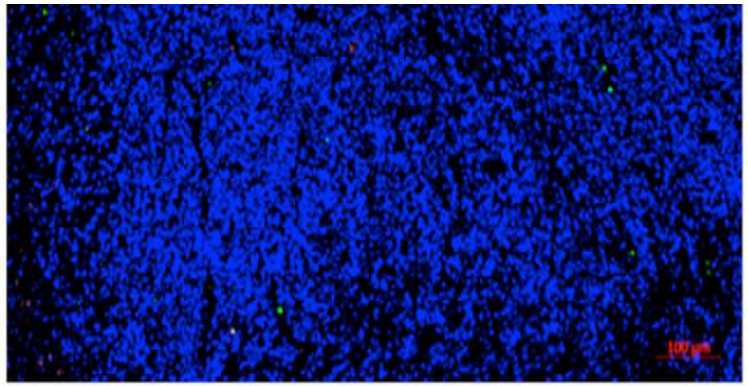
Treatment	# Mice with Tumor Volume <300mm^3
PBS Control	0/16
R-DOTAP	0/8
PDS0101	3/16
Bintrafusp alfa	0/16
NHS-IL12	6/16
PDS0101+Bintrafusp alfa	5/16
PDS0101+NHS-IL12	10/16
NHS-IL12+Bintrafusp alfa	8/16
PDS0101+NHS-IL12+Bintrafusp alfa	13/17

Treatment	T-cell Clones per 25% of TCR Repertoire (Avg)
PBS Control	18
PDS0101	12
Bintrafusp alfa	22
NHS-IL12	25
PDS0101+Bintrafusp alfa	8
PDS0101+NHS-IL12	6
NHS-IL12+Bintrafusp alfa	18
PDS0101+NHS-IL12+ Bintrafusp alfa	3

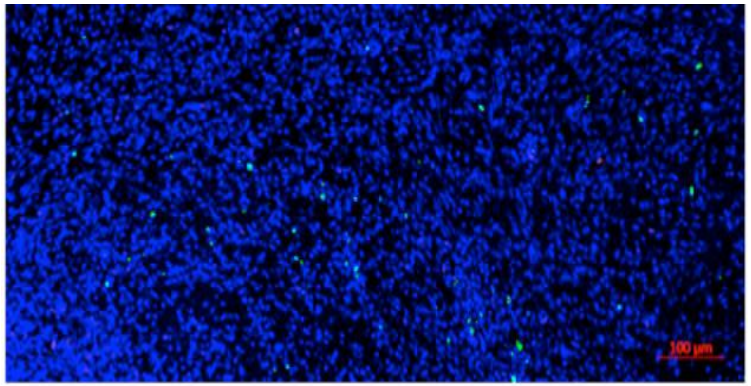
Source: Smalley Rumfield…Schlom, Jochems. J Immunother Cancer. 2020

PDS0301 (NHS-IL12) Accumulates in Tumors and Promotes PDS0101 Induced CD8 and CD4 T Cell Infiltration and Expansion in Tumors – Maximum T Cell Accumulation in Tumor with All Three Agents

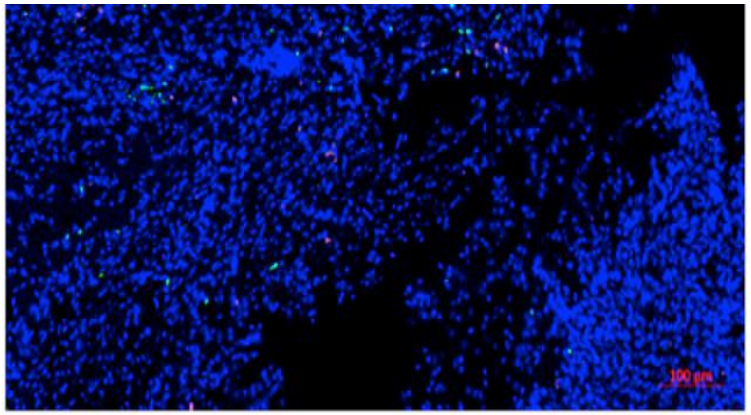
PBS Control



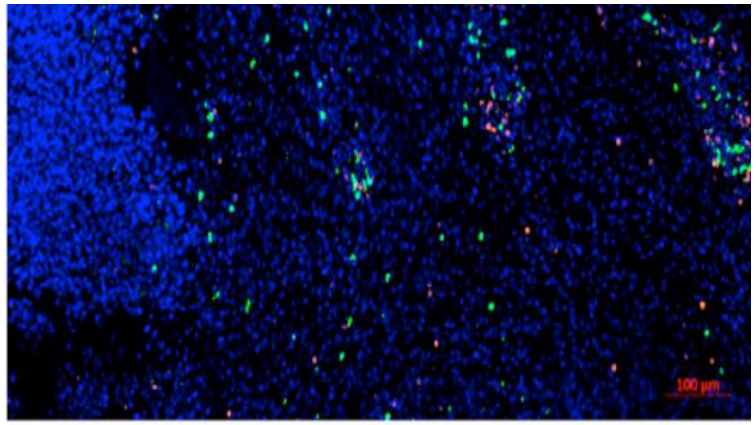
PDS0301 (NHS-IL12)



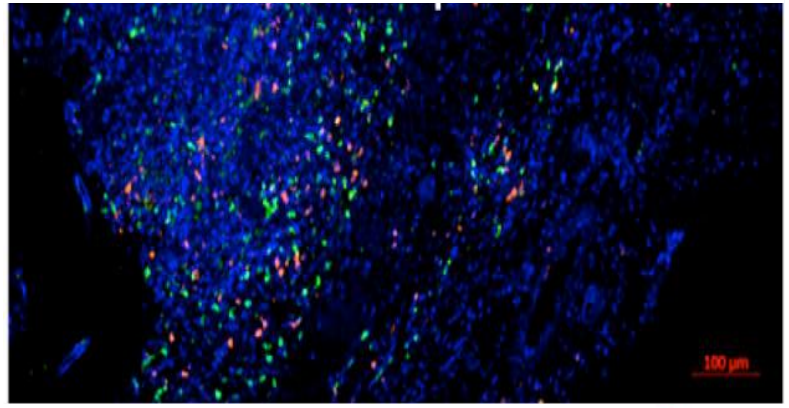
PDS0101 vaccine



PDS0101 + PDS0301

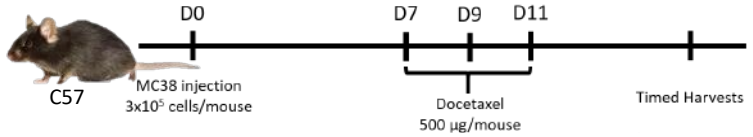


PDS0101 + PDS0301 + checkpoint inhibitor

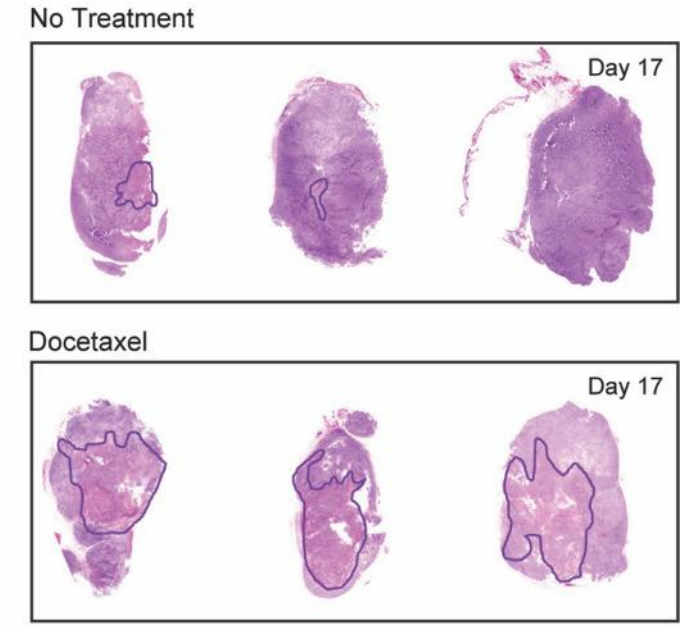


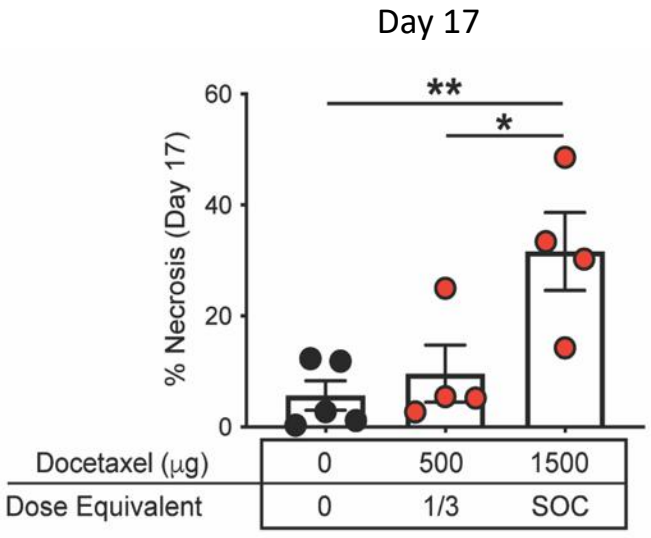
CD4: Green
CD8: Red
DAPI: Blue

Hypothesis: Necrosis-inducing Agents Will Increase NHS-IL12 Targeting to the Tumor and Increase Immune Activation

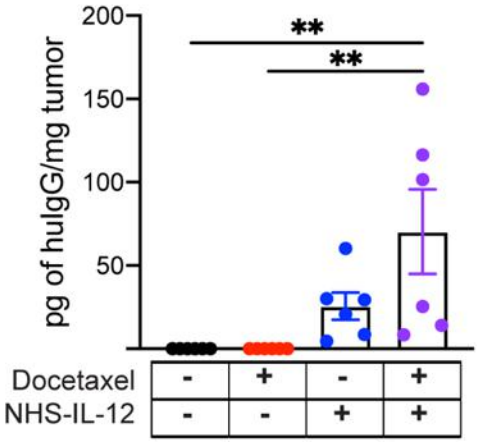


Docetaxel causes necrosis in a dose-specific manner

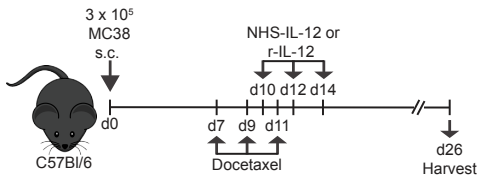


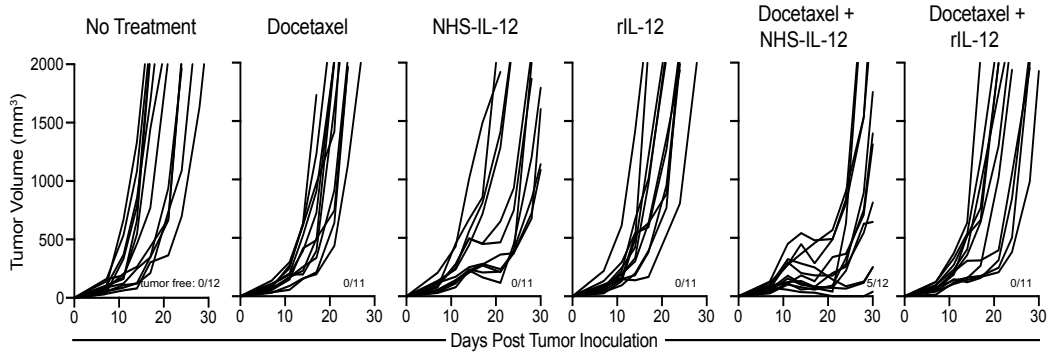


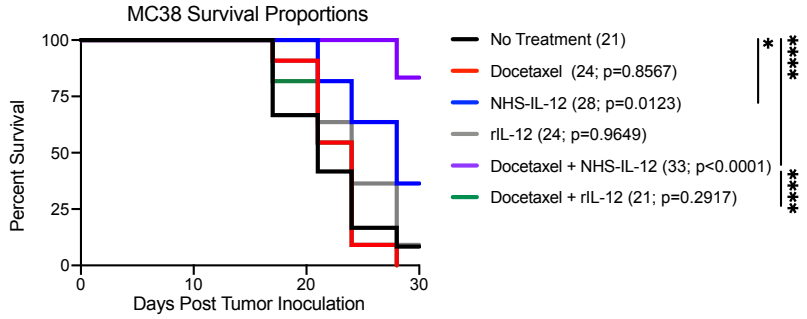
Tumoral NHS-IL12

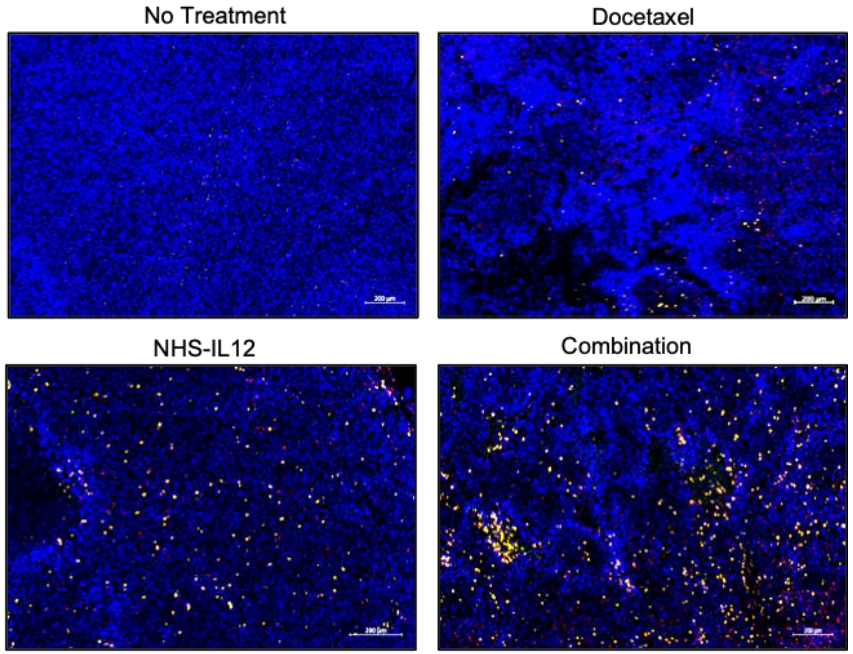


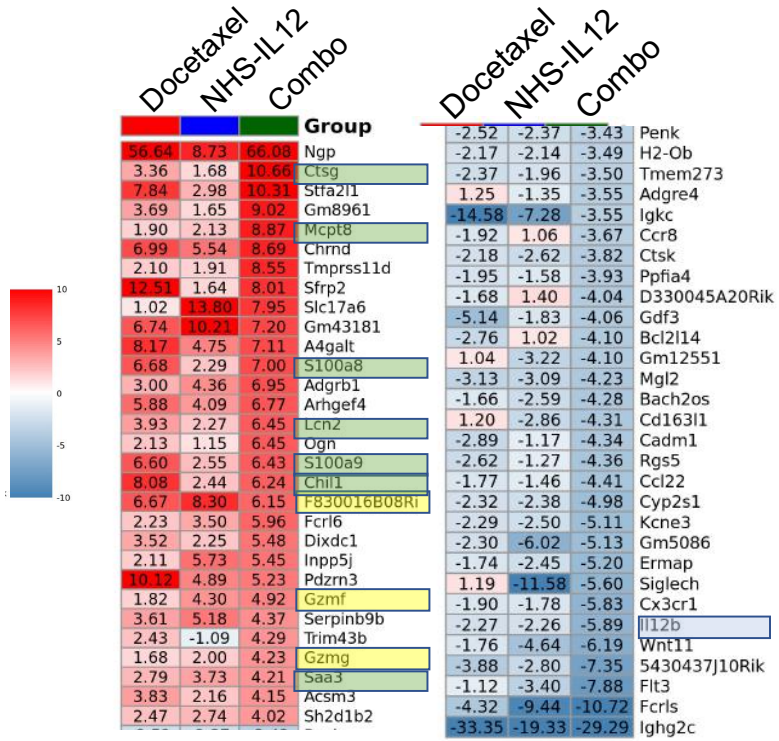
Anti-tumor Activity of Docetaxel + NHS-IL12



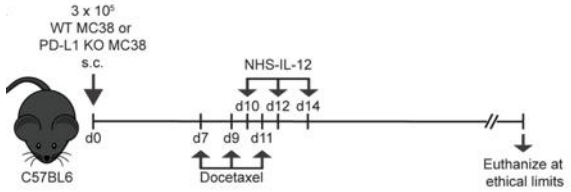




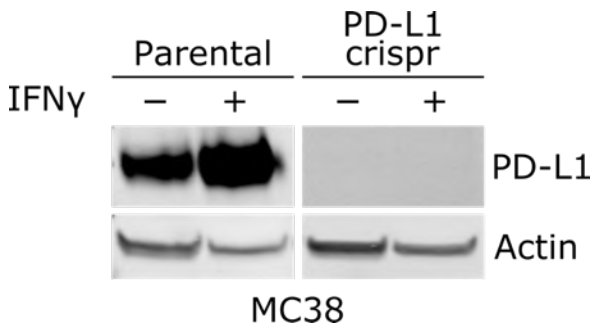


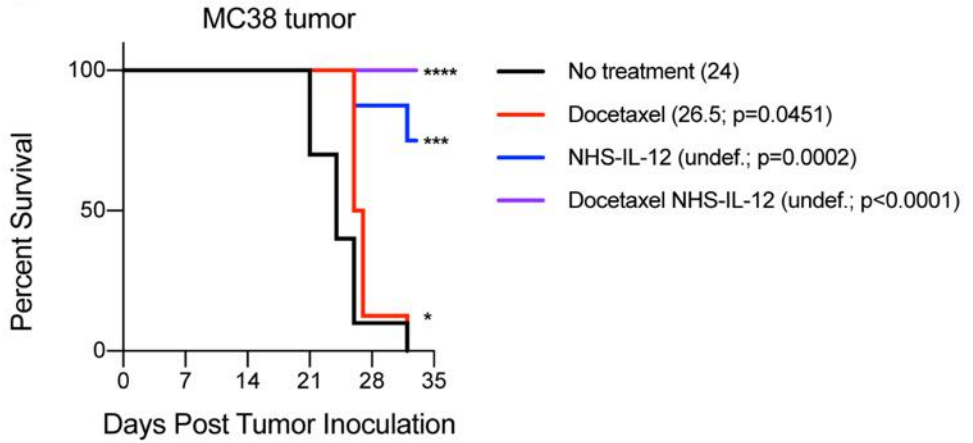


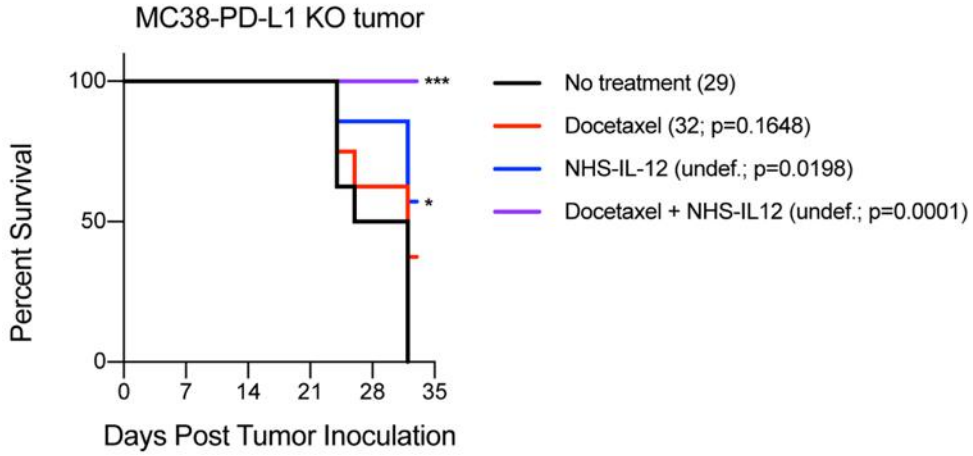
Docetaxel and NHS-IL-12 Combination Therapy Independent of PD-L1 Tumor Expression



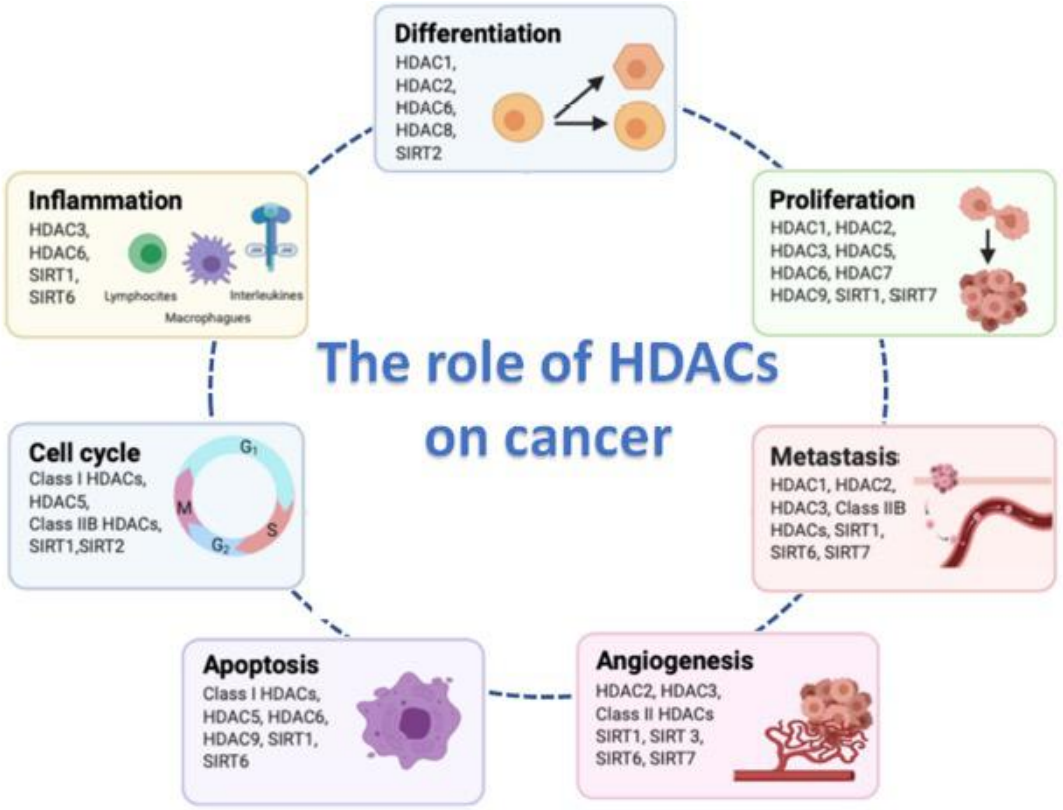
- MC38-PD-L1 KO: MC38 cells were co-transfected recombinant Cas9 and a RNA targeting murine PD-L1
- PD-L1 negative cells were cloned and used in subsequent studies
- Model of Primary Checkpoint Resistance
- Cells made and characterized by Dr. Duane Hamilton







Exploiting Immunotherapy Combinations With HDAC Inhibition



FDA-approved HDACi	Indication
Vorinostat	Cutaneous T cell lymphoma
Romidepsin	Cutaneous & peripheral T cell lymphoma
Belinostat	Peripheral T cell lymphoma
Tucidinostat	Cutaneous T cell lymphoma
Panobinostat	Multiple myeloma

HDACi in solid tumors

Combining epigenetic drugs with other therapies for solid tumours — past lessons and future promise

Daphné Morel[1,5], Daniel Jeffery[2,5], Sandrine Aspeslagh[3], Geneviève Almouzni[2,5] and Sophie Postel-Vinay[1,4,5]**

VOLUME 17 | FEBRUARY 2020 |
NATURE REVIEWS | CLINICAL ONCOLOGY

Source: Hontecillas-Prieto,et al. Front Genet., 2020

Exploiting Immunotherapy Combinations with NHS-IL12

nature COMMUNICATIONS

NATURE COMMUNICATIONS | (2021)12:5151 | https://doi.org/10.1038/s41467-021-25393-x

https://doi.org/10.1038/s41467-021-25393-x OPEN

Tumour-targeted interleukin-12 and entinostat combination therapy improves cancer survival by reprogramming the tumour immune cell landscape

Kristin C. Hicks[1], Paul L. Chariou[1], Yohei Ozawa[1], Christine M. Minnar[1], Karin M. Knudson[1], Thomas J. Meyer[2], Jing Bian[2], Margaret Cam[2], Jeffrey Schlom[1,3]✉ & Sofia R. Gameiro[1,3]

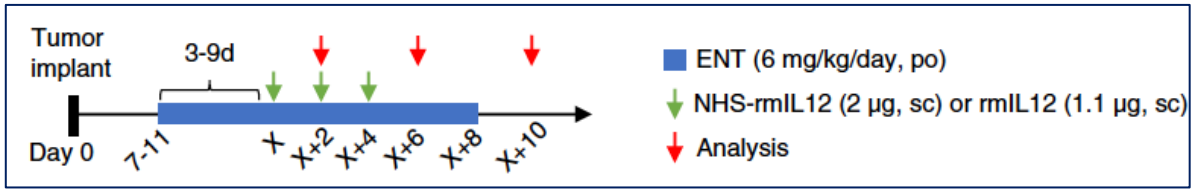
ABSTRACT

Poorly inflamed carcinomas do not respond well to immune checkpoint blockade. Converting the tumour microenvironment into a functionally inflamed immune hub would extend the clinical benefit of immune therapy to a larger proportion of cancer patients. Here we show, by using comprehensive single-cell transcriptome, proteome, and immune cell analysis, that Entinostat, a class I histone deacetylase inhibitor, facilitates accumulation of the necrosis-targeted recombinant murine immune-cytokine, NHS-rmIL12, in experimental mouse colon carcinomas and poorly immunogenic breast tumours. This combination therapy reprograms the tumour innate and adaptive immune milieu to an inflamed landscape, where the concerted action of highly functional $CD8^+$ T cells and activated neutrophils drive macrophage M1-like polarization, leading to complete tumour eradication in 41.7%-100% of cases. Biomarker signature of favourable overall survival in multiple human tumor types shows close resemblance to the immune pattern generated by Entinostat/NHS-rmIL12 combination therapy. Collectively, these findings provide a rationale for combining NHS-IL12 with Entinostat in the clinical setting.

Exploiting Immunotherapy Combinations with NHS-IL12

Entinostat plus NHS-IL12

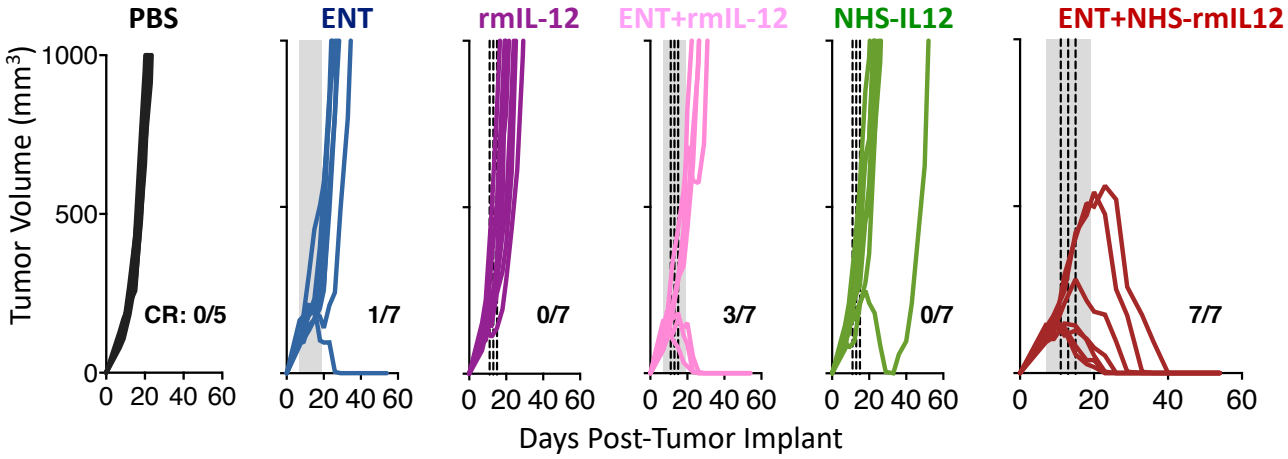
Kristin Hicks



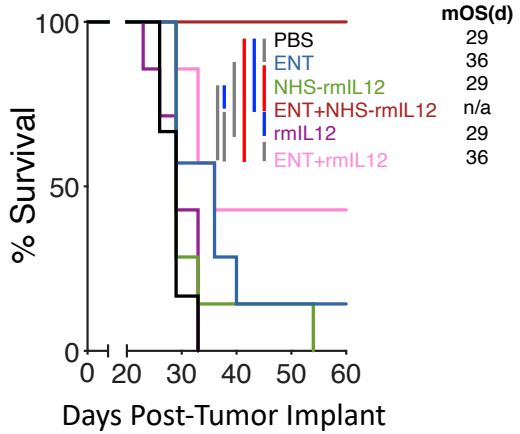
Tumour-targeted interleukin-12 and entinostat combination therapy improves cancer survival by reprogramming the tumour immune cell landscape

Kristin C. Hicks[1], Paul L. Chariou[1], Yohei Ozawa[1], Christine M. Minnar[1], Karin M. Knudson[1], Thomas J. Meyer[2], Jing Bian[2], Margaret Cam[2], Jeffrey Schlom[1,3✉] & Sofia R. Gameiro[1,3]

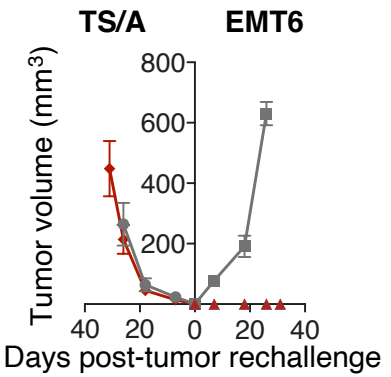
EMT6 (BrCa)



Survival



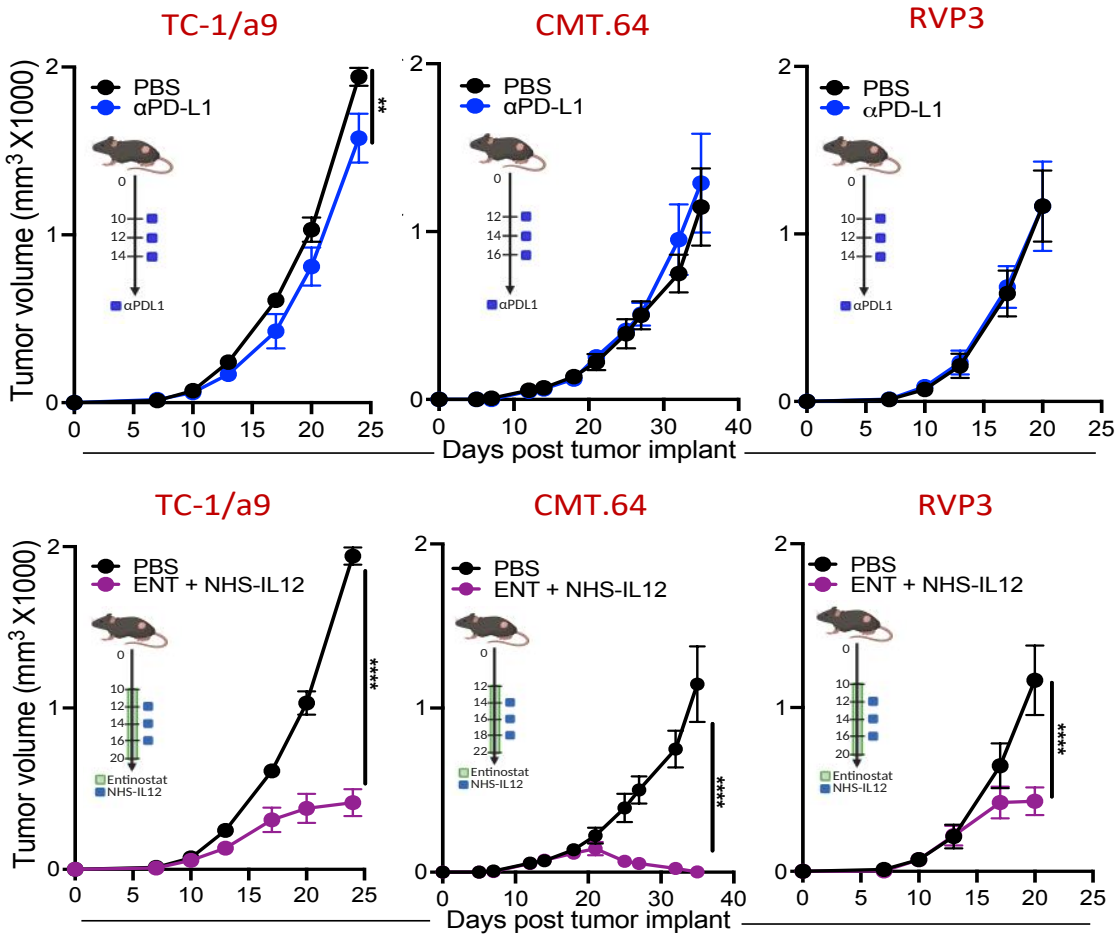
Tumor Rechallenge



PDS Biotechnology

Source: Hicks…Schlom, Gameiro. Nat Commun, 2021

Can NHS-IL12 Plus Entinostat Overcome αPD-1/-L1 Refractory Tumors Due to Defects in APM/IFNγ Signaling?



	TC-1/a9	CMT.64	RVP3
TGI:	79%	100%	63%
Cures:	40%	100%	20%

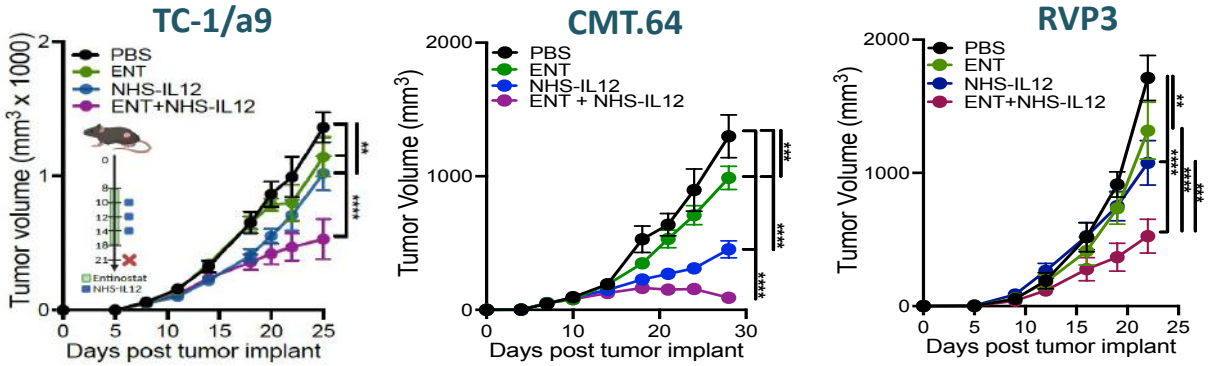
Tumor-targeted interleukin-12 synergizes with entinostat to overcome PD-1/PD-L1 blockade-resistant tumors harboring MHC-I and APM deficiencies

Christine M Minnar, Paul L Chariou, Lucas A Horn, Kristin C Hicks, Claudia Palena, Jeffrey Schlom, Sofia R Gameiro

J Immunother Cancer 2022;**10**:e004561. doi:10.1136/jitc-2022-004561

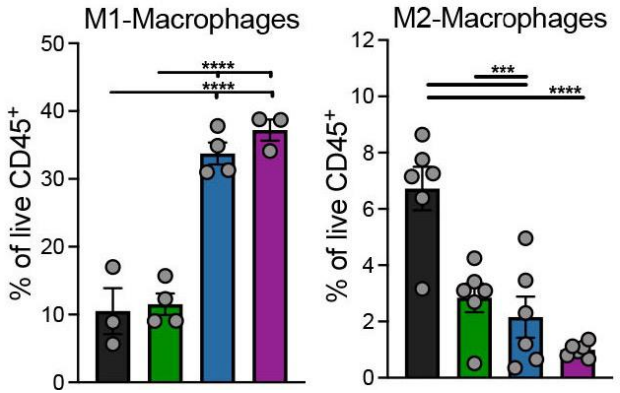
Source: Minnar...Schlom, Gameiro. J Immunother Cancer, 2022

NHS-IL12 Synergizes with Entinostat to Suppress αPD1/αPDL1 Refractory Tumors

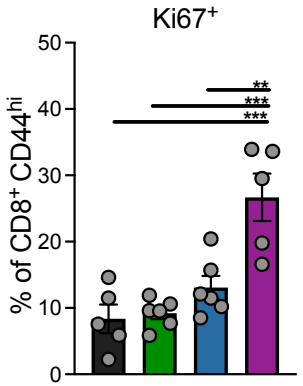


TC-1/a9 TME

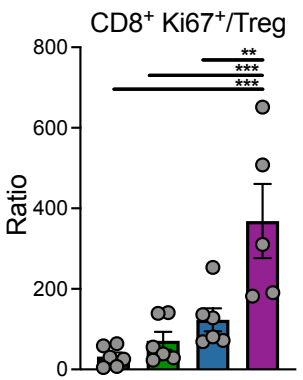
M2 to M1 shift

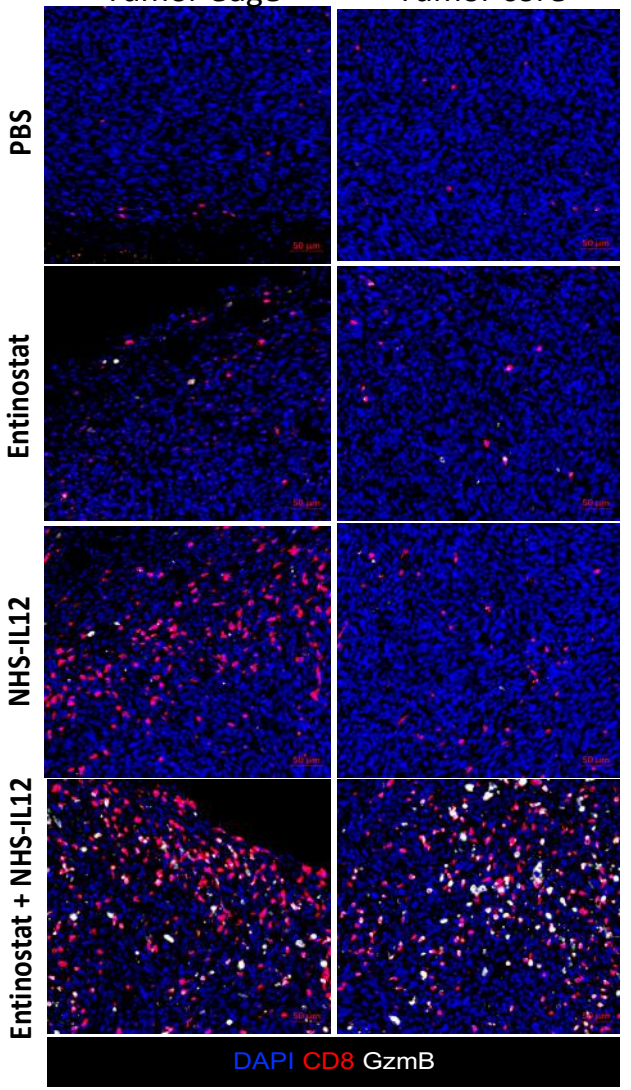


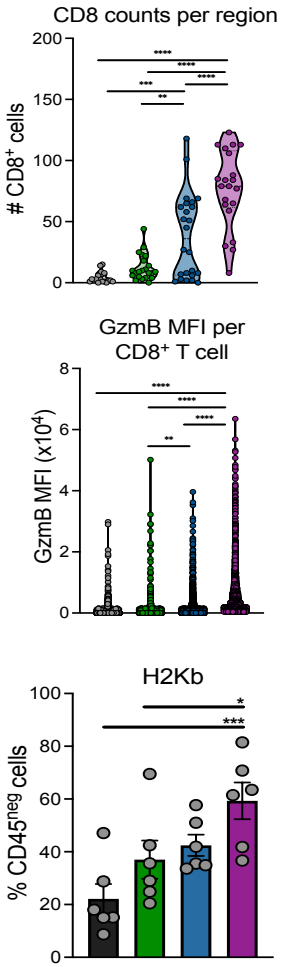
Activated CD8⁺ TILs



Increased CD8/Tregs

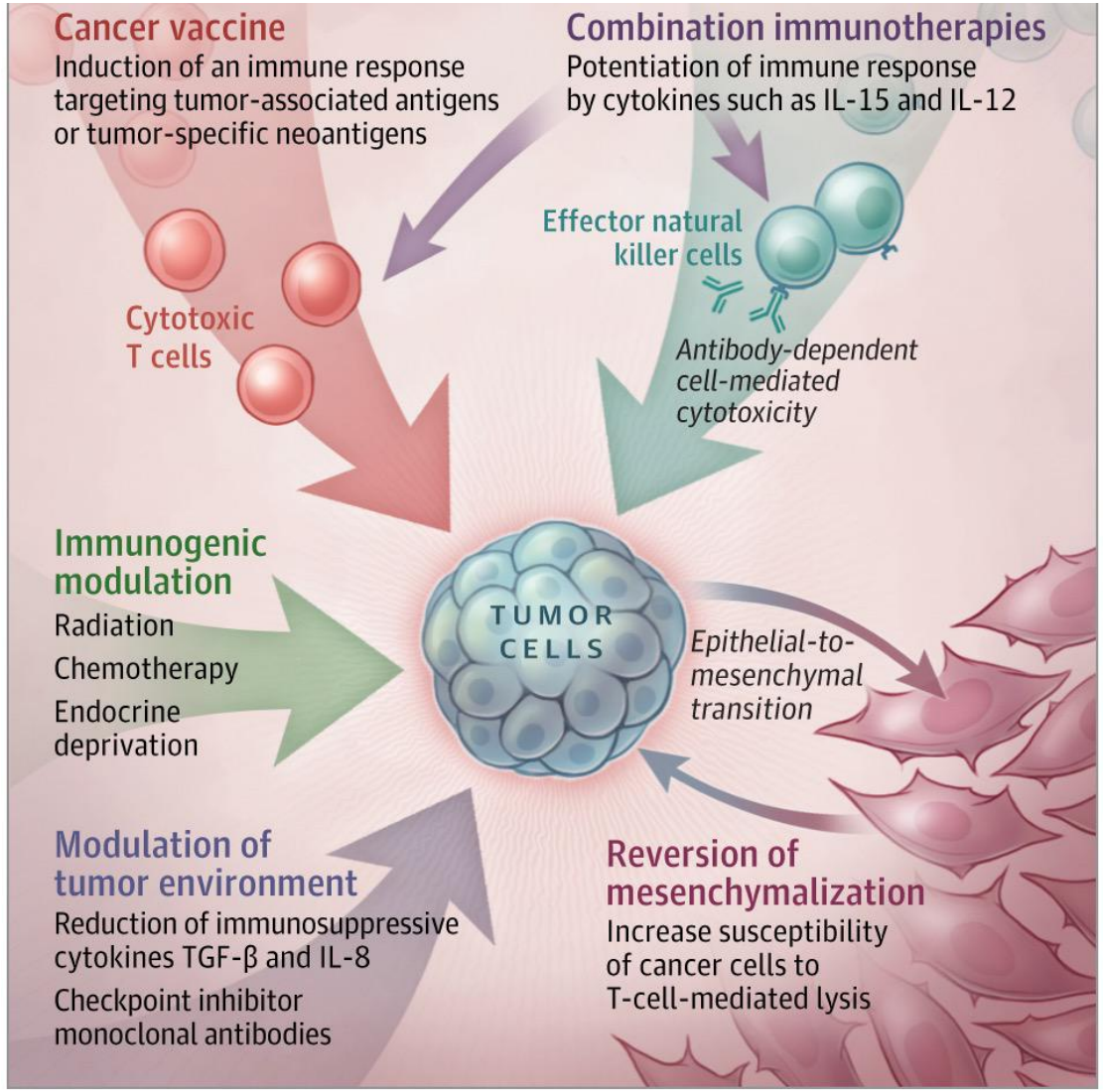




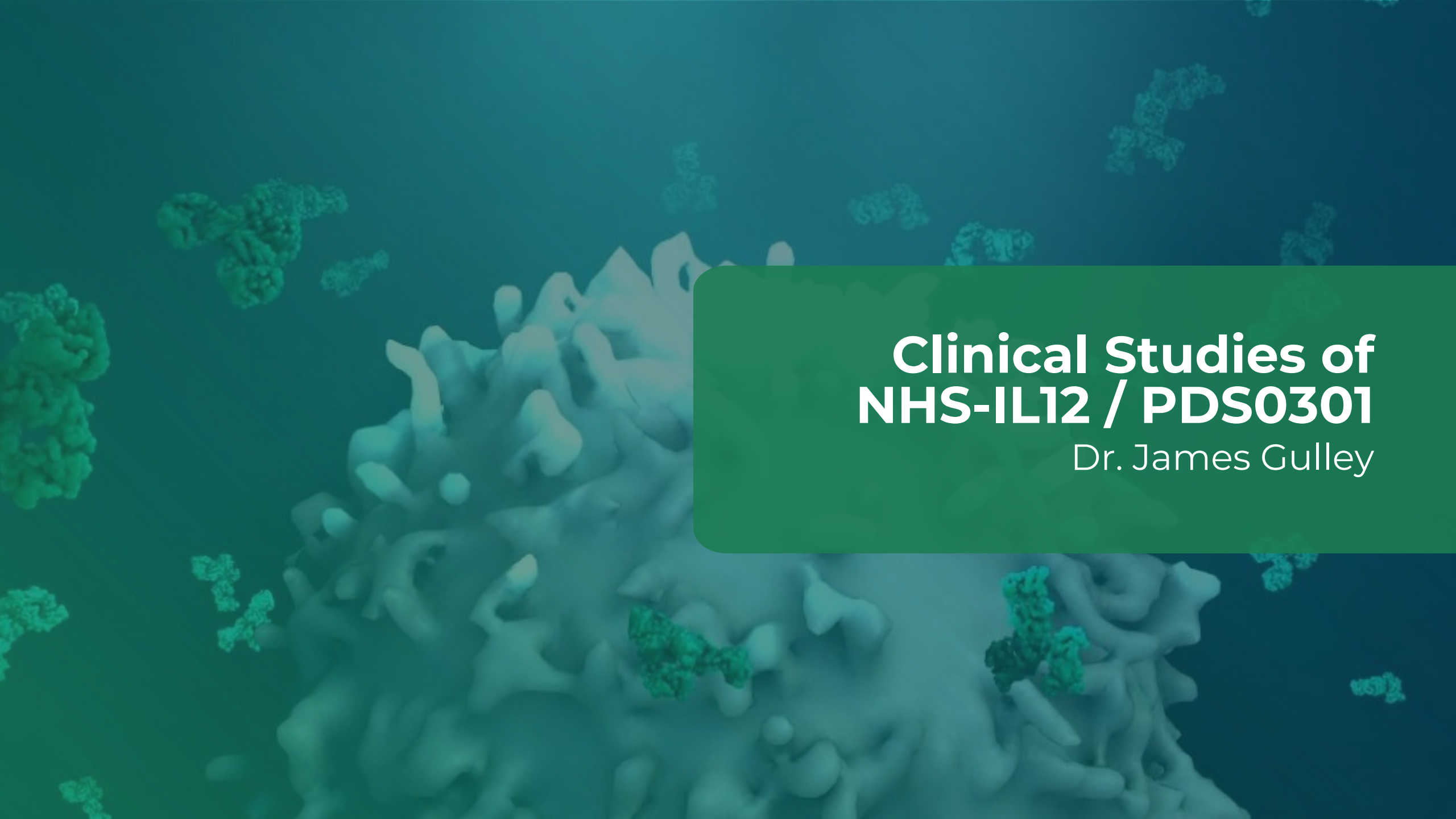


PDS Biotechnology

Components of Effective Cancer Immunotherapy



Source: Schlom and Gulley. JAMA, 2018



Clinical Studies of NHS-IL12 / PDS0301

Dr. James Gulley

NCI Phase 1: First in Human (FIH) Study

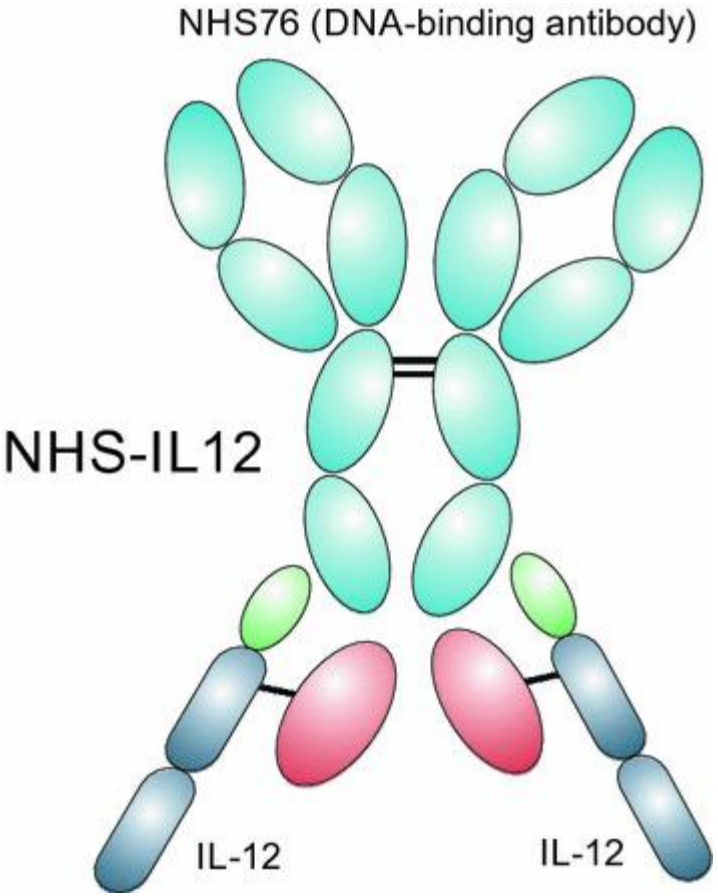
Clinical Trials: Immunotherapy

Clinical Cancer Research

First-in-Human Phase I Trial of a Tumor-Targeted Cytokine (NHS-IL12) in Subjects with Metastatic Solid Tumors

Julius Strauss[1], Christopher R. Heery[2], Joseph W. Kim[3], Caroline Jochems[1], Renee N. Donahue[1], Agnes S. Montgomery[4], Sheri McMahon[5], Elizabeth Lamping[5], Jennifer L. Marté[6], Ravi A. Madan[6], Marijo Bilusic[6], Matthew R. Silver[7], Elisa Bertotti[7], Jeffrey Schlom[1], and James L. Gulley[6]

- Tumor targeted cytokine (binds DNA in areas of necrosis)
- Demonstrated safety and biologic activity
- MTD 16.8 μg/kg s.c. every 28 days



NCT01417546

Source: Clinical Cancer Research, 2019

NCI Phase 1: FIH Study

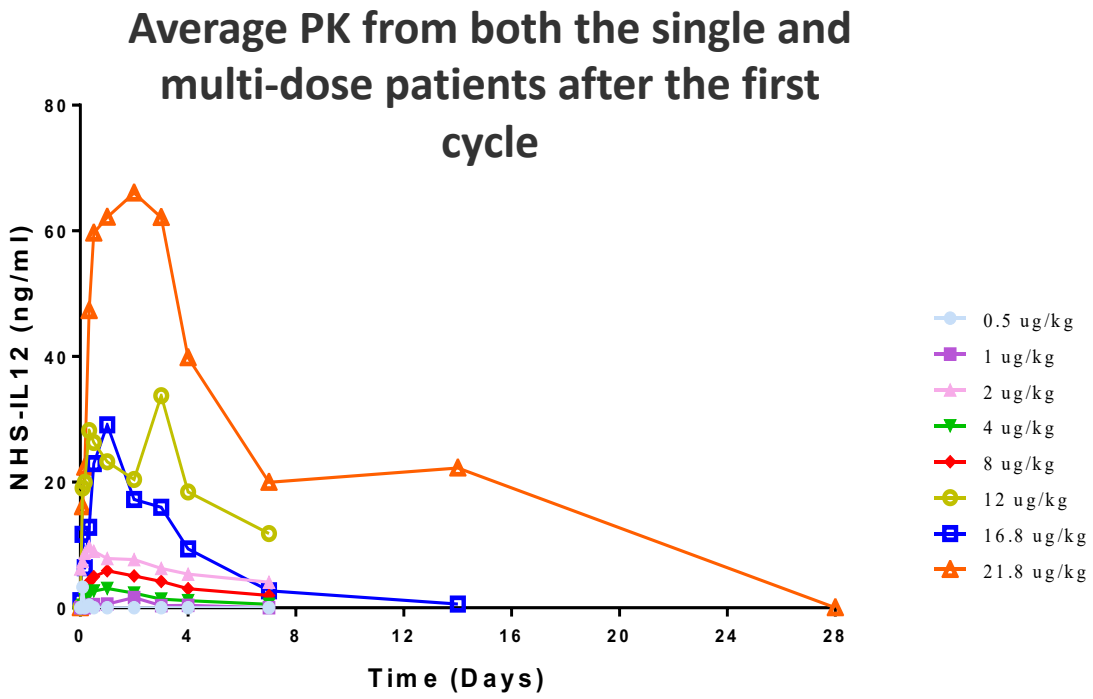
- Phase I Study Design (Open Label)
  - Assess the safety, PK and immune impact
  - 3+3 dose-escalation in solid tumors
    - (SAD & MAD portions)
  - Dosing Schedule: Q4W
  - s.c. administration
  - 6 week DLT period
- Primary Objective
  - MTD
- Secondary Objectives
  - PK of subcutaneously administered NHS-IL12
  - Immunogenicity
  - To determine immune response, including frequency of immune cell subtypes infiltrating tumor tissue (CD8 memory/effector cells, CD4 memory/effector cells, Tregs, NK cells, DCs), and activation of T lymphocytes against relevant tumor-associated antigens as measured by tetramer and/or ELISPOT analysis

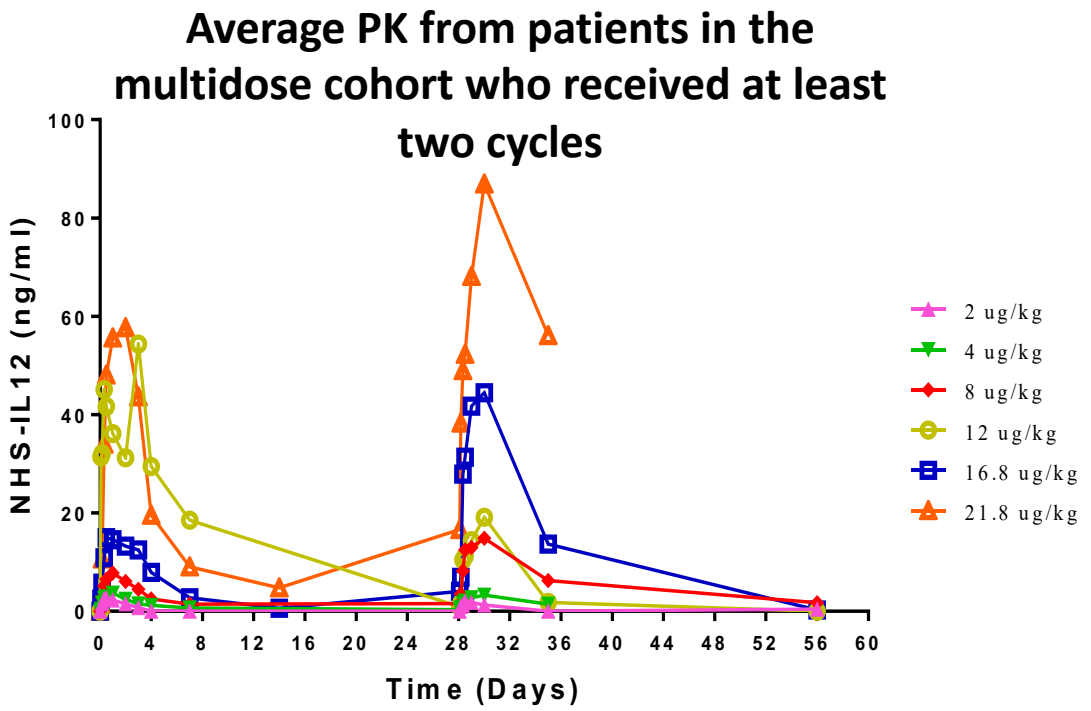
Dose Level* (mcg/kg)	# of pts	Tumor Types	# of pts	Treatment duration (MD), # of cycles	Tumor Types
0.1	3	Kaposi, Breast, Transitional			
0.5	3	CRC (n=2), Mesothelioma			
1.0	4	CRC (n=4)			
2.0	4	CRC (n=2), Rectal, Pancreatic	4	1, 1, 4, 5	NSCLC (n=3), Renal
4.0	3	CRC, Gallbladder, Lung	4	2, 2, 2, 9	Rectal, Pancreatic, Gallbladder, Prostate
8.0	3	Pancreatic, NEC lung, Esoph (sq)	3	3, 5, 6	CRC (n=2), Pancreatic
12.0	2	Adeno Ca (tongue), Breast	4	1, 3, 3, 14	Prostate (n=2), Thymoma, Anal
16.8 (MTD)			17	1, 1, 2, 2, 2, 2, 2, 2, 3, 4, 6	PDAC, Ovarian (n=3), Breast, Adeno Ca intestinal, Prostate (n=3), Chordoma (n=3), CRC (n=5), Cholangio Ca
21.8			6	1, 2, 2, 2, 3, 6	CRC (n=3), Rhabdomyosarcoma, Ovarian, Adeno Ca intestine
	22 Total		**37 Total**		

NCT01417546

*Doses are stated as exact dose in units (eg, mcg/kg) rather than as a percentage

NCI Phase 1 Study: PK Data





PK data: Trend for increased exposure with increasing dose with a high degree of inter-subject variability.

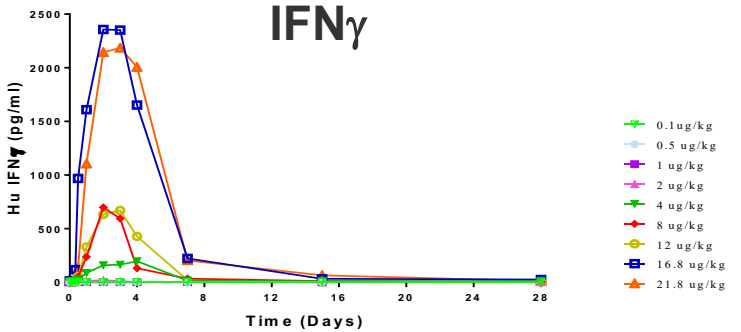
- New PK assay to be introduced in subsequent studies
- ADA testing to be conducted in Q2 2016 with new validated method

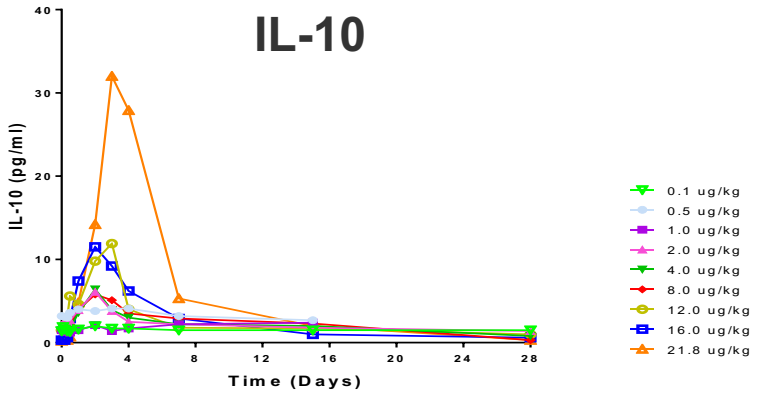
NCT01417546

NCI Phase 1: INF-γ and IL-10 Response to NHS IL-12

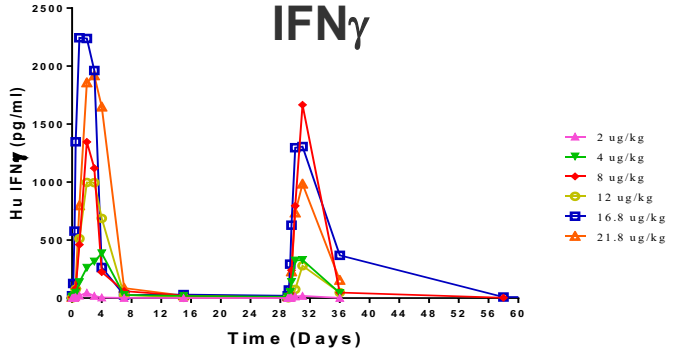
- Dose dependent systemic IFN-g release with trough levels going back to baseline
- Dose dependent IL-10 release with residual levels at Day 14

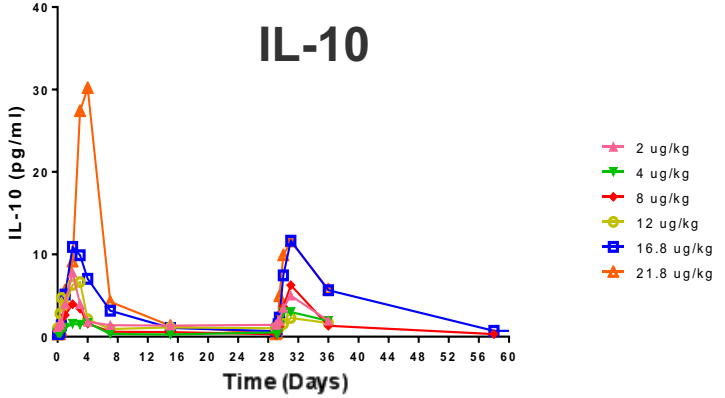
Average serum cytokine levels from both the single and multi-dose patients after the first cycle





Average serum cytokine levels from patients in the multi-dose cohort who received at least two cycles





NCT01417546

NCI Phase 1

The Oncologist, 2023, **XX**, 1–8
https://doi.org/10.1093/oncolo/oyac244
Advance access publication 14 January 2023
Clinical Trial Results

OXFORD

A Phase I Single-Arm Study of Biweekly NHS-IL12 in Patients With Metastatic Solid Tumors

Margaret E. Gatti-Mays[1], Nicholas P. Tschernia[*,2], Julius Strauss[1], Ravi A. Madan[2], Fatima H. Karzai[2], Marijo Bilusic[2], Jason Redman[2], Houssein Abdul Sater[2], Charalampos S. Floudas[1], Nicole J. Toney[1], Renee N. Donahue[1], Caroline Jochems[1], Jennifer L. Marté[2], Deneise Francis[3], Sheri McMahon[3], Elizabeth Lamping[3], Lisa Cordes[2], Jeffrey Schlom[1], James L. Gulley[*,‡,2]

N=13
12 mcg/kg vs. 16.8 mcg/kg s.c. q 2 wk
MTD not exceeded

11 evaluable for clinical activity
6/11 evaluable had stable disease as best response (with 5/11 having PD at first restaging)

NCT01417546

NCI Phase 1: Immune Status at Baseline and Early Changes in the Immune Profile After NHS-IL 12 Associated With Best Overall Response (BOR)

PT	Dose Level (mcg/kg)	Age	Sex	Cancer Type	BOR	Baseline		% Change D14 vs Pre		% Change D28 vs Pre			
						IL-12 p70 (pg/ml)	Non Classical Monocytes	Immature NK	DP NK	Immature NK	CD8	CM CD8	EM CD8
60	12.0	65	F	Colon	PD	0.3	3.8	-42	+130	-15	-10	-53	-30
67	16.8	44	F	Cervical	PD	0.5	4.9	-33	-18	-59	-39	-21	-37
69	16.8	64	F	Cervical	PD	0.7	5.5	+2	+23				
70	16.8	51	F	Colon	PD	0.8	3.2	-46	-44	-53	+5	+4	0
71	16.8	71	M	Prostate	PD	0.3	6.0	-33	+13	-58	-36	-33	-44
63	12.0	35	F	Cervical	SD	0.5	1.1	+52	+342	+32	+22	+51	+35
64	12.0	72	M	Prostate	SD	1.9	2.1	+10	+211	+42	+25	+11	-7
65	12.0	56	M	Prostate	SD	1.7	2.2	+65	+98	+136	-21	-16	-22
66	12.0	79	M	Prostate	SD	1.0	3.3	+10	+516	-24	+31	+62	+49
68	16.8	54	F	Vaginal	SD	2.1	1.0	-32	+23	-43	+14	+20	+30
72	16.8	69	M	Prostate	SD	1.5	2.1	+32	+330	0	+19	-16	+57
Patients treated with high exposure of NHS-IL12 (Q2 weeks)					*Median PD*	*0.5*	*4.4*	*-33*	*+18*	*-53*	*-10*	*-21*	*-30*
					Median SD	*1.7*	*2.1*	*+10*	*+211*	*0*	*+19*	*+11*	*+30*
					p-value	***0.0173***	***0.0087***	***0.0087***	***0.0173***	***0.0381***	***0.0381***	***0.0381***	***0.0381***

Low High

NCT01417546

PDS Biotechnology

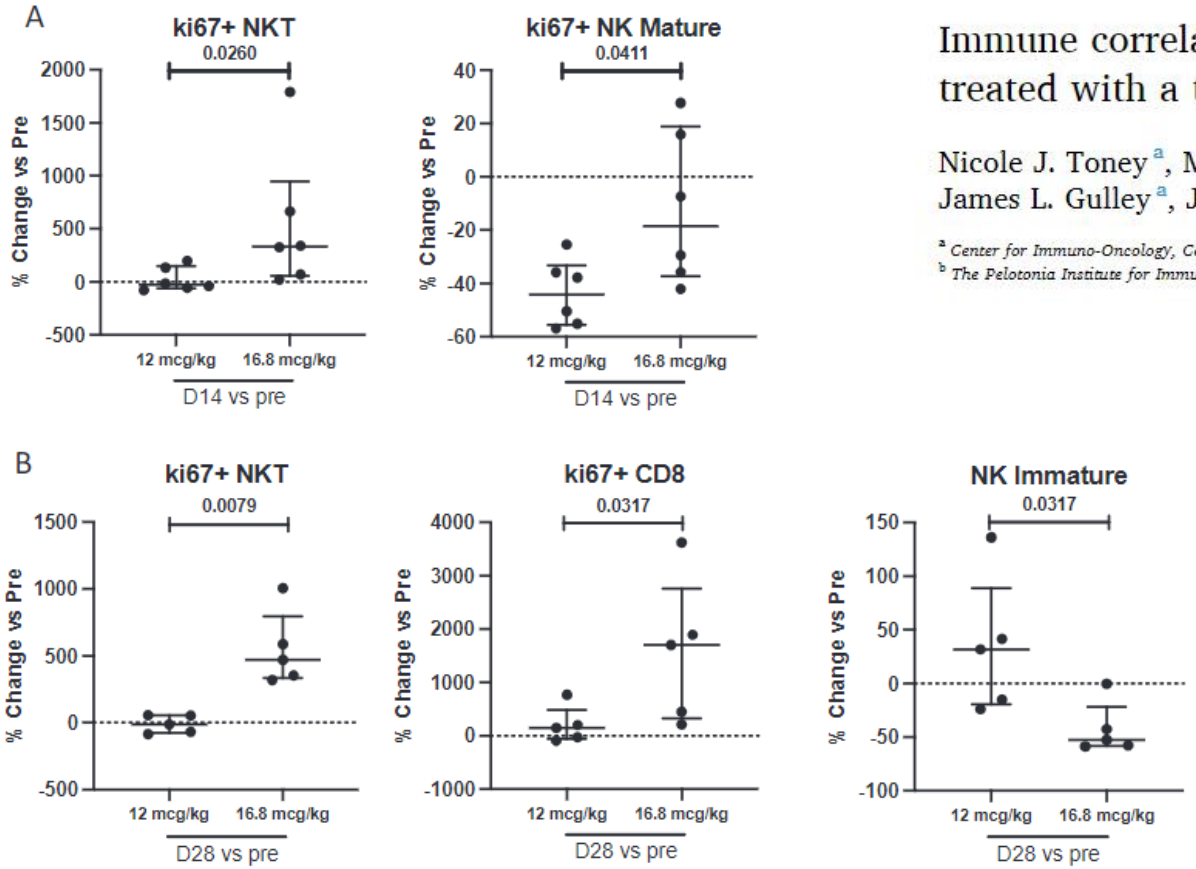
Source: Gatti-Mays, et al. The Oncologist, 2023, Toney, et al. Int Immunopharm., 2023

International Immunopharmacology 116 (2023) 109736

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp



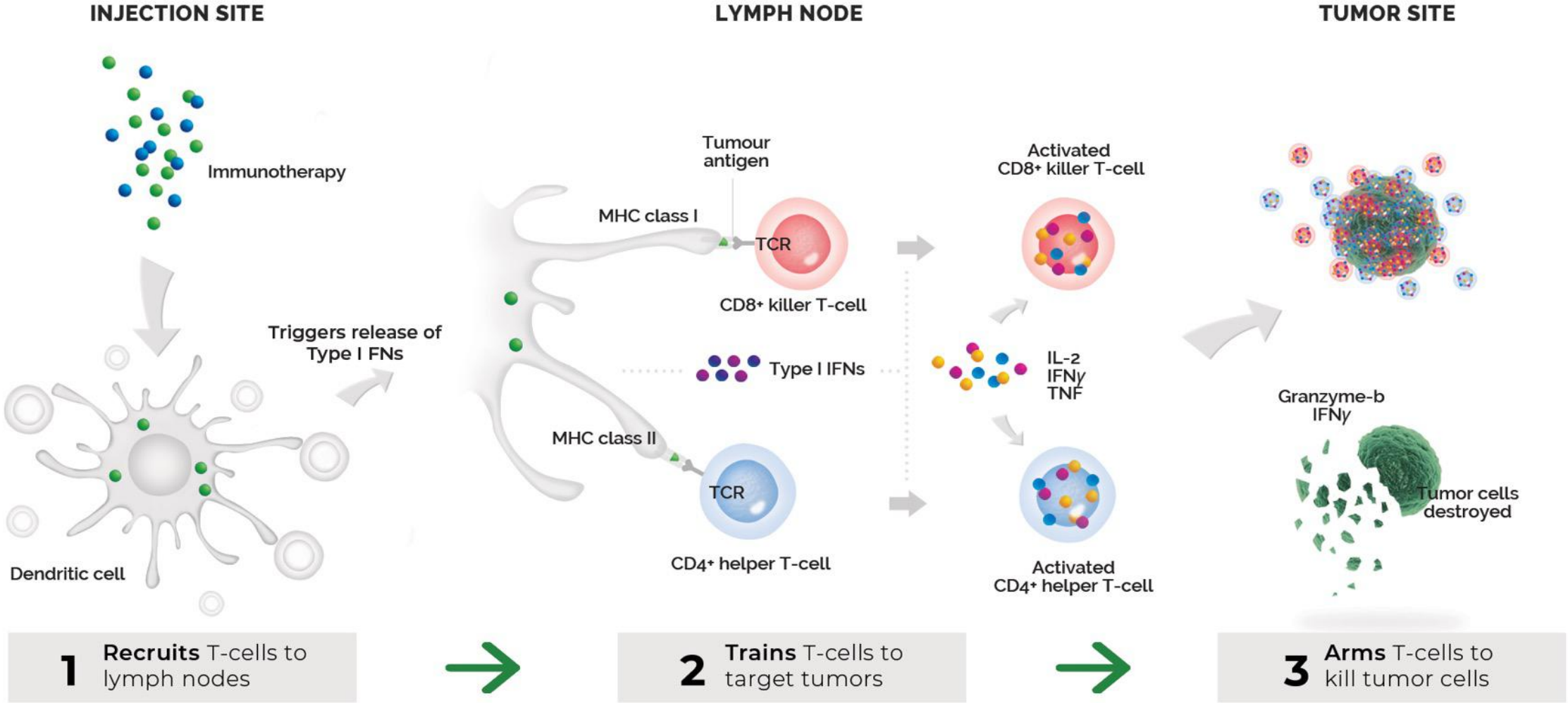
Immune correlates with response in patients with metastatic solid tumors treated with a tumor targeting immunocytokine NHS-IL12

Nicole J. Toney [a], Margaret E. Gatti-Mays [b], Nicholas P. Tschernia [a], Julius Strauss [a], James L. Gulley [a], Jeffrey Schlom [a,*], Renee N. Donahue [a,*]

[a] Center for Immuno-Oncology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA
[b] The Pelotonia Institute for Immuno-Oncology, Division of Medical Oncology, The Ohio State University, Columbus, OH, USA

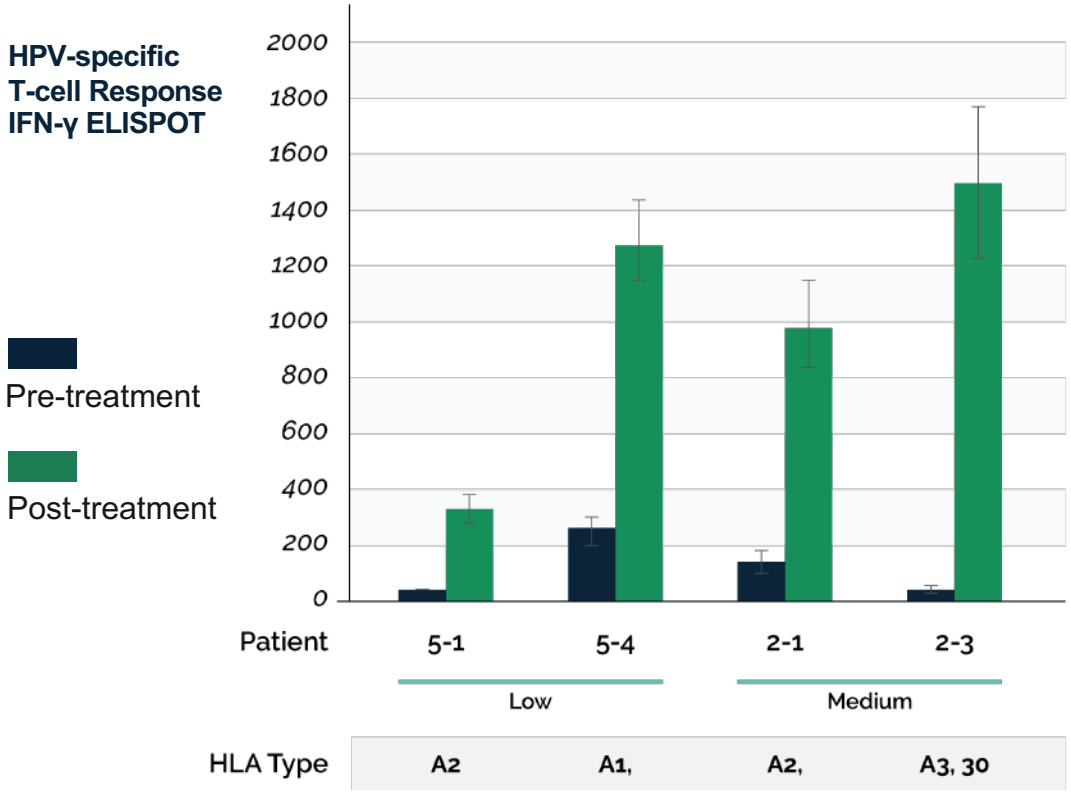
Versamune® Platform

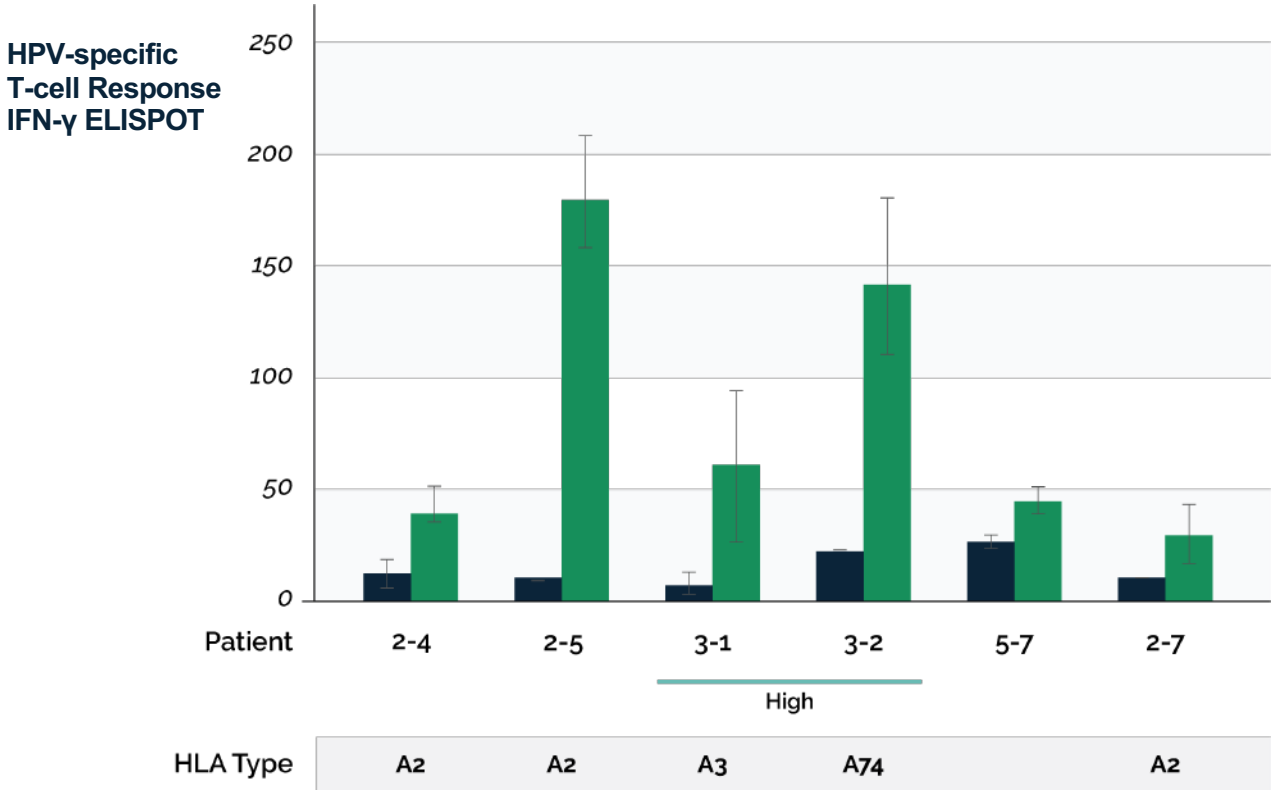
Versamune® generates right type, potency and quantity of killer T cells



References: Gandhapudi SK, et al. 2019. Antigen priming with enantiospecific cationic lipid nanoparticles induces potent antitumor CTL responses through novel induction of a Type I IFN response. J Immunol. 202 (12): 3524-3536. Smalley Rumfield C et al. 2020. Immunomodulation to enhance the efficacy of an HPV therapeutic vaccine. J. for ImmunoTherapy of Cancer 8:e000612.

Versamune®-HPV (PDS0101) Phase 1 Clinical Trial: Confirmation of unique potential to induce rapid and strong CD4 and CD8 T-cell responses against a viral target (HPV16) 14 days post-vaccination

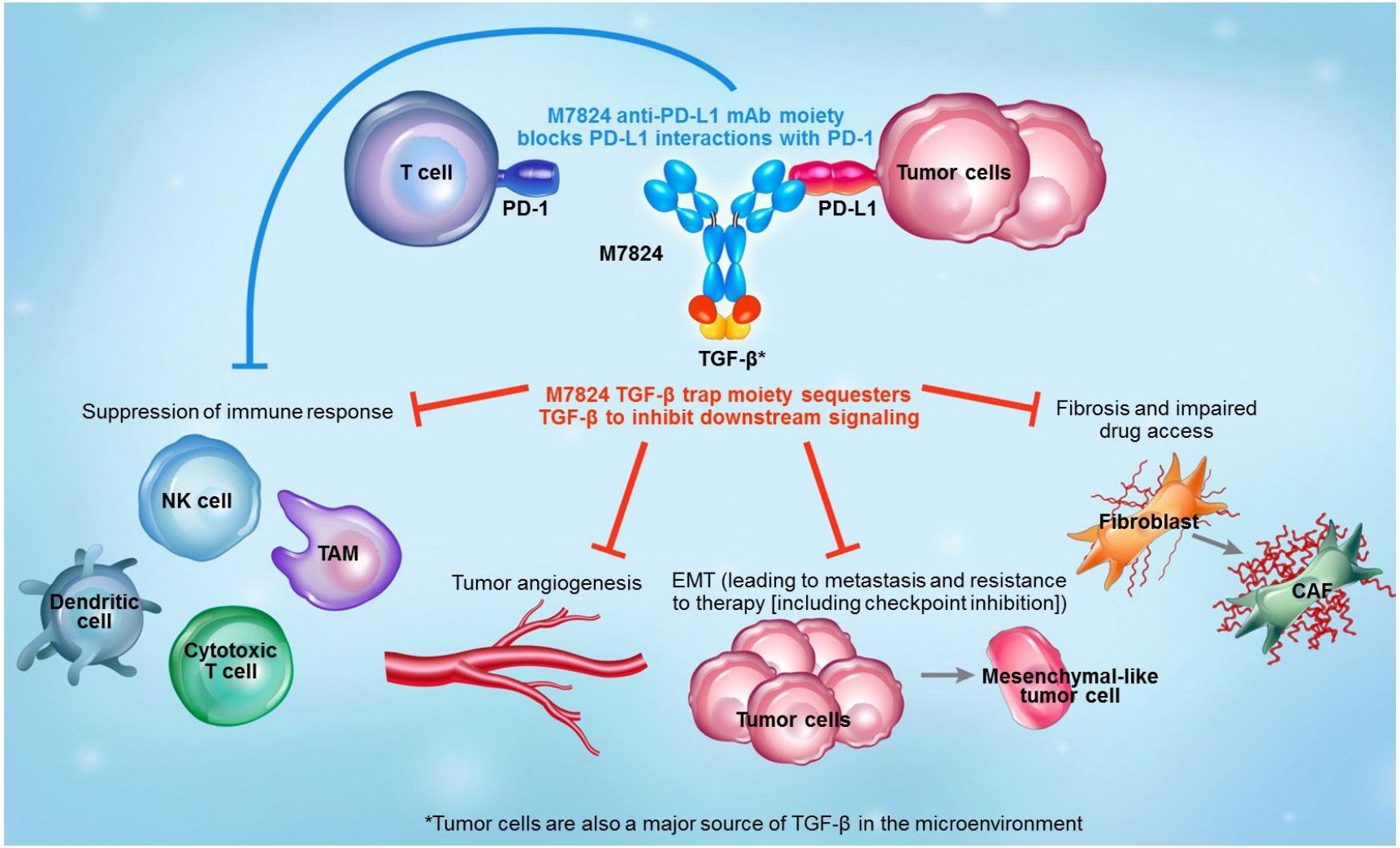




- Strong virus-specific CD8 T-cell responses were also confirmed by Granzyme-b ELISPOT (data not shown)
- Safe in all subjects: Mild transient vaccine site reactions without systemic toxicity

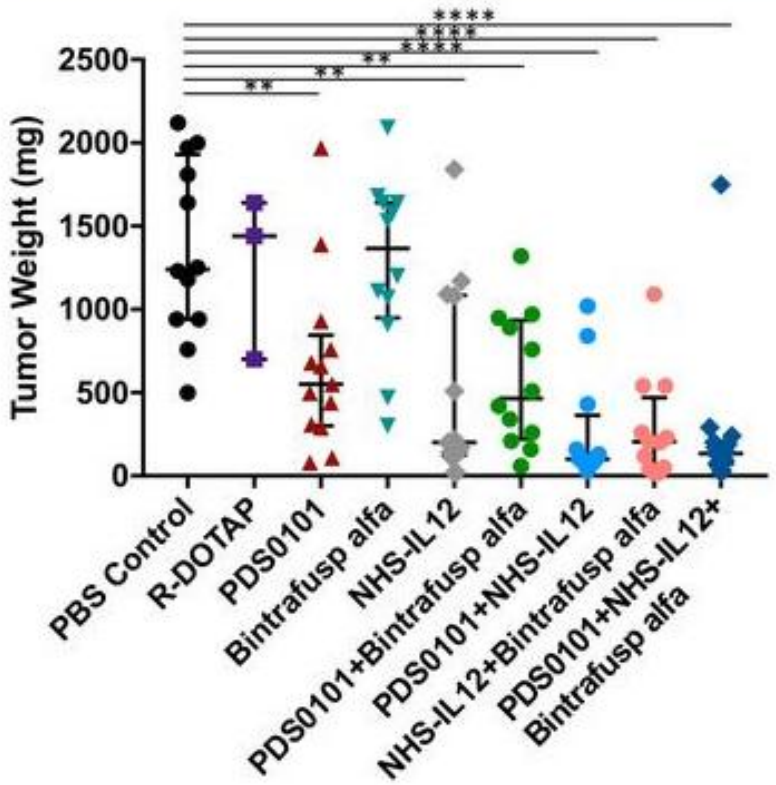
Source: *Wood LV. et al, SITC **2019**, (O19) Abstract ID 12533*

Bintrafusp Alfa

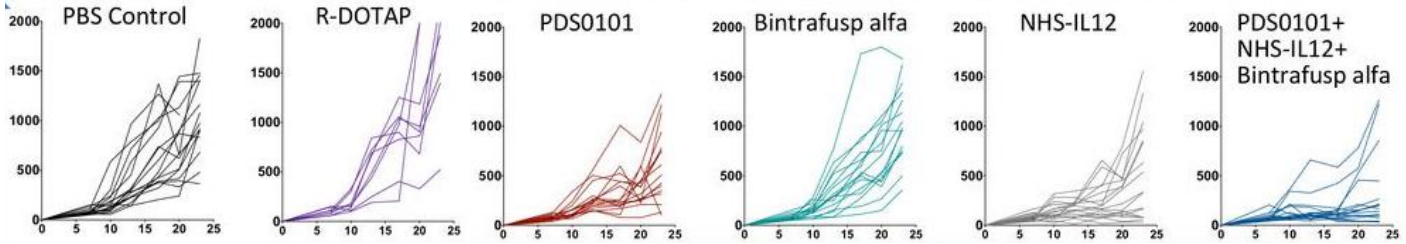


Source: Phase I: Strauss…Gulley. *Clin Cancer Res*. 2018

The combination of PDS0101, bintrafusp alfa and NHS-IL12 (PDS0301) resulted in tumor control in the HPV+ TC-1 syngeneic tumor model



Treatment	# Mice with Tumor Volume <300mm^3
PBS Control	0/16
R-DOTAP	0/8
PDS0101	3/16
Bintrafusp alfa	0/16
NHS-IL12	6/16
PDS0101+Bintrafusp alfa	5/16
PDS0101+NHS-IL12	10/16
NHS-IL12+Bintrafusp alfa	8/16
PDS0101+NHS-IL12+Bintrafusp alfa	13/17



Source: Claire Smalley Rumfield et al. J Immunother Cancer 2020;8:e000612

NCI Triple Combination Study Design

- Patients with advanced HPV-related cancers received the combination of
  - bintrafusp alfa at 1200 mg flat dose i.v. q 2wks,
  - M9241(NHS-IL12/PDS0301) at 16.8 mcg/kg s.c. q 4 wks or 8 mcg/kg s.c. q 4 weeks and
  - PDS0101 given as two separate 0.5 ml s.c. injections q 4 wks
- HPV genotyping was done with PCR based assays (BD Onclarity or Molecular MD) if testing not already done

Population

- Cervical
- Anal
- P16+ oropharyngeal
- Other HPV-associated

Endpoints

Primary: ORR
Secondary: safety

Effective Translation from Preclinical to Human: PDS0101 + PDS0301 + Checkpoint Inhibitor Shows Clinical Activity

Phase 2 Trial Correlates with Preclinical Results Demonstrating Improved Shrinkage of HPV16+ Tumors with the Triple Combination in Multiple Types of HPV-Associated Cancers

Checkpoint inhibitor refractory patients

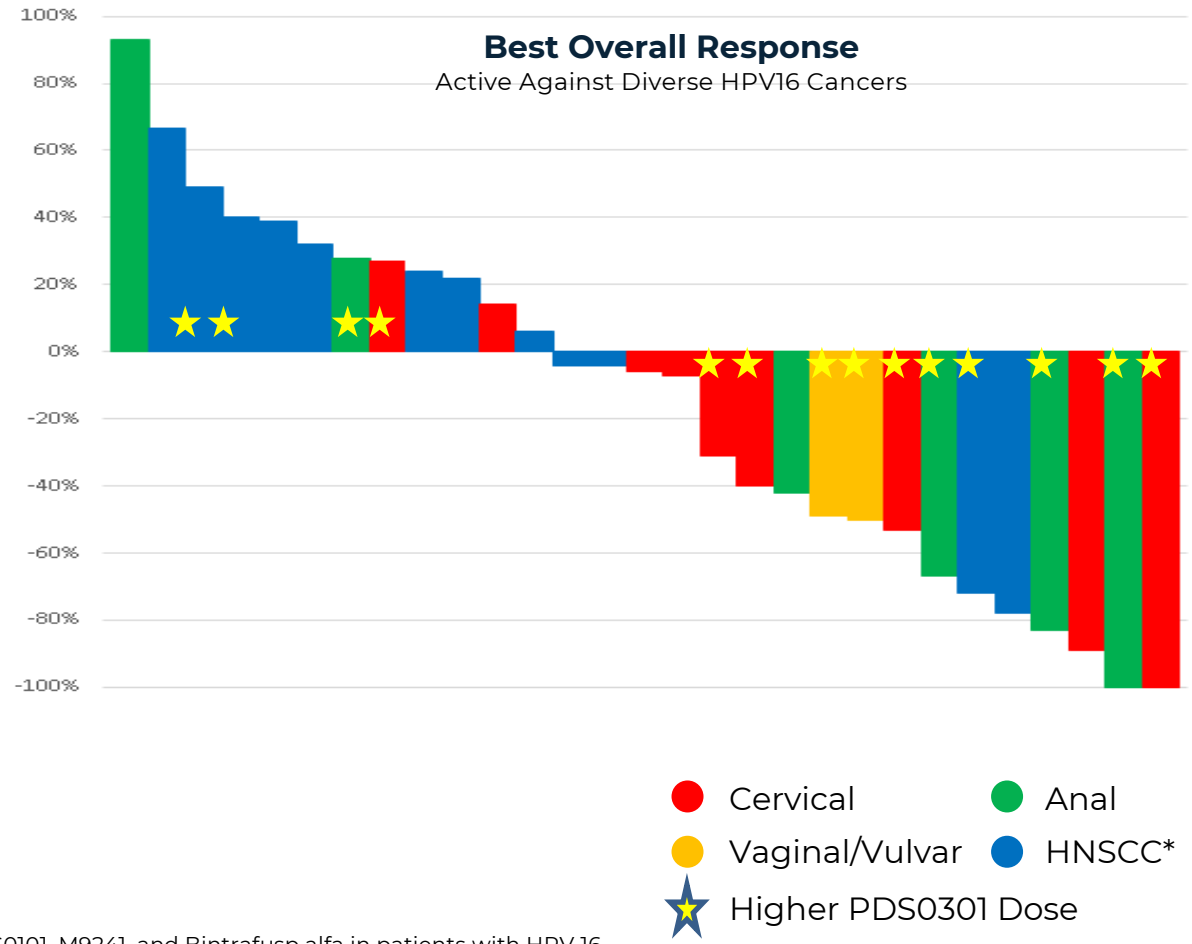
- Efficacy data in HPV16-positive patients:
  - Objective response in optimal dose group (high dose PDS0301) - 5/8 (62.5%)[1,2]
  - Median overall survival (OS) is 21 months (all dose groups n=29)[3]

Checkpoint inhibitor naive patients

- Interim data:
  - Objective response - 7/8 (87.5%)[4]
  - Percent of patients alive at median follow-up of 27 months – 6/8 (75.0%)[5]

Safety results (CPI Naïve and Refractory)

- 24/50 (48%) of patients experienced grade 3 and higher adverse events
- 2/50 (4%) experienced grade 4 adverse events



*HNSCC – head and neck squamous cell carcinomas

Reference: Strauss J. et al. Phase II evaluation of the triple combination of PDS0101, M9241, and Bintrafusp alfa in patients with HPV 16 positive malignancies. Presented at: American Society of Clinical Oncology 2022 Annual Meeting; June 3-7, 2022; Virtual. Abstract: 2518. Best Overall Response is defined by RECIST 1.1

Effective Translation from Preclinical to Human: PDS0101 + PDS0301 + Checkpoint Inhibitor Shows Clinical Activity

Phase 2 Trial Correlates with Preclinical Results Demonstrating Improved Shrinkage of HPV16+ Tumors with the Triple Combination in ICI Naïve and Refractory Patients

Checkpoint inhibitor refractory patients

- Efficacy data in HP
  - Objective response in optimal dose group (high dose PDS0301) - 5/8 (62.5%)[1,2]
  - Median overall survival (OS) is 21 months (all dose groups n=29)[3]

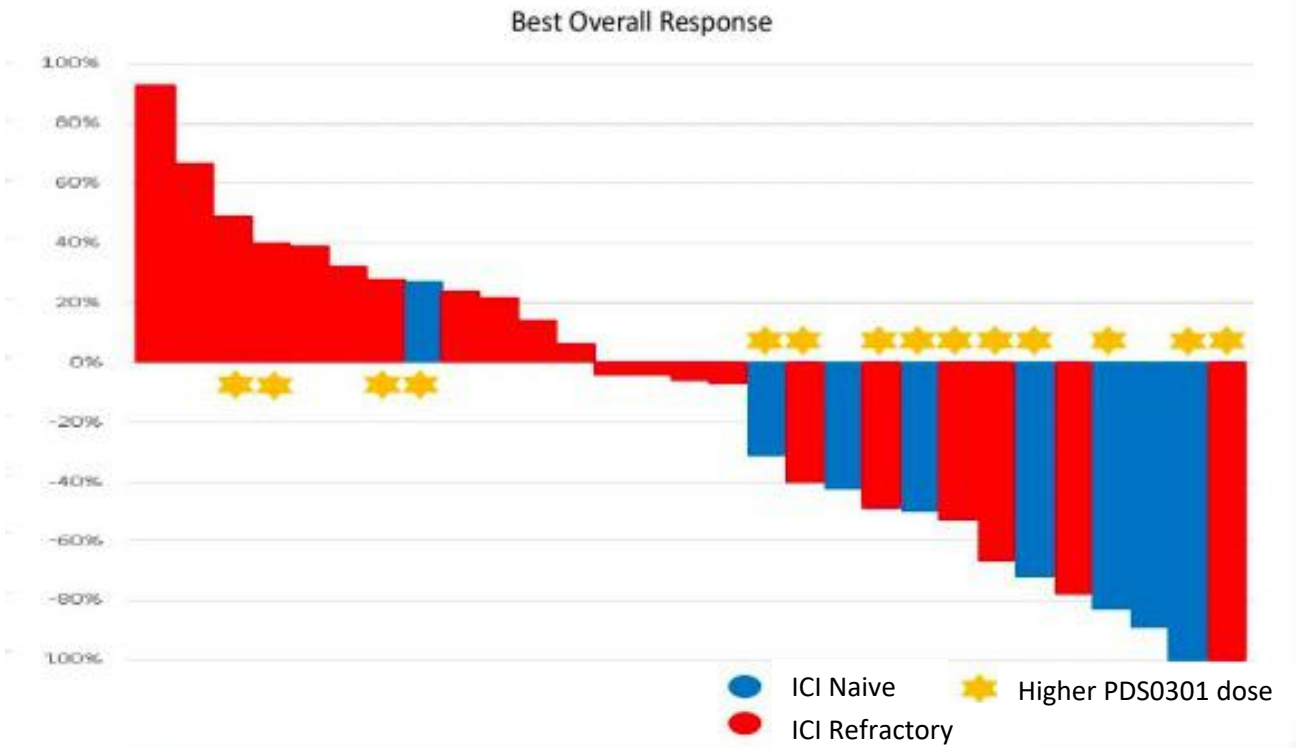
Checkpoint inhibitor <u>naive</u> patients

- Interim data:
  - Objective response - 7/8 (87.5%)[4]
  - Percent of patients alive at median follow-up of 27 months – 6/8 (75.0%)[5]

Safety results (CPI Naïve and Refractory)

- 24/50 (48%) of patients experienced grade 3 and higher adverse events
- 2/50 (4%) experienced grade 4 adverse events

Best Overall Response
Active in ICI Naïve and Refractory Patients



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Best Overall Response is defined by RECIST 1.1

NCI Publications Involving NHS-IL12

- Tumor-targeted interleukin-12 synergizes with entinostat to overcome PD-1/PD-L1 blockade-resistant tumors harboring MHC-I and APM deficiencies. J ImmunoTher Cancer. 2022
- Cure of syngeneic carcinomas with targeted IL-12 through obligate reprogramming of lymphoid and myeloid immunity. JCI Insight. 2022.
- Tumour-targeted interleukin-12 and entinostat combination therapy improves cancer survival by reprogramming the tumour immune cell landscape. Nat Commun. 2021.
- NHS-IL12, a tumor-targeting immunocytokine [review]. Immunotargets Ther. 2021.
- Efficient tumor clearance and diversified immunity through neoepitope vaccines and combinatorial immunotherapy. Cancer Immunol Res. 2019.
- Temporal changes within the (bladder) tumor microenvironment that accompany the therapeutic effects of the immunocytokine NHS-IL12. J Immunother Cancer. 2019.
- Enhanced antitumor effects by combining an IL-12/anti-DNA fusion protein with avelumab, an anti-PD-L1 antibody. Oncotarget. 2017.
- First-in-human phase I trial of a tumor-targeted cytokine (NHS-IL12) in subjects with metastatic solid tumors. Clin Cancer Res. 2019.
- A phase 1 single arm study of bi-weekly NHS-IL12 in patients with metastatic solid tumors. The Oncologist. 2023.
- Immune correlates with response in patients with metastatic solid tumors treated with a tumor targeting immunocytokine NHS-IL12. Int Immunopharm. 2023.

Panel Discussion

Closing Remarks

Dr. Lauren V. Wood