ImmunoScience Academy

Partnering for Education & Optimizing Treatment in ImmunoScience

www.immunoscienceacademy.be

Hot topics – Experts Panel Session

Prof Eric Van Cutsem, MD, PhD
Digestive Oncology
UZ Leuven

Mercury number ONCBE1908737-09
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Disclaimer: Any off-label data shown are used to support the educational message of the presentation and not intended to endorse use of any drug in any way

Experts

Expert: Prof Dr R. Schots, UZ Brussel

Haematology

Expert: Prof Dr P. Coulie, De Duve Institute UCL

Immunology

Expert: Prof Dr B. Neyns, UZ Brussel

Medical Oncology

The views and opinions expressed in these presentations are **those** of the experts... Assumptions made are **not** necessarily reflective of the position of BMS

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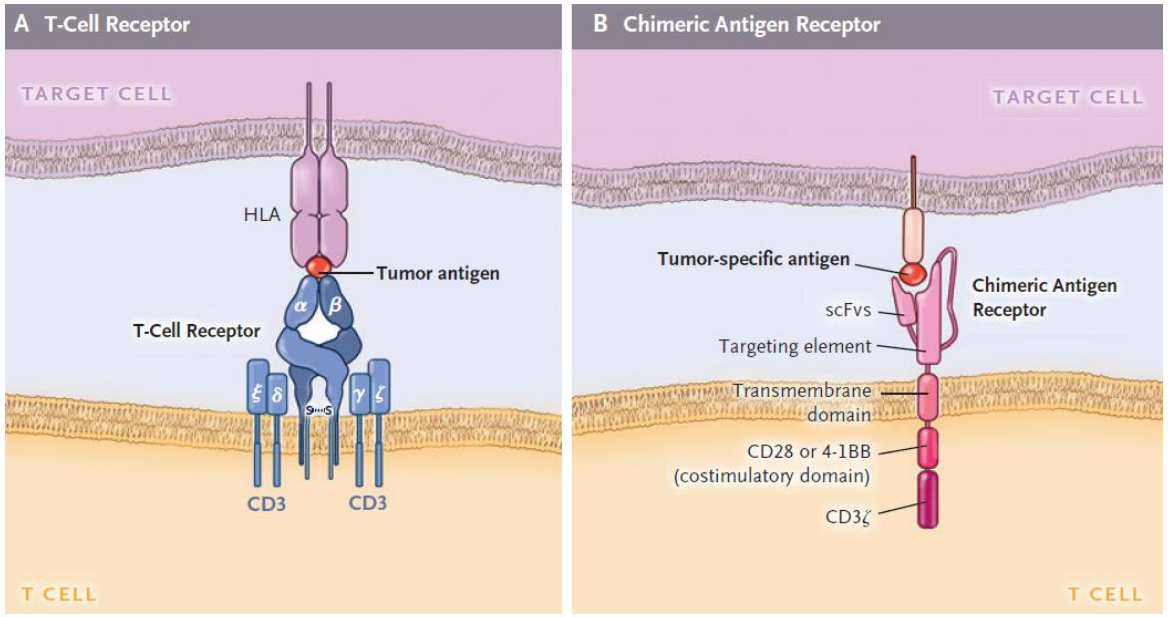
CAR T cells in hemato-oncology

Prof. R. Schots

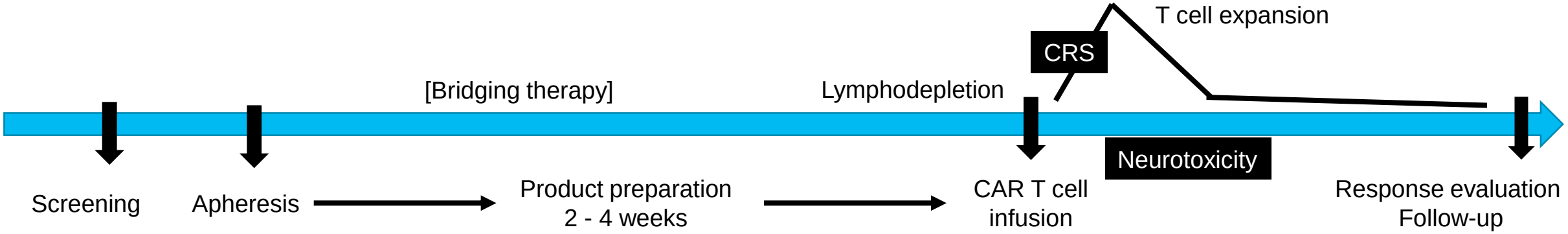
CAR T cell therapy



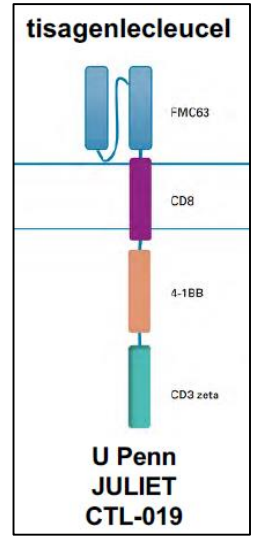
scFv single chain variable domain
HLA-independent T cell activation against cancer cells

Costimulatory domain (CD28 of 4-1BB)
Enhances proliferation, cytotoxicity and persistence of CAR T cells

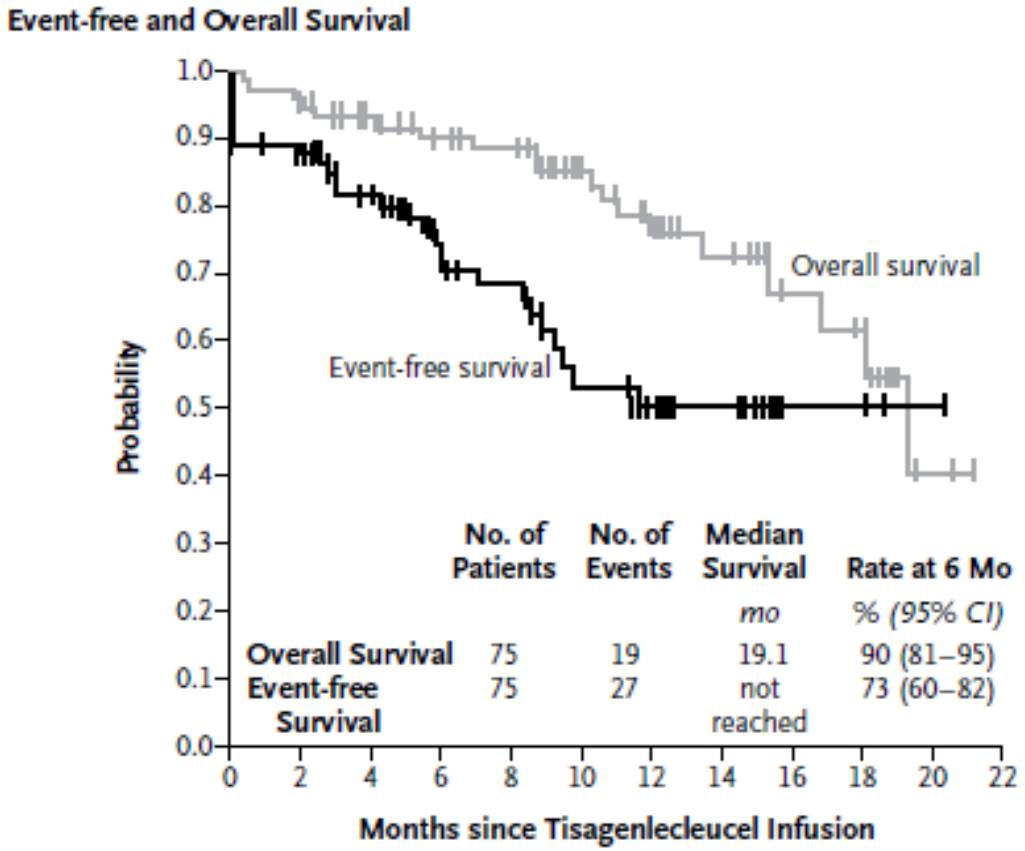
CD3-zeta domain
Proliferation, activation and cytotoxicity of CAR T cells



Anti-CD19 CAR T cell therapy in rel/refr ALL



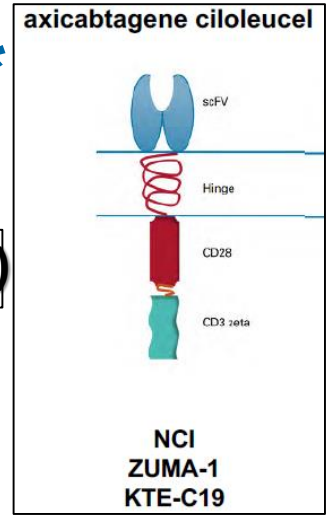
ELIANA trial (Tisagenlecleucel - Kymriah®



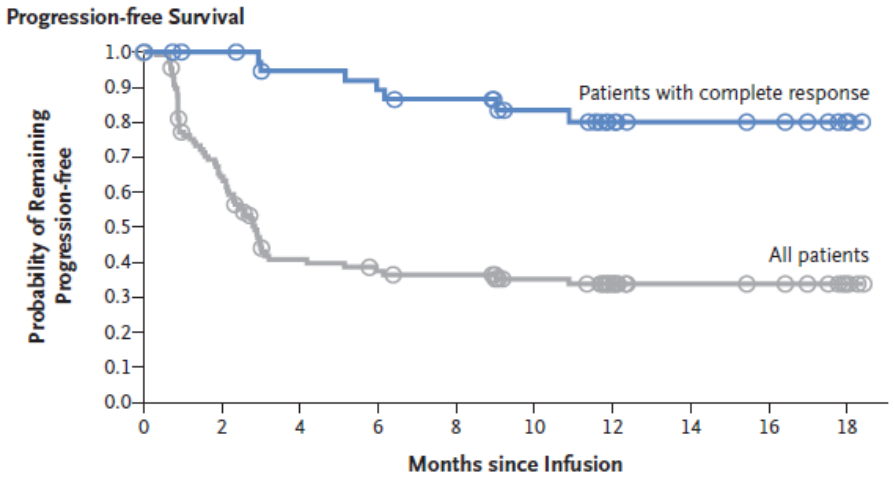
Maude et al. NEJM 2018; 378: 439-448

- Age 3 - 21 years
- 92 pts enrolled - 75 pts received infusion
- ORR = 81%
- CR/CRi = 60%/21% (all evaluated for MRD were neg)
- 80% of patients MRDneg at 3 mths remain in CR > 2 years
- No relation between cell dose and
  - Expansion
  - Clinical responses
- Persistence of tisagenlecleucel in blood for up to 20 mths

Anti-CD19 CAR T cell therapy in advanced lymphoma*



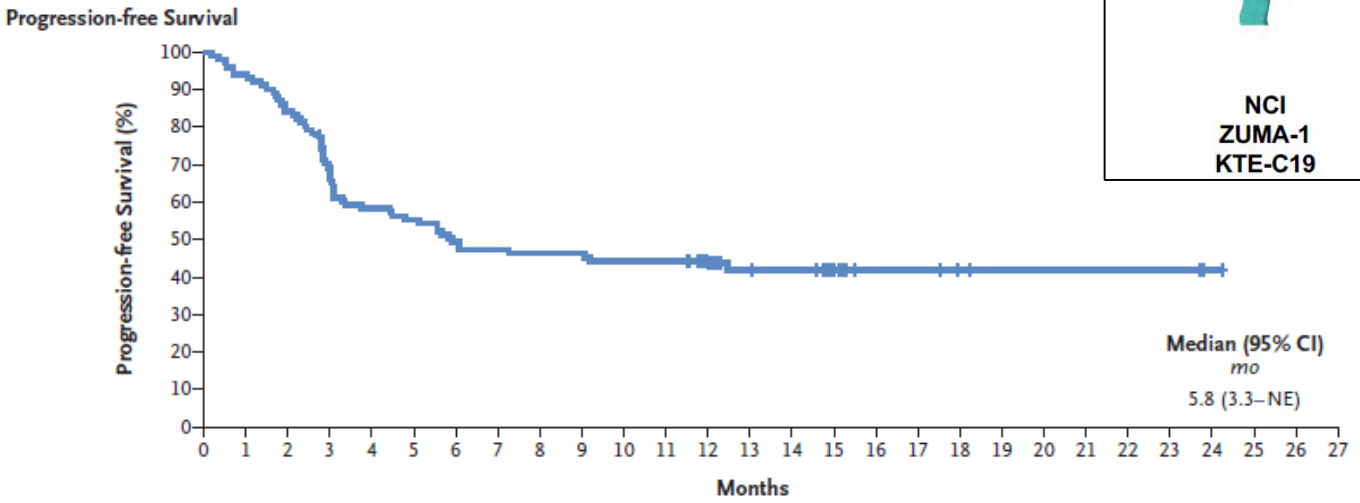
JULIET trial (Tisagenlecleucel - Kymriah®)



Schuster et al. NEJM 2019; 380: 45-56

- 165 enrolled - 111 pts received infusion - 93 evaluable
  - ORR = 52%
  - CR = 40% → 79% relapse-free at 12 mths
  - No association between responses and
    - CD19 expression on tumor cells
    - Expression immune checkpoint inhibitors

ZUMA-1 trial (axicabtagene ciloleucel - Yescarta®)



Neelapu et al. NEJM 2017; 377: 2531-2544

- 111 enrolled - 101 pts received infusion
  - ORR = 82%
  - CR = 54% → 77% CCR
- Higher CAR T levels in blood associated with response

*Expected ORR = 26% (CR 7%) and OS at 2 yrs = 20% (SCHOLAR-1 study (Crump et al. Blood 2017; 130: 1800-1808)

Tisagenleceucel reimbursement

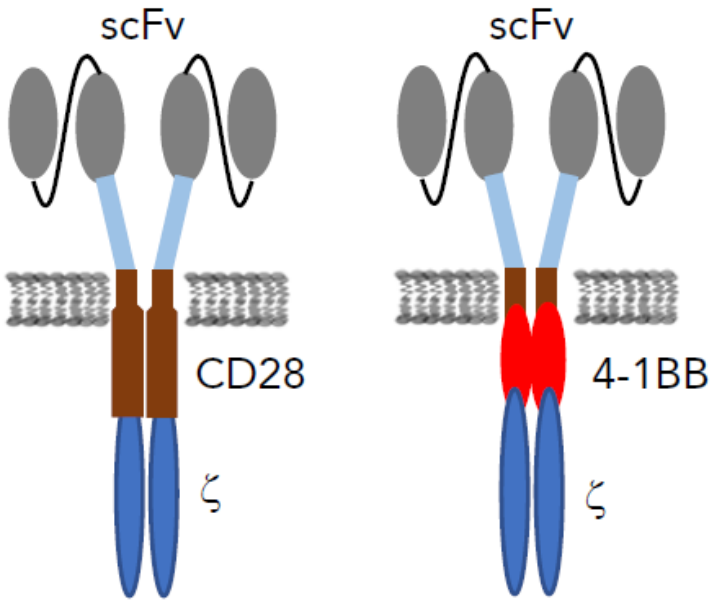
- Relapsed/refractory acute B cel lymphoblastic leukemia
  - Children and adults up to 25 years
- Diffuse large B cel lymphoma
  - Having been treated with at least 2 lines of systemic treatment
- One single infusion is reimbursed
- 4 centers accredited in Belgium
  - UZ Gent, UZ Gasthuisberg KUL, CHU Liège and St Luc UCL
- Expensive treatment!
  - 320 000 E

Toxicity of CAR T cell therapy

- Cytokine release syndrome (CRS)
  - Cytokine “storm” associated with T cell expansion
  - Related to CAR T dose level
  - Symptoms = fever, tachycardia, hypotension, hypoxia
  - Within first week after CAR T infusion
  - Incidence = 50-90% (20-25% grade ≥ 3)
  - Early intervention with tocilizumab + steroids reduces grade ≥ 3 incidence to < 5% (with no effect on CAR T efficacy) (Topp et al. ASH 2019; abstract n° 243)
- Neurotoxicity
  - Mechanism poorly understood (endothelial cell activation? blood-brain-barrier? cytokines?)
  - Mostly related to anti-CD19 CAR T cell protocols
  - Symptoms = confusion, tremor, aphasia, encephalopathy, seizures, cerebral edema
  - First weeks after CAR T infusion
  - Incidence = > 60% (50% ≥ grade 3), generally transient
  - Treatment = steroids, supportive
- Other

Ongoing progress

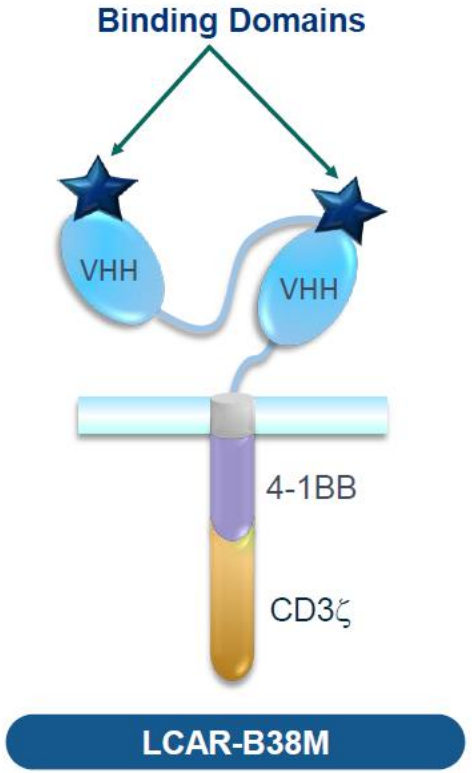
Design of CARs



- New targets: CD20, CD22, CD38, CD37
- Double costimulation (CD28/4-1BB)
- Inducible cytokine secretion (IL-12, IL-18)
- Bispecific CARs (e.g. CD19/CD20, CD19/CD22, CD38/BCMA)
- Fully human CARs (→ prolonged persistence)

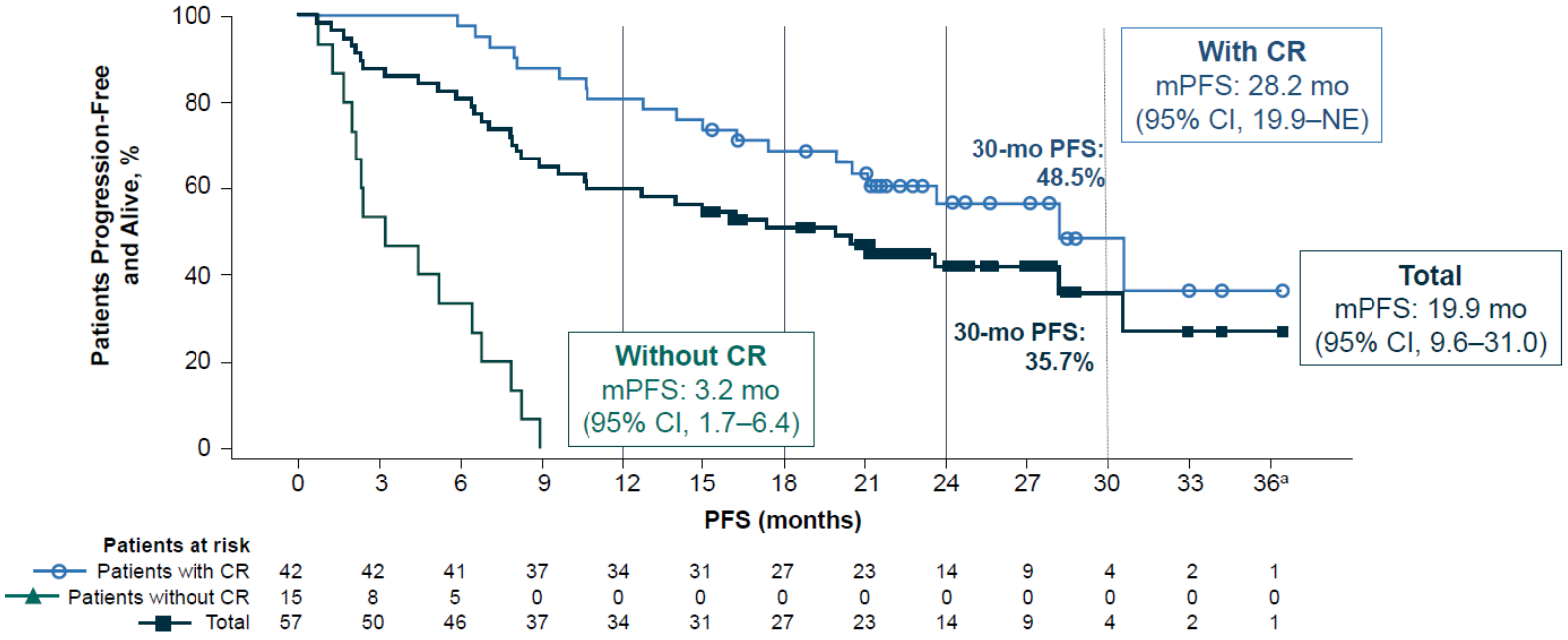
- scFv recognizing 2 epitopes of target antigen

LEGEND-2 (rel/refr MM)



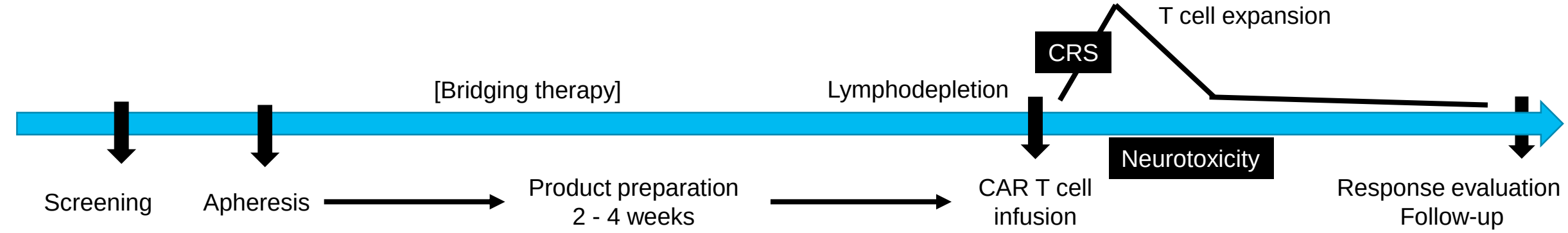
Progression-Free Survival

- PFS prolonged over 2 years for patients achieving CR (median follow-up, 25 mo)



Wang et al. ASH 2019; abstr 579

Ongoing progress



- Allogeneic CAR T cells (“off-the-shelf”)
- “Point of care” CAR T cell production

- Enrich T cells for central memory-like phenotype
- CD4/CD8 fixed composition at infusion (Liso-cel – Seattle)
- …..

Management of toxicities

- Sequential infusion (antiCD19 → anti-BCMA)
- Increasing persistence (e.g. pembroluzimab)
- Combinations..

Summary

- High response rates in patients with advanced hematological malignancies
- Responses are profound and durable but relapses do occur
- Toxicities (CRS, neurological, immune deficiency, ..) are managable
- Improvement at several levels is tested in phase I/II trials
- Phase 3 trials are ongoing
- CAR T cell therapy is likely to be introduced at an earlier stage in high-risk patients
- Cost should go down!

Regional delivery of mesothelin-targeted CAR T cells for pleural cancers: safety and preliminary efficacy in combination with anti-PD-1 agent

2019 ASCO Annual Meeting, Chicago

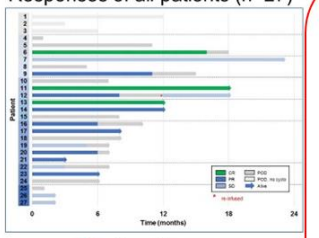
Memorial Sloan Kettering Cancer Center

Prasad S. Adusumilli, Marjorie G Zauderer, Valerie W Rusch, Roisin E O'Cearbhaill, Amy Zhu, Daniel Ngai, Erin McGee, Navin Chintala, John Messinger, Waseem Cheema, Elizabeth F Halton, Claudia R Diamonte, John Pineda, Alain Vincent, Shanu Modi, Steve Solomon, David R Jones, Renier J Brentjens, Isabelle C Riviere, Michel W Sadelain

Mesothelin-targeted CAR T-cell therapy

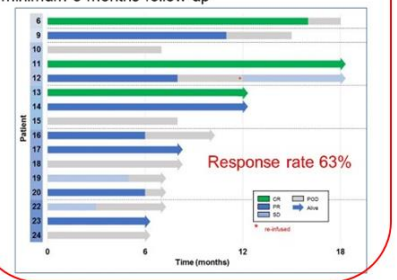
Clinical responses with and without addition of anti-PD-1 antibody

Responses of all patients (n=27)



CR – Complete response
PR – Partial response
SD – Stable disease
POD – Progression of disease

Responses of mesothelioma patients (n=16) that received Cyclophosphamide and CAR T-cells and at least 3 doses of anti-PD1 antibody with minimum 3 months follow-up



Intrapleural CAR T cells + systemic anti-PD1 antibody administration are well tolerated

On-target, off-tumor toxicity monitoring

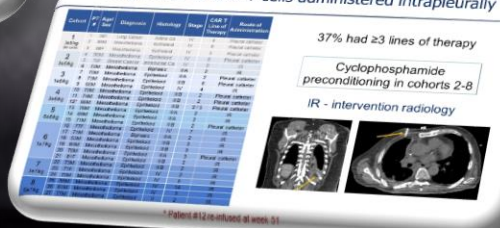
Monitored by	Method
Clinical	Pleuritis, Pericarditis, Peritonitis
Laboratory	Serum Troponin level
Cardiac	EKG, Echocardiogram
Imaging	CXR, CT, PET
Pathology	Biopsy

Adverse event	Grade	# of patients
Fever and chills	1	6
CRS	1	3
Malaise	1	1
Non-cardiac chest discomfort	1	1
Pain	1	1
Fever	2	1
CRS	2	1
Confusion	2	1
Febrile neutropenia (related to cyclophosphamide)	3	1

No evidence of CAR T-cell related AEs ≥Grade 2 (CTCAE V.4)
- No neurotoxicity
- No cytokine release syndrome (CRS)
- No on-target, off-tumor toxicity

Following anti-PD1 agent administration -
- 2 patients developed SOB (grades 2 & 3)
- One patient Rx with IL-6 blockade (two doses) and steroids, currently off oxygen
- One patient treated with short term steroids (3 doses), back on anti-PD1 agent

Single dose of CAR T cells administered intrapleurally



37% had ≥3 lines of therapy

Cyclophosphamide preconditioning in cohorts 2-8

IR - intervention radiology

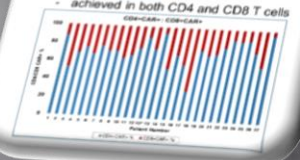
NCT02414269

Intrapleural administration

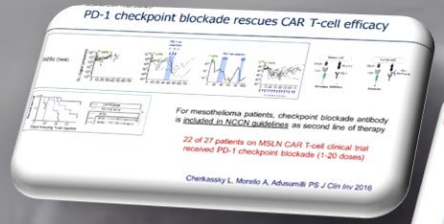
27 patients treated

Mesothelioma, pleural metastatic lung and breast cancers

CAR T-cell transduction is successful
- in all patients
- achieved in both CD4 and CD8 T cells



PD-1 checkpoint blockade rescues CAR T-cell efficacy

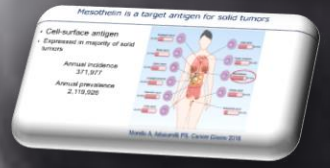


For mesothelioma patients, checkpoint blockade antibody is included in NCCN guidelines as second line of therapy

22 of 27 patients on MSLN CAR T-cell clinical trial received PD-1 checkpoint blockade (1-20 doses)

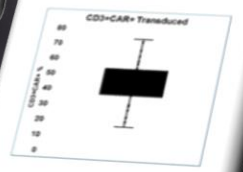
Cherkassky L, Morello A, Adusumilli PS J Clin Inv 2016

Mesothelin is a target antigen for solid tumors



iCasM28z CAR

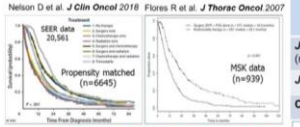
Fully human mesothelin CAR to reduce immunogenicity



Epithelioid mesothelioma patients survival

From diagnosis

Nelson D et al. *J Clin Oncol* 2018 Flores R et al. *J Thorac Oncol* 2007



Overall survival (OS) following **trimodality therapy in epithelioid** mesothelioma patients

	months
JCO (national database, n=242)	23.4
JTO (MSK) (n=207)	20.1
Current trial (n=23)	NR

NR – median survival not reached in 24 months follow up period

Since CAR T-cell infusion

All patients (n=23)		Sub cohort (n=16)	
6-month OS	90.3%	6-month OS	100%
1-year OS	74.1%	1-year OS	80.2%
Median follow up	8.4 months	Median follow up	11.8 months

(this is a phase I trial designed to investigate safety)

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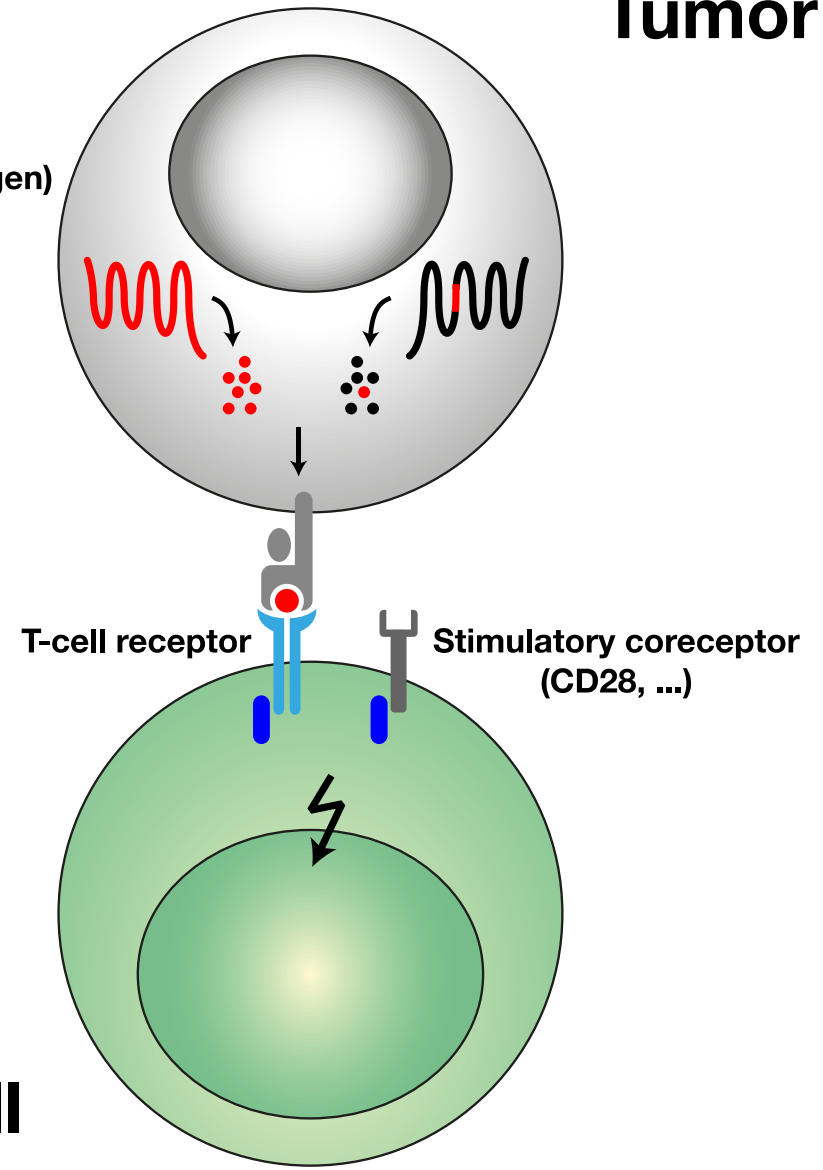
CAR T cells: more difficult for solid tumors

Prof Dr P. Coulie, De Duve Institute UCL Immunology

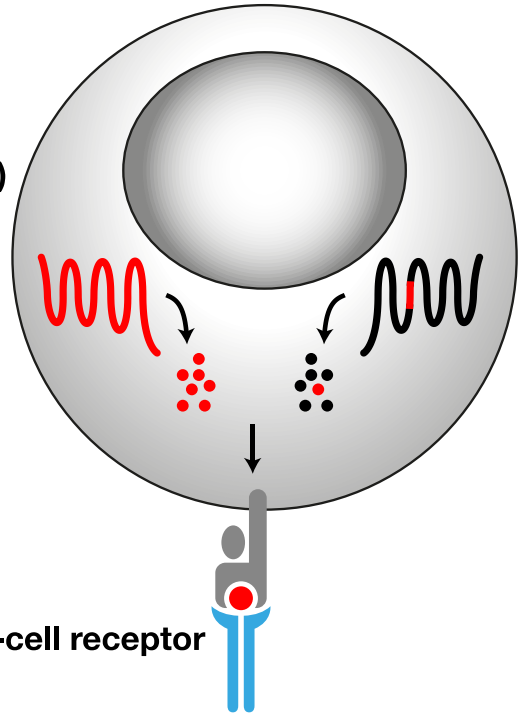
Tumor cell

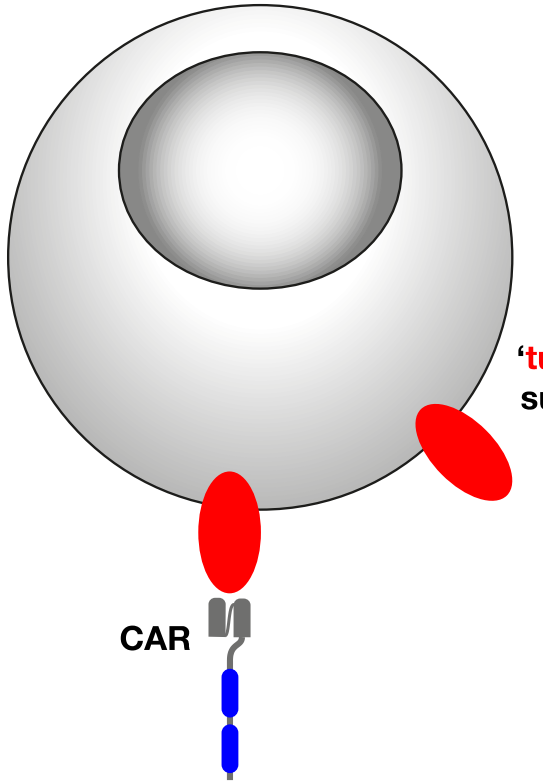
tumor-specific
protein,
peptide
or amino acid (neoantigen)



T-cell

tumor-specific
protein,
peptide
or amino acid (neoantigen)





'tumor-specific'
surface protein

Frequent
Several per tumor cell

Rare
But possible with some
differentiation antigens
on dispensible cells (!)

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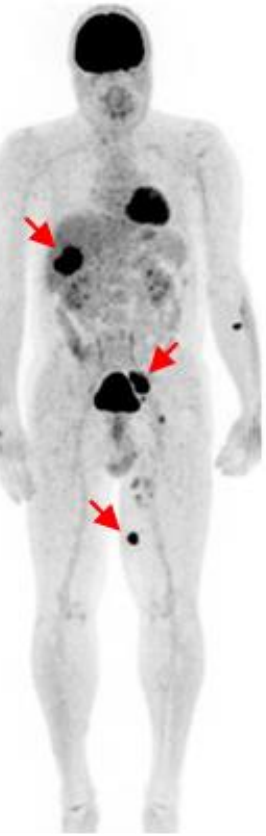
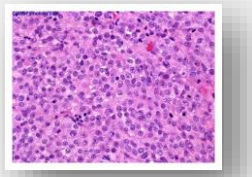
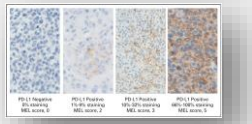
Professor Bart Neyns MD PhD
Head of the Department of Medical Oncology
Universitair Ziekenhuis Brussel
Brussels, Belgium



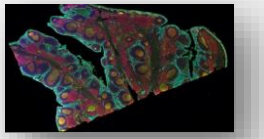
Baseline



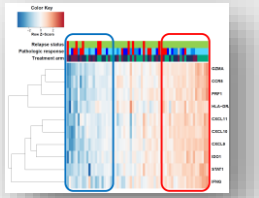
Conventional histopathology



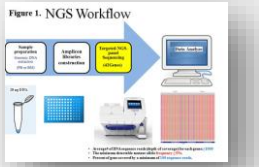
IHC (e.g. PD-L1, CD8+, …)



Multiplex IF



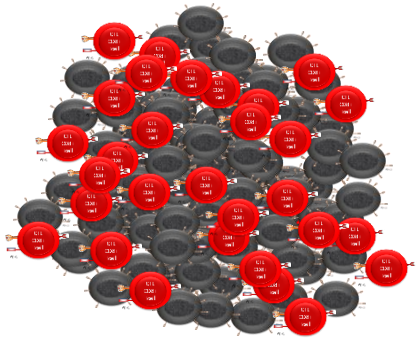
Gene Expression Profiling



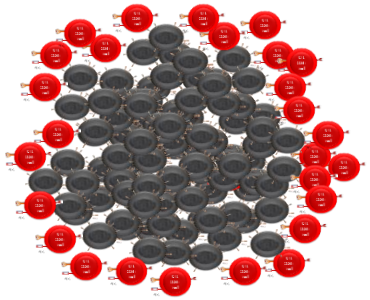
Mutation analysis (TMB)

Immune-cell repertoire

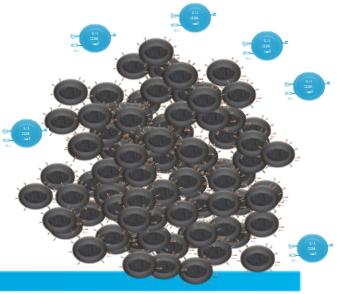
T-Cell Inflammed
Tumor Microenvironment
"Hot Tumor"

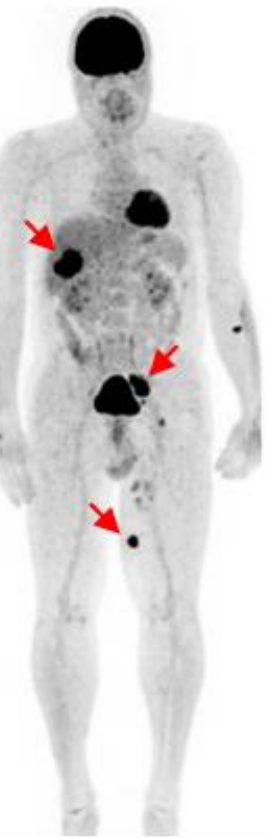


T-Cell Excluded
"Cold Tumor"

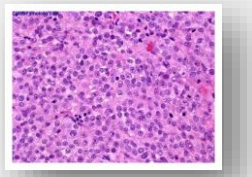


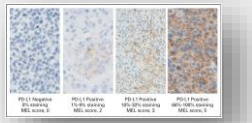
T-Cell Neglected
"Cold Tumor"

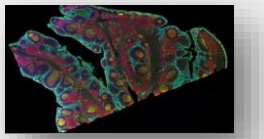


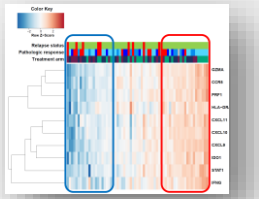


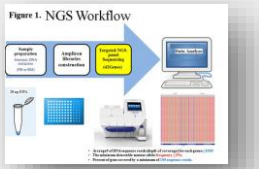
Baseline









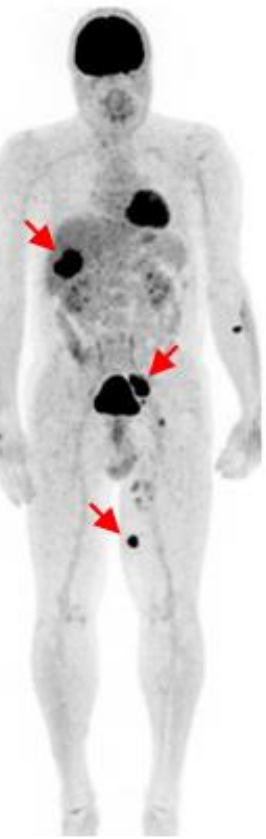


T-Cell Inflammed
Tumor Microenvironment
"Hot Tumor"

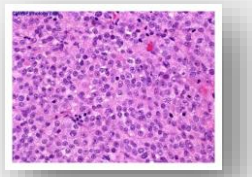
T-Cell Excluded
"Cold Tumor"

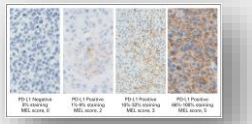
T-Cell Neglected
"Cold Tumor"

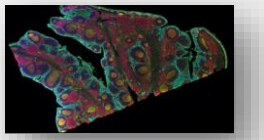
PD-1/PD-L1
As the Unique
"Gatekeeper"

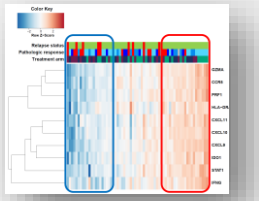


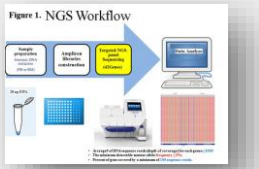
Baseline









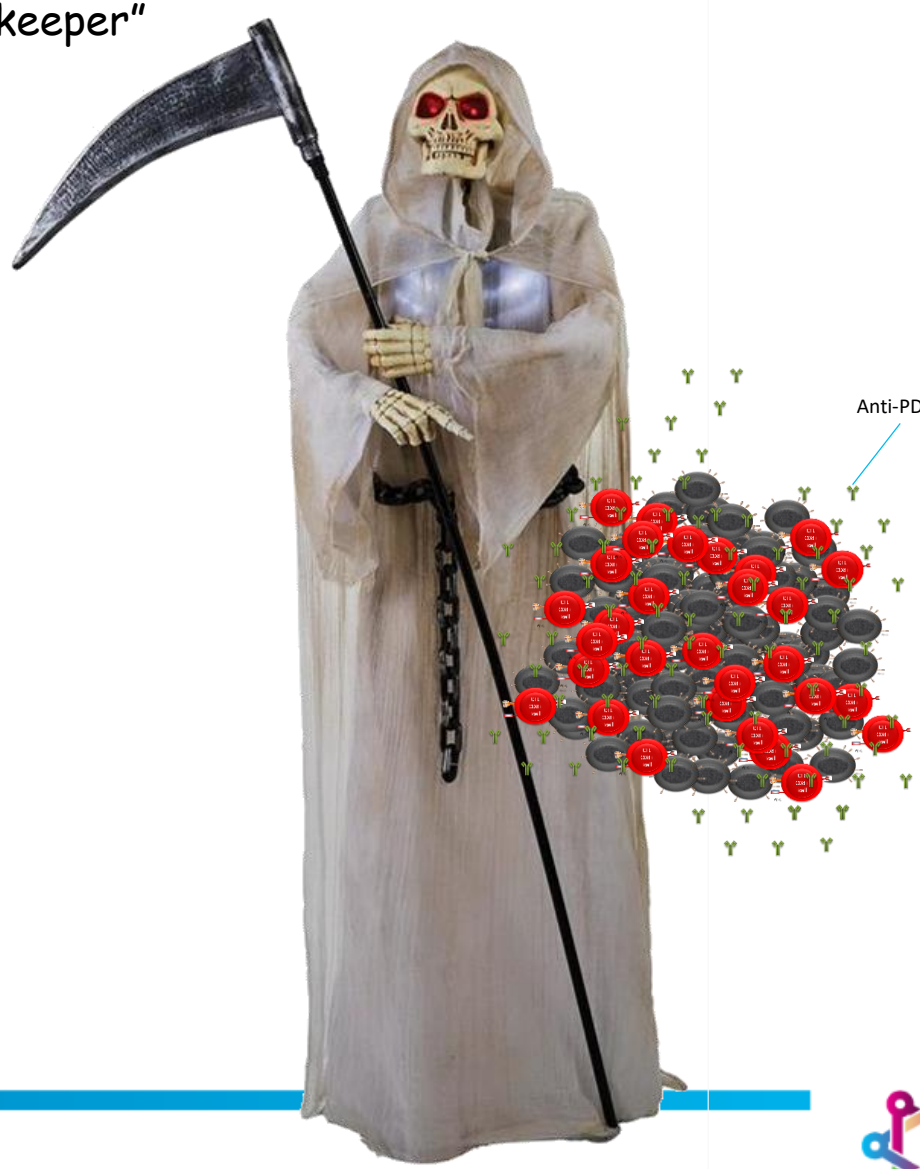


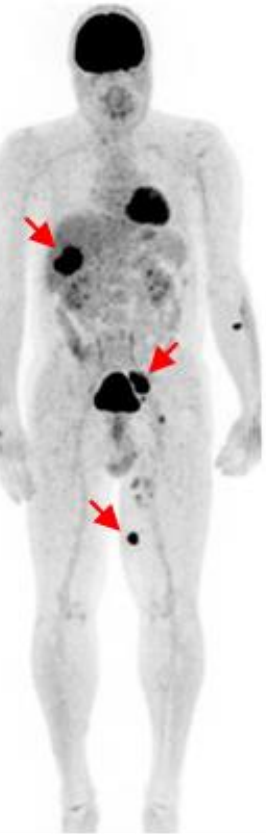
T-Cell Inflammed
Tumor Microenvironment
"Hot Tumor"

T-Cell Excluded
"Cold Tumor"

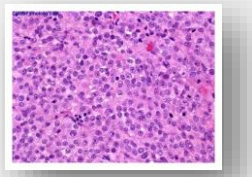
T-Cell Neglected
"Cold Tumor"

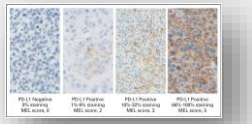
PD-1/PD-L1
As the Unique
"Gatekeeper"

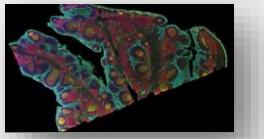


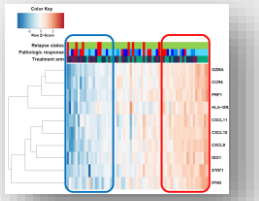


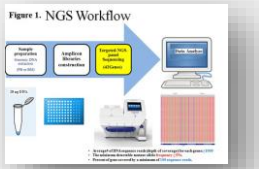
Baseline











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"Cold Tumor"

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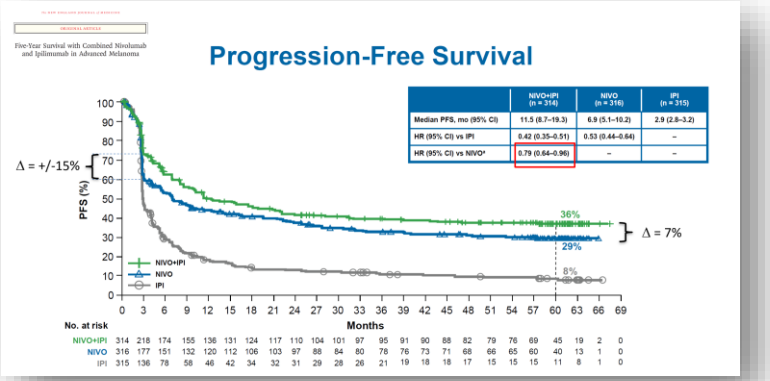
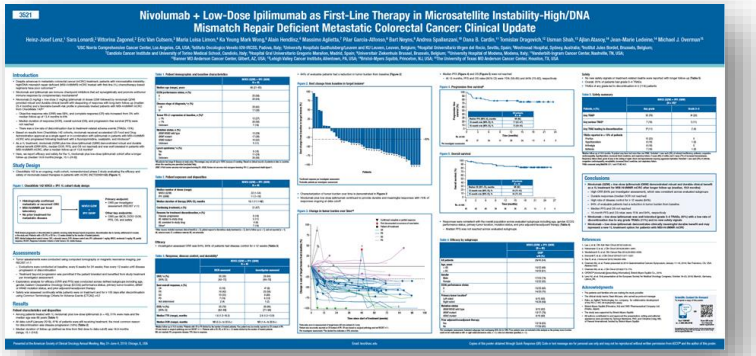
PD-1/PD-L1
As the Unique
"Gatekeeper"

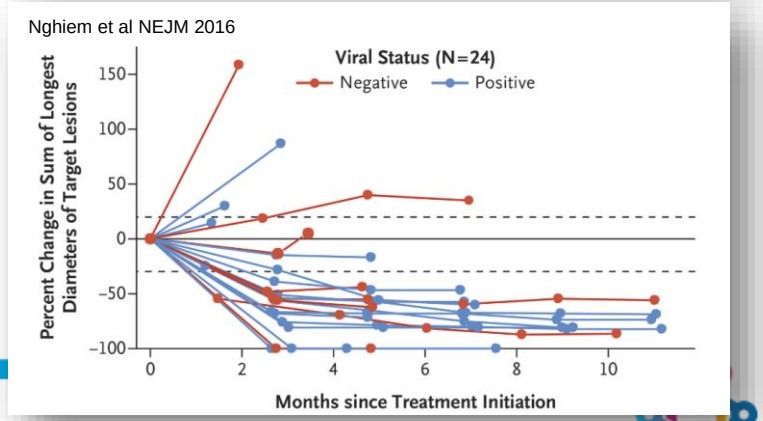
Melanoma

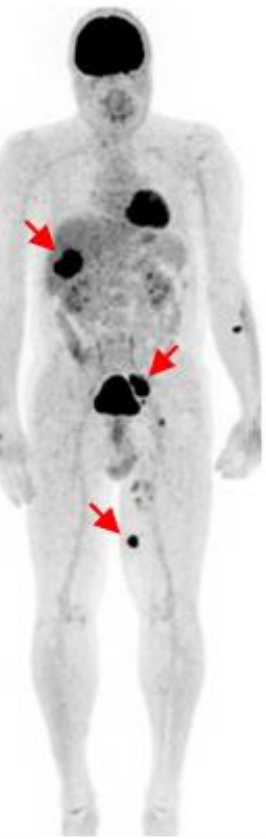


MSI-H CRC

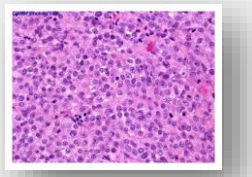


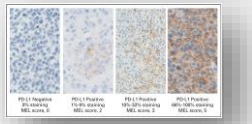
MCC

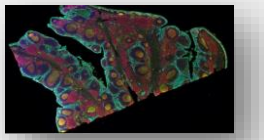


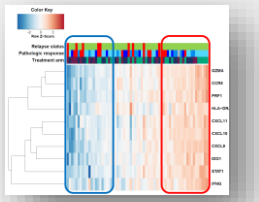


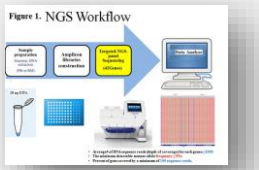
Baseline











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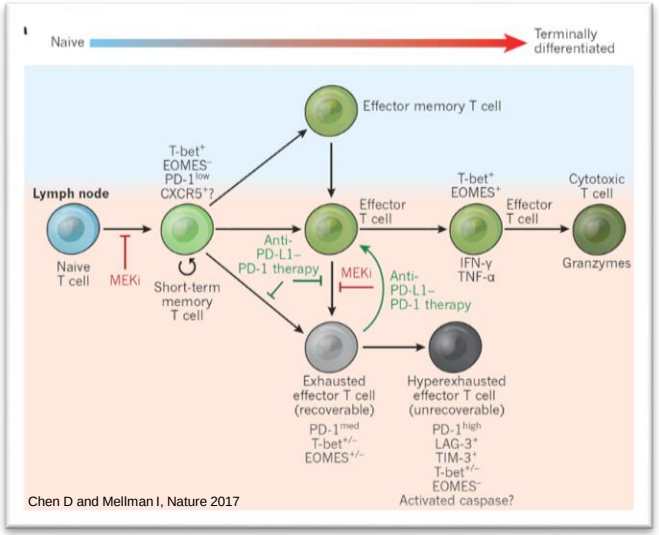
"Cold Tumor"

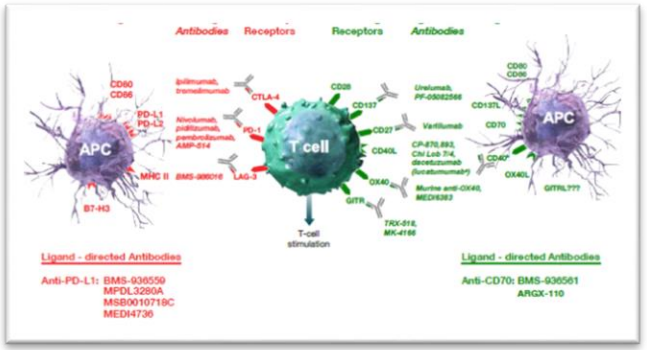
T-Cell Neglected
"Cold Tumor"

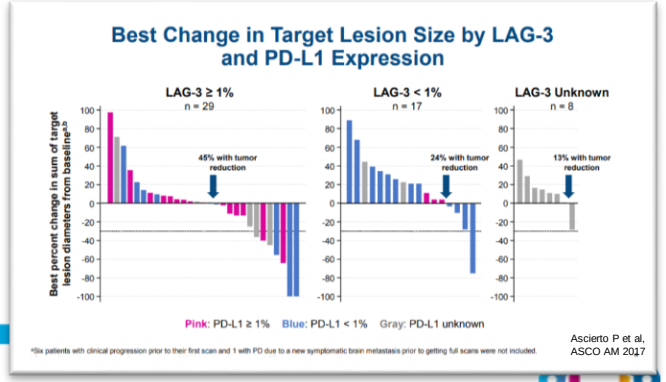
PD-1/PD-L1
As the Unique
"Gatekeeper"

PD-1/PD-L1
Plus additional
ICI

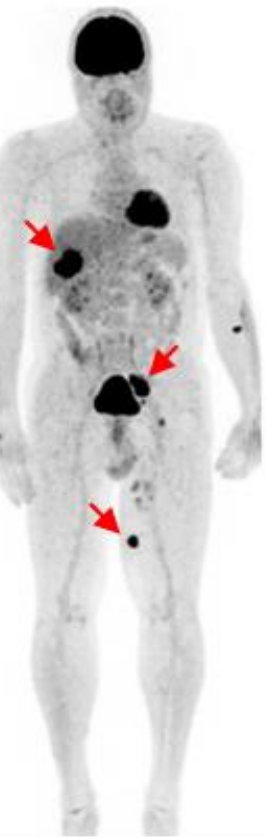


Chen D and Mellman I, Nature 2017

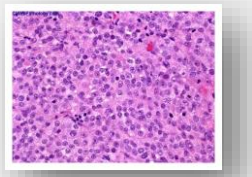


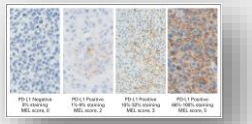


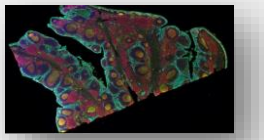
Ascierto P et al, ASCO AM 2017

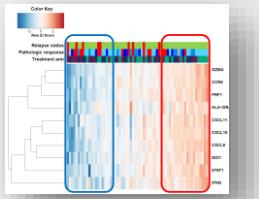


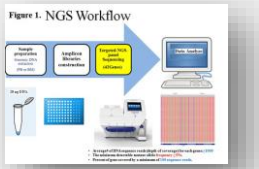
Baseline











T-Cell Inflammed
Tumor Microenvironment
"Hot Tumor"

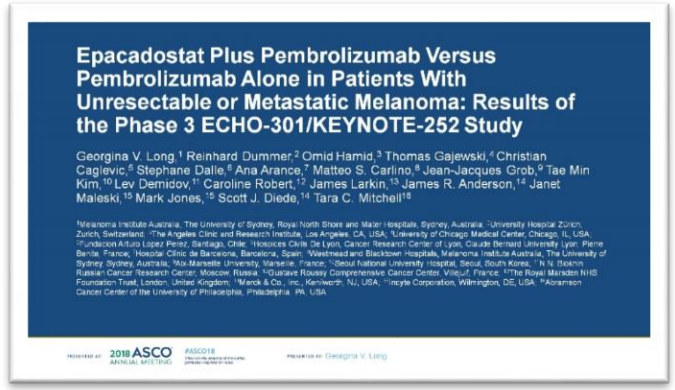
PD-1/PD-L1
As the Unique
"Gatekeeper"

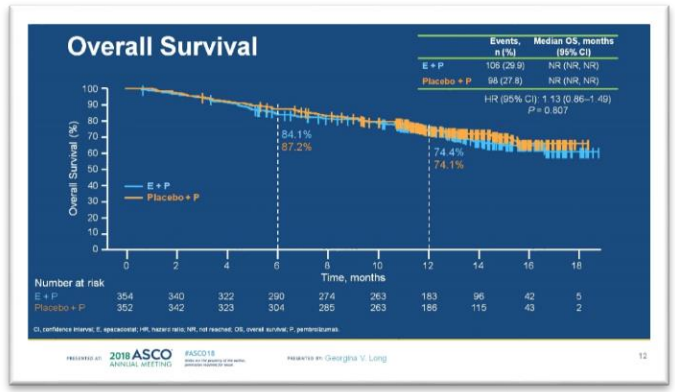
Additional
ICI

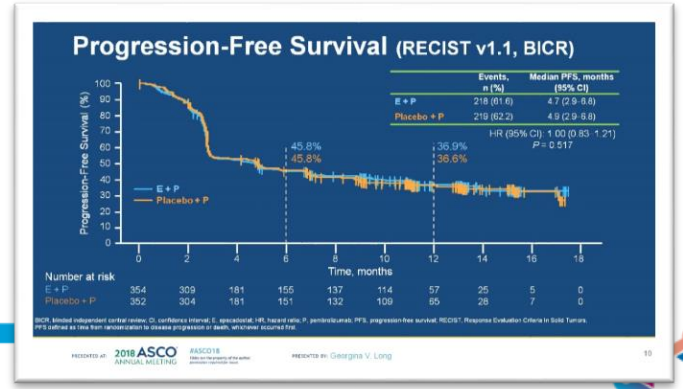
IDO1, Treg, …

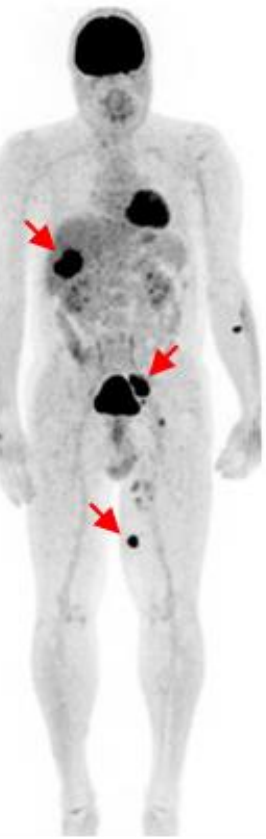
T-Cell Excluded
"Cold Tumor"

T-Cell Neglected
"Cold Tumor"

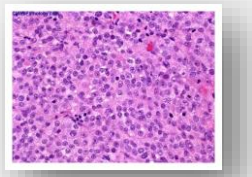


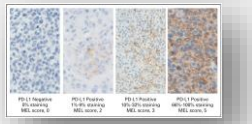


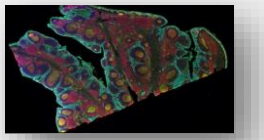


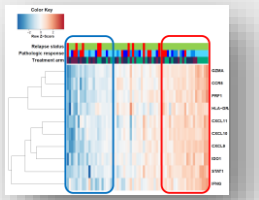


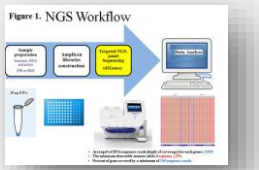
Baseline











T-Cell Inflammed
Tumor Microenvironment
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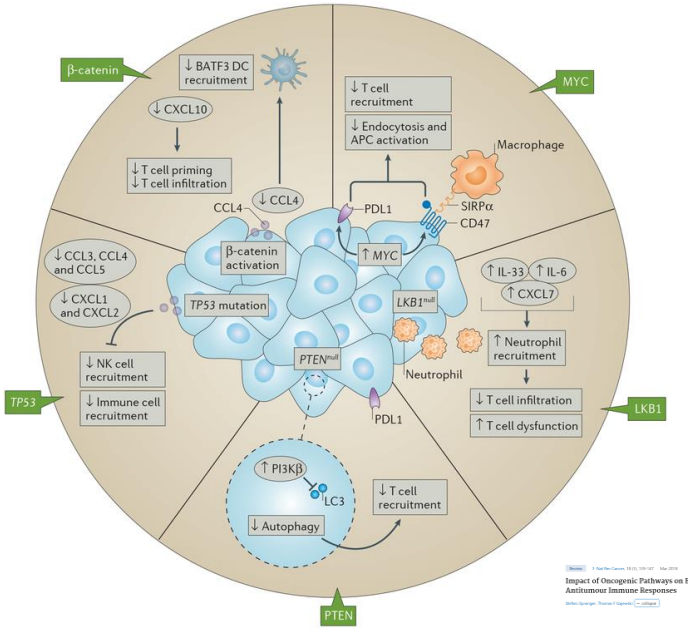
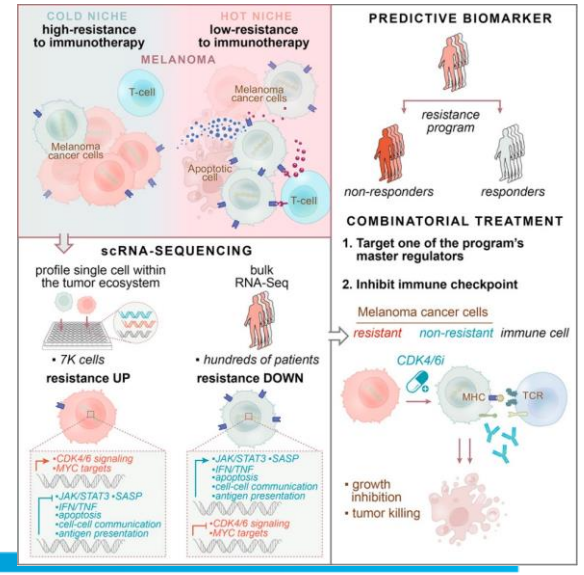
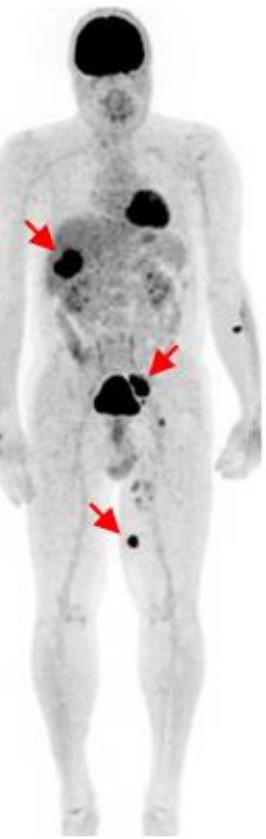
T-Cell Neglected
"Cold Tumor"

Genetic
Oncogenic pathway activation
[Constitutive Resistance to IO]

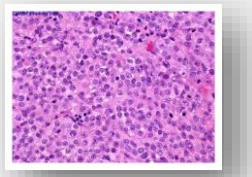
Epigenetic
Tumor transcriptinal program
[Acquired Resistance to IO]

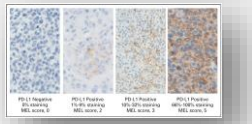


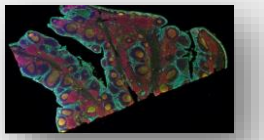


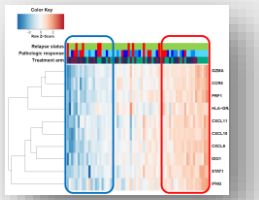


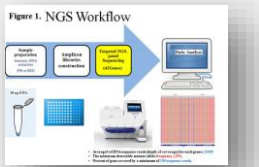
Baseline











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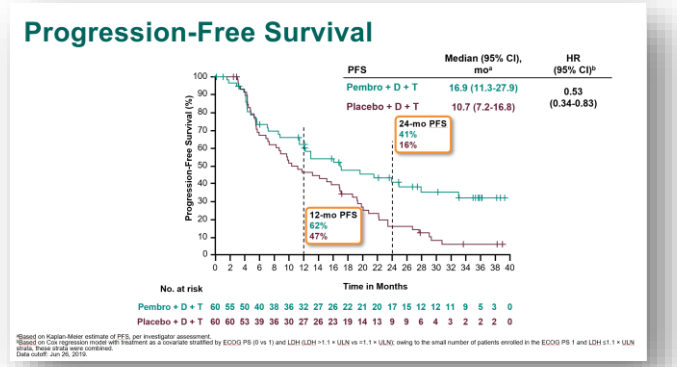
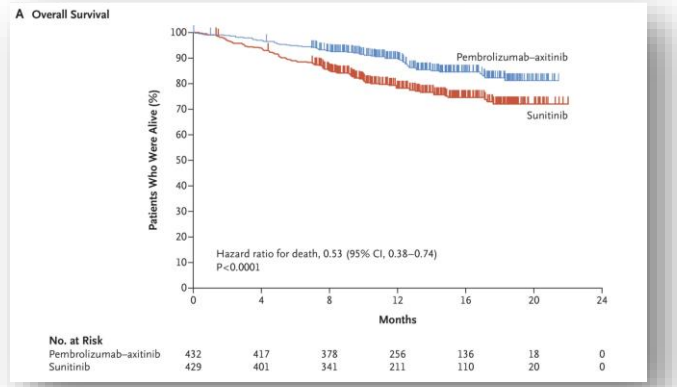
Genetic
Oncogenic pathway activation
[Constitutive Resistance to IO]

Epigenetic
Tumor transcriptinal program
[Acquired Resistance to IO]

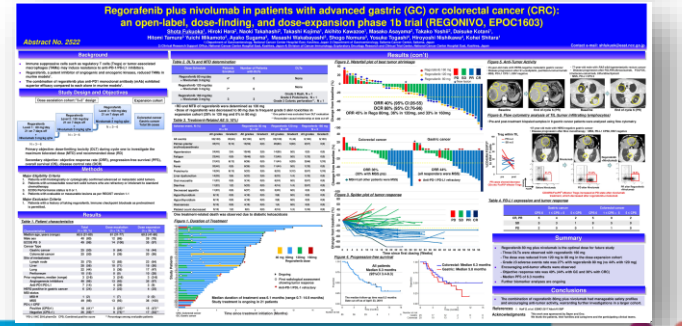
Melanoma



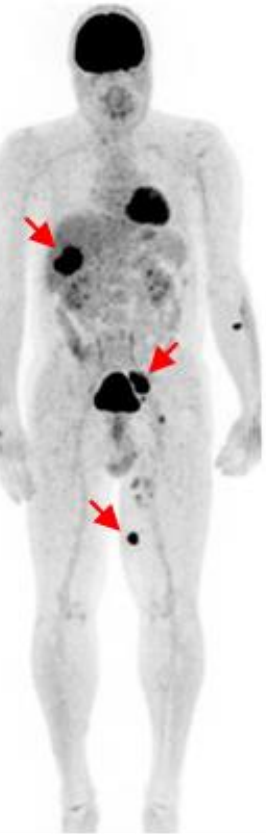
RCC



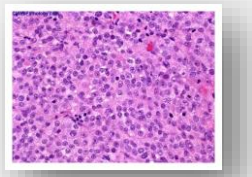
MSS CRC

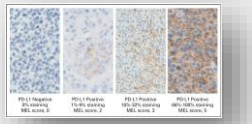


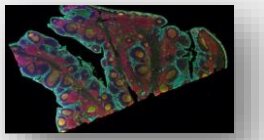
Pier F. Ferrucci et al. SMR AM 2019; Rini et al. NEJM 2019; Fukuoka et al. ASCO AM 2019

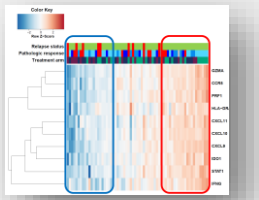


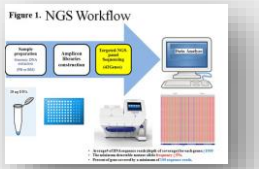
Baseline











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Tumor Microenvironment
"Hot Tumor"

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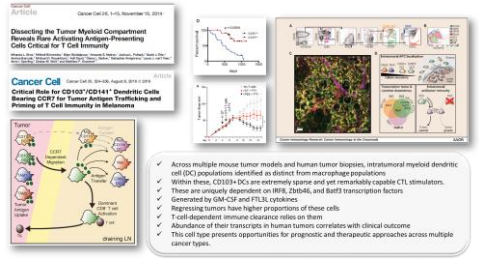
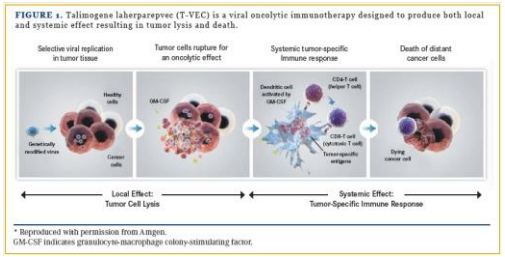
"Cold Tumor"

T-Cell Neglected
"Cold Tumor"

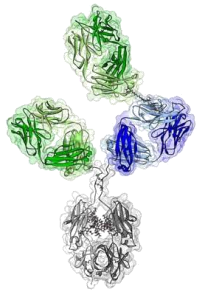


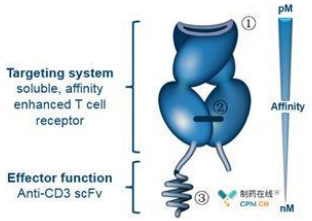
Defective priming

Case Illustration – 80y/o female
PD following pembrolizumab and ipilimumab

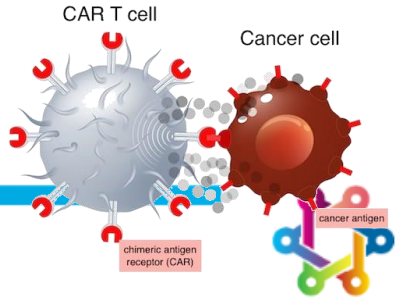


Loss of antigenicity
(Ag-loss, mutations APM-,
Mutations IFN-, STING pathway)





Insufficient foreignness



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Mechanism behind combo superior efficacy

Prof Dr P. Coulie, De Duve Institute UCL Immunology

Rational for combinations: different mechanisms→ less primary or secondary resistance

Almost all resistances have a genetic cause within the tumor cells.

Combination works when the mutations that confer resistances are transmitted independently.

Thus multiple resistant are rare ($10^{-6} \times 10^{-6} = 10^{-12}$ or about 1 kg of tumor)

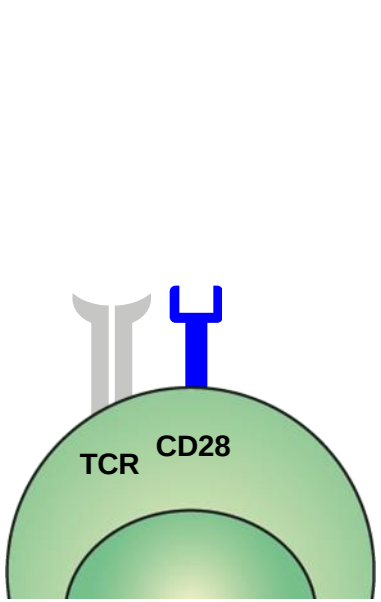
Lymphoid structure

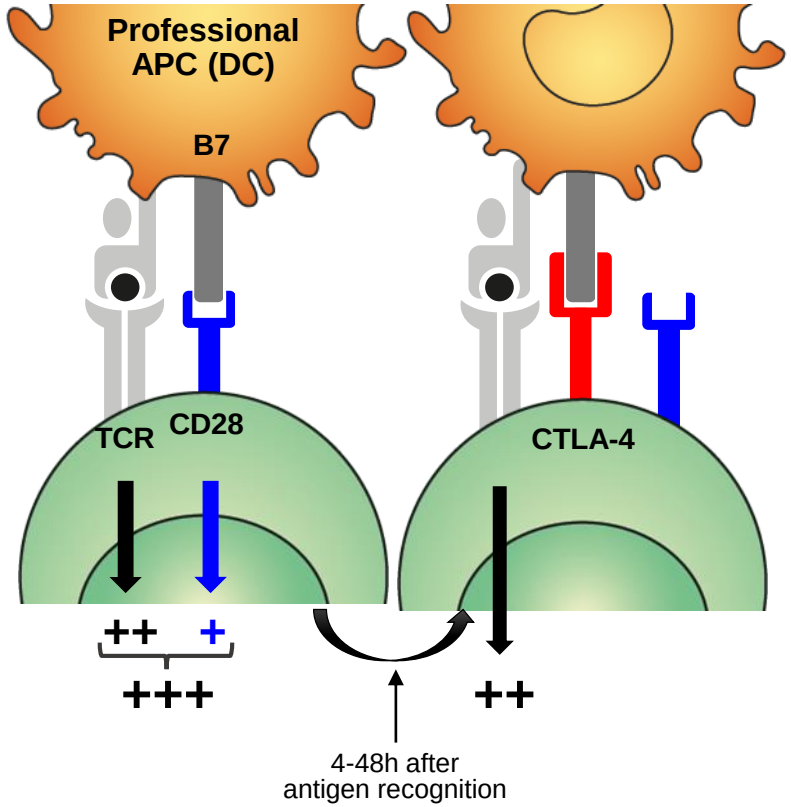
Tumor site

Naive T cell

Priming
(first activation)

Proliferation, differentiation





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Thank you

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