

# Cancer Immunotherapy – Today and Tomorrow

Opening Event of the Athens Comprehensive Cancer Center (ACCC)

Athens, Greece  
December 8<sup>th</sup>, 2017

Guy Ungerechts



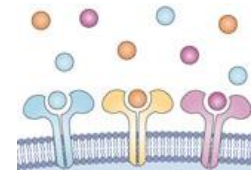
NCT

NATIONALES CENTRUM  
FÜR TUMORERKRANKUNGEN  
HEIDELBERG

# Cancer Immunotherapy Today

- Cytokines + antagonists

INF-alpha/beta, GM-CSF, IL2,...



- Antibodies

Cetuximab, Bevacizumab,...

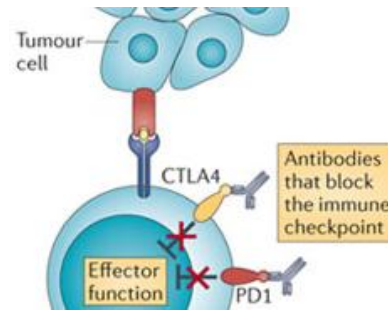


- Vaccines

Peptides, RNAs, Sipuleucel-T, ...

- Immune checkpoint inhibition

Ipilimumab, Nivolumab, Pembrolizumab, Atezolizumab, Avelumab, Durvalumab

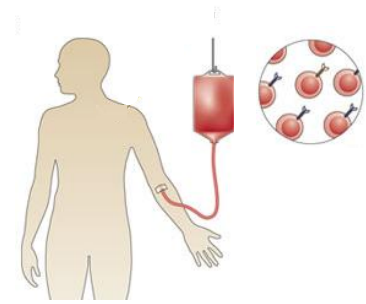


- BiTEs

Blinatumumab...

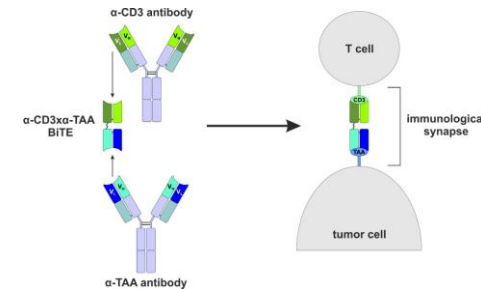
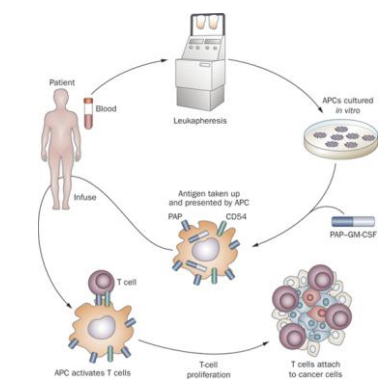
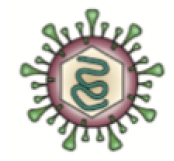
- Adoptive cell transfer

TILs, CARs,...



- Oncolytic Viruses

Imlygic®...



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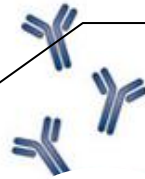
Blinatumumab...

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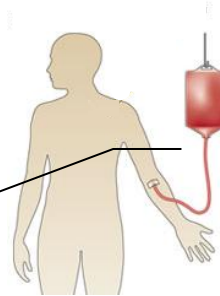
Imlygic®...



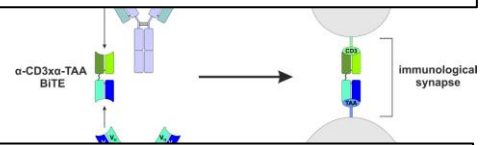
FDA approval in Apr 2010  
Prostate cancer

FDA's accelerated approval program in Dec 2014  
precursor B-cell ALL

FDA approval in Oct 2015  
Melanoma



Tumour cell  
Effect func



# Cancer Immunotherapy Today

- Cytokines + anti-CTLA4

INF-alpha/beta, GM-CSF, IL2, ...

FDA approval Mar 2011 – Melanoma

FDA approval Sep 2014 – Melanoma

- Antibodies

Cetuximab, Bevacizumab, ...

- Vaccines

Peptides, RNAs, Sipuleucel-T, ...

- Immune checkpoint inhibition

Ipilimumab, Nivolumab, Pembrolizumab, Atezolizumab, Avelumab, Durvalumab

FDA approval Dec 2014 – Melanoma

FDA approval May 2016 – Urothelial Ca

- BiTEs

Blinatumumab...

FDA approval May 2017 – Urothelial carcinoma

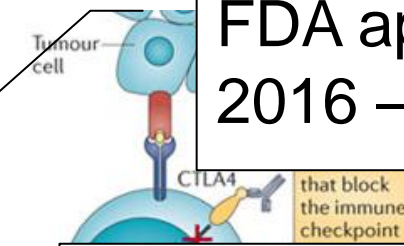
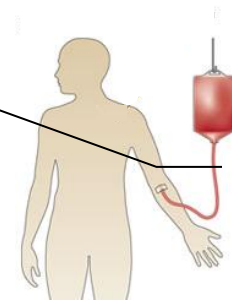
- Adoptive cell transfer

TILs, CARs, ...

FDA approval Mar 2017 - Urothelial carcinoma - Merkel cell carcinoma

- Oncolytic Viruses

Imlygic®...



# Cancer Immunotherapy Today

- Cytokines + antagonists

INF-alpha/beta, GM-CSF, IL2,...

- Antibodies

Cetuximab, Bevacizumab,...

- Vaccines

Peptides, RNAs, Sipuleucel-T, ...

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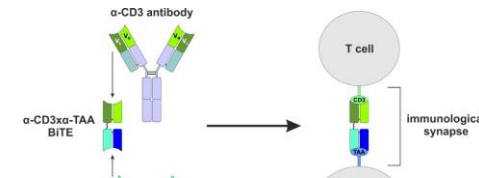
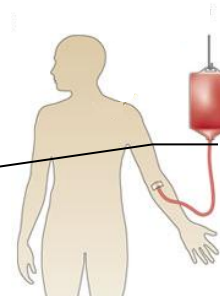
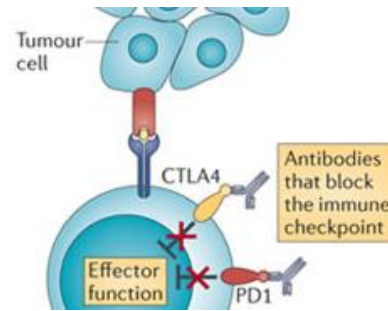
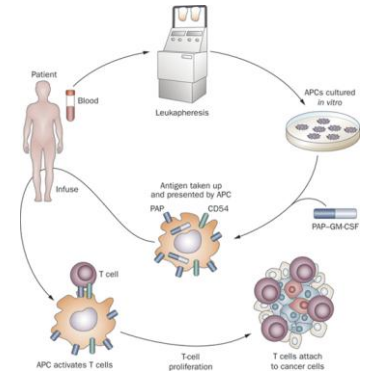
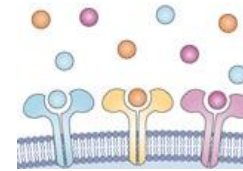
Blinatumumab...

- Adoptive cell transfer

TILs, CARs,...

- Oncolytic Viruses

Imlygic®...



FDA approval Aug 2017 - B-cell precursor ALL

# Cancer Immunotherapy Today

- Cytokines + anti-CTLA-4

INF-alpha/beta, GM-CSF, IL-2, ...

FDA approval Mar 2011 – Melanoma

FDA approval Sep 2014 – Melanoma

- Antibodies

Cetuximab, Bevacizumab, ...

FDA approval Apr 2014  
Prostate Cancer

FDA approval Dec 2014 – Melanoma

- Vaccines

Peptides, RNAs, Sipuleucel-T, ...

FDA approval May 2016 – Urothelial Ca  
Dec 2014

- Immune checkpoint inhibition

Ipilimumab, Nivolumab, Pembrolizumab, Atezolizumab, Avelumab, Durvalumab

FDA approval May 2017 – Urothelial carcinoma

- BiTEs

Blinatumumab...

FDA approval Aug 2017 - B-cell precursor ALL

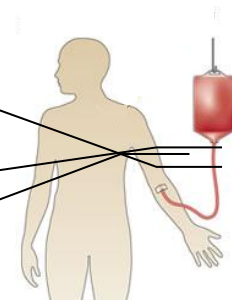
- Adoptive cell transfer

TILs, CARs, ...

FDA approval Aug 2017 - Merkel cell carcinoma

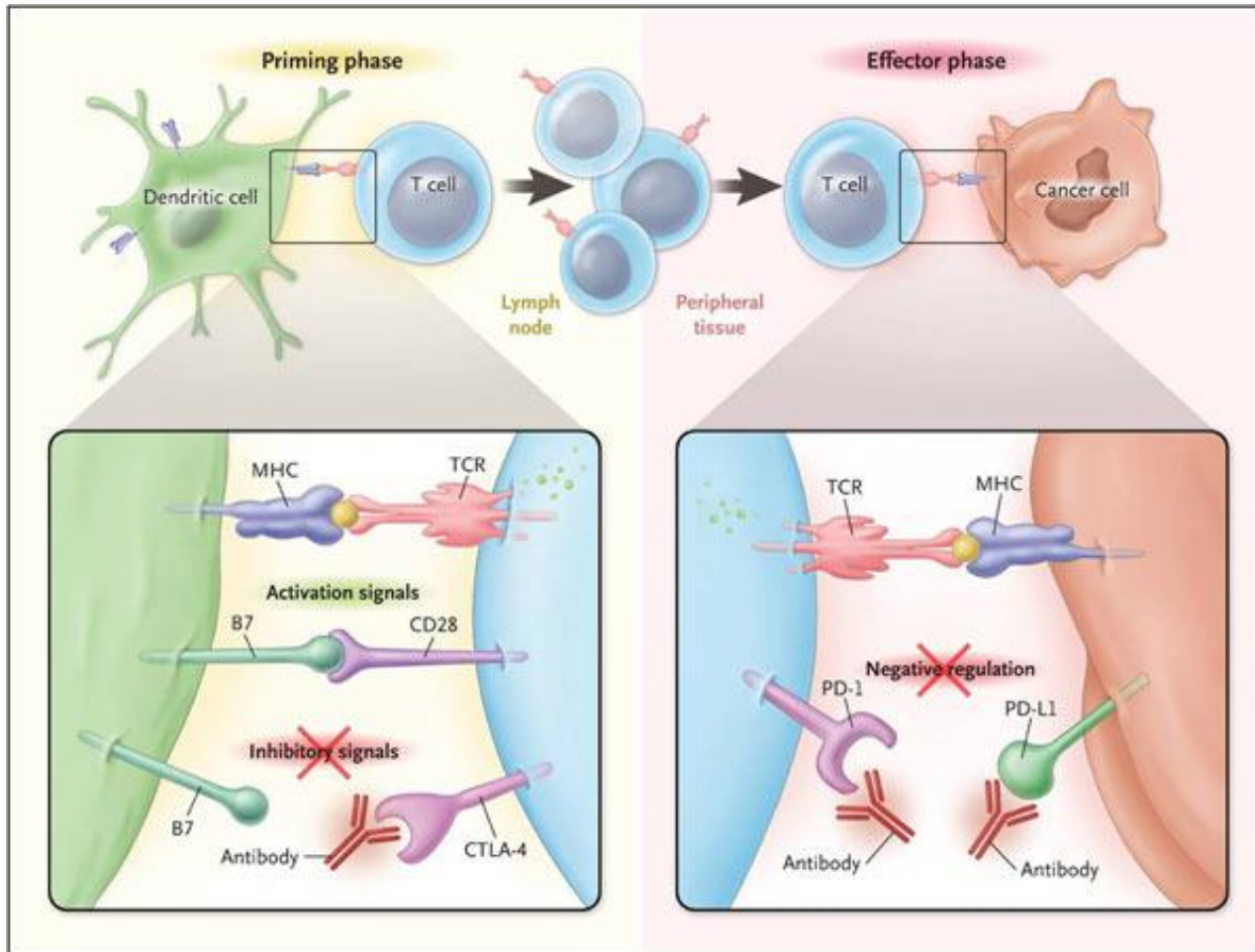
- Oncolytic Viruses

Imlygic®...



# Cancer Immunotherapy today

## Immune Checkpoint Inhibition



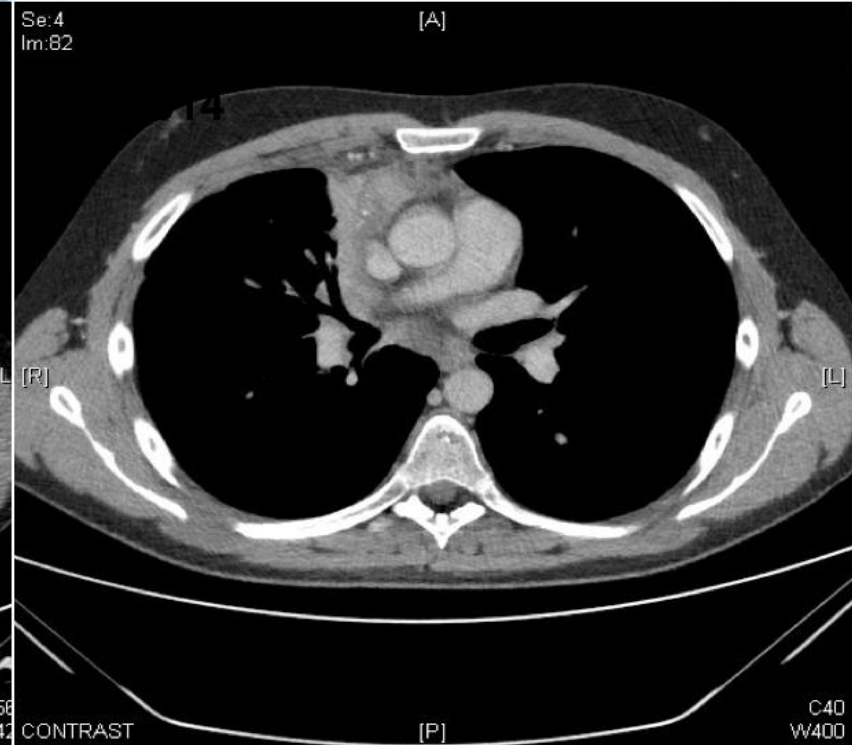
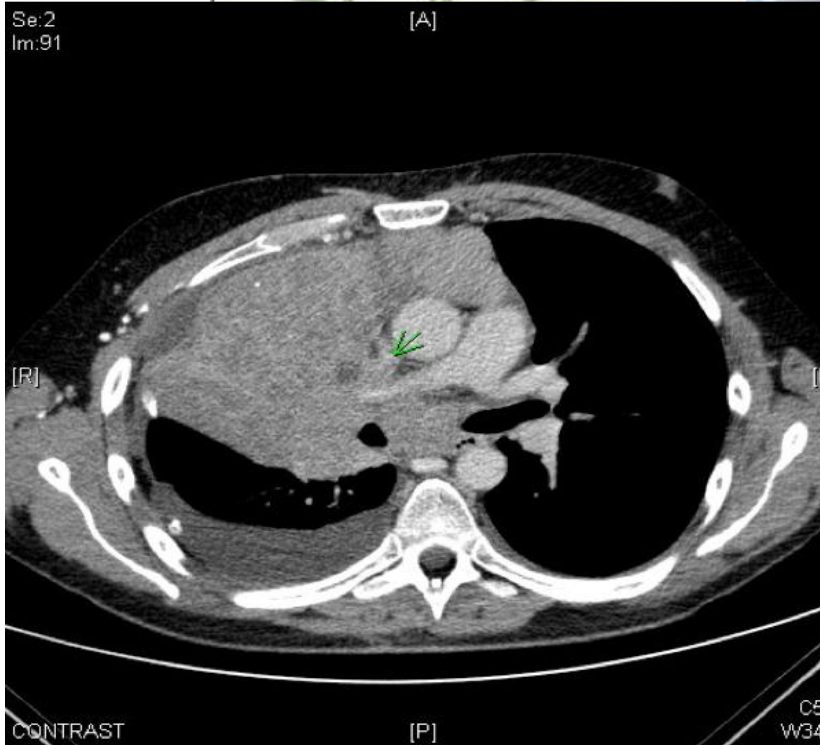
→ anti CTLA4

→ anti PD-1/PD-L1

Ribas, New England Journal of Medicine, 2012

# Cancer Immunotherapy today

## Immune Checkpoint Inhibition



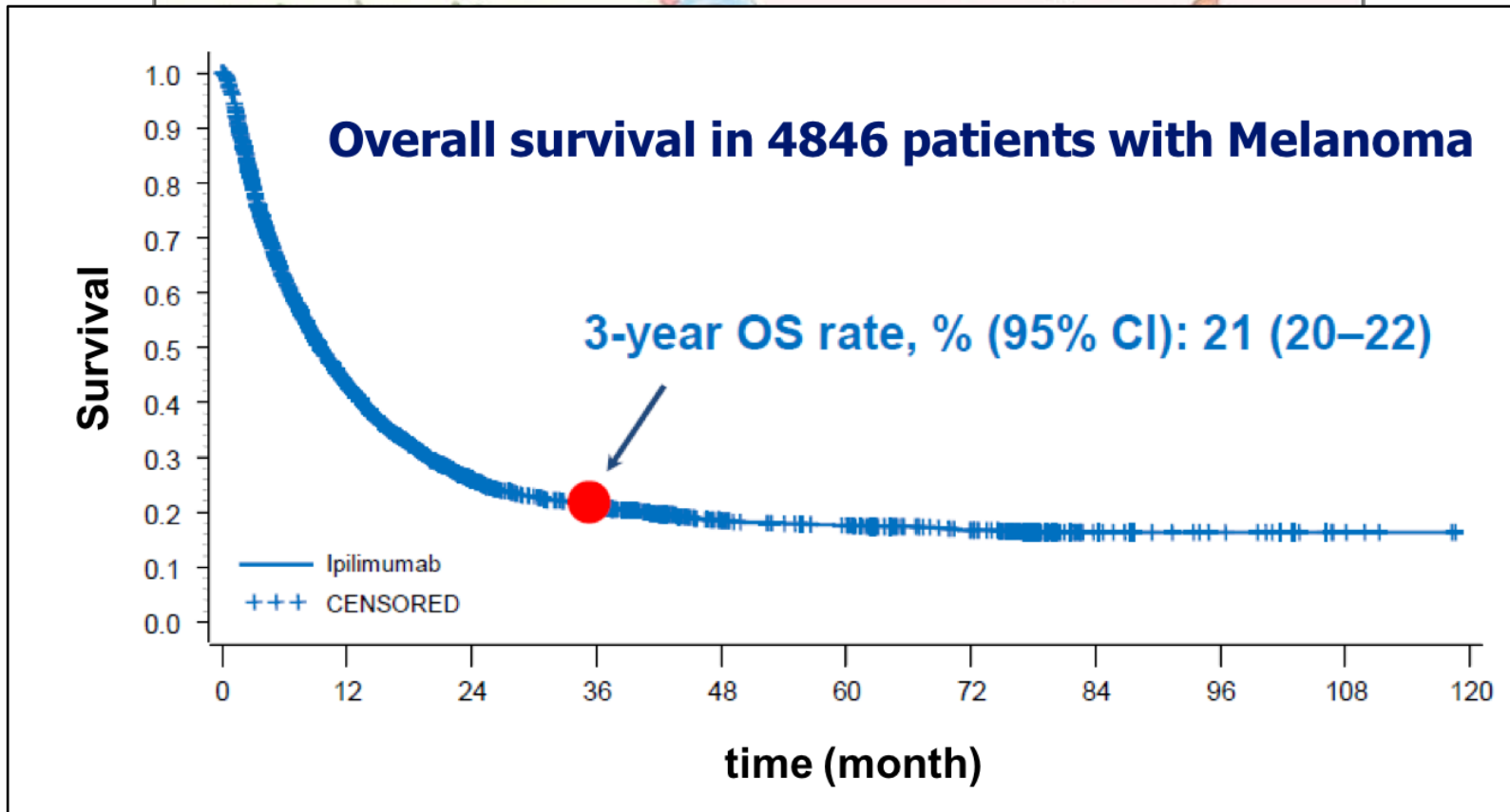
- male, 27 yr
- NSCLC (extensive disease)
- Refractory to standard CTX
- 05-09/2014: 9x anti-PDL-1 (MEDI4736)
- 09/2014: Restaging: PR (-74 %)

→ anti PD-1/PD-L1



# Cancer Immunotherapy today

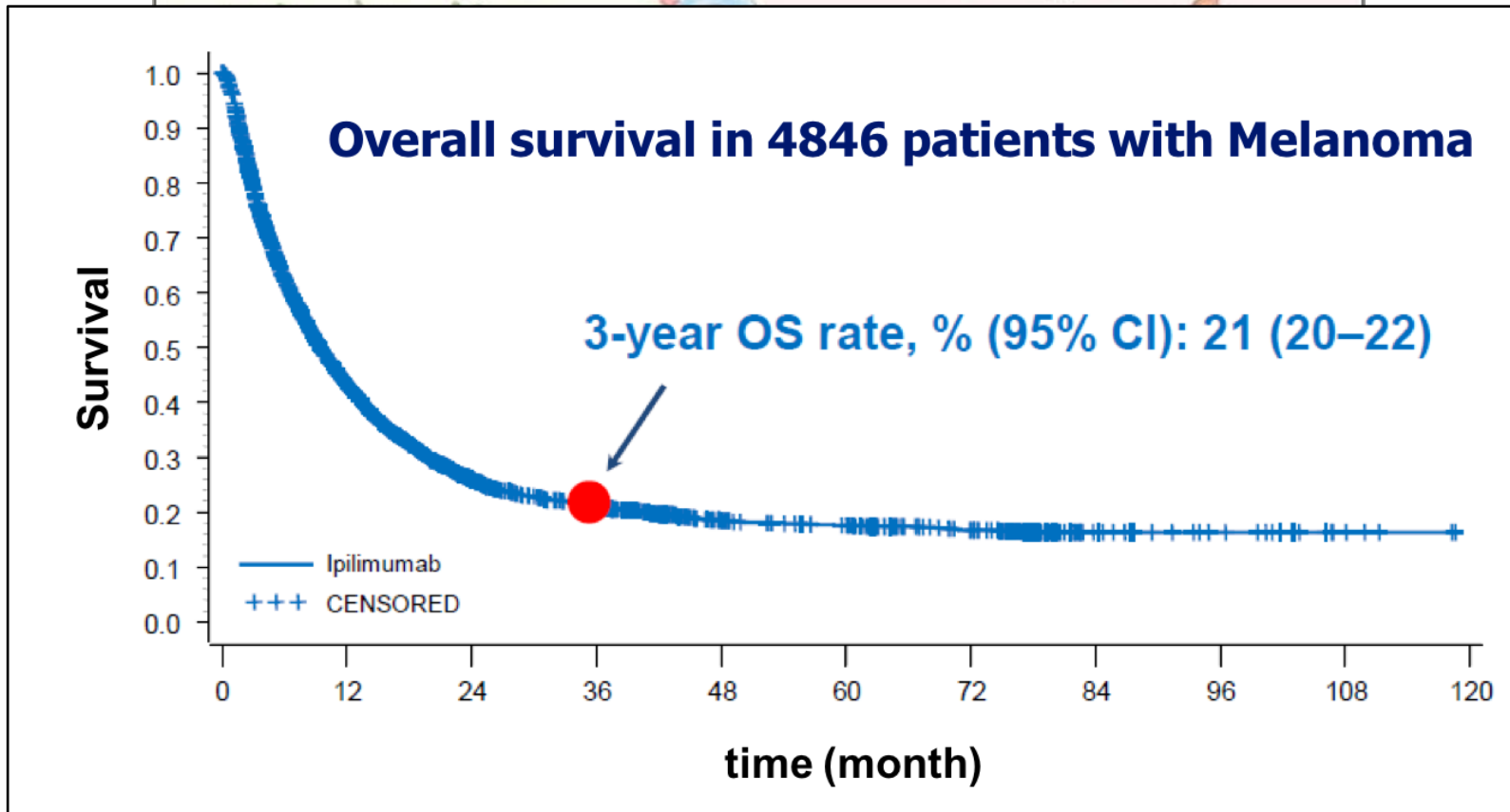
## Immune Checkpoint Inhibition



→ anti CTLA4

# Cancer Immunotherapy today

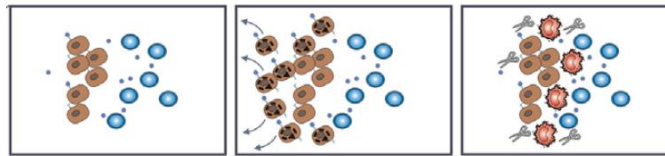
## Immune Checkpoint Inhibition



→ anti CTLA4

# Cancer Immunotherapy tomorrow

Combination of checkpoint inhibition with CCR5 inhibition in refractory CRC



CCL5 is produced by lymphocytes

CCL5 promotes tumor cell growth and invasion

CCL5 leads to MMP production by macrophages

Baseline-CT

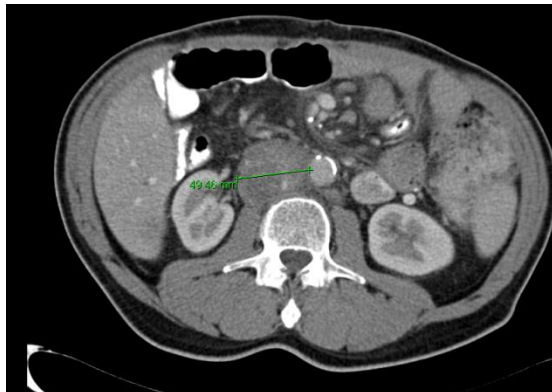
3 cycles PD1 + CCR5-inhibitor

6 cycles PD1 + CCR5-inhibitor

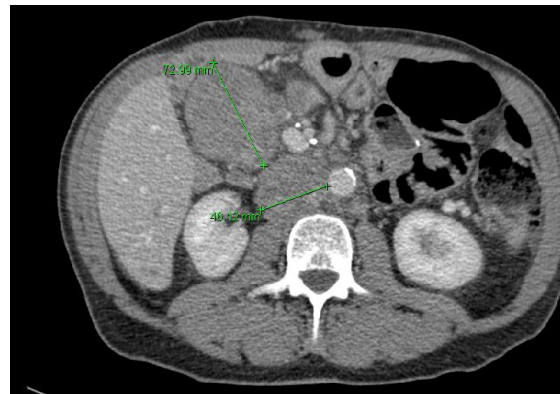
CT Abd 10.09.2014

CT Abd 20.01.2015

CT Abd 20.03.2015



LN-Bulk 49,46 mm



LN-Bulk 46,12 mm

newLN-Bulk 72,99 mm



LN-Bulk 30,64 mm

newLN-Bulk 38,27 mm

Halama et al. Cancer Cell 2016

# Cancer Immunotherapy tomorrow

Combination of checkpoint inhibition with CCR2/5 inhibition

## Prospective clinical trials @NCT are starting

- CRC and PDAC second line:
  - Ipilimumab + nivolumab + CCR5 antagonist
- CRC last line:
  - Pembrolizumab + CCR5 antagonist
- CRC and PDAC:
  - Chemotherapy + CCR2/5 antagonist

# Cancer Immunotherapy tomorrow

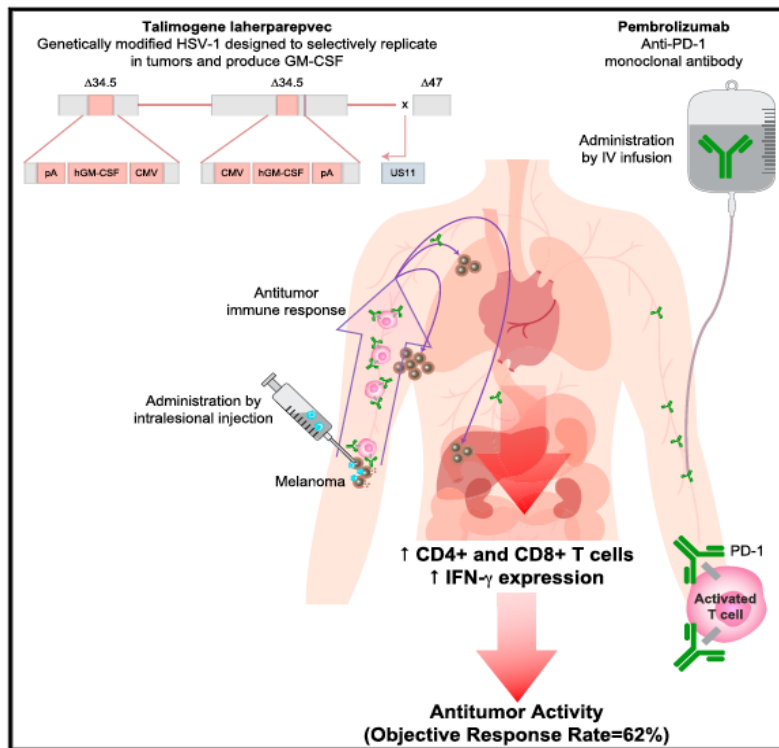
Combination of checkpoint inhibition with virotherapy

Article

Cell

## Oncolytic Virotherapy Promotes Intratumoral T Cell Infiltration and Improves Anti-PD-1 Immunotherapy

Graphical Abstract



Authors

Antoni Ribas, Reinhard Dummer, Igor Puzanov, ..., Jennifer Gansert, F. Stephen Hodi, Georgina V. Long

Correspondence

aribas@mednet.ucla.edu

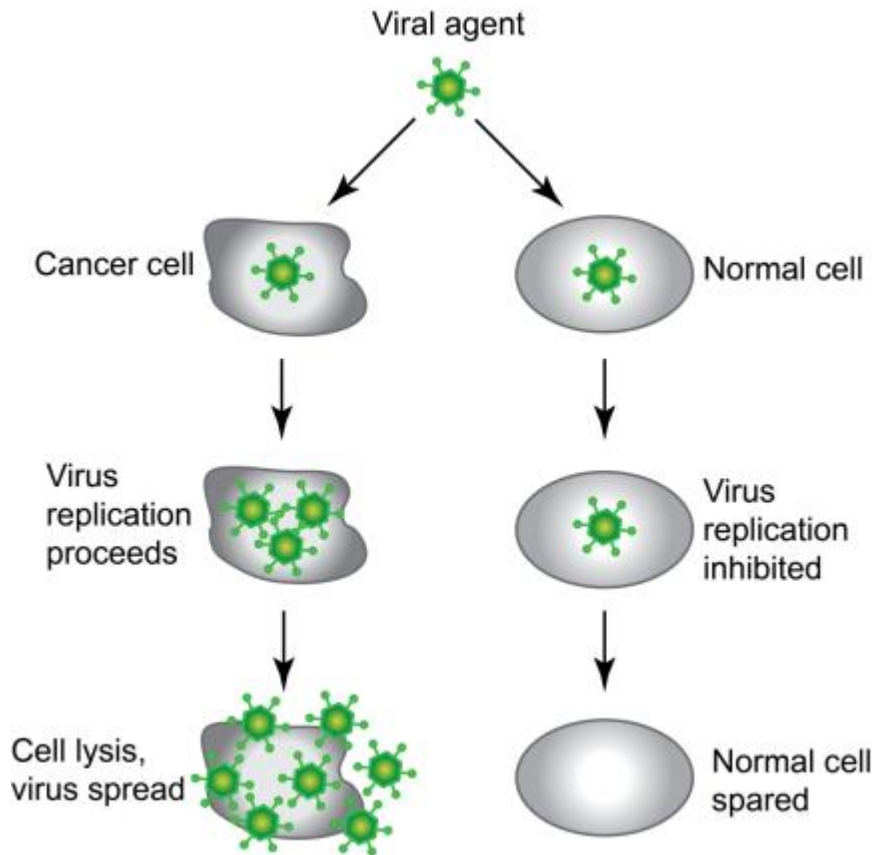
In Brief

In combination with anti-PD-1 therapy, intratumoral injection of an oncolytic virus engineered to enhance immune recognition of cancer resulted in a high response rate in patients with advanced melanoma.

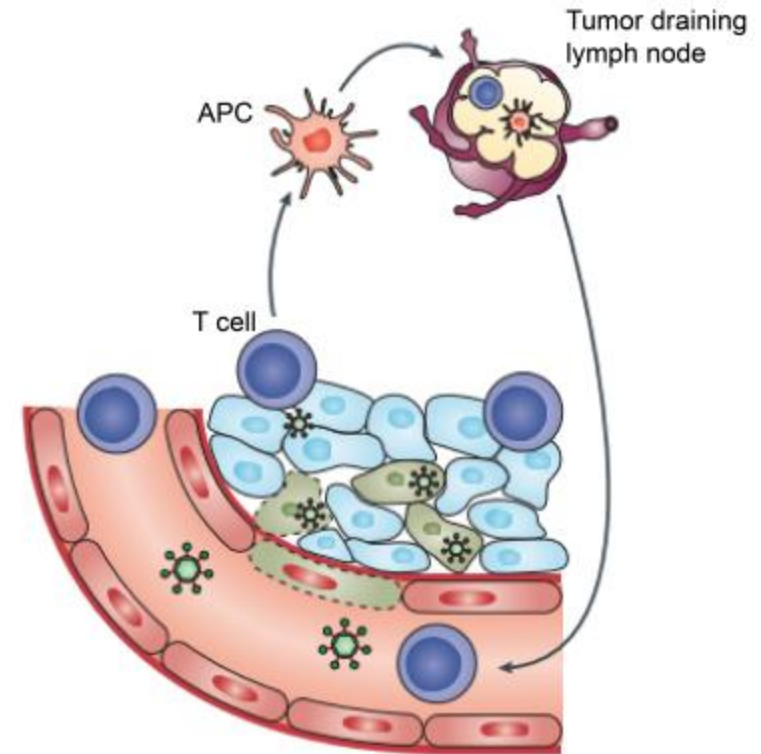
Ribas et al., Cell 2017

# Principles of Virotherapy

## I. Direct oncolysis



## II. Activation of tumor-specific immune response



→ Targeted immunomodulation / *in situ* vaccination

# Cancer Immunotherapy tomorrow

Combination of checkpoint inhibition with virotherapy

Phase Ib trial T-VEC + Pembrolizumab (21 patients)

→ Phase III trial is ongoing

- Common adverse events: fatigue, fevers, chills
- **No dose-limiting toxicities**
- **Confirmed objective response rate: 62%**
- **Complete response rate 33% (irRC)**
- Response associated with increased CD8+ T cells and IFN- $\gamma$  expression after treatment

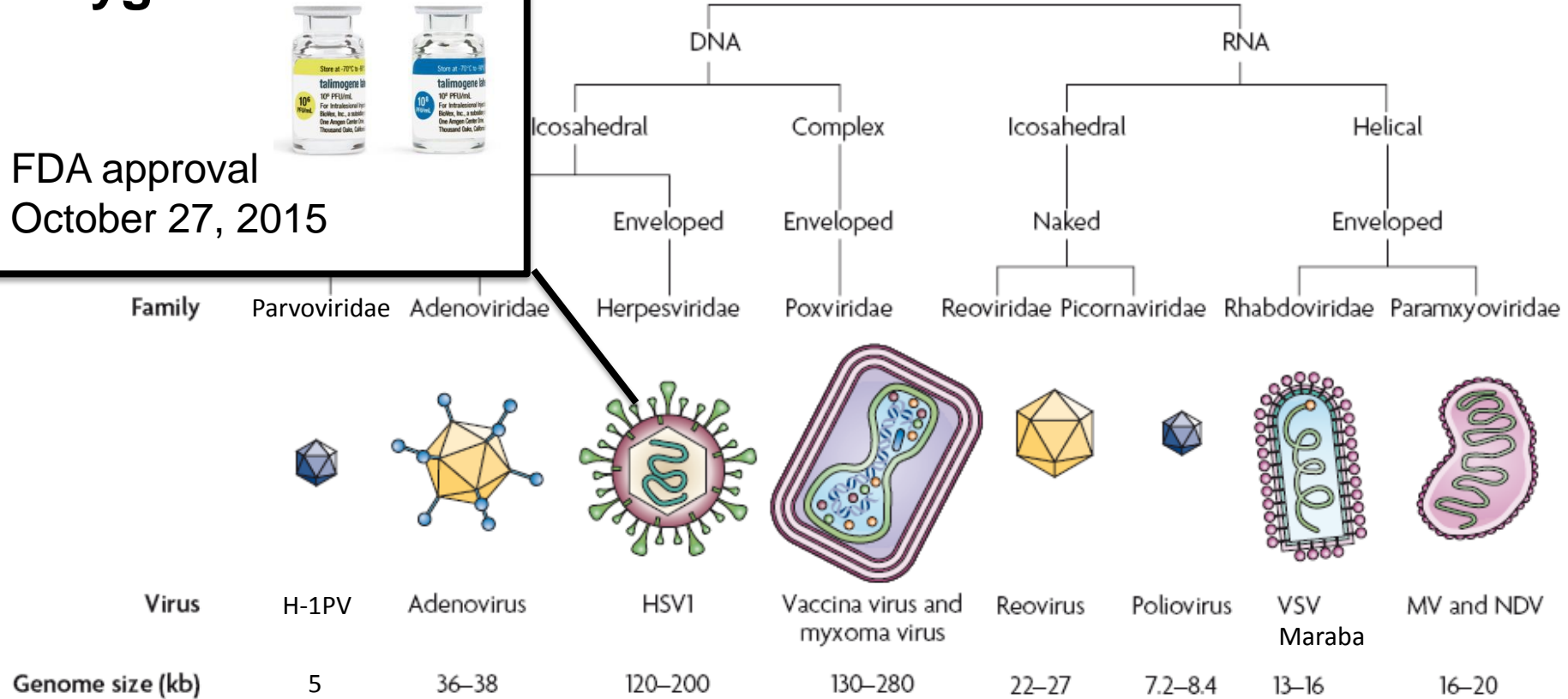
# Cancer Immunotherapy tomorrow

## Oncolytic Viruses

**Imlygic®**



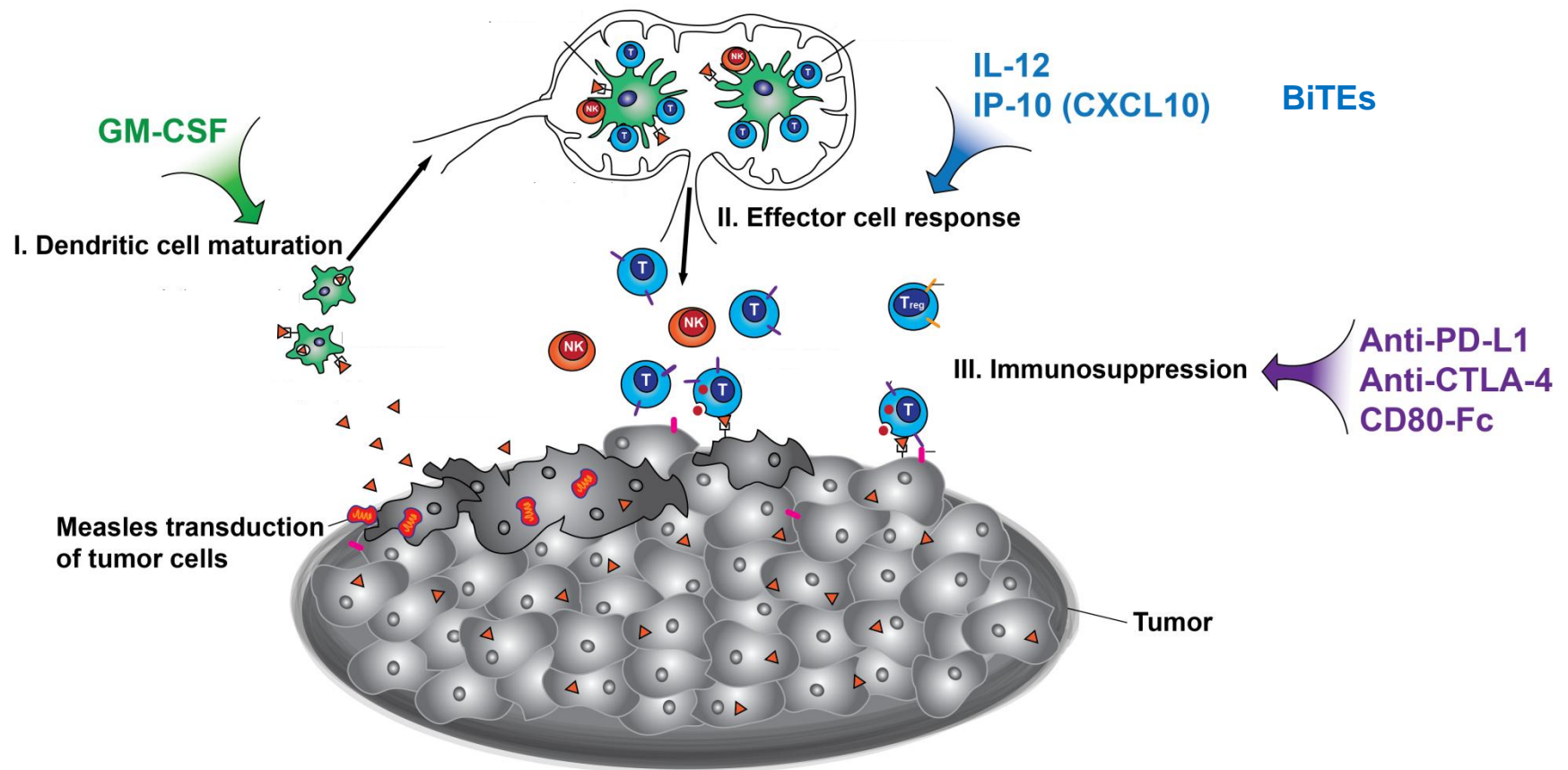
FDA approval  
October 27, 2015



adapted from Nature Reviews Microbiology 6, 1529-540 (2008)

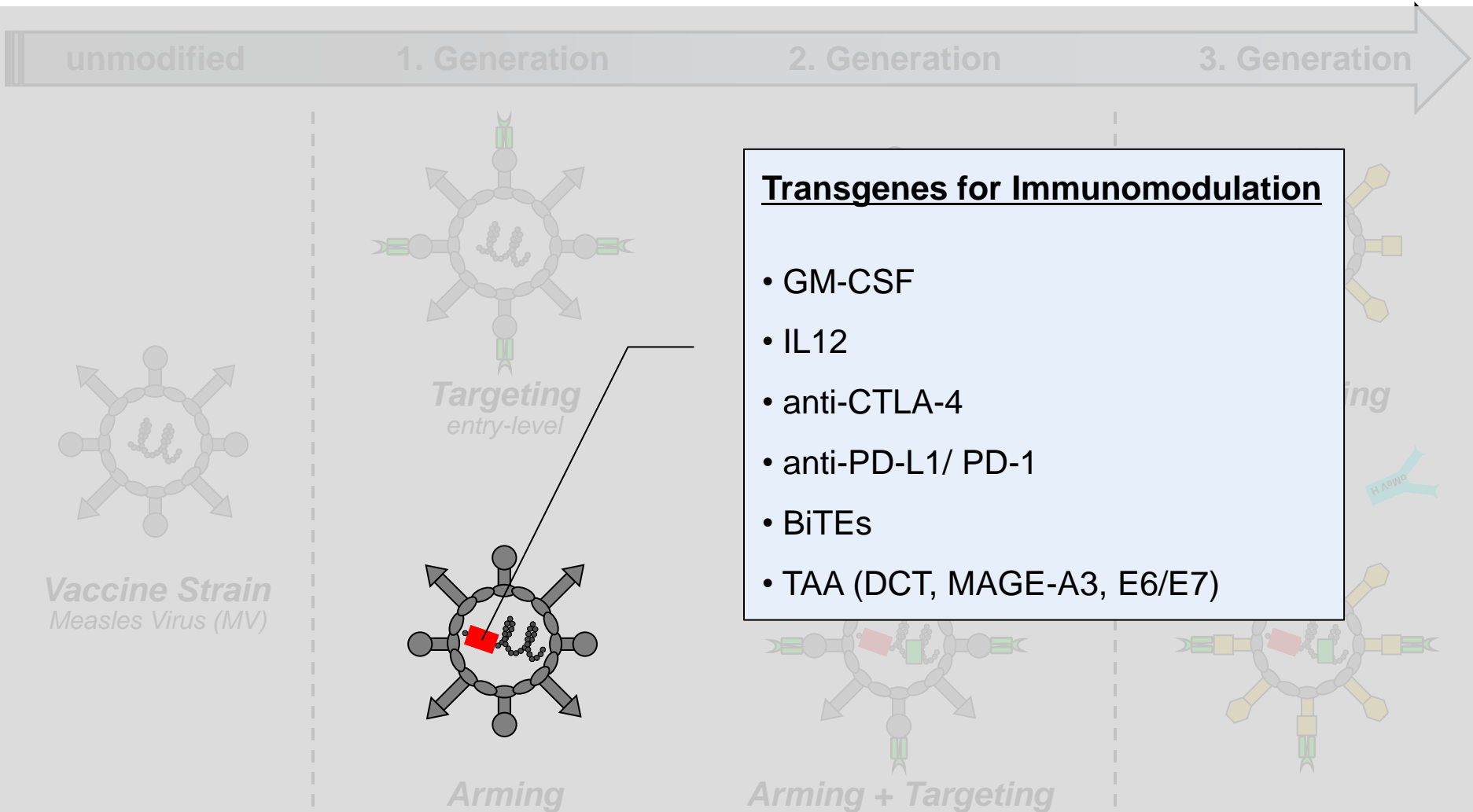


# Oncolytic Viruses can support different phases of anti-tumor immune responses



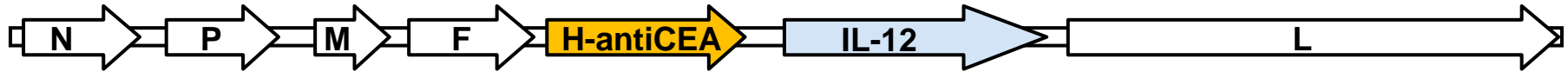
Courtesy of Rūta Veinalde, adapted from Mellman et al., 2011. *Nature*, 480(7378):480-9.

# Engineering Measles Virus

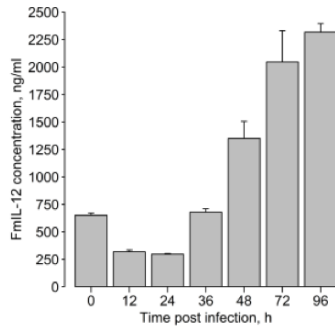


 MV-H	 single-chain antibody	 immunomodulatory transgenes	 CDV-H
Grossardt et al., <i>Human Gene Therapy</i> 2013			
 anti-MV antibodies	 anti-MV antibodies		 CDV-F
Engeland et al., <i>Molecular Therapy</i> 2014			
 anti-MV antibodies			
Veinalde et al., <i>Oncoimmunology</i> 2017			

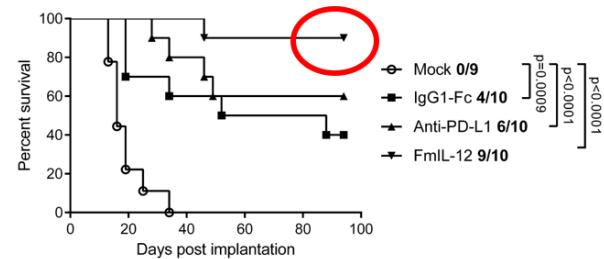
# MV encoding IL-12



MC38cea in vitro



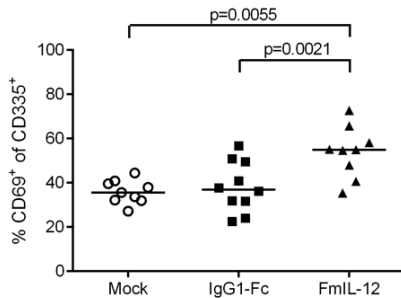
MC38cea in C57BL/6J



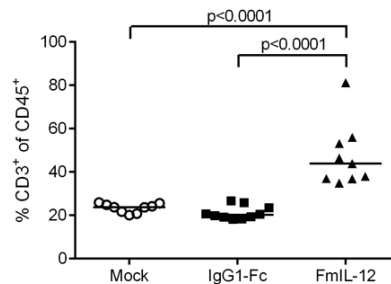
→ high IL-12 expression levels

→ prolonged survival / 90% CR

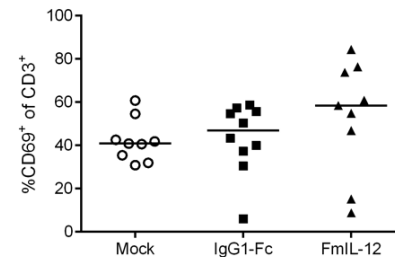
Activated NK cells



T cells

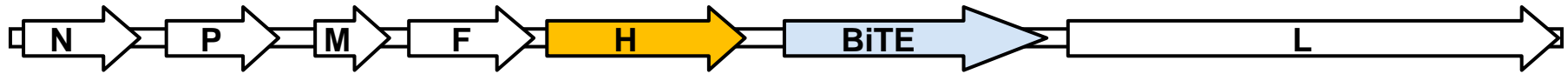


Activated cytotoxic T cells

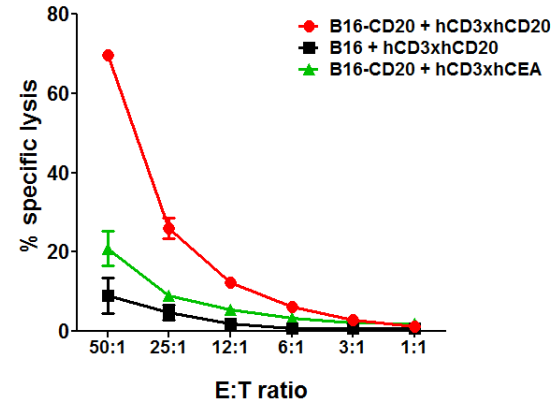
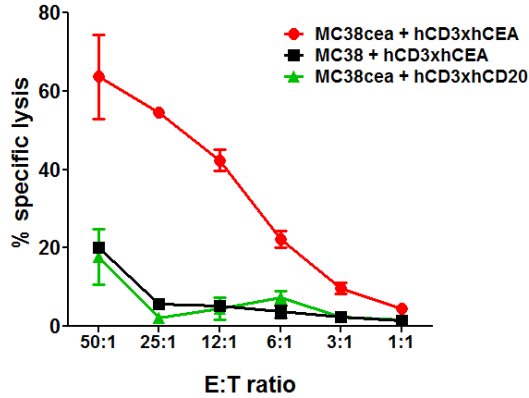


→ efficient T and NK cell activation!

# Measles with more BiTE...

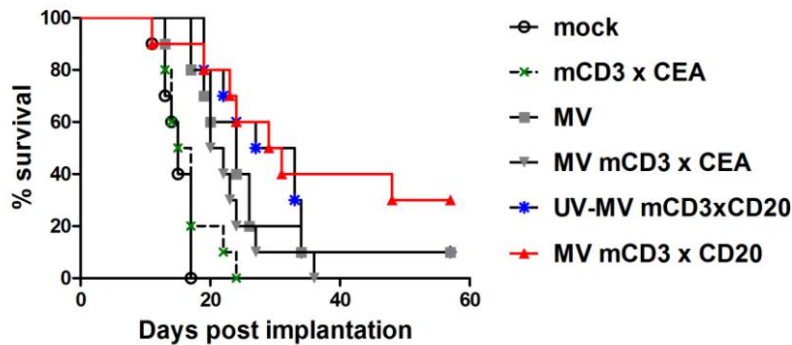


*in vitro*

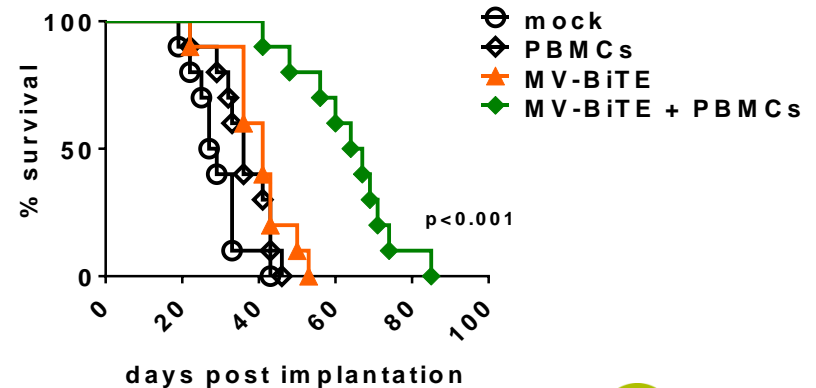


## B16-CD20: T cell-neglected Tumor

*in vivo*

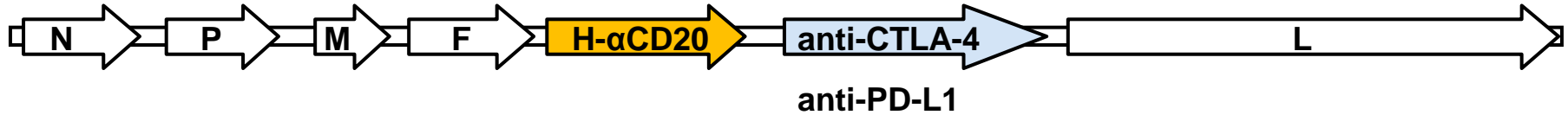


## Patient-derived xenograft (colon carcinoma spheroid cultures)

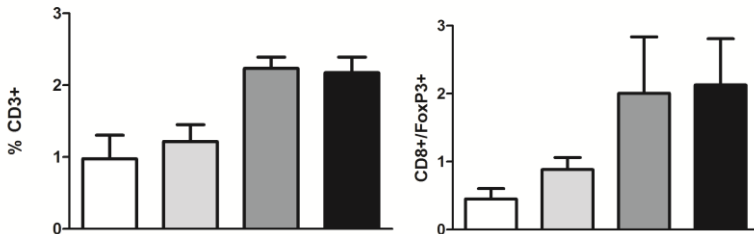


# MV encoding ICI

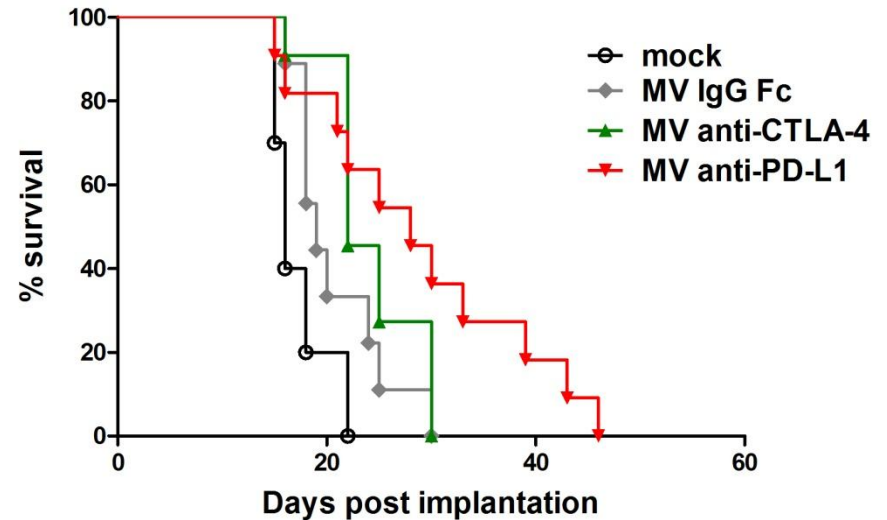
## Mouse model: C57/BL6; B16-CD20



- mock
- ▒ MV-IgG Fc
- MV-aCTLA-4
- MV-aPD-L1



- increased CD3+
- decreased Treg
- increased Teff/Treg



- prolonged survival

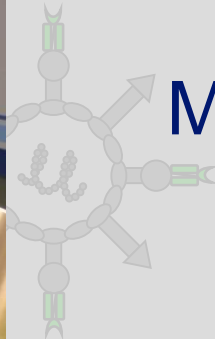
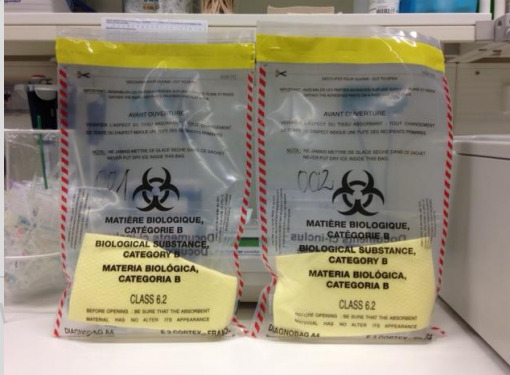
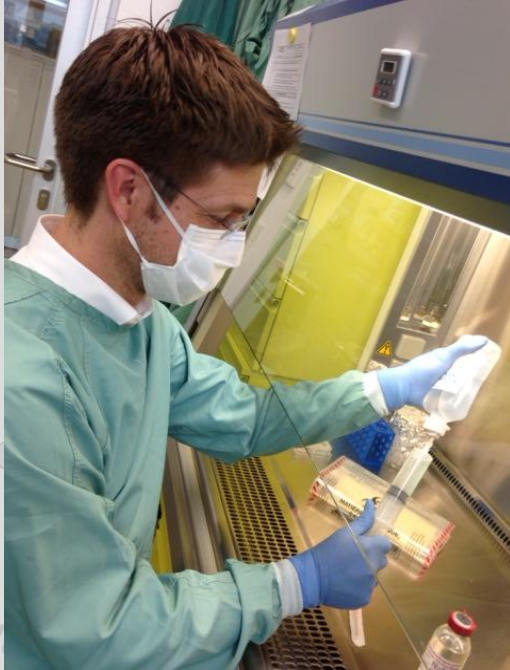
# Translation - Clinical Trial Development

unmodified

1. Generation

2. Generation

3. Generation



targeting  
entry-level

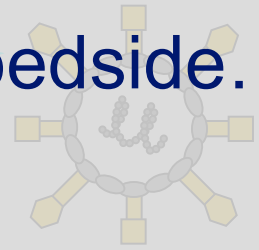
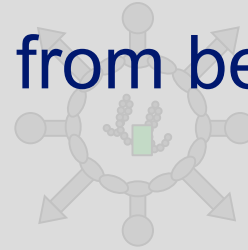


arming

suicide/i

anti-MV antibodies

Moving from bench to bedside...



MV-F

microRNA target site

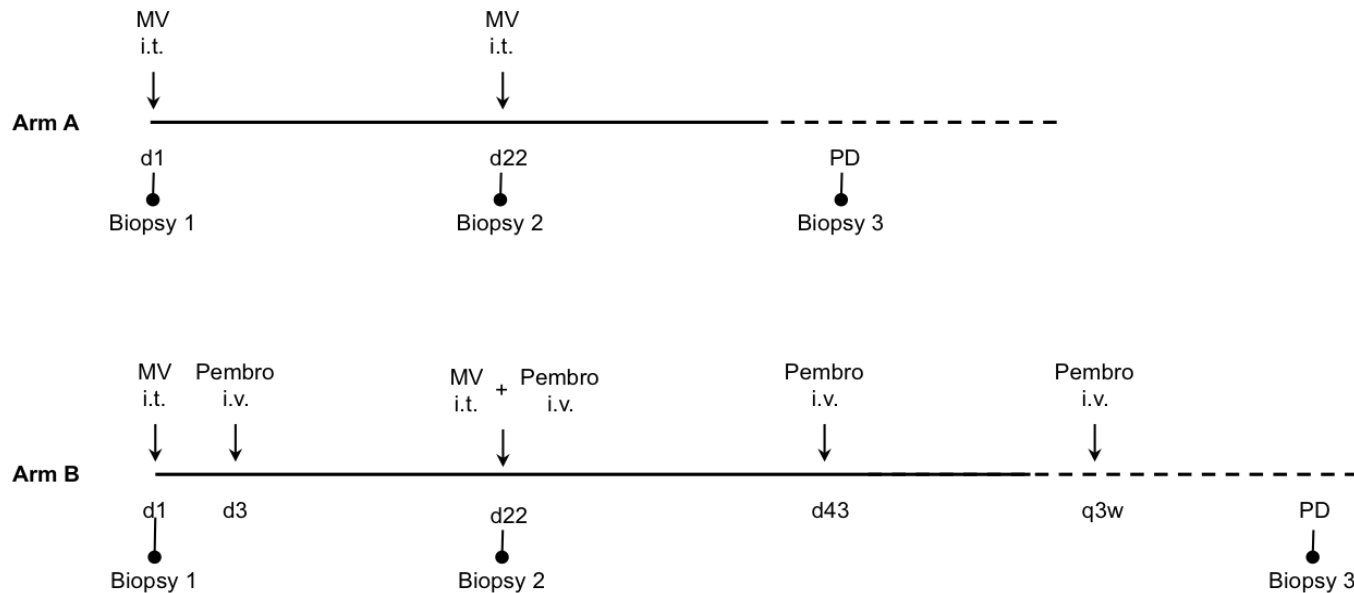
CDV-F



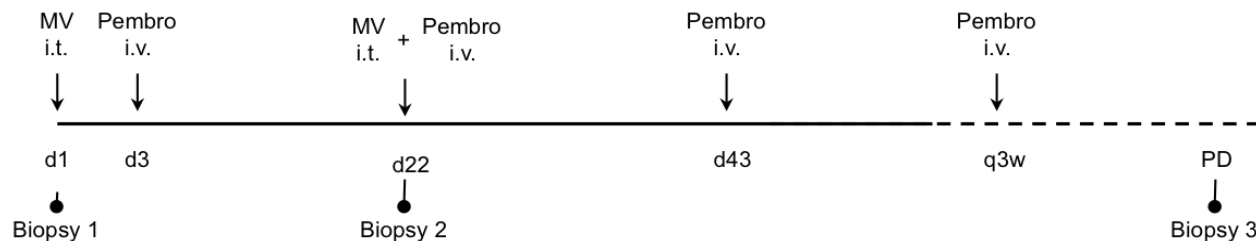
# Phase Ib/II Study Measles Virus + Pembrolizumab

FPI: Q2 2018 @ NCT

## Phase Ib

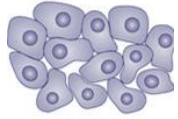


## Phase II



# Translational Research Program

EXPLORATORY OBJECTIVE: Identify **immunological** and **molecular** signatures predicting clinical response



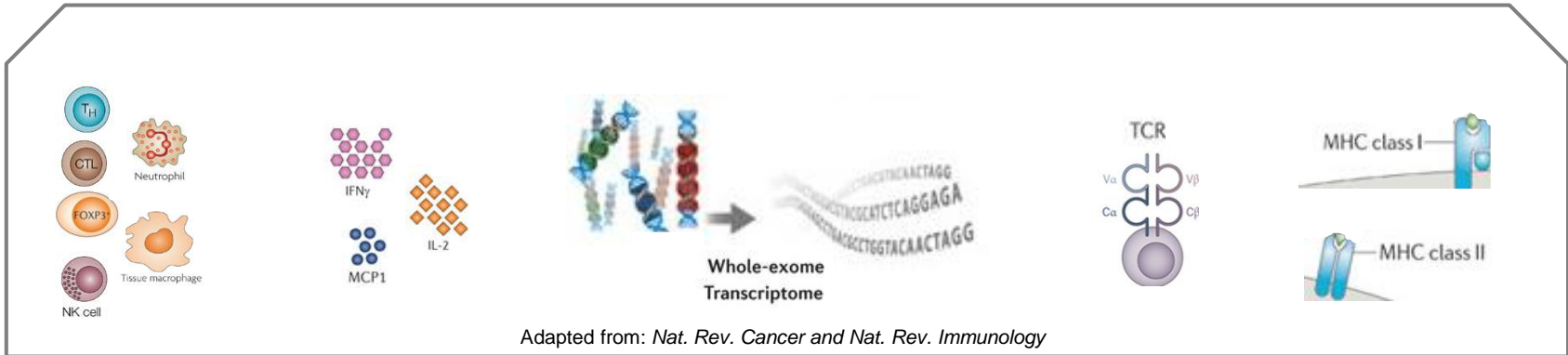
1<sup>st</sup> Biopsy  
prior treatment



2<sup>nd</sup> Biopsy  
after 2-3 weeks



3<sup>rd</sup> Biopsy  
at time of PD



- Quantification of immune cell subsets and cytokine/chemokine profiles
- TCR sequencing to define the T cell clonotypic repertoire
- Sequential exome/transcriptome analyses of tumor biopsies
- Analysis of genetic germline background, including MHC I and MHC II alleles

- ▶ local immunological microenvironment
- ▶ predictive score
- ▶ neoepitopes triggering mutation-specific responses
- ▶ predictive MHC haplotypes



# Cancer Immunotherapy tomorrow

Growing number of new and combinatorical approaches

- Cytokines + antagonists

INF, GM-CSF, CCR2/5i, IL2, IL12...

- Antibodies

Cetuximab, Bevacizumab,...

- Vaccines

Personalized RNA mutanome vaccines...

- Immune checkpoint inhibition

Ipilimumab, Nivolumab, Pembrolizumab, Atezolizumab, Avelumab, Durvalumab, ...LAG-3, TIM-3, ...

- BiTEs, BiKEs, TriKEs...

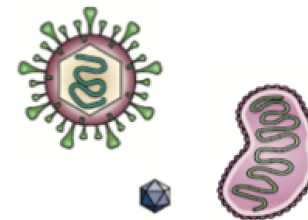
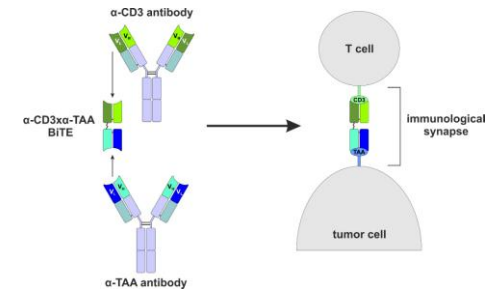
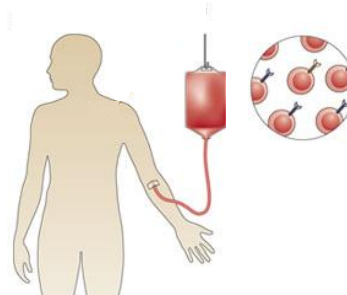
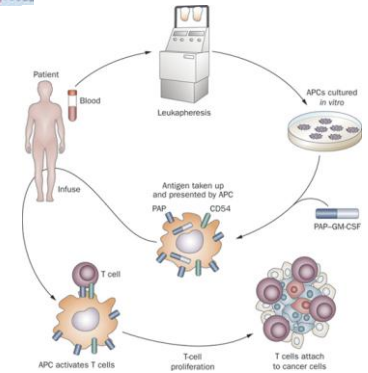
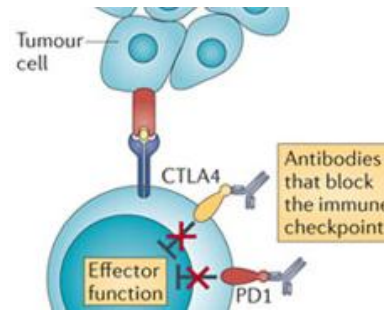
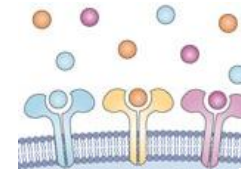
Blinatumumab...

- Adoptive cell transfer

TILs, CARs,...

- Oncolytic Viruses

Imlygic®, Parvo H-1, Measles viruses...



# Cancer Immunotherapy tomorrow

Growing number of new and combinatorical approaches

- **Cytokines + antagonists**

INF, GM-CSF, CCR2/5i, IL2, IL12...

- **Antibodies**

Cetuximab, Bevacizumab,...

- **Vaccines**

Personalized RNA mutanome vaccines ...

- **Immune checkpoint inhibition**

Ipilimumab, Nivolumab, Pembrolizumab, Atezolizumab, Avelumab, Durvalumab, ...LAG-3, TIM-3...

- **BiTEs, BiKEs, TriKEs...**

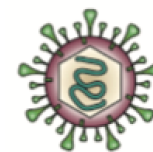
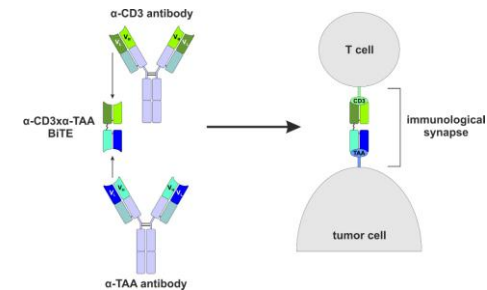
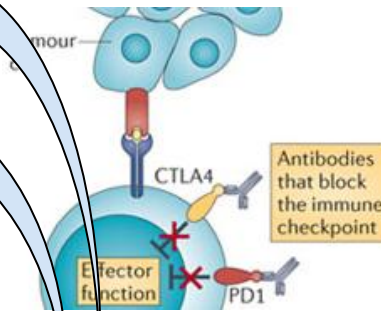
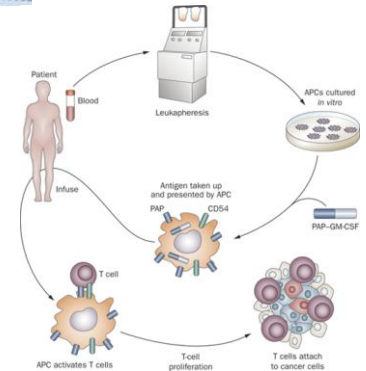
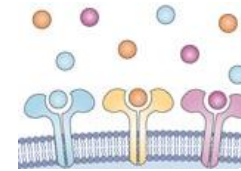
Blinatumumab...

- **Adoptive cell transfer**

TILs, CARs,...

- **Oncolytic Viruses**

Imlygic®, Parvo H-1, Measles viruses...



# Summary

Immunotherapy will be changing paradigms!

- Identify and understand both immunological and molecular signatures
- Development of new concepts / substances (e.g. Personalized RNA mutanome vaccines, CARs, TriKEs, OVs, RTx as an immune adjuvant)
- Growing number of combination options!

# Thank you!

