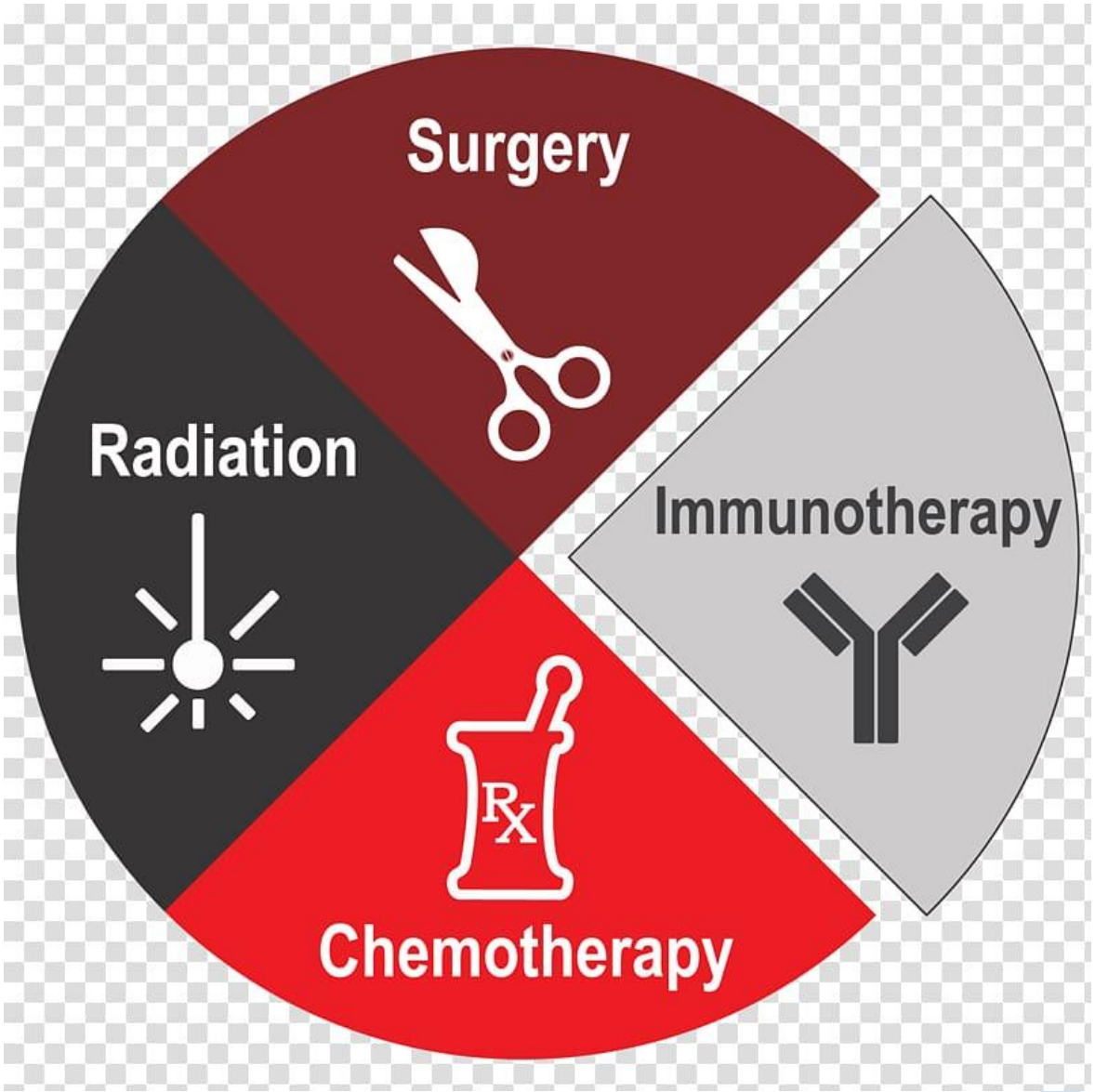
The evolving field of cancer

Suraj Saksena, PhD, HCLD (NRCC)
Science & Technology Leader
BD Biosciences, San Jose CA


Chemotherapy


Surgery
Radiation
Immunotherapy
Rx
Chemotherapy


Science
20 December 2013 | $10
Breakthrough of the Year
Cancer Immunotherapy
T cells on the attack
AAAS


nature
THE INTERNATIONAL WEEKLY JOURNAL OF SCIENCE
Antitumour immunity enhanced by inhibiting PD-L1/PD-1 and identifying mutant neo-antigens
IMMUNE-CHECKPOINT BLOCKADE IN
CANCER
PEER REVIEW
ACCEPT YOUR OWN PAPER
How some scientists are duping the system
MICROSCOPY
THE CASE FOR AIMING HIGHER
Atomic resolution is there for the taking
ENERGY
'NIGHT-TIME' COOLING BY DAY
New materials enable radiative cooling in sunlight


The lingering legacy of Deepwater Horizon
The future of human genome editing
Drilling into engine oil antiwear films
Science
$10
3 APRIL 2015
AAAS
SPECIAL ISSUE
Cancer Immunology and Immunotherapy


TIME
What if your immune system could be taught to kill cancer?
Inside the brutally selective, hugely expensive, lifesaving trials of immunotherapy.
By Alice Park


Cancer
Free

FACT OF THE DAY

"

[After immunotherapy] ... they didn't find any cancer at all."

– **JIMMY CARTER**
Former U.S. President

Emily Whitehead: Miracles do happen!

Age 5 in 2012: gum bleeds, bruises on body, excruciating pain in legs- diagnosed with B-ALL; relapsed twice after intensive rounds of chemotherapy

Age 12 in 2019: 7 years cancer free!

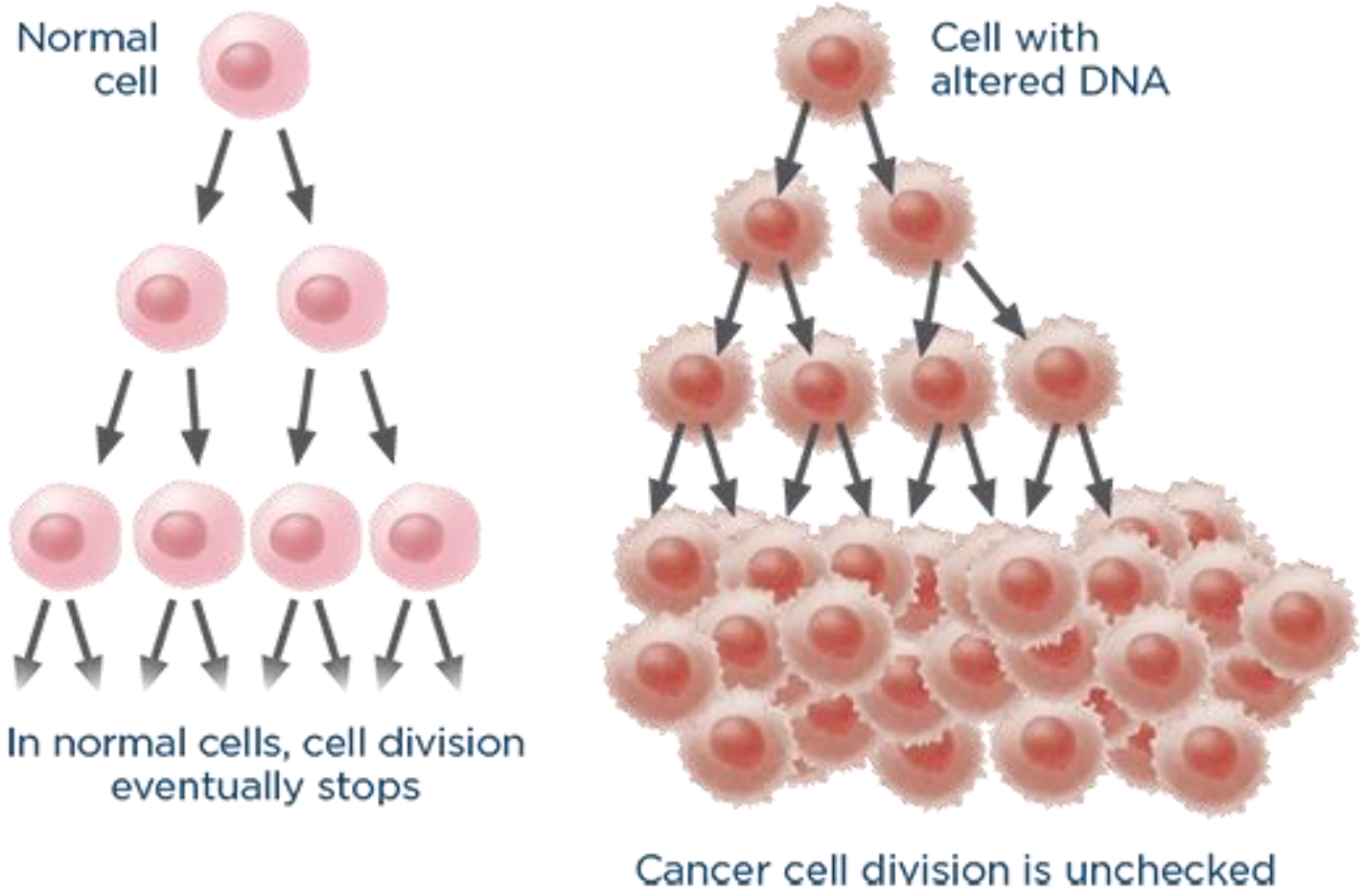
Dr. Carl June (U. Penn)

Dr. Stephen Grupp (Oncologist)

Children’s Hospital of Philadelphia (CHOP)

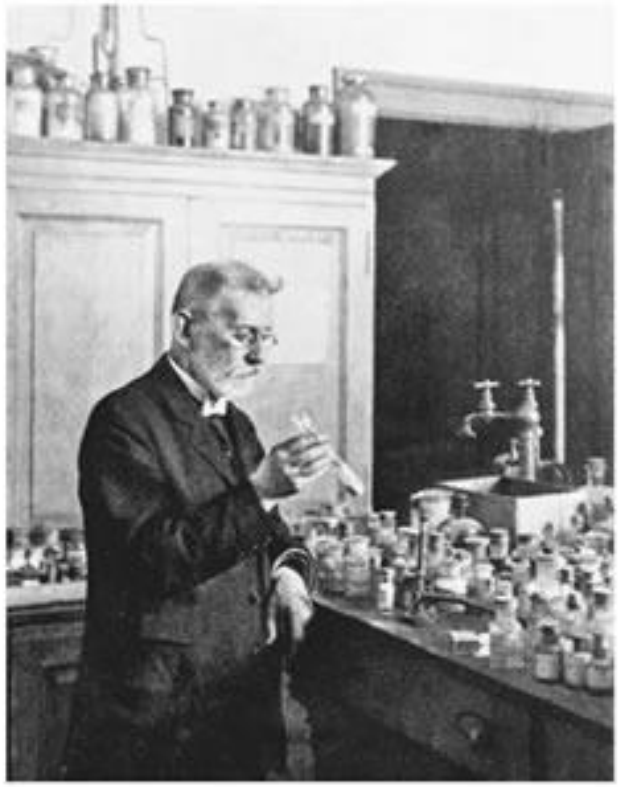
Immunotherapy: *Treatment to boost or restore the ability of the immune system to fight cancer*

HOW CANCER CELLS GROW AND DIVIDE

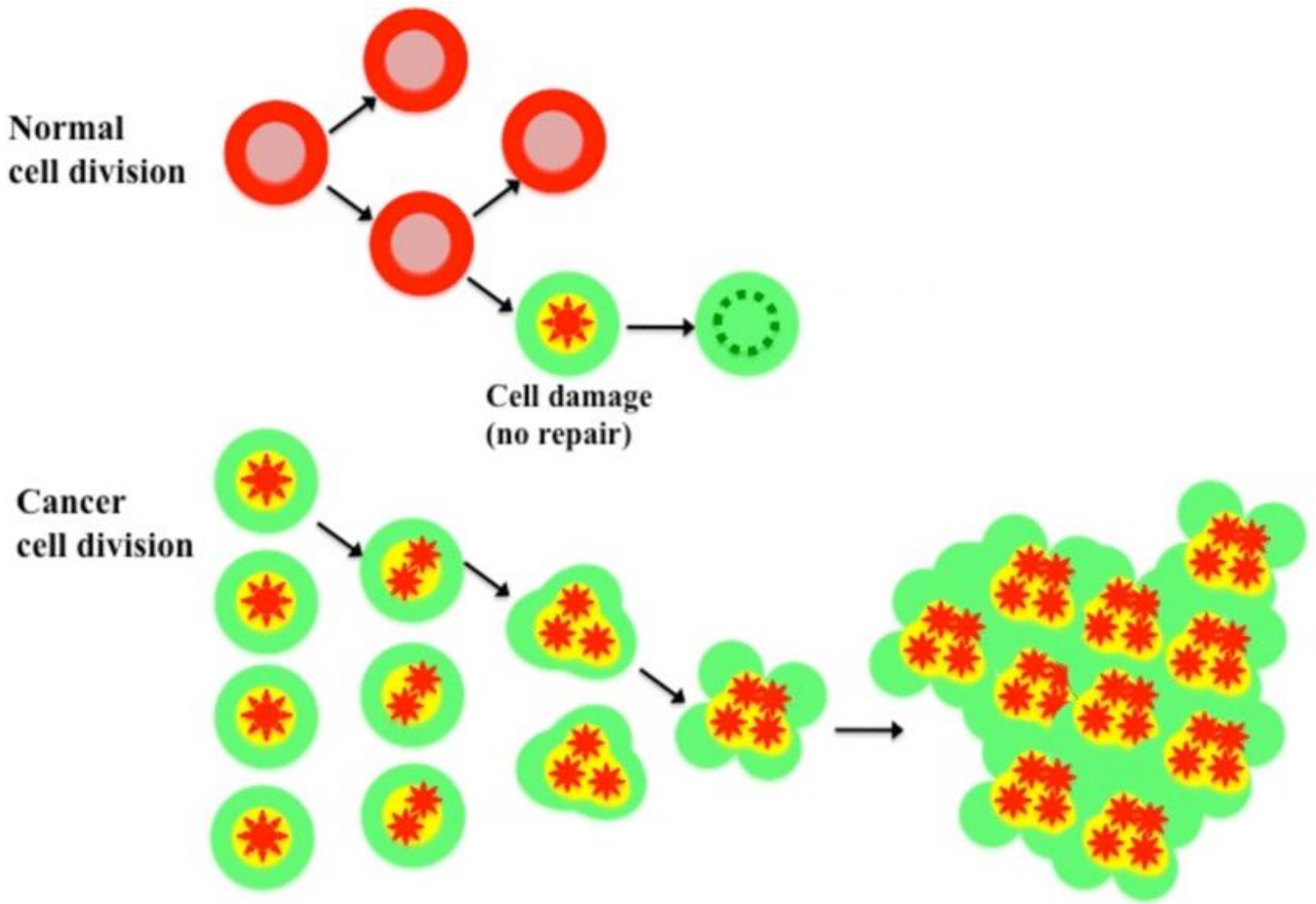


Frank Mac Farlane Burnet

Paul Ehrlich



Lewis Thomas


Normal
cell division
Cell damage
(no repair)
Cancer
cell division

Dynamics Between Cancer and the Immune System

In a dynamic process, the immune system can either

Suppress tumor growth, development & survival

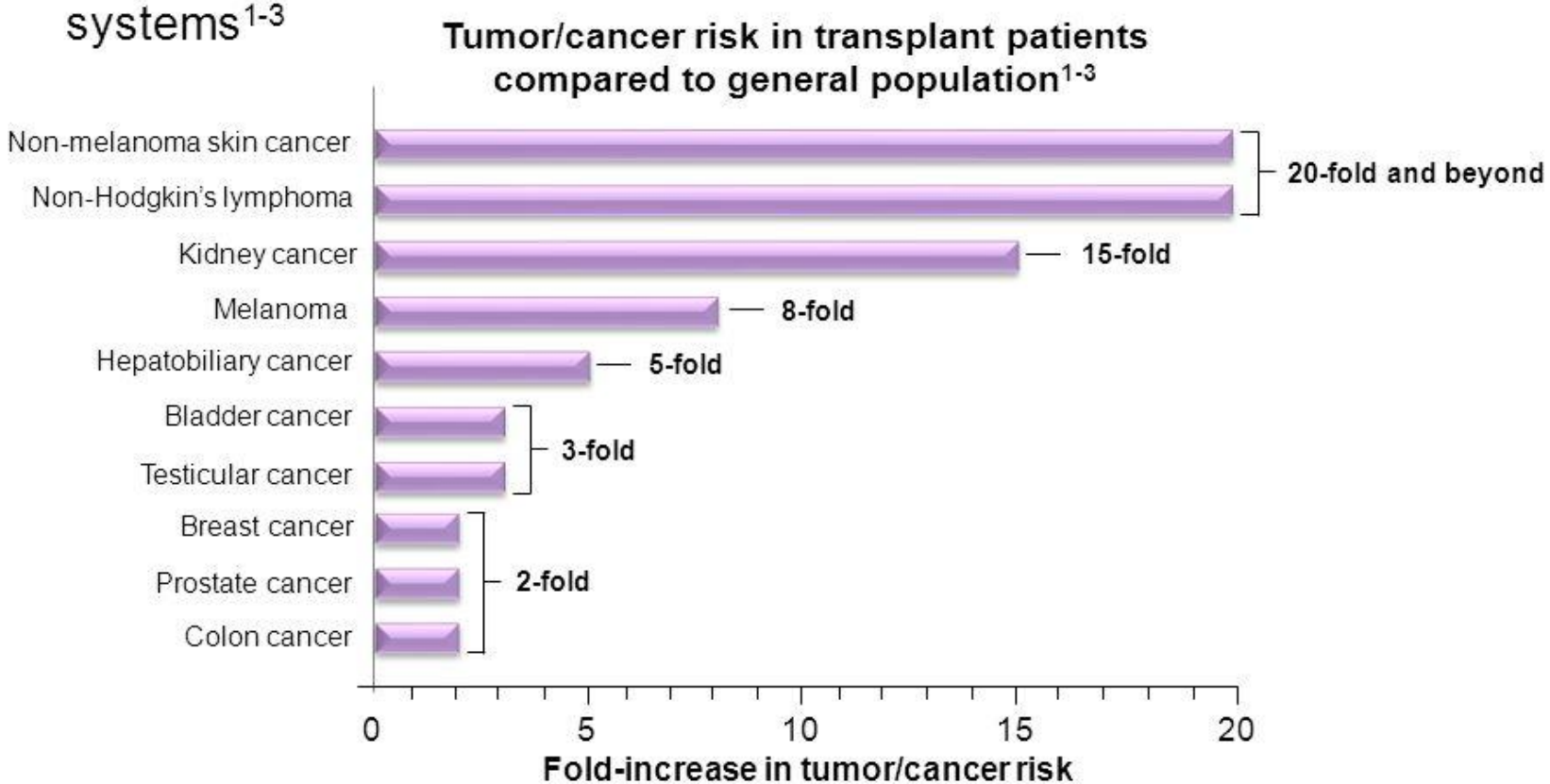
-----OR-----

Allow tumor growth

Dunn GP, Schreiber RD, et al. *Nat Rev Immunol.* 2006;6(11):836-848.

Increased Incidence of Cancer in Immunocompromised Individuals

- Malignant tumors develop in individuals with compromised immune systems[1-3]



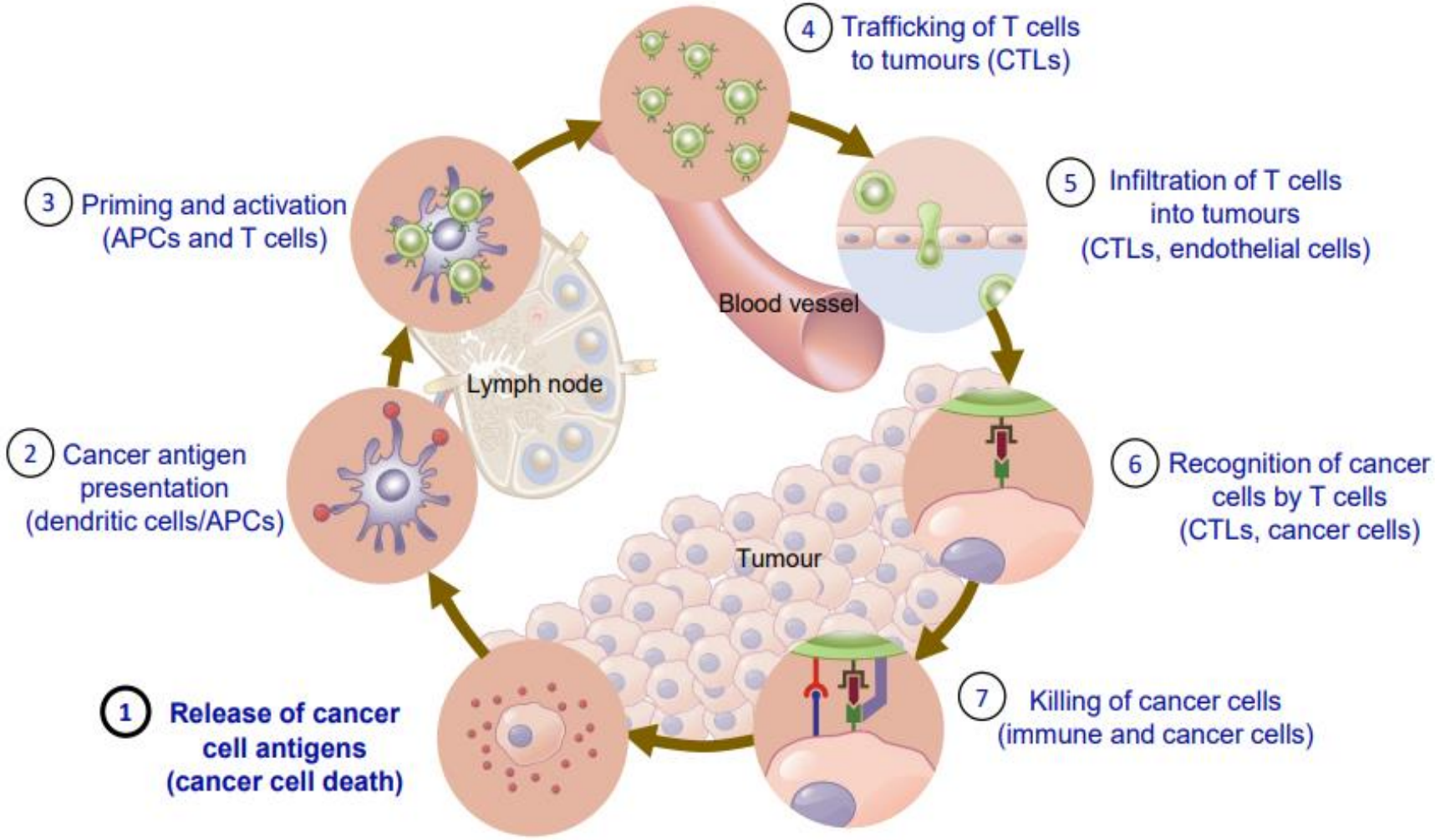
1. Kasiske BL, Wang C, et al. *Am J Transplant*. 2004;4(6):905-913.
2. Le Mire L, Wojnarowska F, et al. *Br J Dermatol*. 2006;154(3):472-477.
3. Abbas AK, Lichtman AH. *Basic Immunology*. 3rd ed. 2011.

Oncology meets Immunology: The Cancer Immunity Cycle

Daniel S Chen & Ira Mellman

Immunity Vol. 39 1-10 (2013)

The Cancer Immunity Cycle

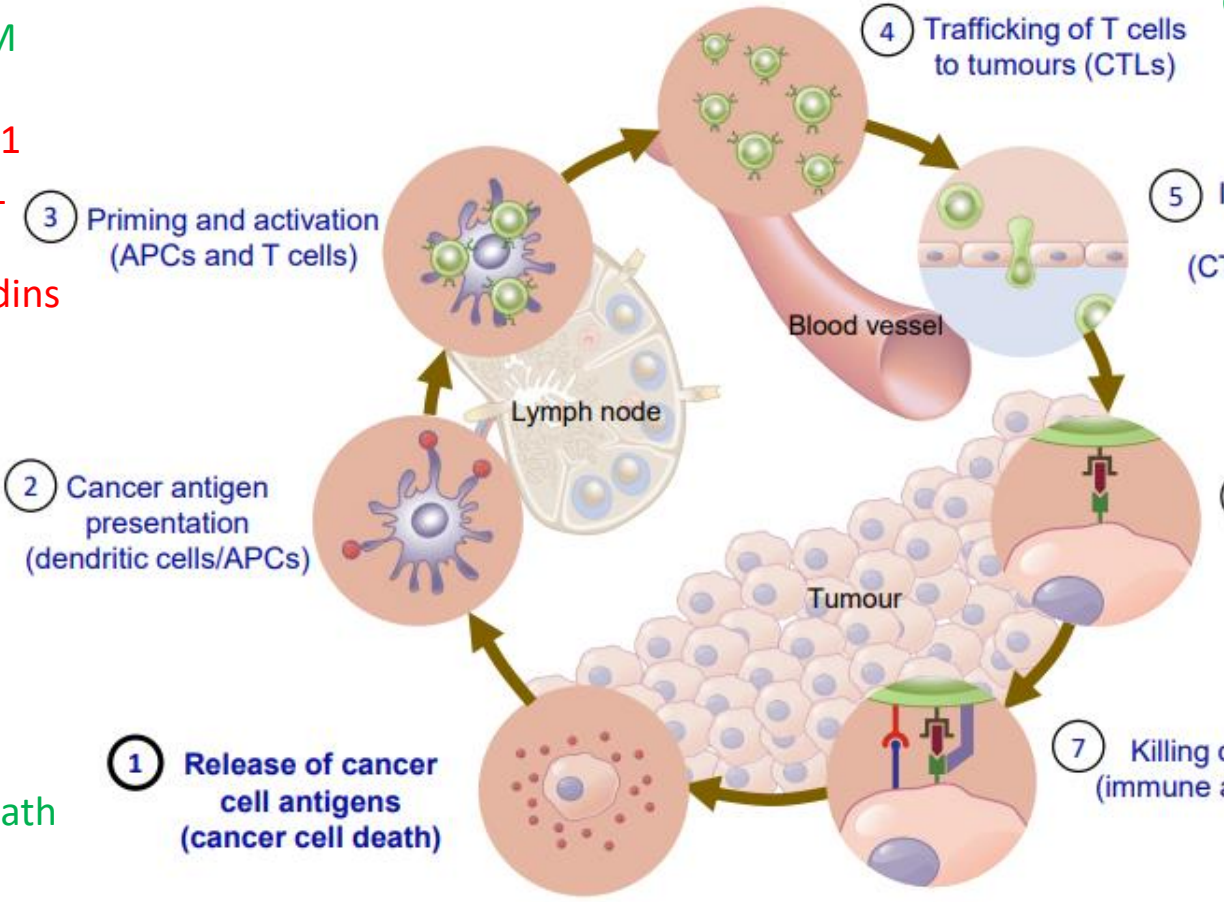


Chen & Mellman. 2013

CD28/B7.1
CD137/CD137L
OX40/OX40L
CD27/CD70
GITR, HVEM
IL-2, IL-12
CTLA-4/B7.1
PD-1/PD-L1
PDL1/B7.1
Prostaglandins

TNF-α, IFN-α
CD40/CD154
IL-1, ATP
TLR, HMGB1
IL-10, IL-4, IL-13

Immunogenic cell death
Tolergenic cell death



CX3CL1
CXCL9
CXCL10
CCL5

LFA1/ICAM1
Selectins
VEGF
Endothelin β receptor

TCR
Reduced p-MHC on cancer cells

IFN-γ, T cell granule content
PD-1/PD-L1, LAG-3, TIM-3, PD-L1/B7.1, IDO, TGFβ, BTLA, VISTA, B7-H4, Arginase

Chen & Mellman. 2013

Types of Cancer Immunotherapy

- Vaccines
- Oncolytic Virus Therapy
- Adoptive Cell Therapy
- Immune Checkpoint Inhibitors

Types of Cancer Immunotherapy

Vaccines

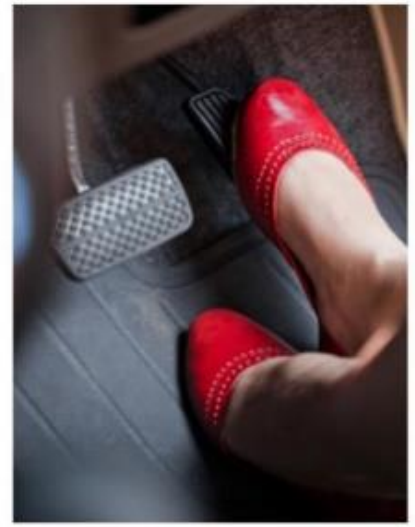
Oncolytic Virus Therapy

Adoptive Cell Therapy

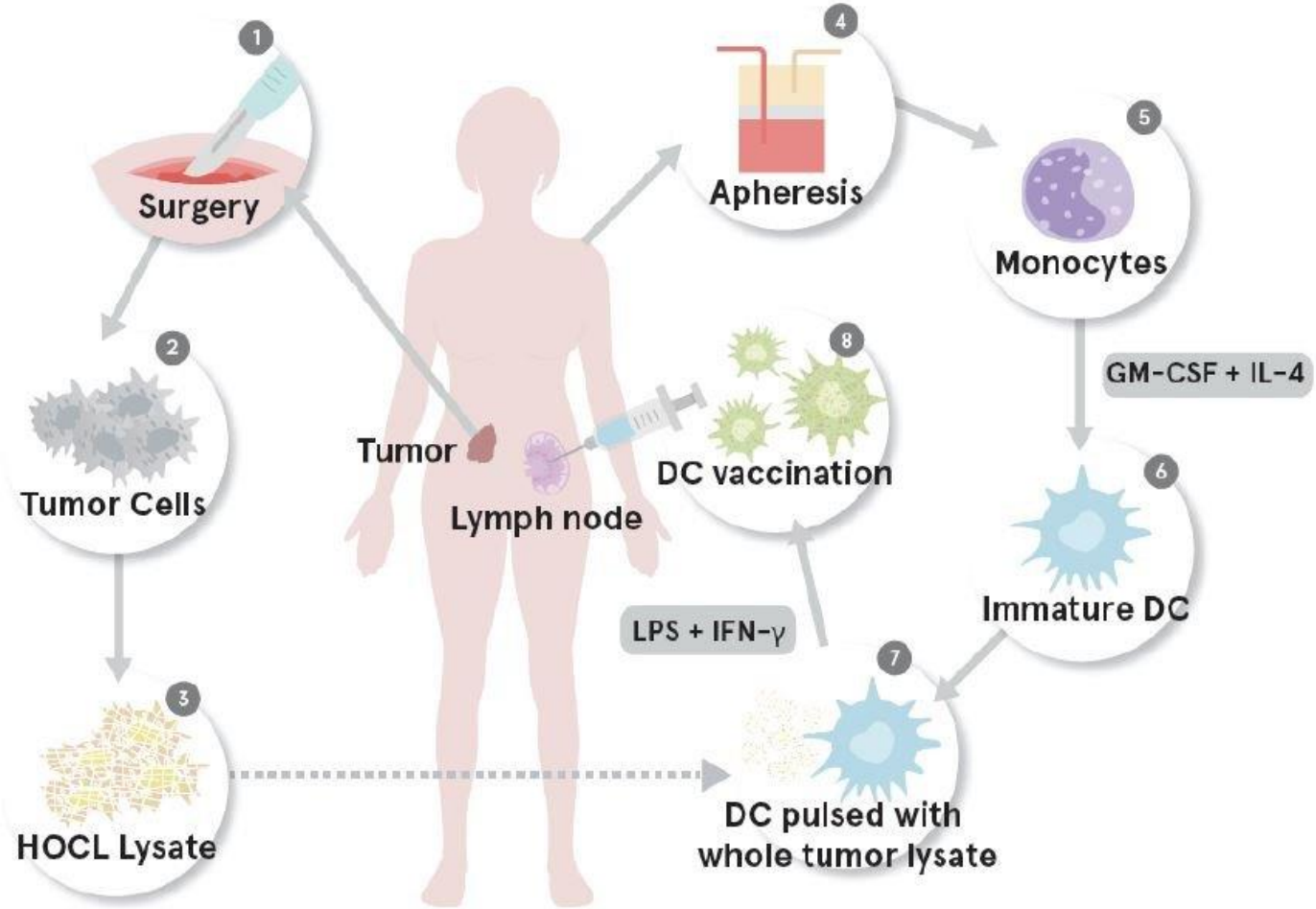
Immune Checkpoint Inhibitors

DC-based vaccines (Increased antigen presentation to T cells)

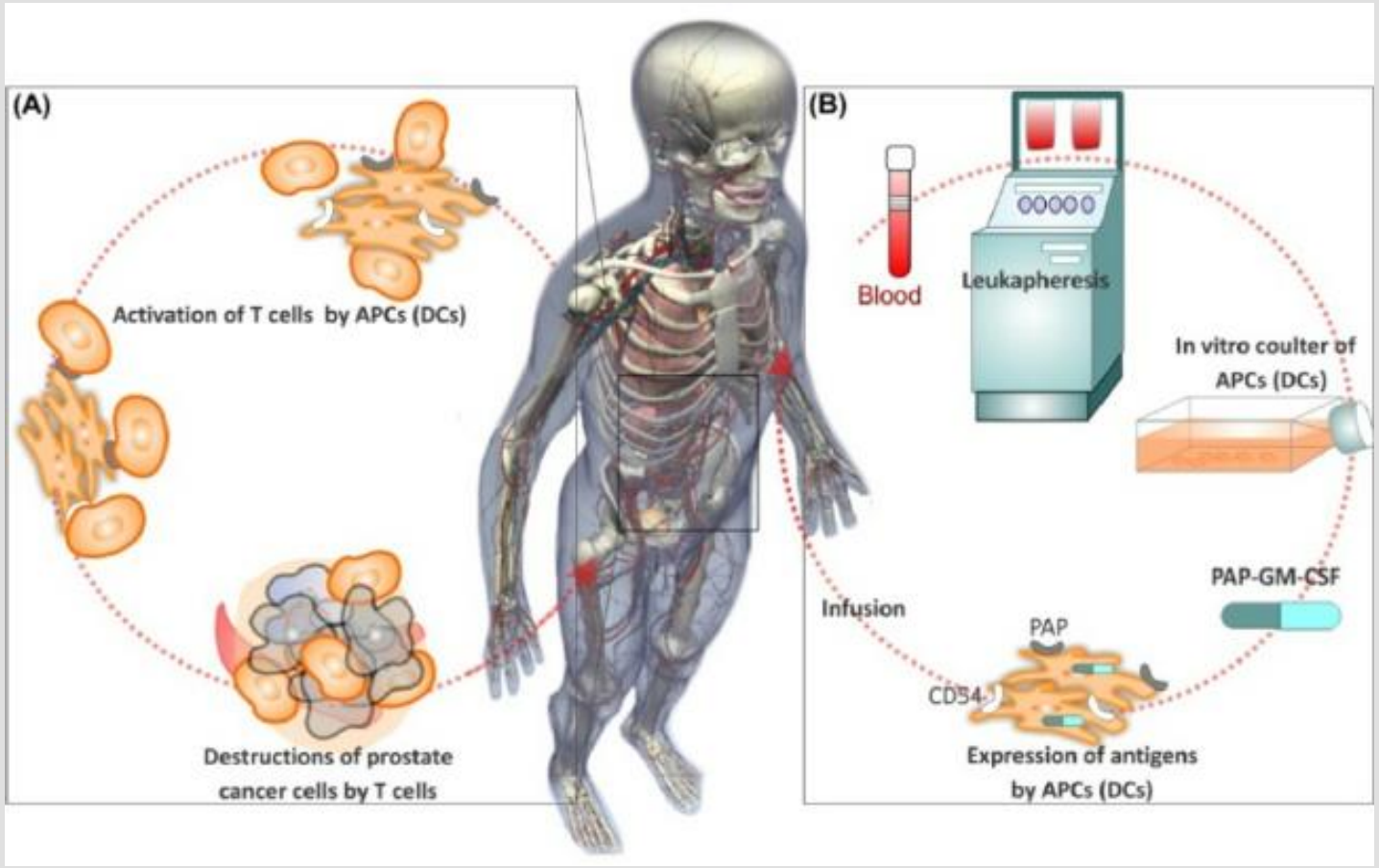
Vaccinate with tumor antigens (protein, DNA, RNA)



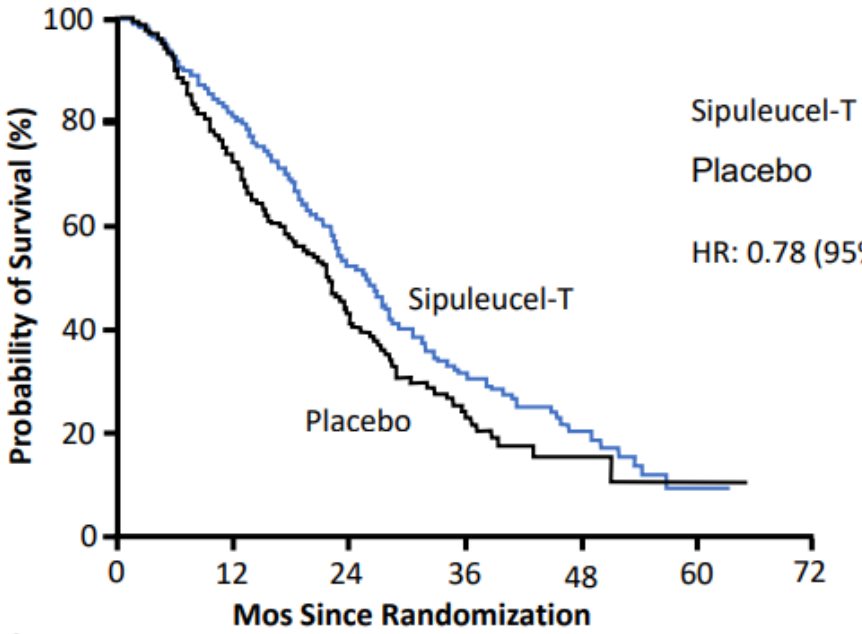
Dendritic Cell (DC)-based Vaccines



Sipuleucel-T (Provenge): Cellular Immunotherapy for the treatment of mCRPC



IMPACT: OS With Sipuleucel-T vs Placebo



Pts at Risk, n						
Sipuleucel-T	341	274	129	49	14	1
Placebo	171	123	55	19	4	1

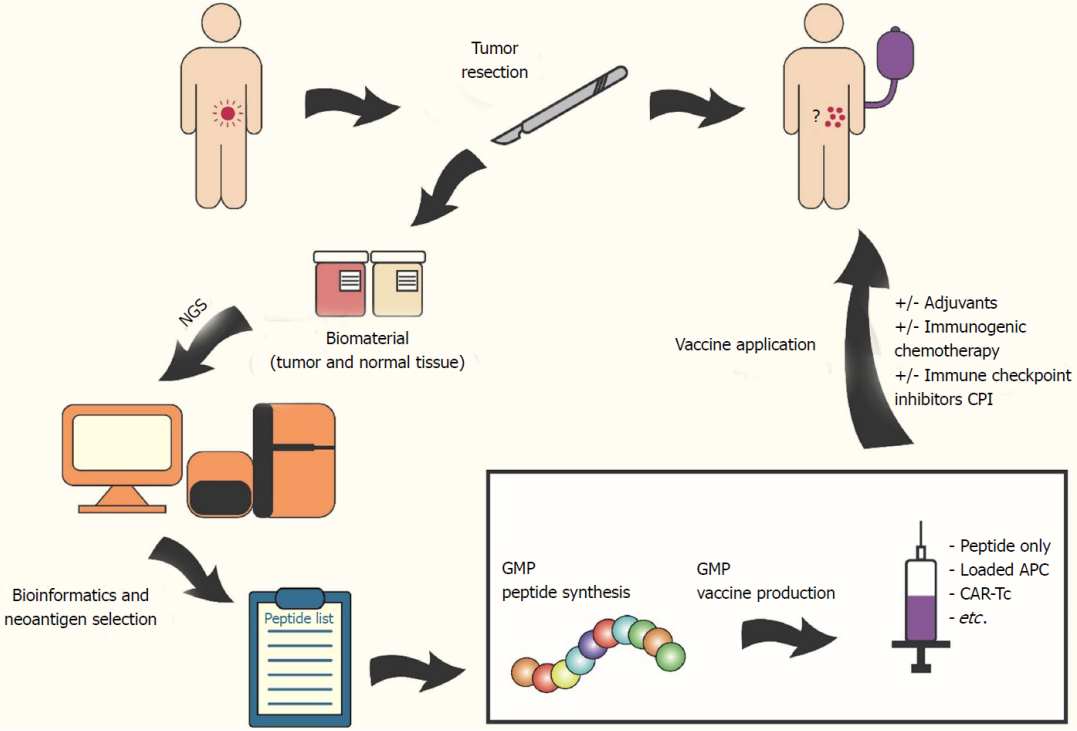
	Median OS, Mos
Sipuleucel-T	25.8
Placebo	21.7

HR: 0.78 (95% CI: 0.61-0.98; *P* = .03)

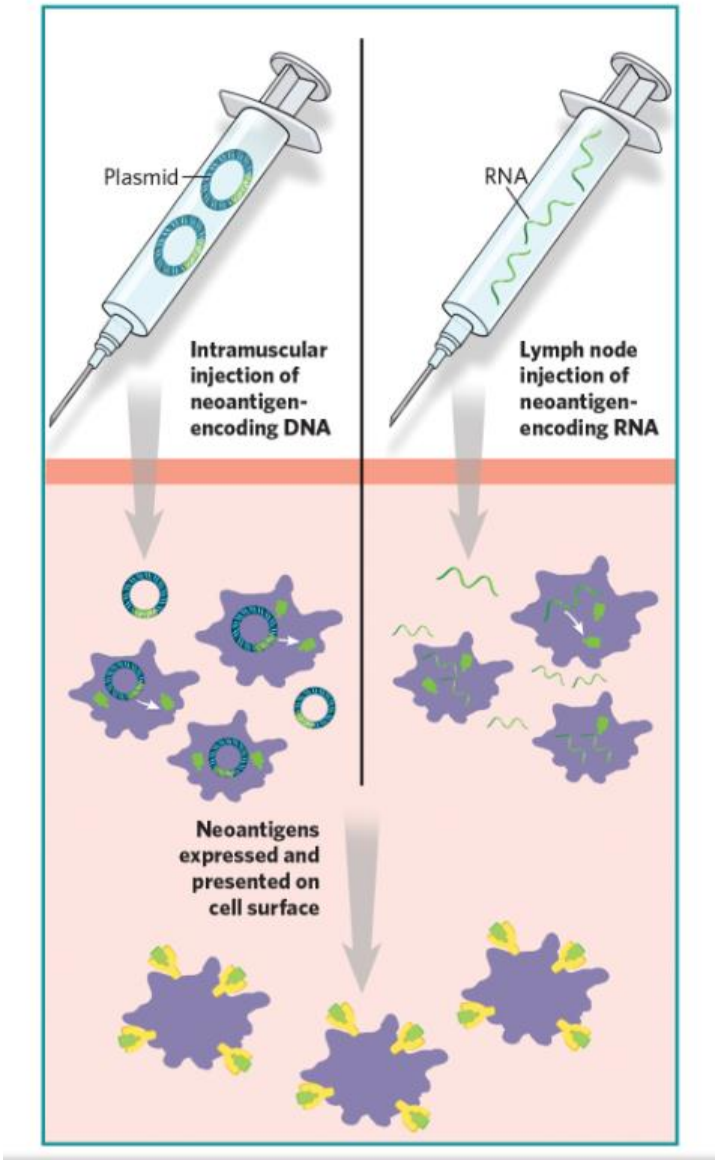
Sipuleucel-T was approved by the FDA on April 30, 2010, for the treatment of metastatic prostate cancer.

Kantoff P, et al. N Engl J Med. 2010.

Vaccination with tumor antigens



DNA & RNA-based vaccines



Types of Cancer Immunotherapy

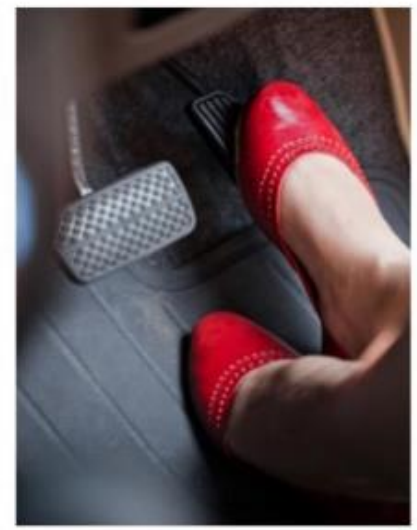
Vaccines

Immune Checkpoint Inhibitors

Oncolytic Virus Therapy

Adoptive Cell Therapy

Administration of oncolytic viruses for systemic autoimmunity



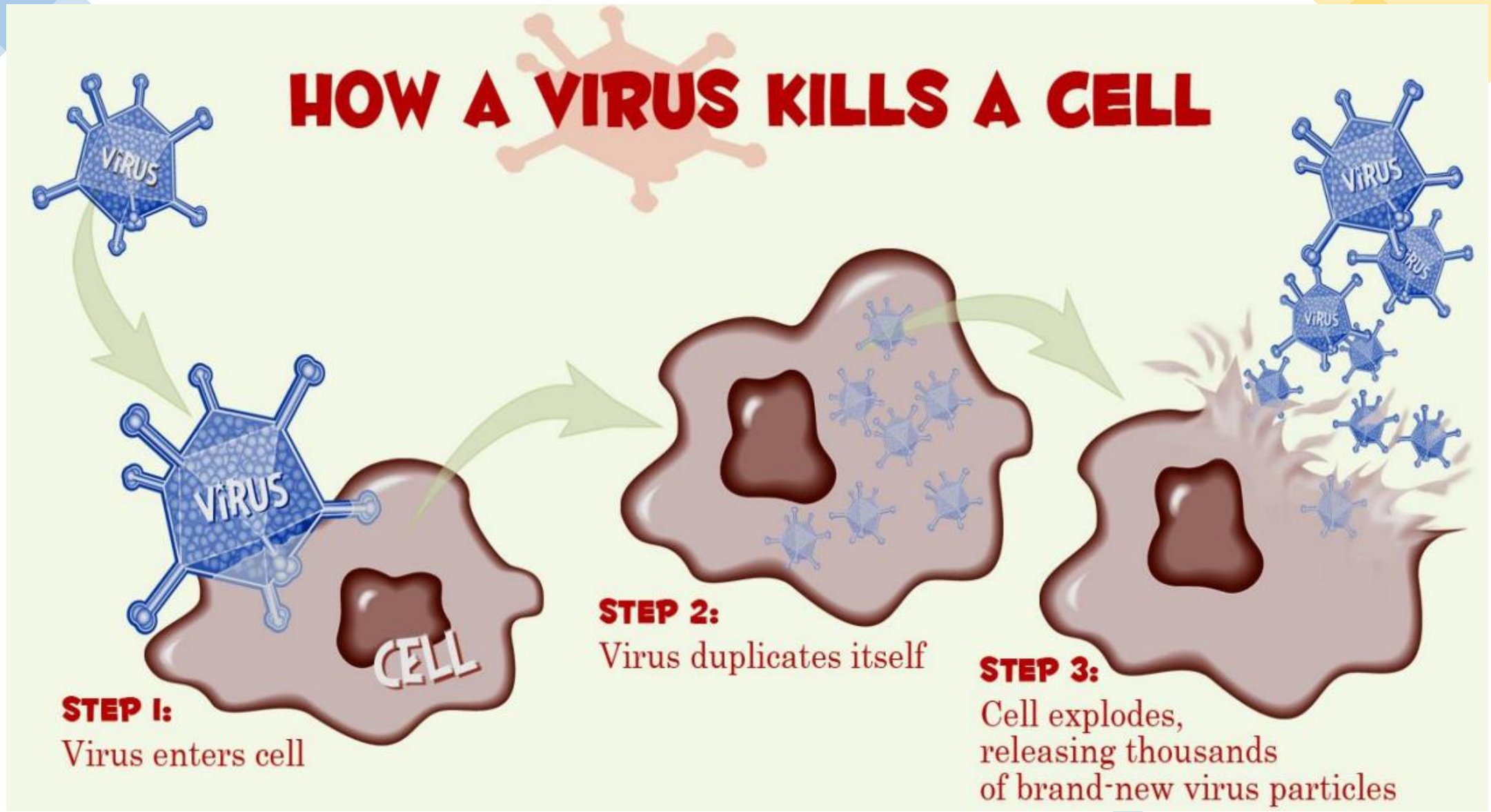
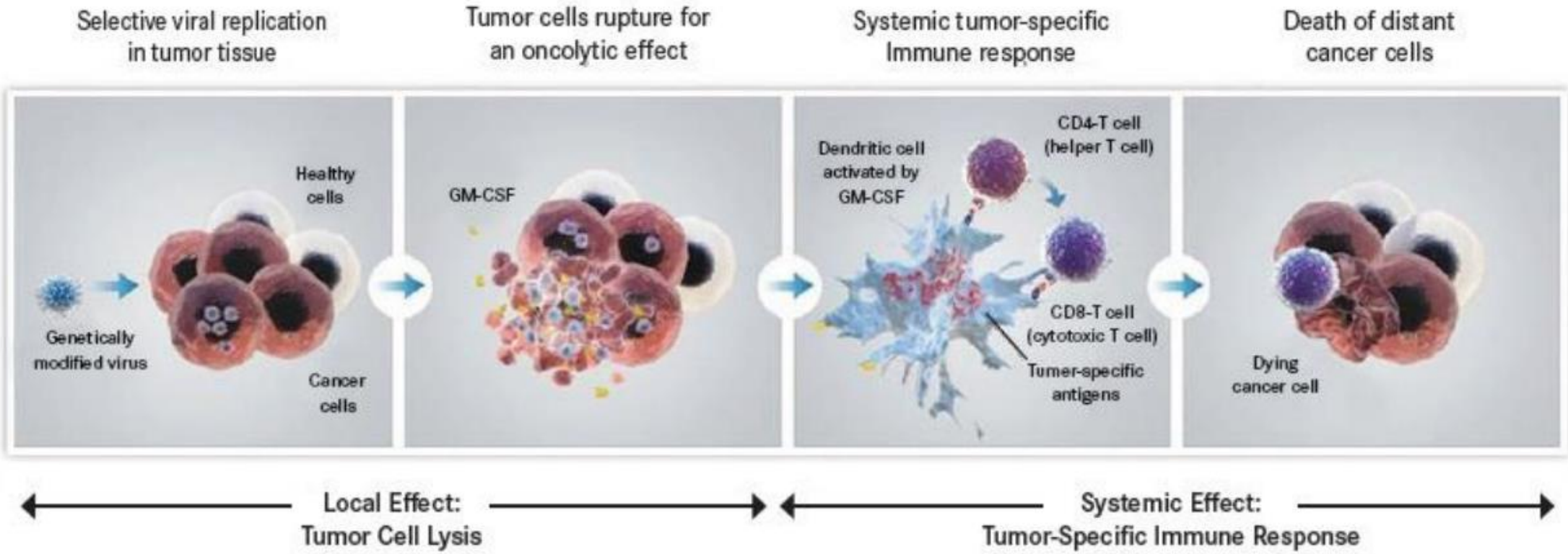

HOW A VIRUS KILLS A CELL
VIRUS
VIRUS
CELL
STEP 1:
Virus enters cell
STEP 2:
Virus duplicates itself
VIRUS
VIRUS
VIRUS
STEP 3:
Cell explodes,
releasing thousands
of brand-new virus particles

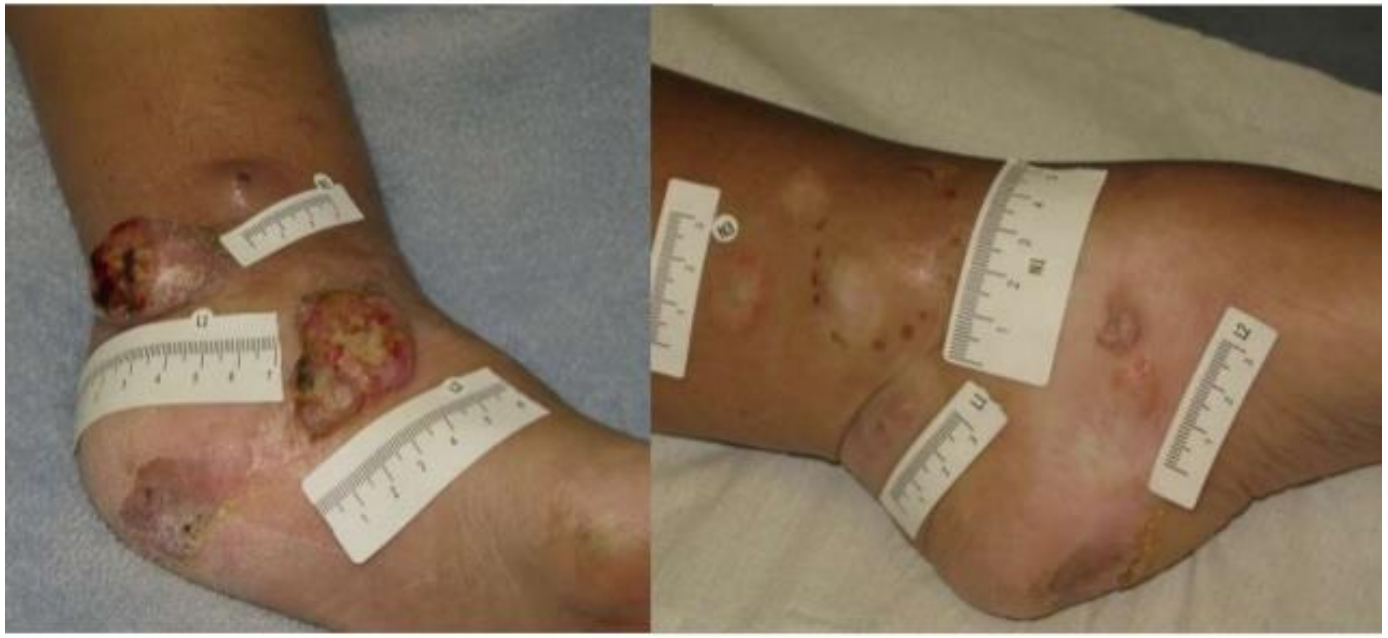
FIGURE 1. Talimogene laherparepvec (T-VEC) is a viral oncolytic immunotherapy designed to produce both local and systemic effect resulting in tumor lysis and death.



* Reproduced with permission from Amgen.

GM-CSF indicates granulocyte-macrophage colony-stimulating factor.

Talimogene Laherparepvec (T-VEC): FDA Approved for Advanced Melanoma



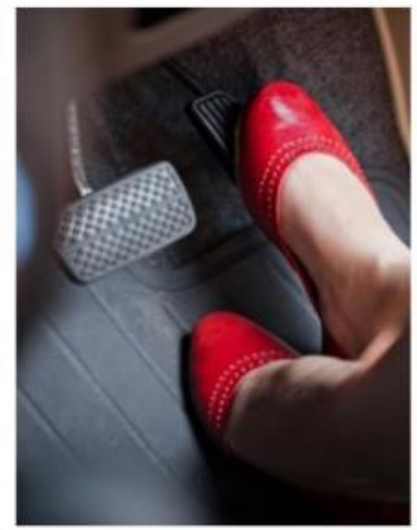
1 month

12 months

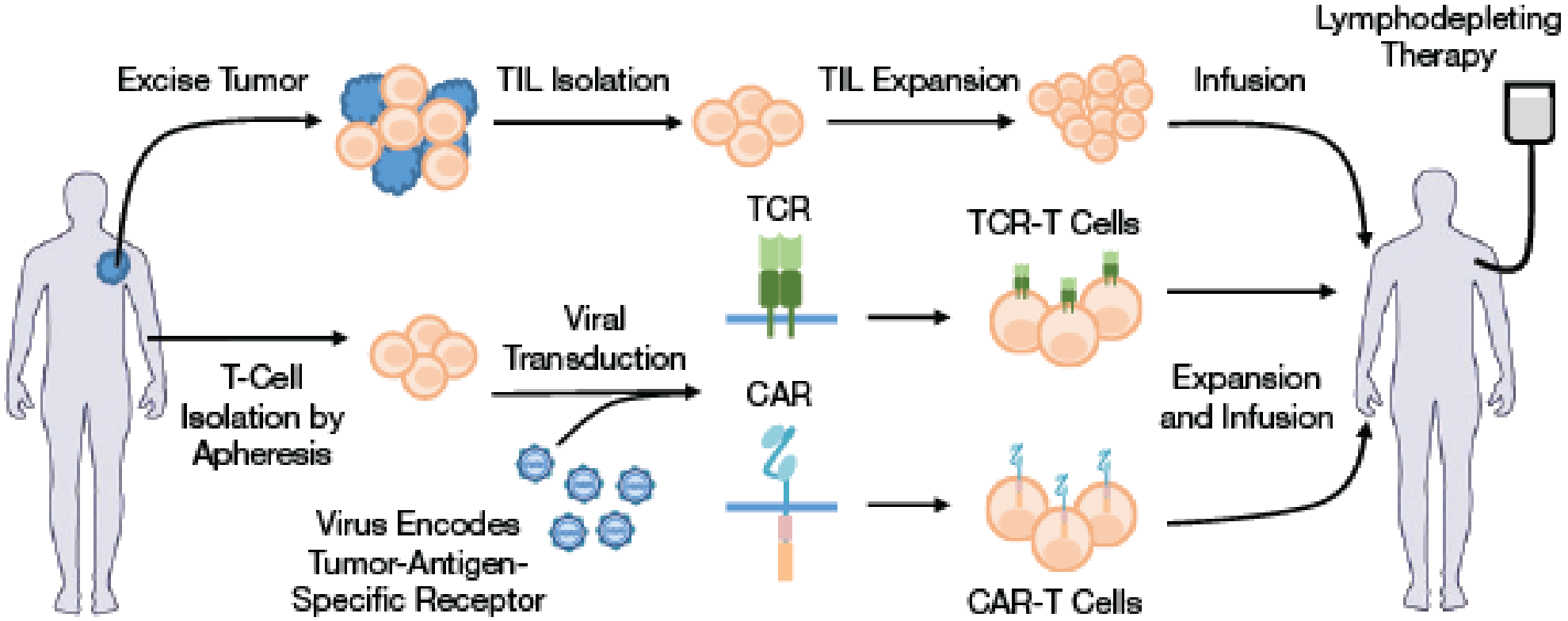
Previously presented at IMWG, 2010

Types of Cancer Immunotherapy

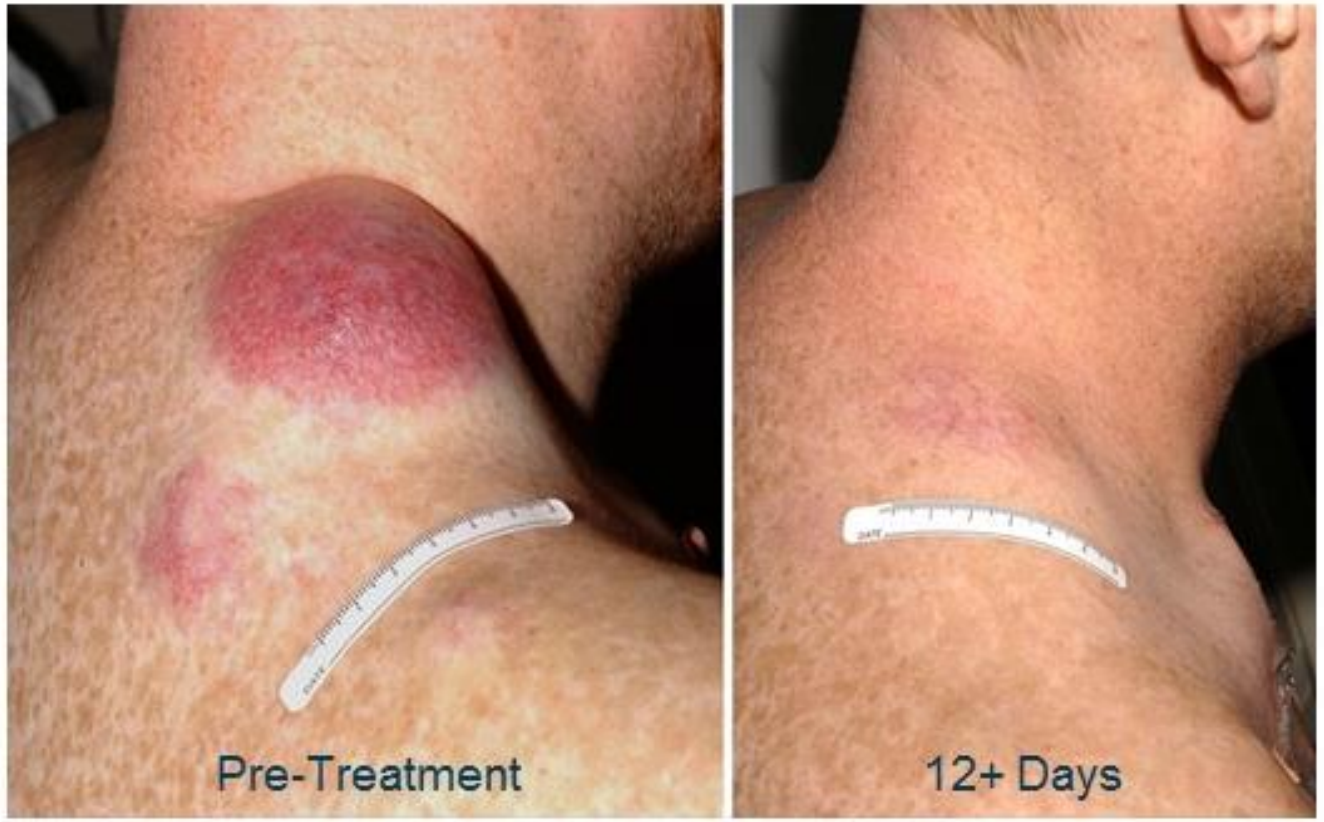
- Vaccines
- Oncolytic Virus Therapy
- Adoptive Cell Therapy
- Immune Checkpoint Inhibitors

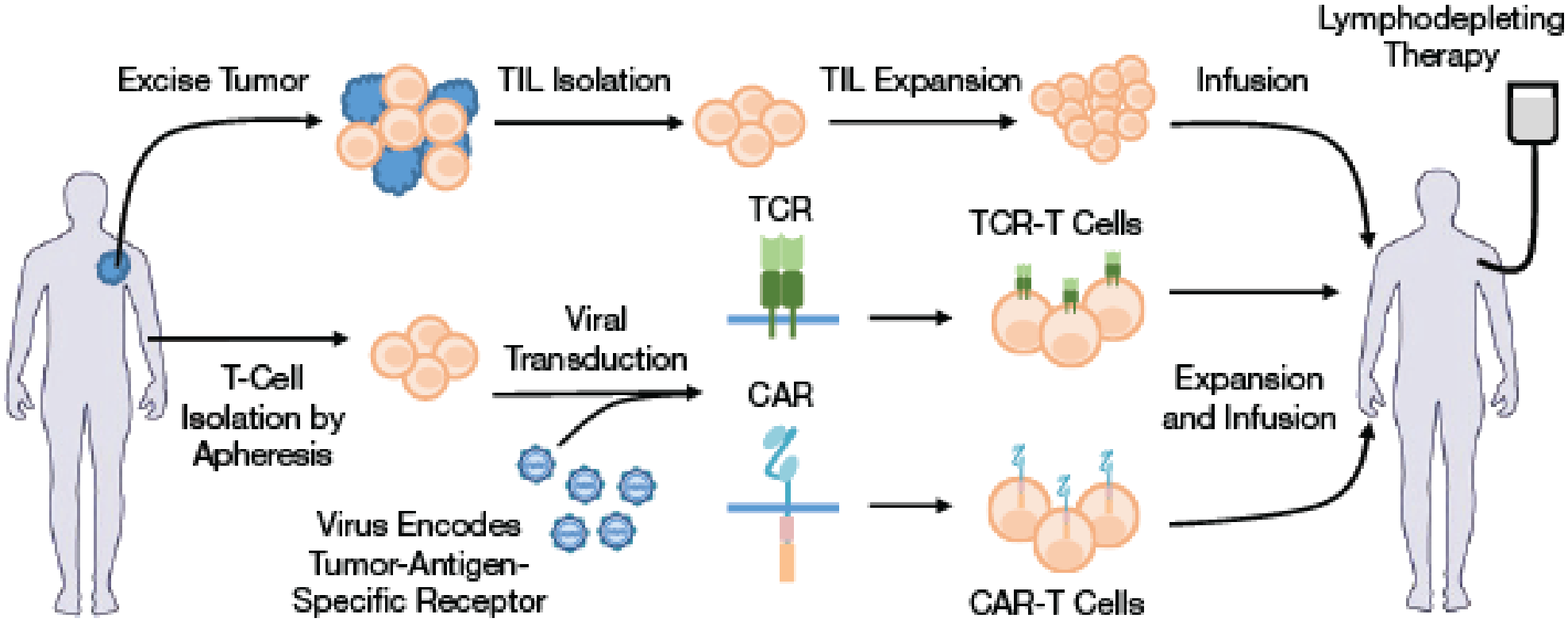


Administration of immune cells directly to the patient


Excise Tumor
TIL Isolation
TIL Expansion
Infusion
Lymphodepleting Therapy
TCR
TCR-T Cells
T-Cell Isolation by Apheresis
Viral Transduction
CAR
Expansion and Infusion
Virus Encodes Tumor-Antigen-Specific Receptor
CAR-T Cells

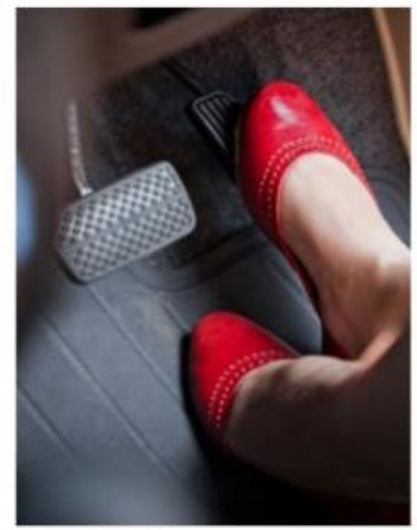
TILs & Melanoma Regression




Excise Tumor
TIL Isolation
TIL Expansion
Infusion
Lymphodepleting Therapy
TCR
TCR-T Cells
T-Cell Isolation by Apheresis
Viral Transduction
CAR
Expansion and Infusion
Virus Encodes Tumor-Antigen-Specific Receptor
CAR-T Cells

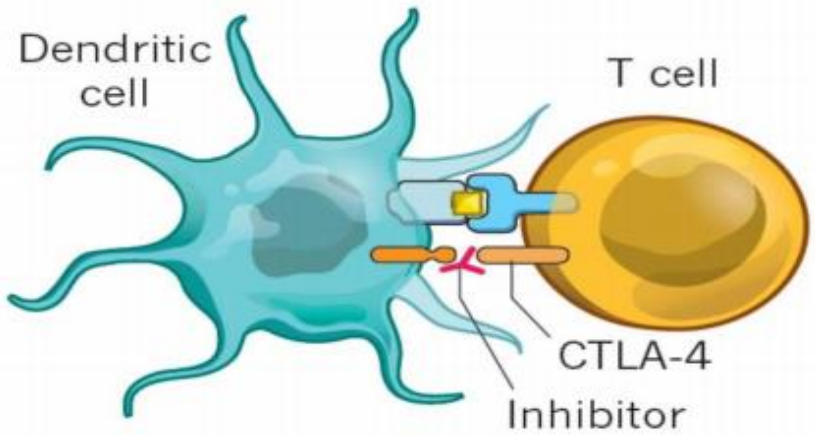
Types of Cancer Immunotherapy

- Vaccines
- Oncolytic Virus Therapy
- Adoptive Cell Therapy
- Immune Checkpoint Inhibitors



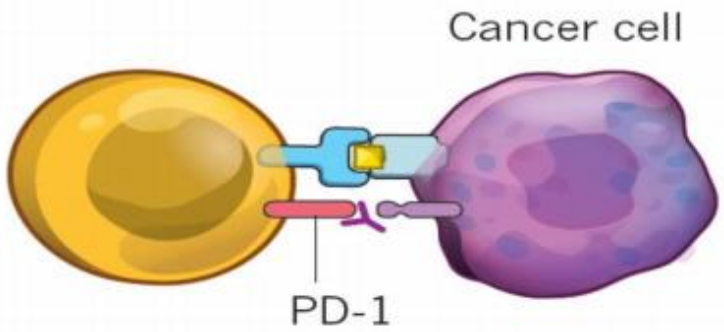
Administration of immune cells directly to the patient

Immune checkpoints inhibitors



The CTLA-4 checkpoint protein prevents dendritic cells from priming T cells to recognize tumours. Inhibitor drugs block the checkpoint.

CTLA-4 blockade (e.g. Ipilimumab)



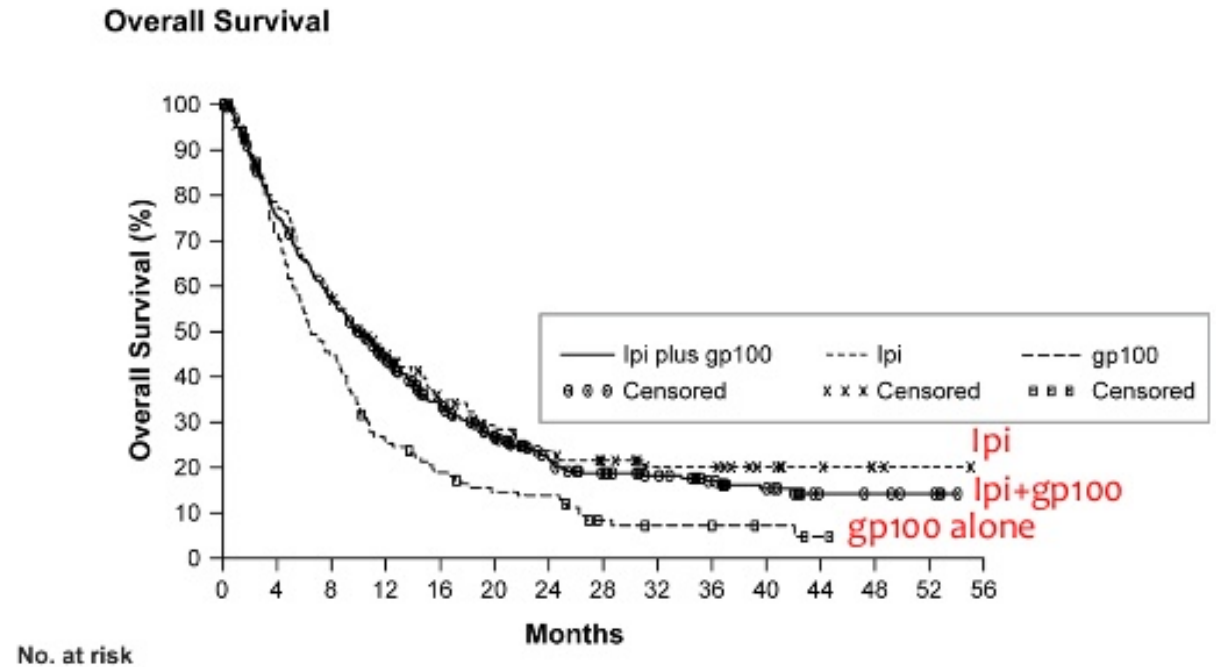
The PD-1 checkpoint protein prevents T cells from attacking cancer cells. The inhibitor drug allows T cells to act.

PD- (L)1 blockade (e.g. Nivolumab, pembrolizumab, Atezolizumab)

Ledford. Nature 508. 24-26

Dawn of the present: Ipilimumab (anti-CTLA4) elicits low frequency but durable responses in metastatic melanoma

- Ipilimumab (ipi) mediates a statistically significant overall survival (OS) advantage in patients with previously treated metastatic melanoma
- Patients who received ipilimumab (ipi) alone or ipi + gp100 peptide vaccine had a median survival of 10.1 months compared to 6.4 months for patients receiving gp100 peptide vaccine alone
- Pilot trials with ipi in RCC, prostate cancer as well as NSCLC are underway

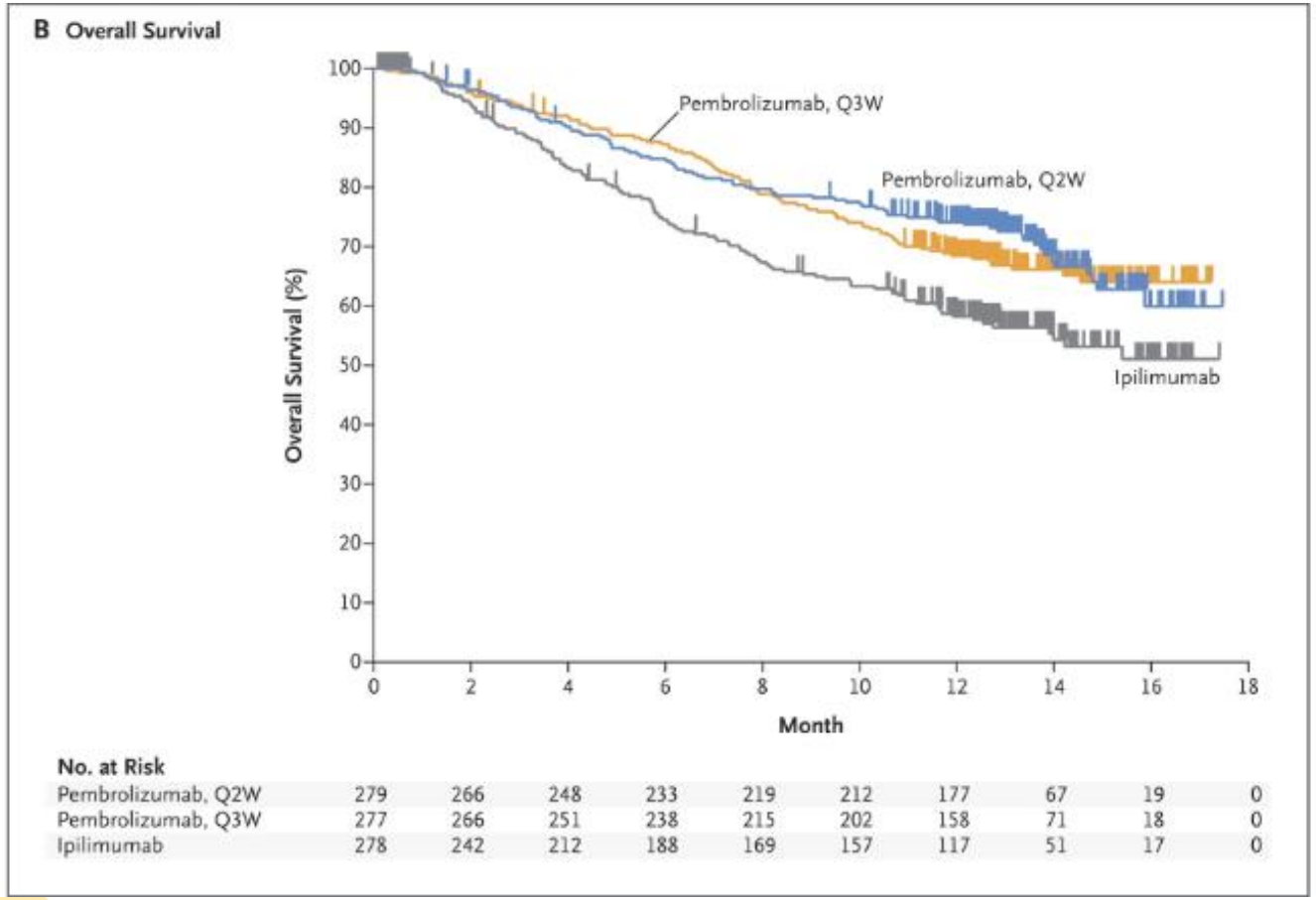


No. at risk

Ipi plus gp100	403	297	223	163	115	81	54	42	33	24	17	7	6	4	0
Ipi	137	106	79	56	38	30	24	18	13	13	8	5	2	1	0
gp100	136	93	58	32	23	17	16	7	5	5	3	1	0	0	0

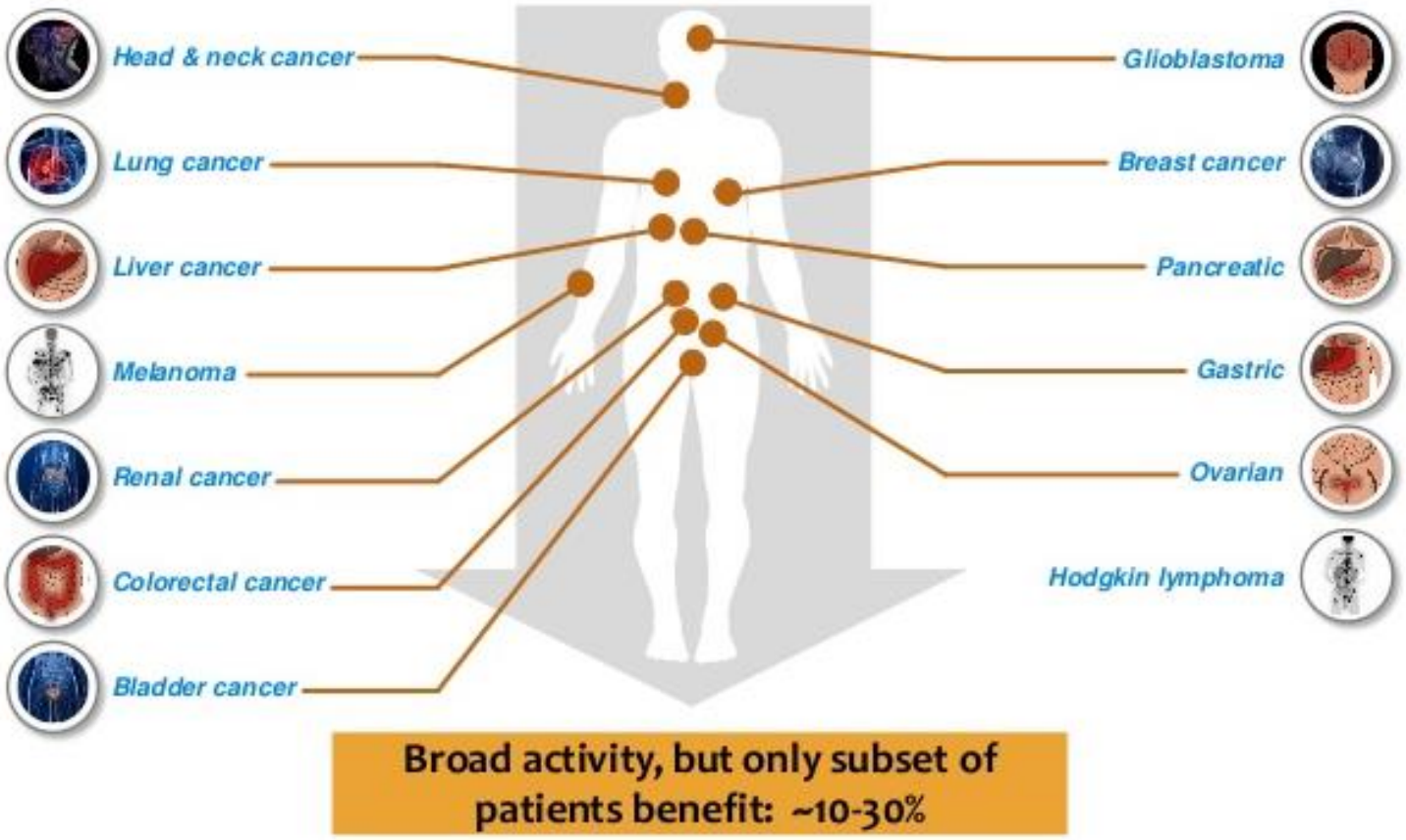
Hodi et al (2010) NEJM

Pembrolizumab (anti-PD-1) versus Ipilimumab (anti-CTLA4) in advanced melanoma



No. at Risk										
Pembrolizumab, Q2W	279	266	248	233	219	212	177	67	19	0
Pembrolizumab, Q3W	277	266	251	238	215	202	158	71	18	0
Ipilimumab	278	242	212	188	169	157	117	51	17	0

Broad activity for anti-PD-1/PD-L1 in human cancer

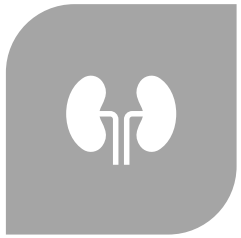


Other IC Blockade Therapies:

- **Multiple other IC pathways have been identified: LAG3, TIM3, TIGIT, VISTA, BTLA**
- **Therapies targeting LAG3 are the furthest along in clinical development (mono & combo)**
- **Several TIM3 antagonists are in pre-clinical development**
- **Numerous other immune check point agents are currently under development**

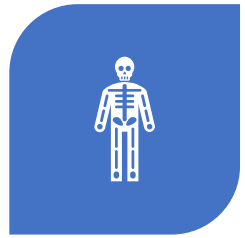
Combination Therapies:

ADVANCED CANCERS MAY RESPOND TO MONOTHERAPY, BUT FOR THE MAJORITY, MONOTHERAPY MAY BE INEFFECTIVE



COMPLETE REMISSION AND CURES FOR CANCER PATIENTS, THE COMBINATION OF MULTIPLE THERAPEUTIC APPROACHES MAY BE REQUIRED

COMBINING IC BLOCKADE THERAPIES IS THE NEW TREND



IPI-NIVO STUDY: IPI (ANTI-CTLA-4) + NIVO (ANTI- PD1) : TUMOR REGRESSION IN 50% PATIENTS WITH ADVANCED MELANOMA

PATIENTS WITH PREVIOUSLY UNTREATED METASTATIC MELANOMA WHO RECEIVED IPI + NIVO SHOWED AN OBJECTIVE RESPONSE RATE OF 61% COMPARED TO 11% SEEN IN PATIENTS TREATED WITH IPI ALONE

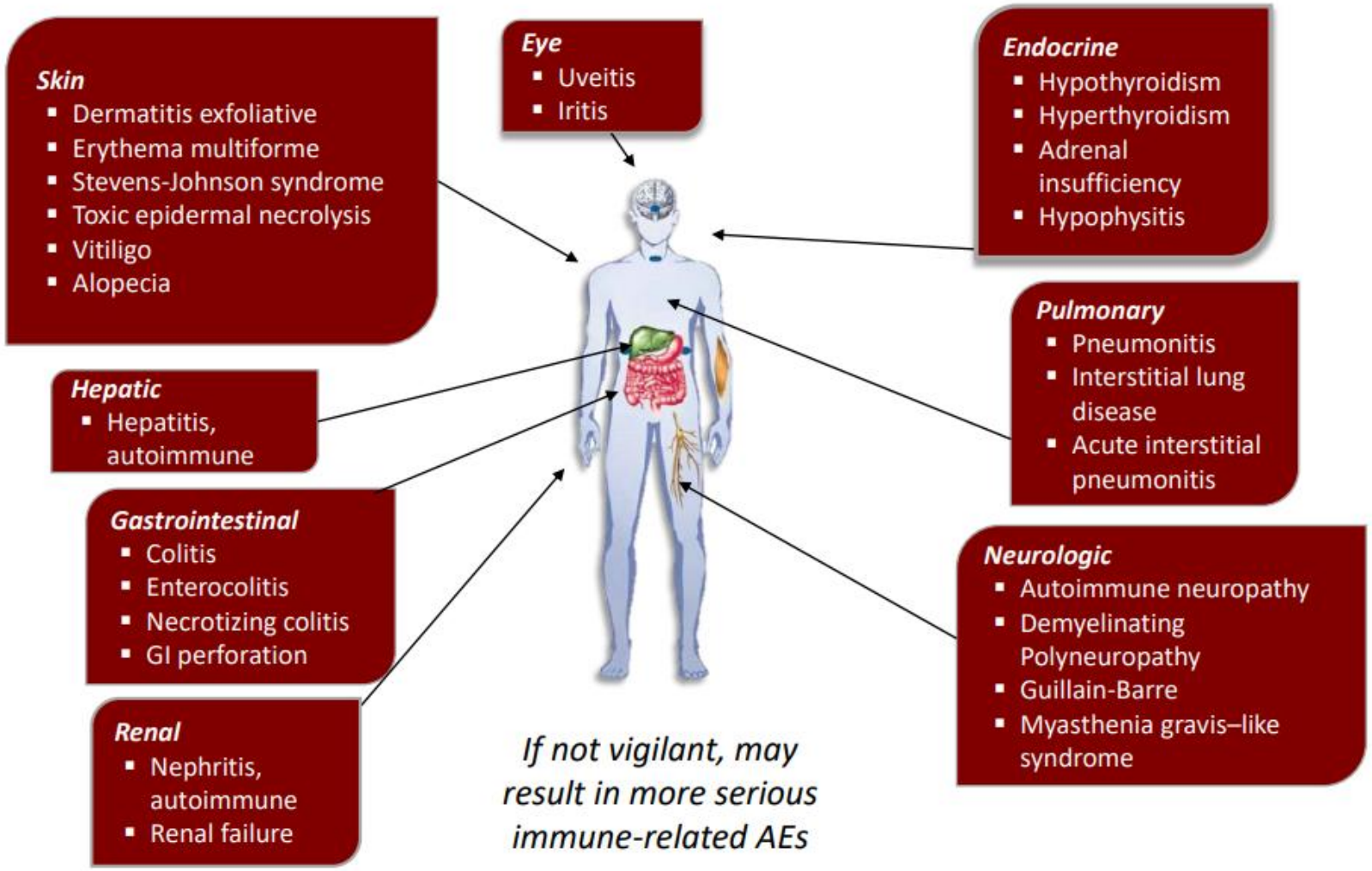
IC Inhibitors + Conventional Therapies:

Chemotherapy may boost the immunotherapies by modifying the immunosuppressive tumor environment: Cyclophosphamide is known to deplete Treg cells; Paclitaxel & 5FU eliminate MDSCs

For melanoma patients with the B-raf V600E mutation: trials looking at combining FDA-approved B-raf inhibitors (Zelboraf) with anti-CTLA-4 (Ipi) and anti-PD1 are underway

VEGF enhances the number of immunosuppressive Tregs and MDSCs in the tumor, while reducing the intratumoral flux of lymphocytes and suppressing DC maturation: combining IC inhibitors + VEGF inhibitors

Immune-Related AEs With Immunotherapy



Immune-Mediated Hepatitis: Symptom Surveillance

- Monitor LFTs at baseline and prior to each dose of treatment
- Pts with abnormal LFTs should be monitored more frequently
- Hepatotoxicity appears worse when ipilimumab combined other drugs[1-3]

1. Robert C, et al. N Engl J Med. 2011;364:2517-2526.
2. Ribas A, et al. N Engl J Med. 2013;368:1365-1366.
3. Wolchok JD, et al. Ann Oncol. 2013;24:2174-2180.

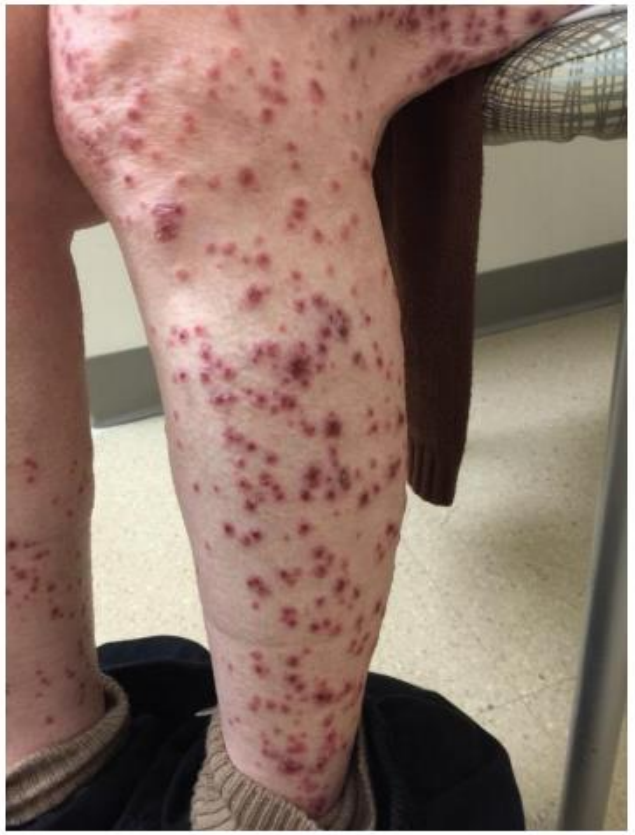
Immune-Mediated Hepatitis: Symptom Management

- Rule out other causes of LFT abnormalities
- Increase LFT monitoring
- Corticosteroid treatment with grade ≥ 2 LFTs (prolonged taper may be required)
- Mycophenolate may be useful
- LFT abnormalities appear to be dose dependent

LFT	Grade 1	Grade 2	Grade 3	Grade 4
Bilirubin	> ULN to 1.5 x ULN	> 1.5 to 3.0 x ULN	> 3.0 to 10.0 x ULN	> 10.0 x ULN
ALT/AST	> ULN to 2.5 x ULN	> 2.5 to 5.0 x ULN	> 5.0 to 20.0 x ULN	> 20.0 x ULN
Albumin	< LLN to 3 g/dL	< 3 to 2 g/dL	< 2 g/dL	--

Immune-Mediated Dermatitis

- Reported in up to 40% of pts with anti–CTLA-4 and anti–PD-1 agents
- Occasionally severe rashes
- Onset within a few wks of starting or several wks/mos into therapy
- Severity driven by symptoms
- Rule out other etiologies
- Generally not infusion related



Hodi FS, et al. N Engl J Med. 2010;363:711-723.
Image courtesy Matthew M. Burke, MBA, RN, MSN, APRN-BC.

Immune-Mediated Dermatitis: Symptom Management

Severity	Management
Mild/moderate (rash/pruritus)	▪ Topical nonsteroidal cream, antihistamine, oatmeal baths ▪ Skin care, moisturize, sunscreen, avoid sun
Persistent (> 1 wk) or interferes with ADLs	▪ Moderate-potency steroid creams or ▪ Moderate-dose parenteral steroids
Severe	▪ Discontinue treatment ▪ High-dose steroids ▪ Avoid rapid steroid taper

Oncolytic viruses

- Native or engineered viruses that target, infest and kill cancer cells
- Tumor debulking due to tumor infection and induction of immune response
- Viral genome can be modified to increase cytotoxicity and attenuate pathogenicity

Farkona et al. BMC Medicine (2016) 14:73