sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

What's Next for Cancer Immunotherapy?

Hans Hammers MD, PhD

Associate Professor / UT Southwestern

AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE CHAMPION OF THE EMERGENCY PHYSICIAN

ACCC Association of Community Cancer Centers

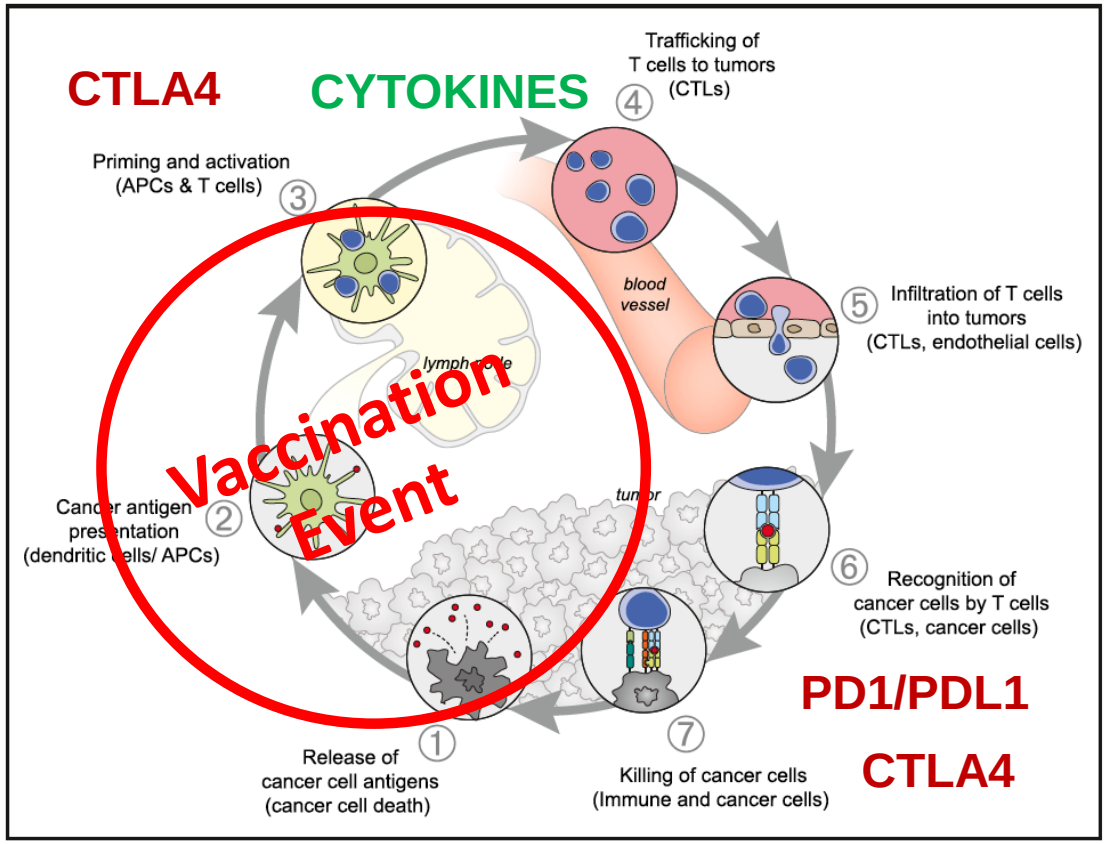
HOPA Hematology/Oncology Pharmacy Association

sitc Society for Immunotherapy of Cancer

Disclosures

- Clinical Research Funding:
  - BMS, Merck
- Consulting:
  - Pfizer, BMS, Exelixis, Eisai, Merck, Armo Biosciences, Novartis, Eli Lilly, Corvus, Surface Oncology
- I will be discussing non-FDA approved indications during my presentation.

Immunity Cycle



T CELLS

Mellman, Chen Immunity Cycle

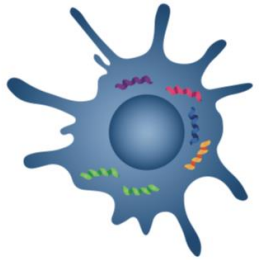
Vaccination Approaches

- Deterministic Approach
  - RNA (e.g. BioNtech)
  - DNA
  - Peptide (e.g. Neon, Immatics)

- Stochastic Approach (typically in-situ)
  - Radiation
  - TLR / Agonists STING

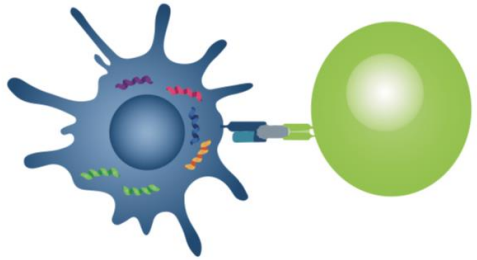
NEO-PV-01 (Peptides)

Cancer Mutations Generate Neoantigens



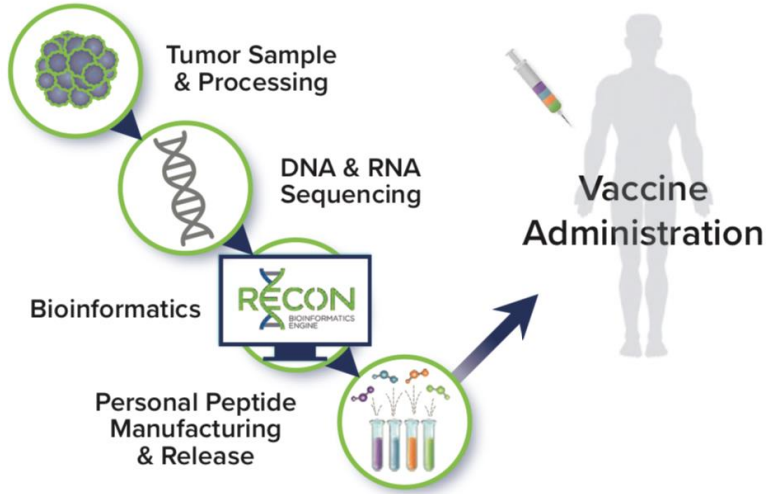
- Tumor mutations expressed as neoantigens
- Neoantigens presented on tumor cell surface via MHC

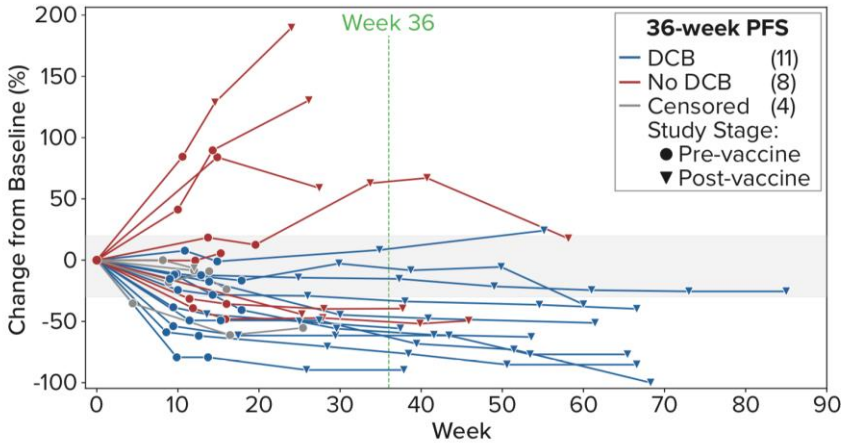
Neoantigens Provide Targets for T cells



- T cells interface with neoantigen peptide: MHC
- Tumor cell recognition & T cell-mediated killing

Manufacture of NEO-PV-01 Personal Neoantigen Vaccine





First Immunotherapy

THE

AMERICAN JOURNAL

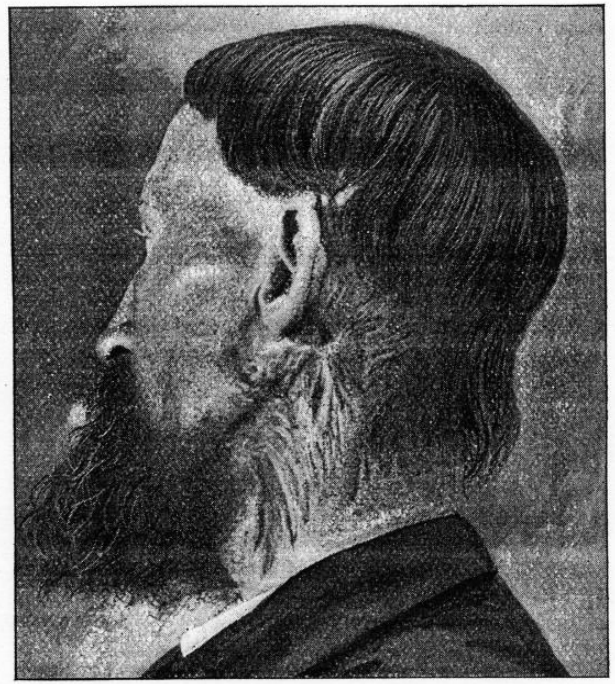
OF THE MEDICAL SCIENCES.

MAY, 1893.

THE TREATMENT OF MALIGNANT TUMORS BY REPEATED INOCULATIONS OF ERYSIPELAS: WITH A REPORT OF TEN ORIGINAL CASES.[1]

By William B. Coley, M.D.,

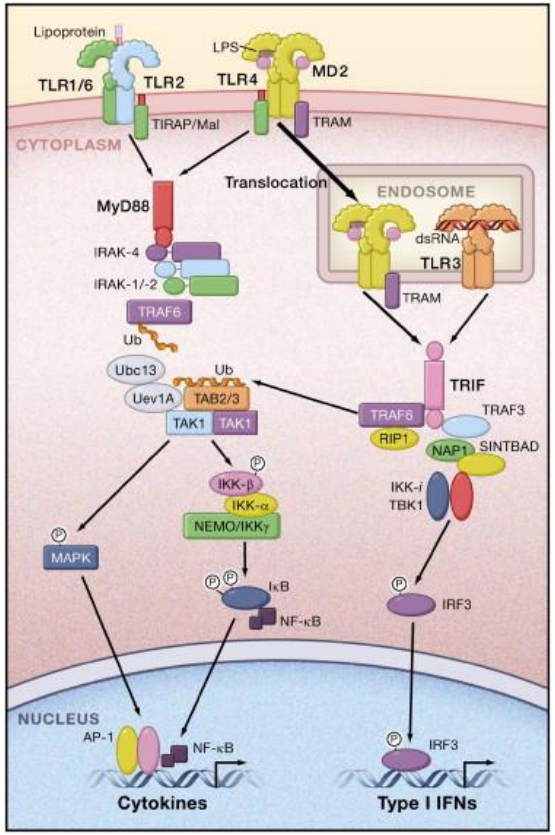
ASSISTANT SURGEON TO THE HOSPITAL FOR RUPTURED AND CRIPPLED; INSTRUCTOR IN SURGERY IN THE POST-GRADUATE MEDICAL SCHOOL, NEW YORK.



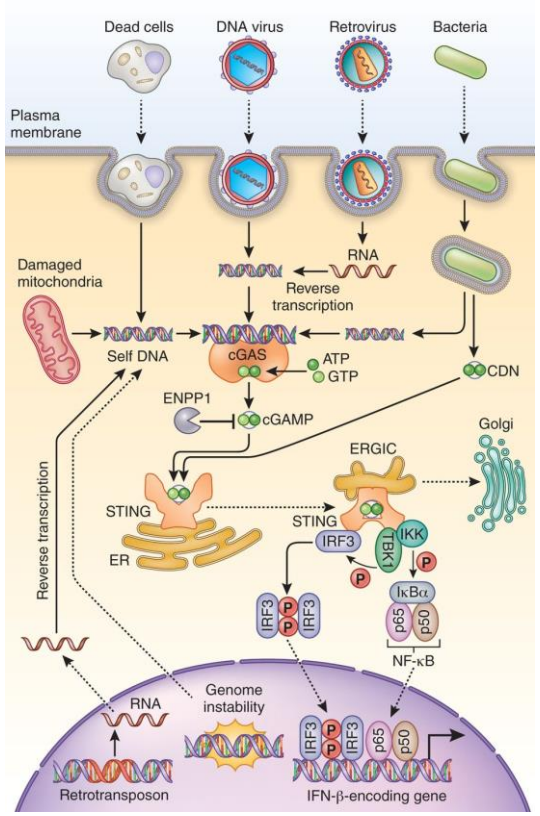
Round-celled sarcoma of neck, cured by erysipelas. Photograph taken seven years after. (Bull's case.)

LPS = Toll Like Receptor 4 agonist

Innate Immune Sensing

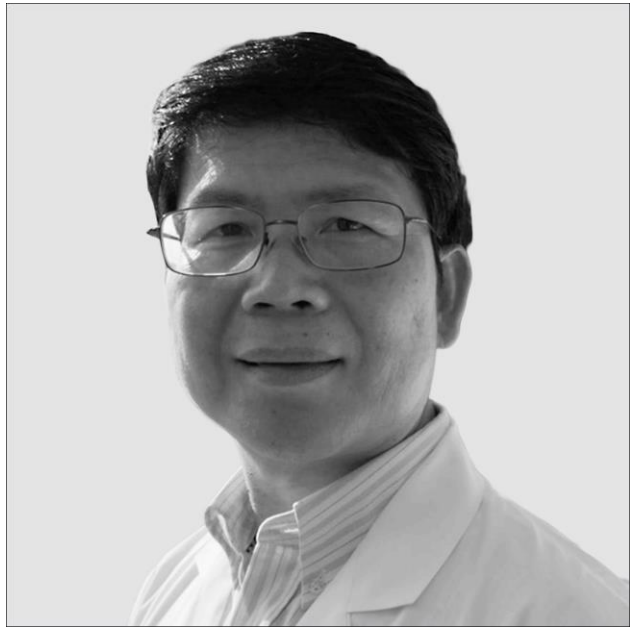


Toll-Like Receptors (TLR)



cGAS-STING pathway

Innate Immune Sensing

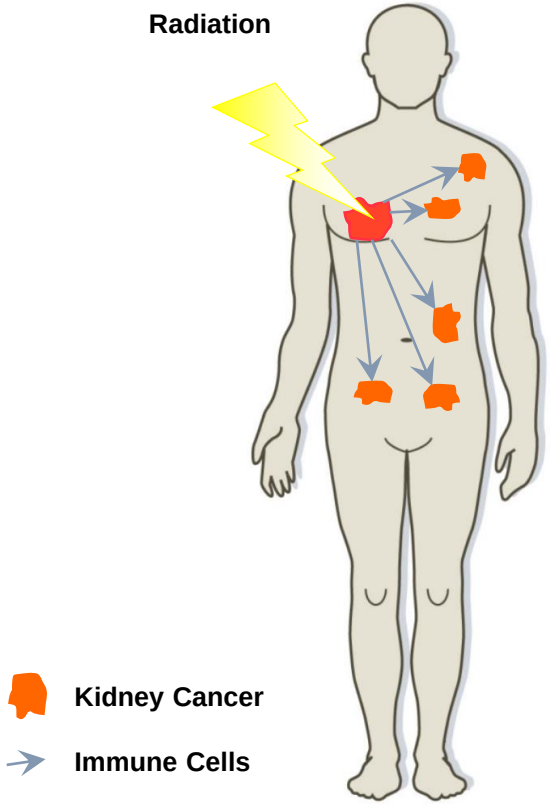


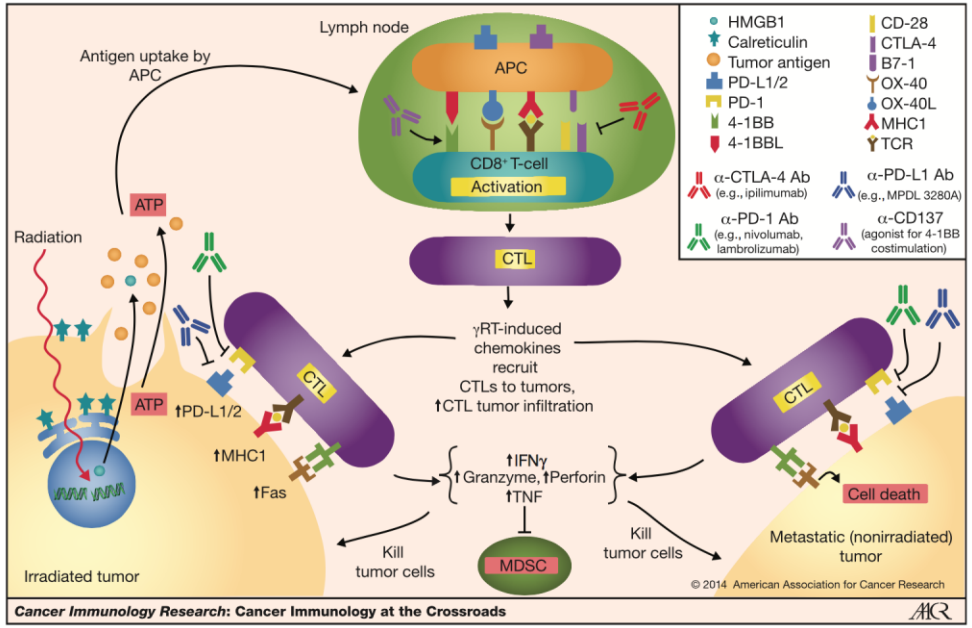
Bruce Beutler
2011 Nobel Price Medicine/Physiology

Zhijian “James” Chen
2019 Breakthrough Prize in Life Sciences

UT Southwestern, Dallas

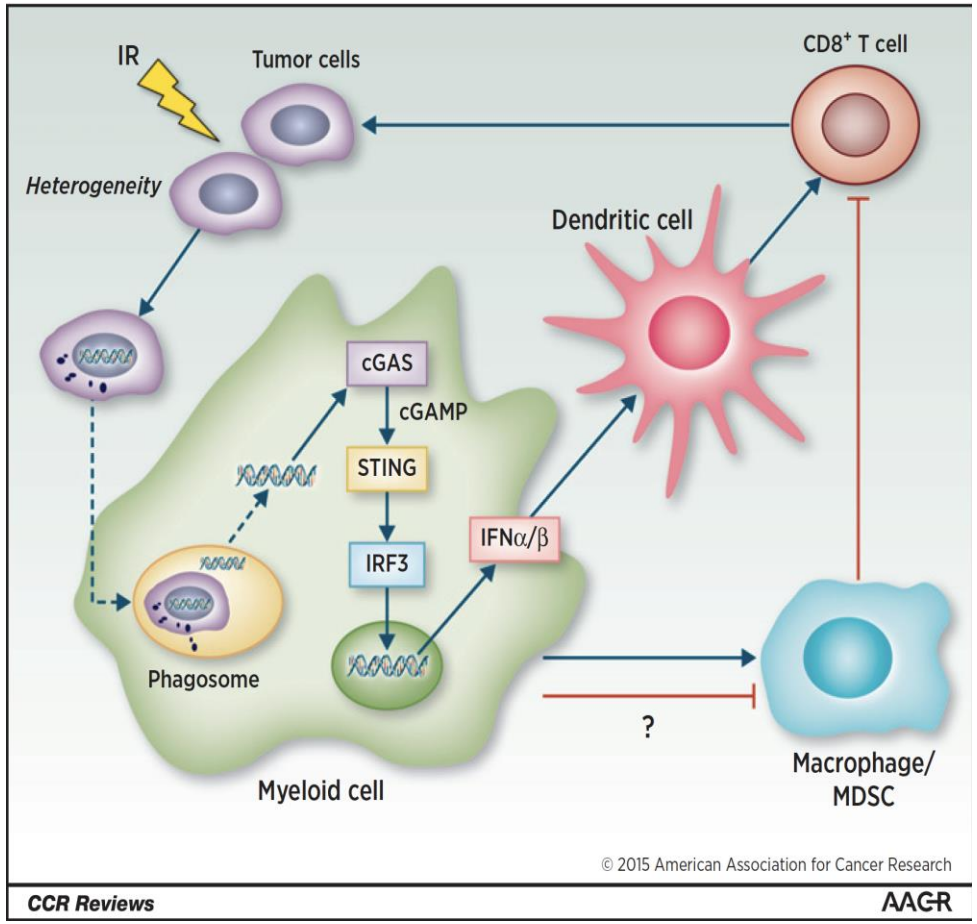
IN SITU VACCINATION WITH SBRT



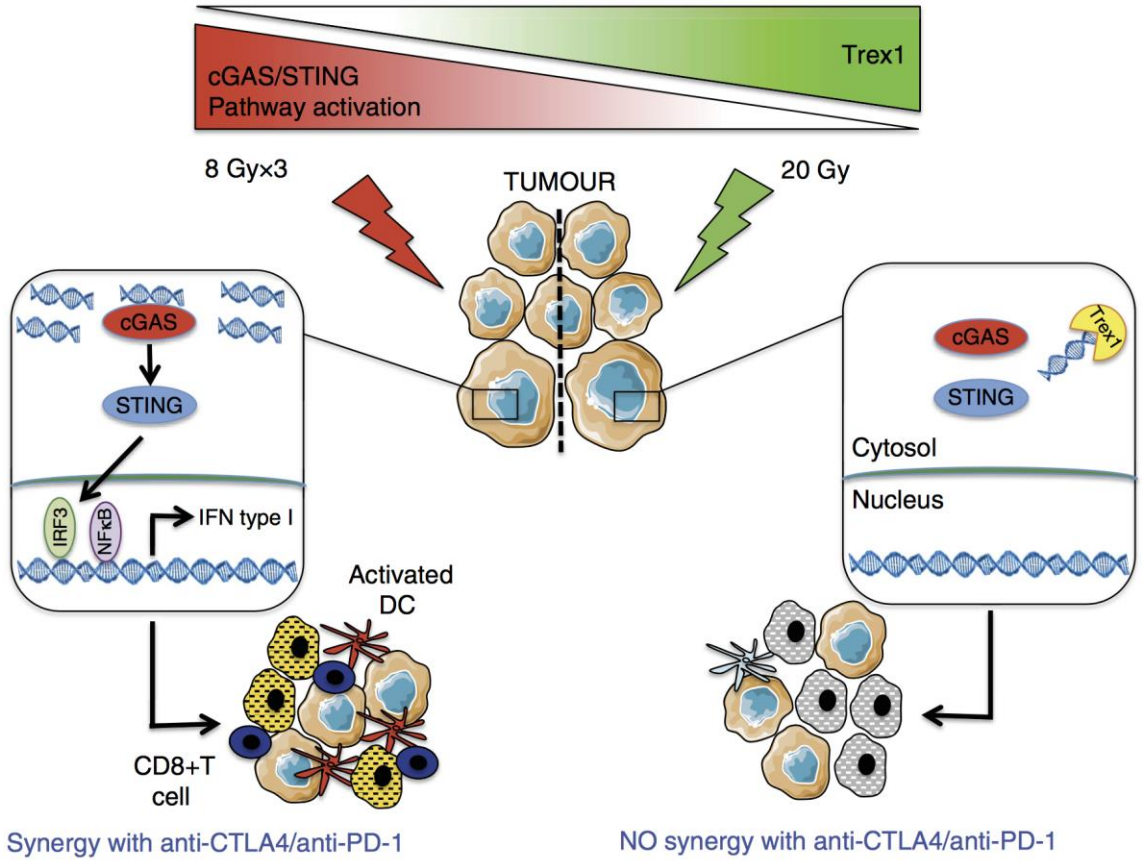


Cancer Immunology Research 2(9); 831–8.

Radiation Induced cGAS-STING

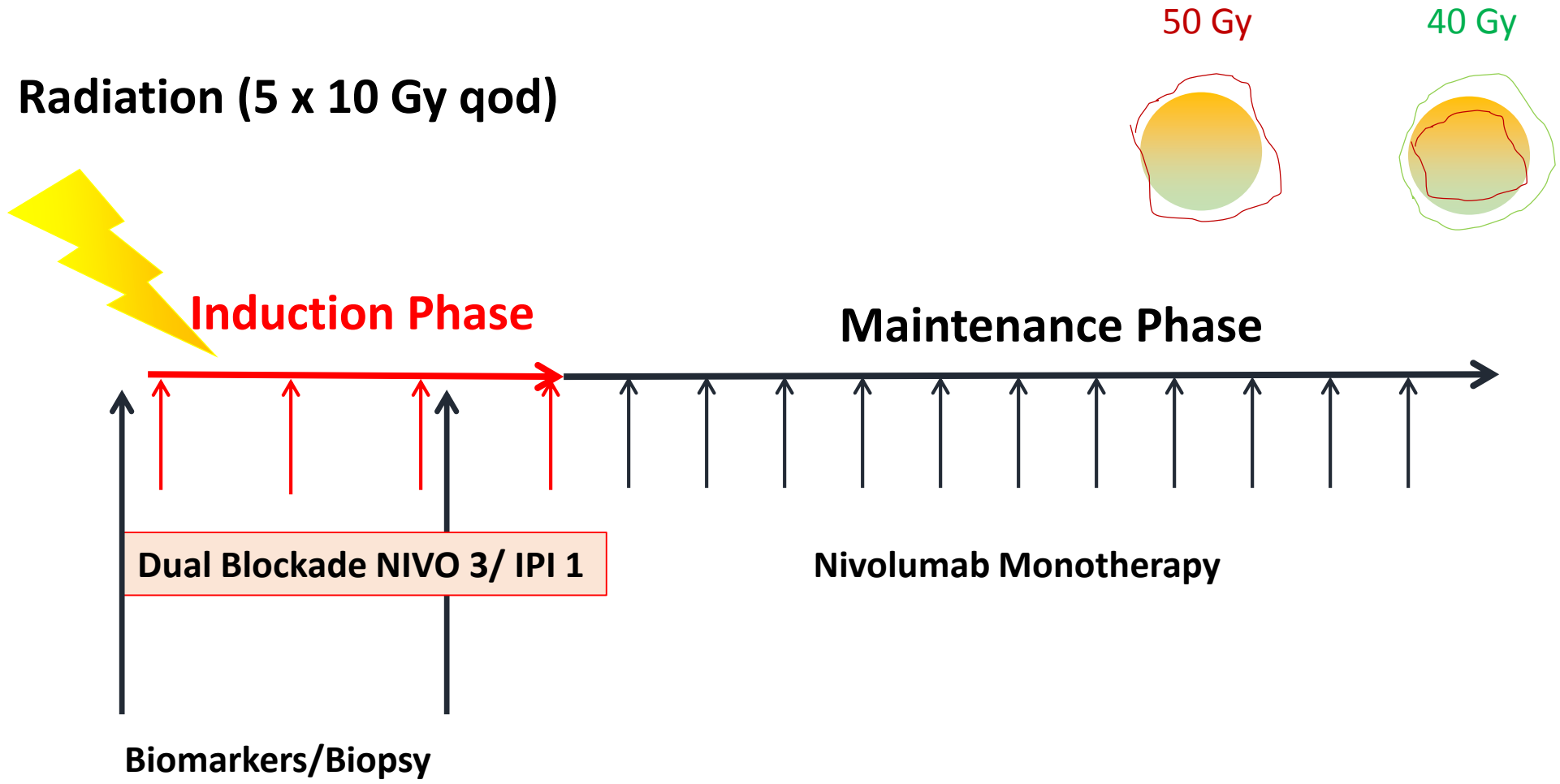


Clin Cancer Res; 22(1) January 1, 2016

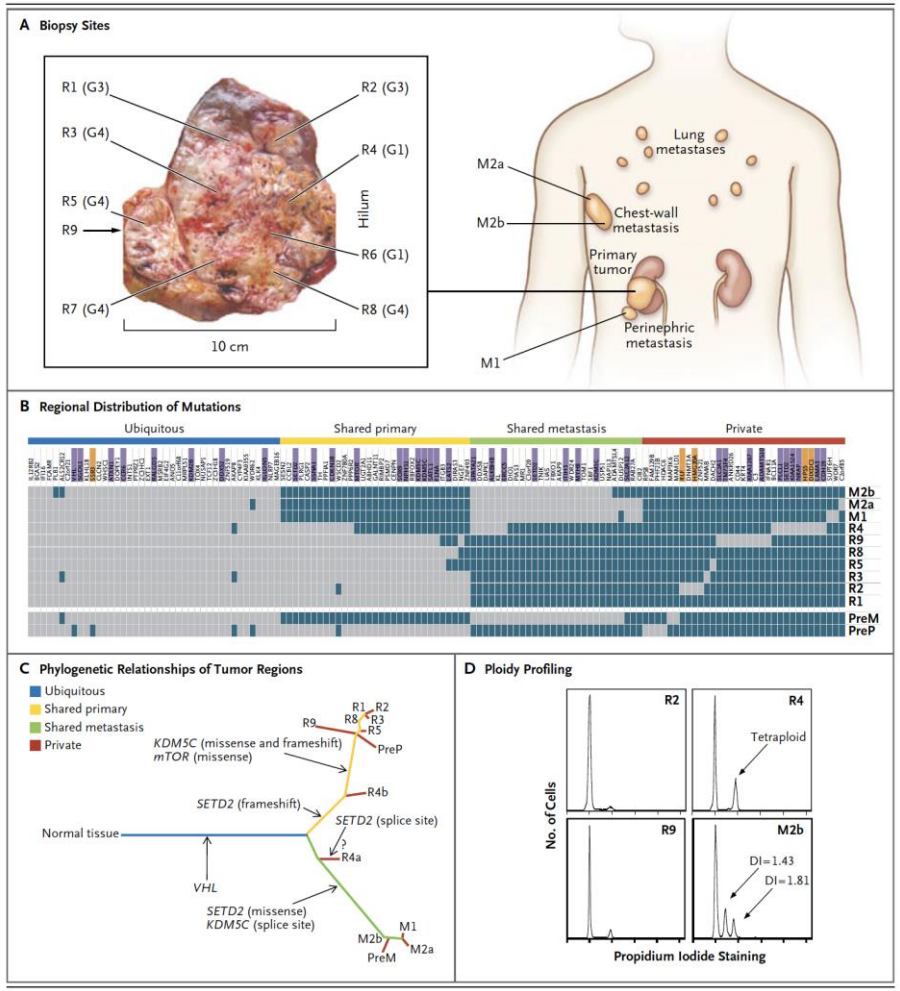


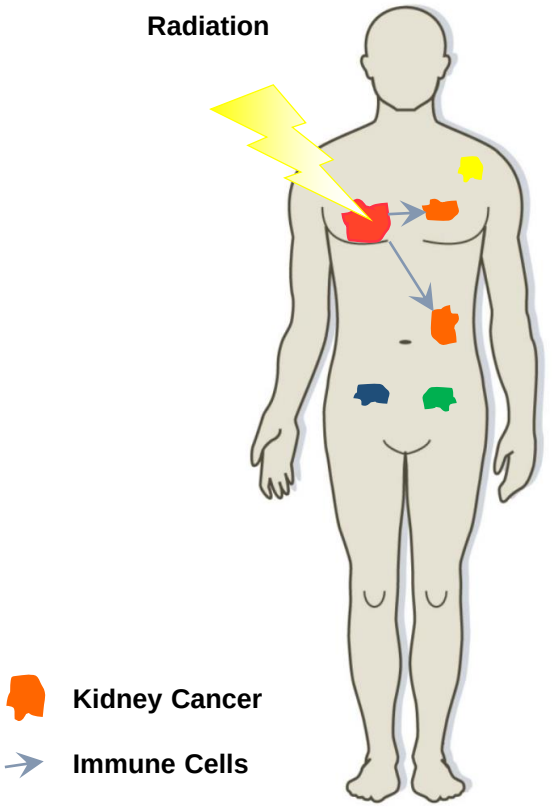
Nat Commun. 2017 Jun 9;8:15618.

RADVAX RCC Trial



Tumor Heterogeneity





Gerlinger et al NEJM

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Immuno-PET

nature COMMUNICATIONS

ARTICLE

DOI: 10.1038/s41467-018-07131-y OPEN

Whole body PD-1 and PD-L1 positron emission tomography in patients with non-small-cell lung cancer

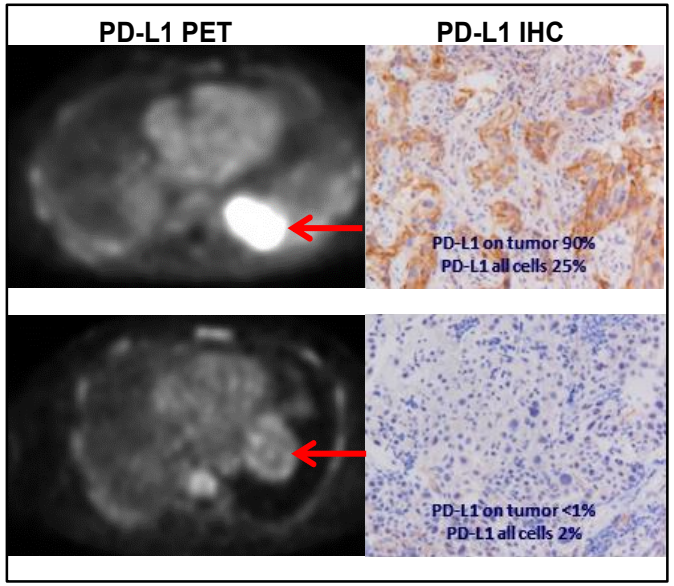
A.N. Niemeijer[1], D. Leung[2], M.C. Huisman[3], I. Bahce[1], O.S. Hoekstra[3], G.A.M.S. van Dongen[3], R. Boellaard[3], S. Du[2], W. Hayes[2], R. Smith[2], A.D. Windhorst[3], N.H. Hendrikse[3], A. Poot[3], D.J. Vugts[3], E. Thunnissen[4], P. Morin[2], D. Lipovsek[2], D.J. Donnelly[2], S.J. Bonacorsi[2], L.M. Velasquez[2], T.D. de Gruijl[5], E.F. Smit[6] & A.J. de Langen[1,6]

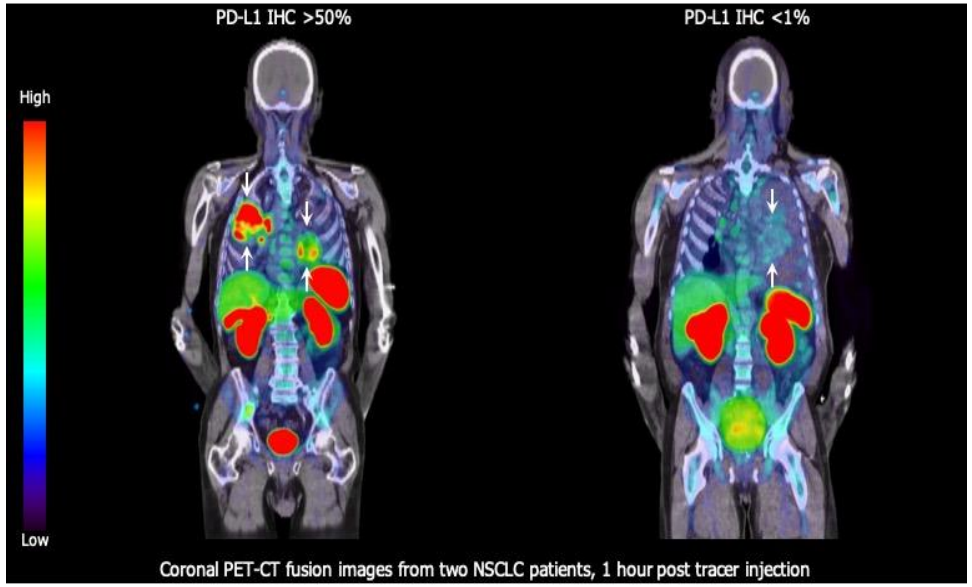
F18-PET PDL1 Imaging (2nd Gen)

Synthesis and Biologic Evaluation of a Novel ^{18}F-Labeled Adnectin as a PET Radioligand for Imaging PD-L1 Expression

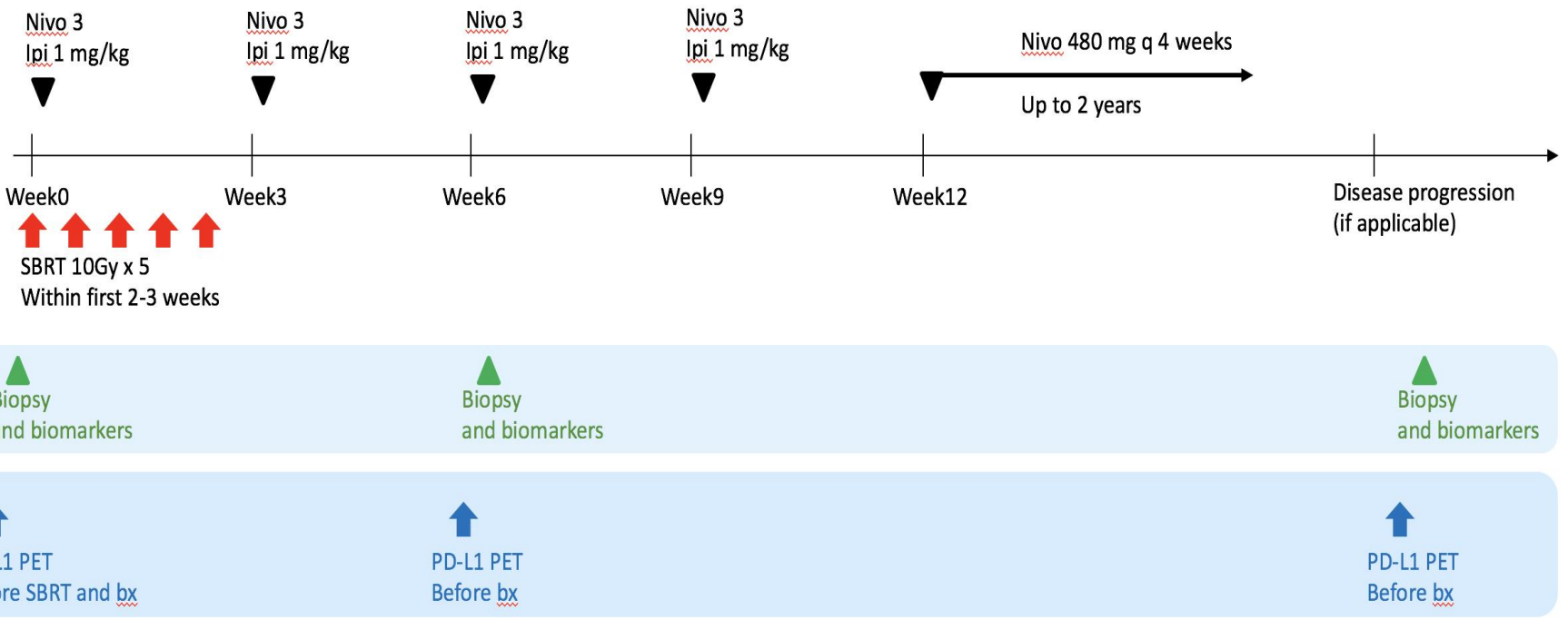
David J. Donnelly*, R. Adam Smith*, Paul Morin*, Daša Lipovšek, Jochem Gokemeijer, Daniel Cohen, Virginie Lafont, Tritin Tran, Erin L. Cole, Martin Wright, Joonyoung Kim, Adrienne Pena, Daniel Kukral, Douglas D. Dischino, Patrick Chow, Jinping Gan, Olufemi Adelakun, Xi-Tao Wang, Kai Cao, David Leung, Samuel J. Bonacorsi Jr., and Wendy Hayes

Bristol-Myers Squibb Research and Development, Princeton, New Jersey





RADVAX RCC II



STING Agonist

Phase Ib study of MIW815 (ADU-S100) in combination with spartalizumab (PDR001) in patients with advanced/metastatic solid tumors or lymphomas (NCT03172936)

Funda Meric-Bernstam,[1] Shahneen Sandhu,[2] Omid Hamid,[3] Anna Spreafico,[4] Stefan Kasper,[5] Reinhard Dummer,[6] Toshio Shimizu,[7] Neeltje Steeghs,[8] Nancy Lewis,[9] Craig Talluto,[10] Sinead Dolan,[10] Andrew Bean,[9] Robert J. Brown,[11] Damian Trujillo,[11] Nitya Nair,[11] Jason J. Luke[12]

[1]Department of Investigational Cancer Therapeutics, MD Anderson Cancer Center, Houston, TX; [2]Peter MacCallum Cancer Centre, Melbourne, Australia; [3]The Angeles Clinic and Research Institute, Los Angeles, CA; [4]Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, Toronto, ON, Canada; [5]Department of Medical Oncology, West German Cancer Centre, University Hospital Essen, Essen, Germany; [6]University of Zurich, Zurich, Switzerland; [7]National Cancer Center Hospital, Tokyo, Japan; [8]Netherlands Cancer Institute, Amsterdam, The Netherlands; [9]Novartis Pharmaceuticals Corporation, East Hanover, NJ; [10]Novartis Institutes for BioMedical Research, Cambridge, MA; [11]Aduro Biotech Inc., Berkeley, CA; [12]The University of Chicago Medicine, Chicago, IL

PRESENTED AT: 2019 ASCO ANNUAL MEETING #ASCO19

PRESENTED BY: Dr Funda Meric-Bernstam

STING Agonist

Preliminary anti-tumor activity

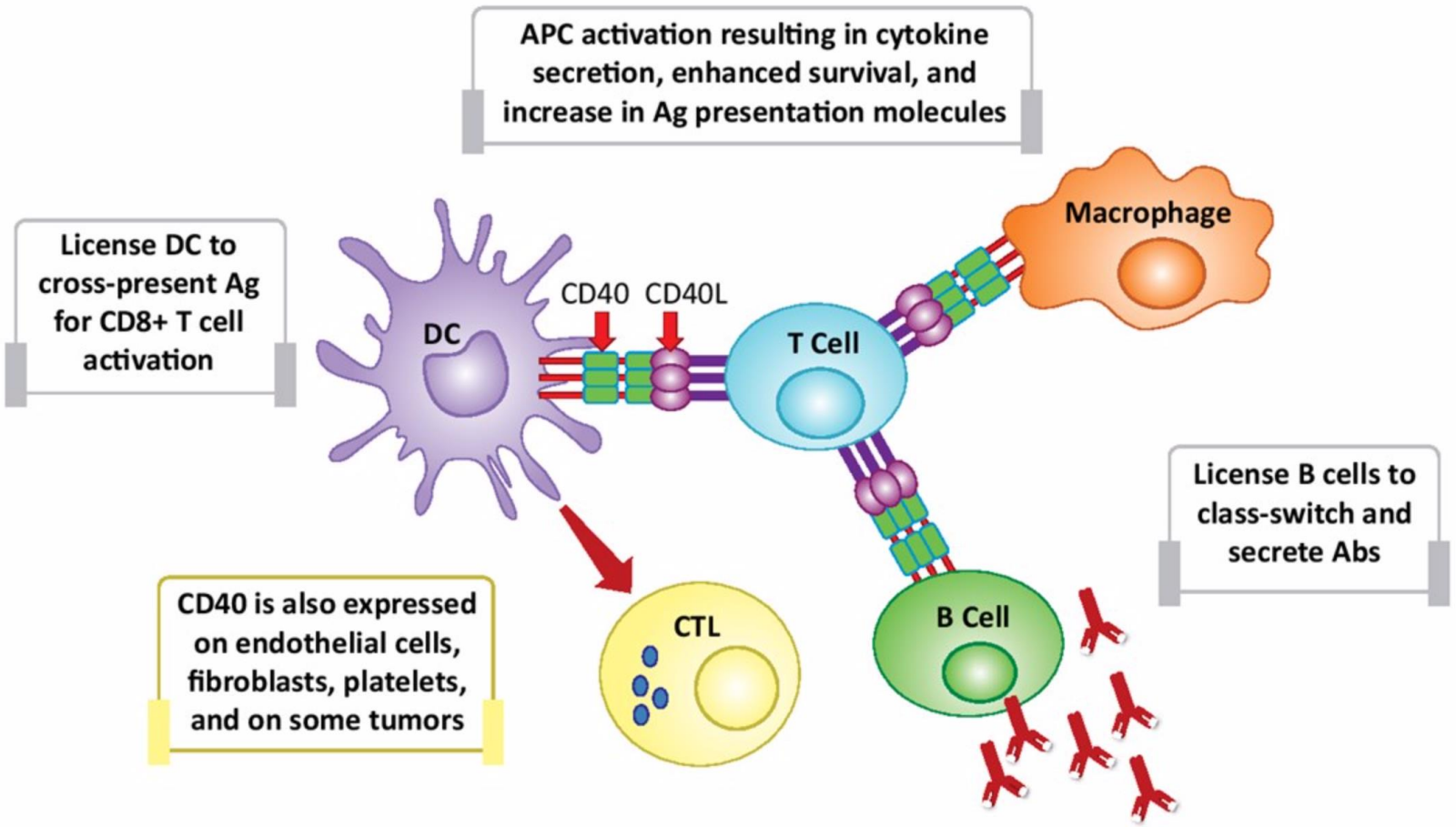
MIW815 (ADU-S100) 3-weeks-on/1-week-off	Confirmed responses were achieved in five patients, one of which was a CR
	• Three of these responses (including the CR) were observed in patients with IO-naive TNBC; these patients are continuing to receive treatment at time of data cut
	  • Two of these patients with TNBC expressed PD-L1 levels of >1% at baseline (data from the third patient are not available)
	• The two remaining responders had previously IO-treated melanoma (of 35 melanoma patients enrolled across the whole study, 7 not yet reimaged)
	• An additional 12 patients achieved SD
	  • Tumor types: Sarcoma, melanoma, SCC skin, breast, lymphoma, and head and neck

MIW815 (ADU-S100) monthly	No patients achieved a response; however, six patients achieved a SD • Tumor types: Ovarian, breast, uveal melanoma, head and neck, and cutaneous melanoma • Four of whom maintained SD for ≥6 months

CRC, colorectal cancer; SCC, squamous cell carcinoma.

Data cut-off: April 5, 2019

Anti-CD40



Anti-CD40

Apexigen

Press Release

Apexigen Presents Clinical Data on CD40 Antibody APX005M in Metastatic Melanoma at the AACR Annual Meeting 2019

- *APX005M and Nivolumab Combination was Well Tolerated and Induced Promising Response Rates in Patients with Metastatic or Unresectable Melanoma Progressing on Anti-PD-1/PD-L1 Therapy*
- *Plenary Session and Late-breaking Poster Presentations Highlight Progress Developing APX005M in Combination Therapy for Difficult-to-Treat Types of Cancer*

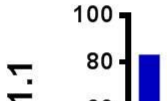
>> In Melanoma 16% PR in PD1 progressors

>> Trial with anti-CSF1 and anti-PD1 enrolling RCC at Yale (Kluger)

Cytokines: PEG-IL2

Stage IV IO-Naïve 1L RCC Cohort Achieved Pre-Specified Efficacy Criteria

Stage 1: ORR 7/11 (64%)
Stage 2: Best Overall Response ORR=12/26 (46%); DCR=20/26 (77%)



Median Time on Study 5.6 Months (N=26)
As of May 29, 2018

Bempegaldesleukin in combination with OPDIVO® (nivolumab)

INDICATION: Renal Cell Carcinoma

PARTNER

Bristol-Myers Squibb

PHASE 3

Data cut: May 29, 2018

PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18

Horizontal dotted lines indicate the thresholds for PD, PR and CR response according to RECIST (version 1.1) criteria; -100% is PR for complete clearance of target lesions. CR is a complete response, "u": Unconfirmed. *Best overall response is PD (SD for target lesions, PD for non-target lesions). §Off study treatment with confirmed PR due to patient decision.

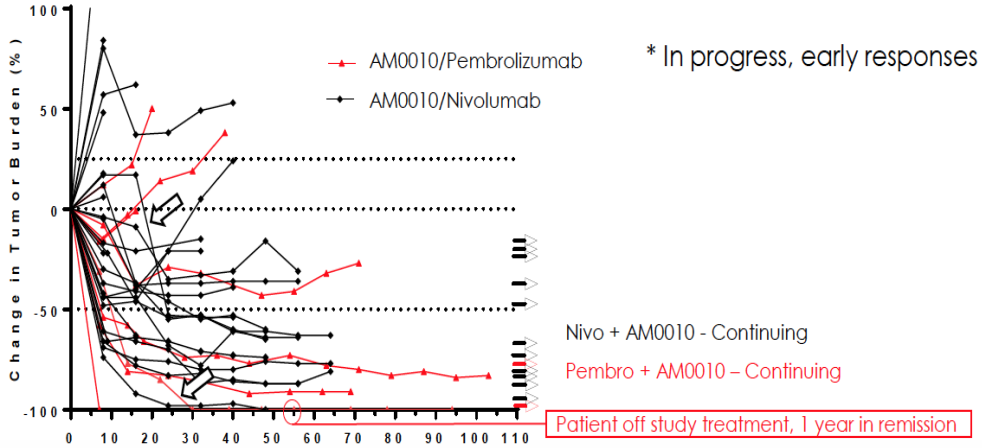
Cytokines: PEG-IL10

AM0010 + Anti-PD-1 in RCC (92% Poor to Intermediate risk)

AM0010 + Anti-PD-1 Shows Significant, Sustained Impact on Tumor Burden

Disease	Treatment Combo (n=Evaluable Patients/ Enrolled Patients)	Prior Therapies Median (Range)	DCR n (%)	ORR (%)	CR (%)	mPFS (Months)	mOS (Months)
RCC	**AM0010** (n=16/19)	3 (0-7)	9 (56%)	4 (25%)	–	1.9	9.8[1]
	AM0010 + pembrolizumab (n=8/8)	2 (0-5)	8 (100%)	4 (50%)	2[4] (25%)	16.7	NR[2]
	AM0010 + nivolumab (n=26/29)	1 (1-3)	21 (81%)	11 (42%)[2]	NR	NR[3]	NR[3]
	AM0010 + anti-PD-1 (n=34/37)	2 (0-5)	29 (85%)	15 (44%) [1]	2[3]		
	Anti-PD-1 mAb (nivolumab) (Motzer et al., JCO 2014)	1	57-65%	20-22%	1	2.7-4.2	25

(1) ORR numbers as of 10/29/2017 (2) Study in progress. Numbers as of August 11, 2017. Median follow-up 26.75 months (range 12.3-29.8); (3) Study in progress. Numbers as of August 11, 2017. Median follow-up 11.1 months (range 0.5-17.3); (4) 2 partial responses with 100% reduction in measurable disease; NR not reached



* In progress, early responses

CAR T Cells

Treatment of metastatic renal cell carcinoma (mRCC) with CAIX CAR-engineered T-cells – a completed study overview

Cor H.J. Lamers*[1], Yarne Klaver*, Jan W. Gratama†, Stefan Sleijfer† and Reno Debets*

*Laboratory of Tumor Immunology, Department of Medical Oncology, Erasmus MC – Cancer Institute, 3015 CN Rotterdam, The Netherlands
†Department of Medical Oncology, Erasmus MC – Cancer Institute, 3015 CN Rotterdam, The Netherlands

Biochem. Soc. Trans. (2016) 44, 951–959; doi:10.1042/BST20160037

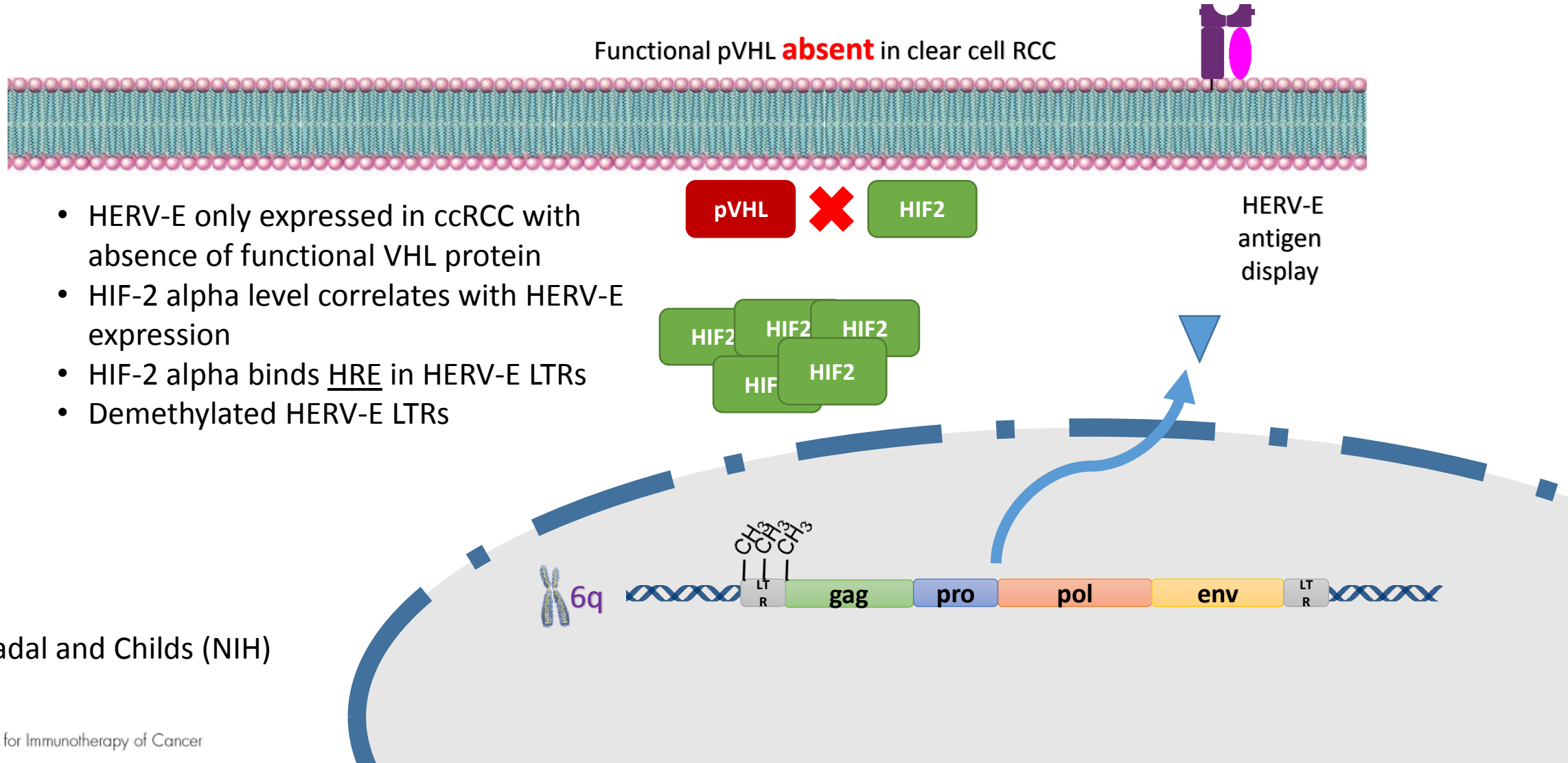
CAR T Cells

- CAR T-cells did not significantly expand in vivo, nor persist >4 weeks post infusion and showed gradually decreasing CAR gene and surface expression [21,22,28].
- Blood cytokine profiles, in particular IFN-γ and IL-6, mirrored CAR T-cell presence and in vivo T-cell activity [21,24].
- CAR T-cells displayed antigen-specific functions [39].
- Patients presented with dose-limiting elevations of liver enzymes in blood highly likely as a consequence of specific recognition of CAIX on lining cells of the bile ducts by CAR T-cells [3,24].
- Blocking CAR by parental mAb (G250) infusion decreased liver enzyme values in blood [24].
- CAR T-cells induced both humoral and cellular immune responses in patients directed against murine Fv domains, and which preceded loss of CAR T-cells [28].

Biochem. Soc. Trans. (2016) 44, 951–959; doi:10.1042/BST20160037

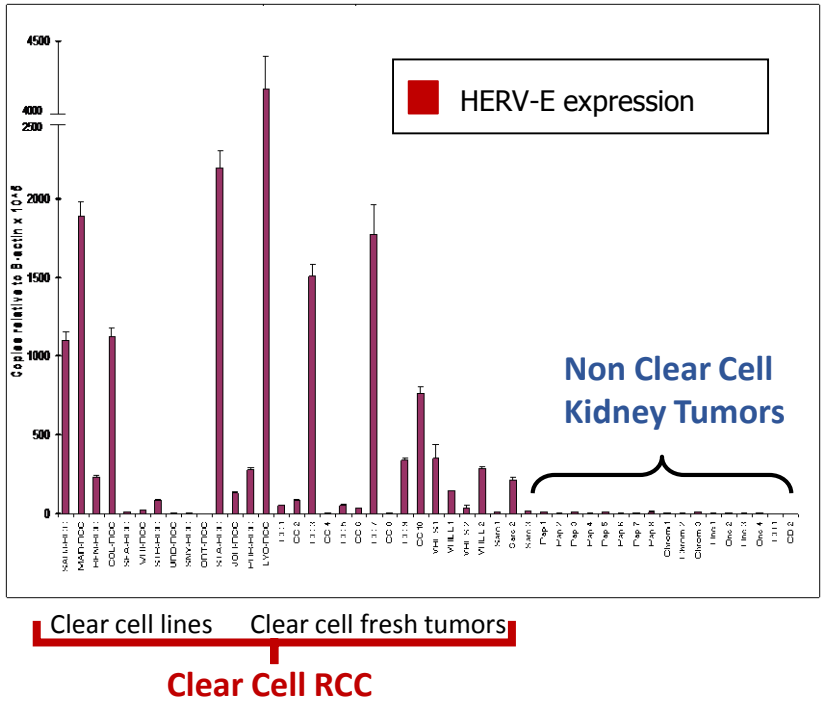
Regulation RCC HERV-E expression in ccRCC

- HERV-E only expressed in ccRCC with absence of functional VHL protein
- HIF-2 alpha level correlates with HERV-E expression
- HIF-2 alpha binds HRE in HERV-E LTRs
- Demethylated HERV-E LTRs

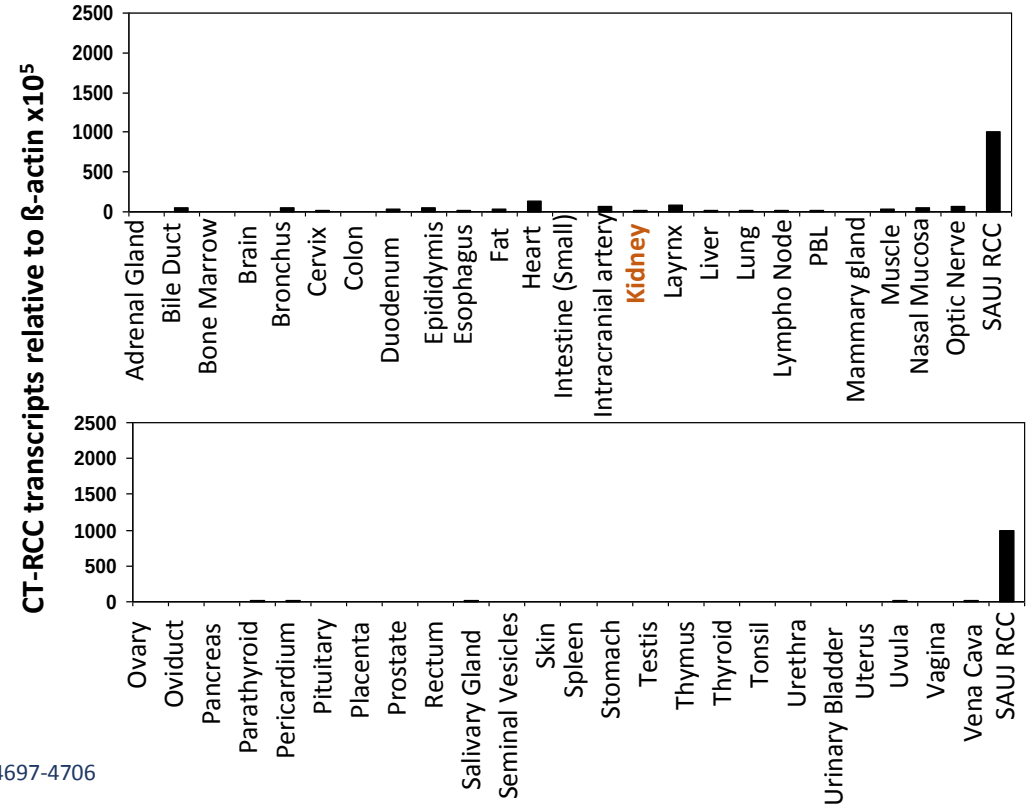


Drs Nadal and Childs (NIH)

CT-RCC HERV-E expression is restricted to the clear cell histology



No CT-RCC HERV-E expression in Normal Tissues



Cherkasova et al. *Oncogene* 2011; 30:4697-4706

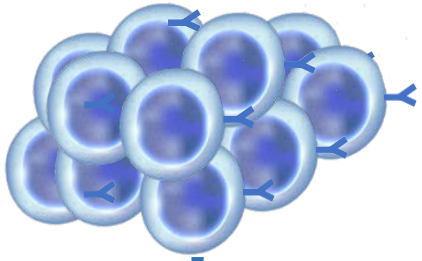
Investigational Plan

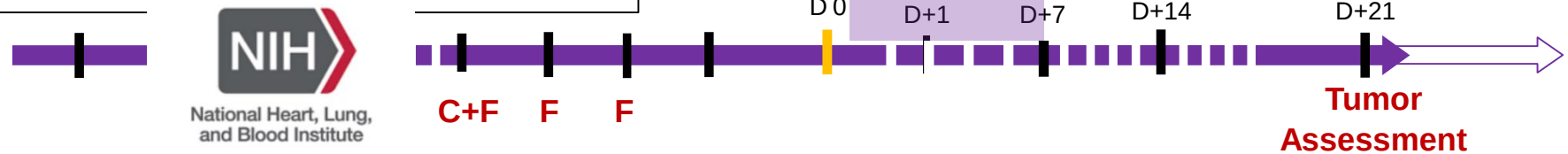
Apheresis → ***In vitro* Generation HERV-E TCR T-cells** → **Cryopreserve Cells at specified dose**

HERV-E TCR transduced T-cells

Lymphodepleting chemotherapy:

C: Cyclophosphamide 1000 mg/m²/day I.V.
F: Fludarabine 30 mg/m²/day I.V.
IL-2: 2,000,000 IU/m² I.V. q12h x 14 doses





Thank you !

@HHammersMD

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