**Σεμινάριο Συνεχιζόμενης Ιατρικής Εκπαίδευσης ΕΕΠΙ&ΜΑ**
**«Ενδιαφέρουσες Εξελίξεις στην Πυρηνική Ιατρική από τα Διεθνή Συνέδρια (EANM, SNMMI, RSNA) – Highlights 2020»**

Αθήνα – Ερρίκος Ντυνάν Hospital Center | Σάββατο, 8 Φεβρουαρίου 2020



# *Ανοσοθεραπεία – Απεικόνιση με τεχνικές Π.Ι.*

Άννα Πασχάλη
Επιμ.Β' Πυρηνικής Ιατρικής
Α.Ν.Θ. "Θεαγένειο"

1800s
Surgery

1900s
Radiation

1940s
Chemotherapy

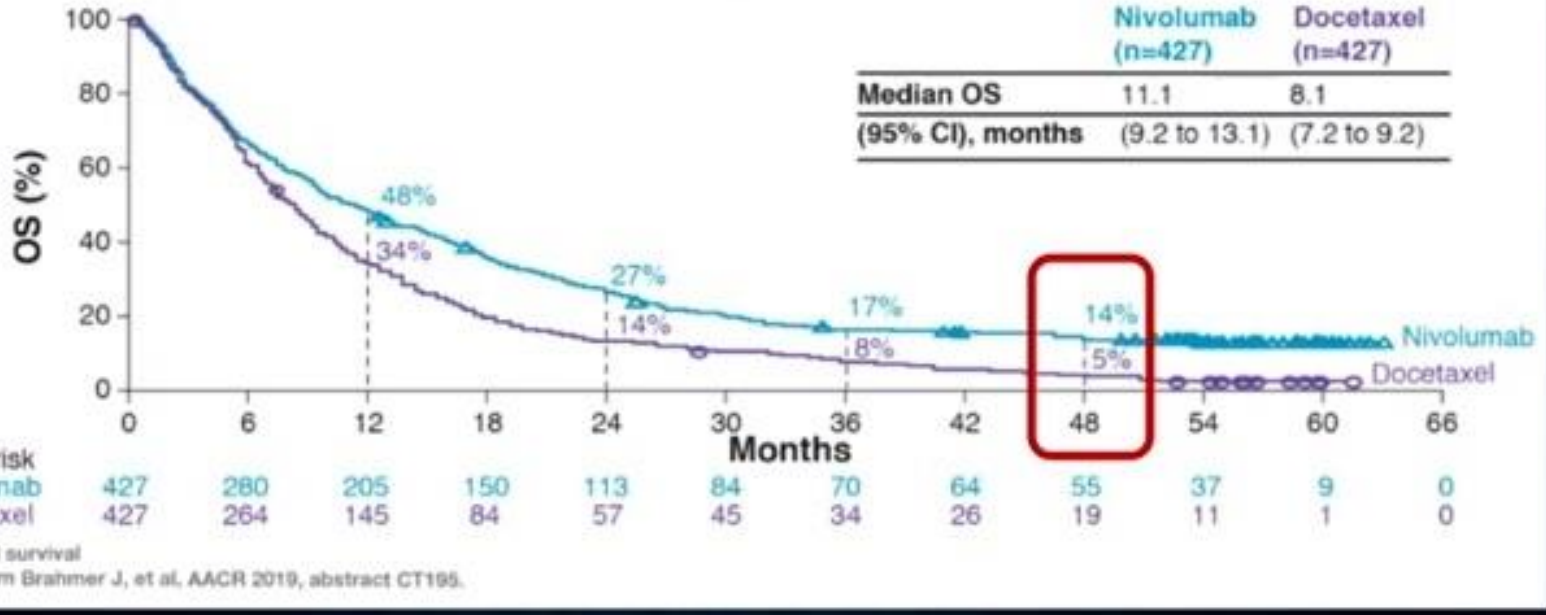
2000s
Targeted Drugs

Today
Immunotherapy

IMMUNO-ONCOLOGY

# LONG TERM SURVIVAL

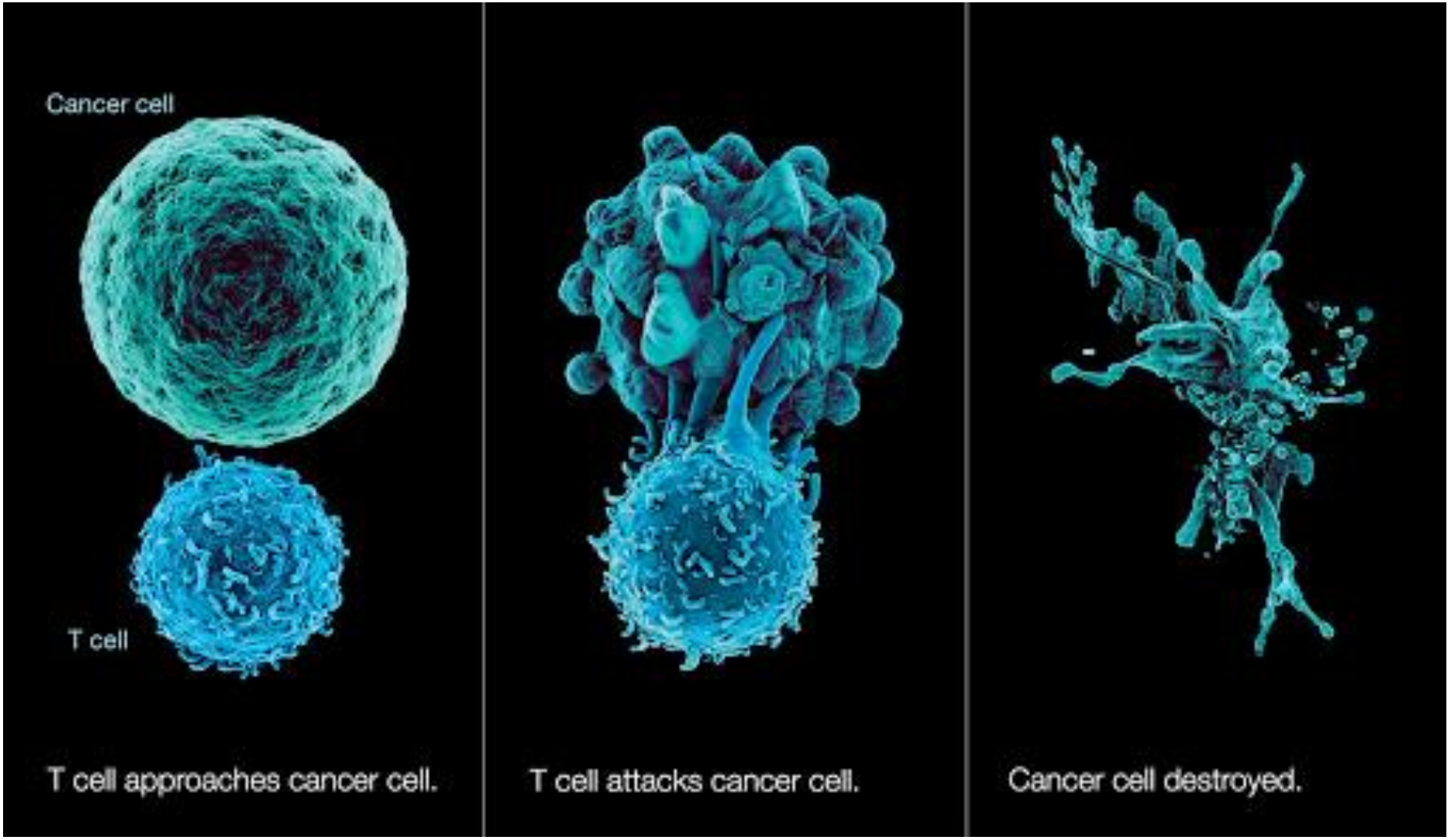
**Figure 2. Pooled analysis of CheckMate 017 and 057 trials: Overall survival**




| | Nivolumab (n=427) | Docetaxel (n=427) |
|---|---|---|
| Median OS | 11.1 | 8.1 |
| (95% CI), months | (9.2 to 13.1) | (7.2 to 9.2) |

OS = overall survival
Adapted from Brahmer J, et al. AACR 2019, abstract CT195.

Brahmer et al. AACR 2019

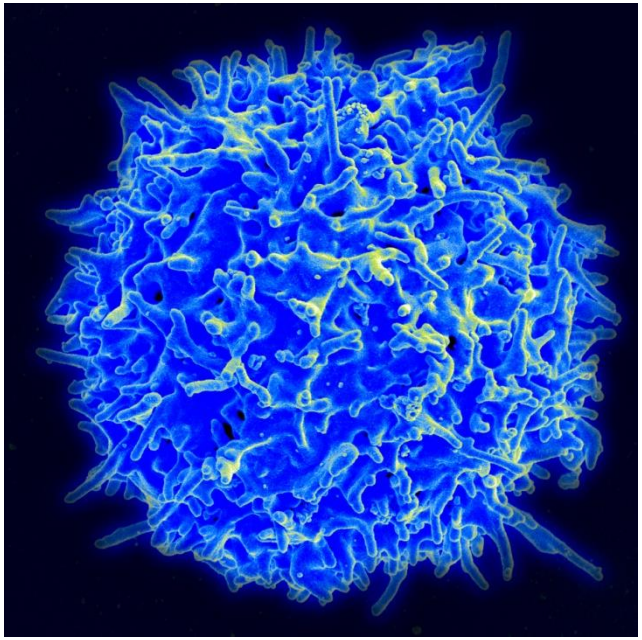

Cancer cell
T cell
T cell approaches cancer cell.
T cell attacks cancer cell.
Cancer cell destroyed.

JANUARY 22, 2020

Share:

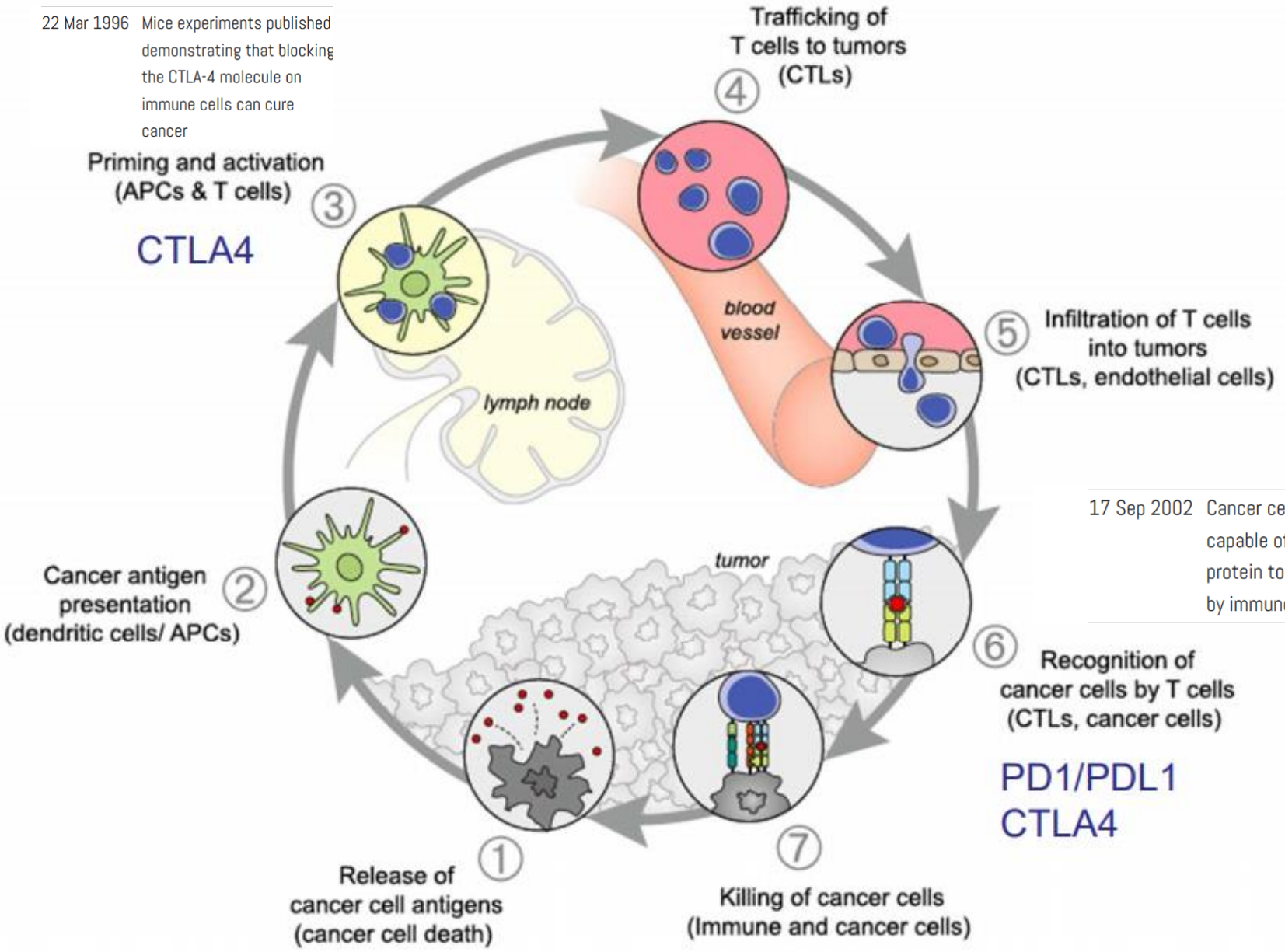
# Remarkable new T-cell discovery can kill several cancer types in the lab

*Researchers have discovered a new type of immune cell receptor that could potentially be used to develop an innovative T-cell cancer therapy. Preliminary results using mice and human cells have been promising. In T-cell therapy, the most common form is CAR-T, where the natural function of T-cells is strengthened to guide them towards tumor cells.*



# Cancer immunity cycle

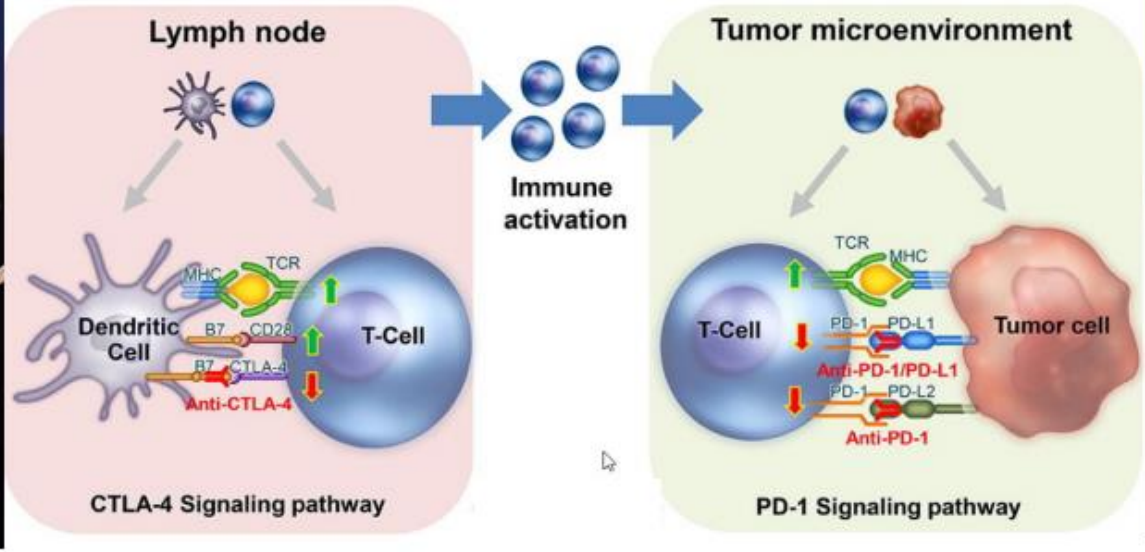
22 Mar 1996 Mice experiments published demonstrating that blocking the CTLA-4 molecule on immune cells can cure cancer




17 Sep 2002 Cancer cells shown to be capable of hijacking PD-1 protein to evade destructior by immune system

**James P. Allison**
**University of Texas MD Anderson Cancer Center**

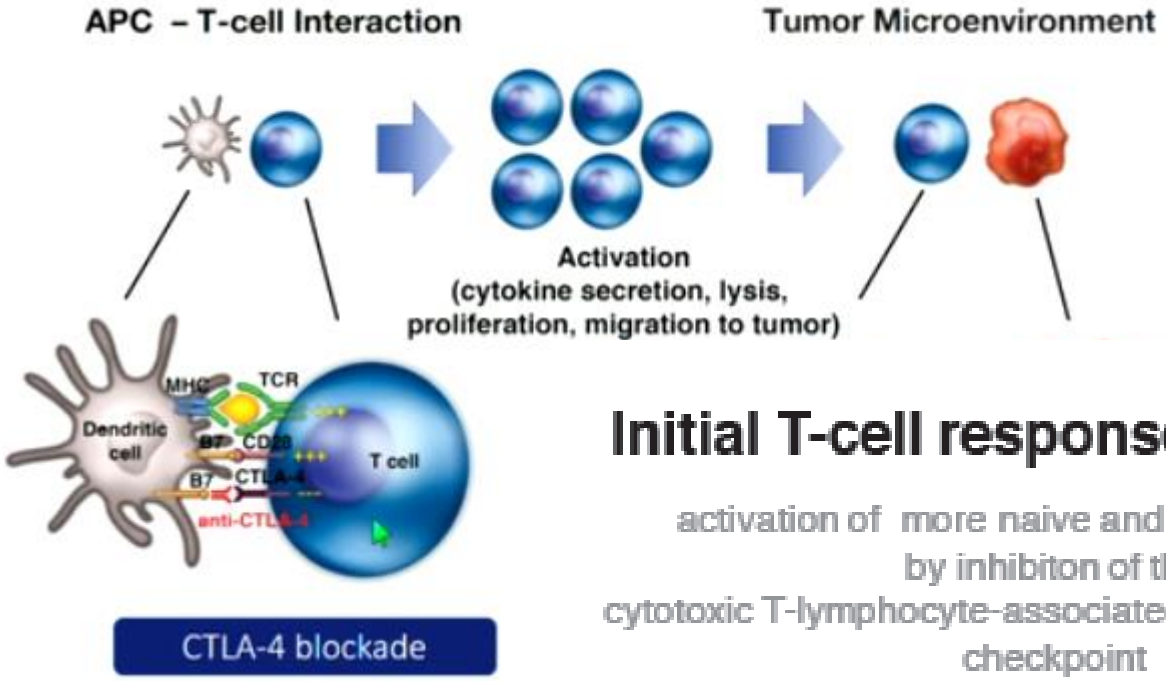
**Tasuku Honjo**
**Kyoto University in Japan**




**«For their discovery of a revolutionary approach to cancer treatment» Nobel Committee, Stockholm, October 1 2018**

# Immune Checkpoint Inhibitors (ICIs)

| | | | |
|---|---|---|---|
| 25 Mar 2011 | First immune checkpoint inhibitor drug targeting CTLA4 (ipilimumab, Yervoy®), approved by the FDA | Allison | Medarex, University of California Berkley |




## Initial T-cell response to antigen

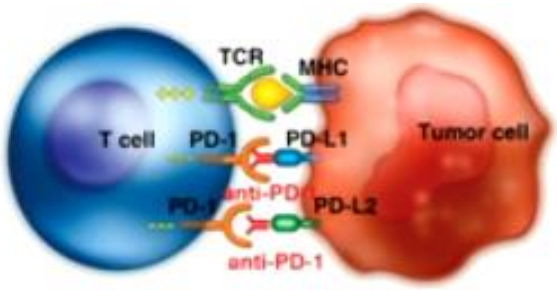
activation of more naive and memory T-cells
by inhibiton of the
cytotoxic T-lymphocyte-associated antigen 4 (CTLA4)
checkpoint

# Immune Checkpoint Inhibitors (ICIs)

| | | | |
|---|---|---|---|
| 22 Dec 2014 | First immune checkpoint inhibitor drug targeting PD-1 approved in US | Honko, Freeman, Lonberg | Medarex, Bristol-Myers Squibb, Ono Pharmaceutical, Kyoto University |

## Regulation of T-cell activity

activation of the immune response
by inhibition of
programmed cell death protein 1 (PD1) and
PD-Liganten 1 and 2 (PDL1,PDL2) checkpoints




**PD1- blockade:**
-pembrolizumab (Keytruda)
- nivolumab (Opdivo)

**PDL1 –blockade:**
-atezolizumab (Tecentriq)
-avelumab (Bavencio)
-durvalumab (Imfinzi)

# U.S. FDA Approved Immune-Checkpoint Inhibitors[1-7]

**Squamous Cell Head & Neck Cancer**
1L/2L after platinum chemotherapy:
- nivolumab or pembrolizumab

**Malignant Melanoma**
Adjuvant ipilimumab, nivolumab, or pembrolizumab
1L ipilimumab, nivolumab, or pembrolizumab
1L combination nivolumab + ipilimumab

**Merkel Cell Carcinoma**
2L avelumab or pembrolizumab

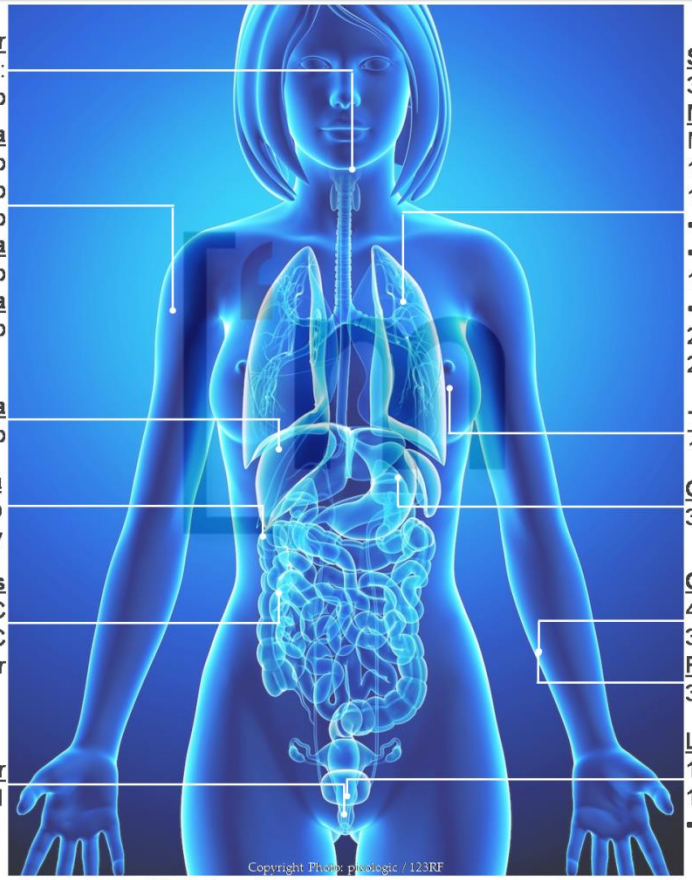
**Cutaneous Squamous Cell Carcinoma**
1L cemiplimab

**Hepatocellular Carcinoma**
2L nivolumab or pembrolizumab after sorafenib

**Adv. Renal Cell Carcinoma**
1L nivolumab plus ipilimumab
2L nivolumab after anti-angiogenic therapy

**MSI-H or dMMR Cancers**
2L nivolumab in CRC
2L nivolumab plus ipilimumab in CRC
2L pembrolizumab in any MSI-H/dMMR cancer

**Cervical Cancer**
2L pembrolizumab CPS≧1




**Small Cell Lung Cancer**
3L nivolumab

**Non-Small Cell Lung Cancer**
Maintenance durvalumab after chemoradiation
1L pembrolizumab TPS≧50%
1L *non-squamous* NSCLC
- pembrolizumab + pemetrexed & platinum-salt
- atezolizumab + bevacizumab, paclitaxel & carboplatin

1L *squamous* NSCLC
- pembrolizumab + carboplatin & (nab-)paclitaxel in

2L pembrolizumab TPS≧1%
2L atezolizumab or nivolumab

**Triple-Negative Breast Cancer**
1L atezolizumab + paclitaxel protein-bound PD-L1≧1%

**Gastric & GEJ Carcinoma**
3L pembrolizumab CPS≧1

**Classical Hodkin Lymphoma**
4L pembrolizumab
3L/4L nivolumab after auto-HSCT and BV

**PMBCL**
3L pembrolizumab

**Locally Adv. or Met. Urothelial Cancer**
1L/2L pembrolizumab,
1L/2L after platinum salt:
- atezolizumab, avelumab, durvalumab, or nivolumab

Updated on 09-Mar-2019 - citations on last page - 

# Immune Checkpoint Inhibitors (ICIs)

**Δεδομένα:**

✓Ανταπόκριση μόνο σε υποομάδες ασθενών.

✓Ανταπόκριση σε μικρό σχετικά ποσοστό σε κάθε ιστολογικό τύπο.

✓Δεν υπάρχουν ακριβείς δείκτες ως προς την επιλογή των ασθενών που θα ωφεληθούν από την θεραπεία.

✓Παρενέργειες (irAEs)


✓Θεραπεία υψηλού κόστους

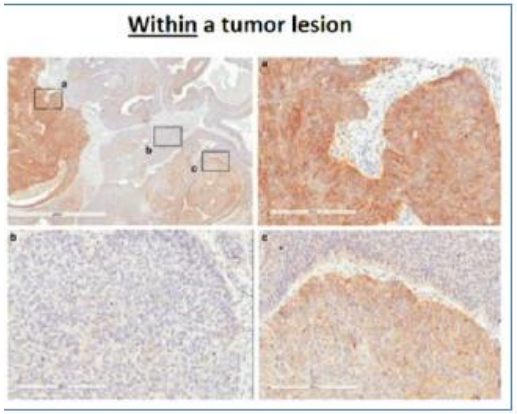
"$100,000 per year," "Combine drugs and it's over $200,000 per year."

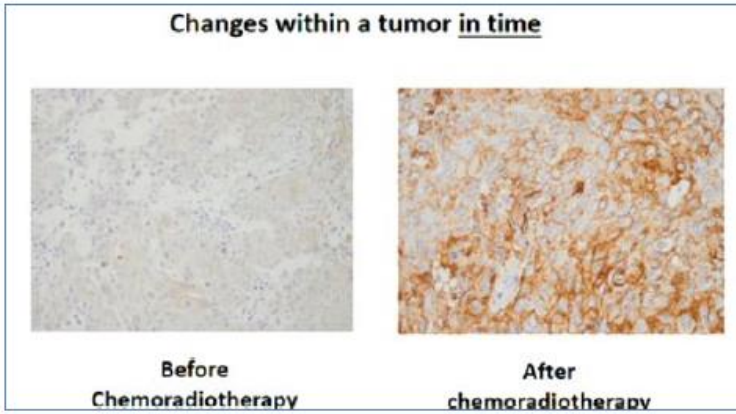
# Immune Checkpoint Inhibitors (ICIs)

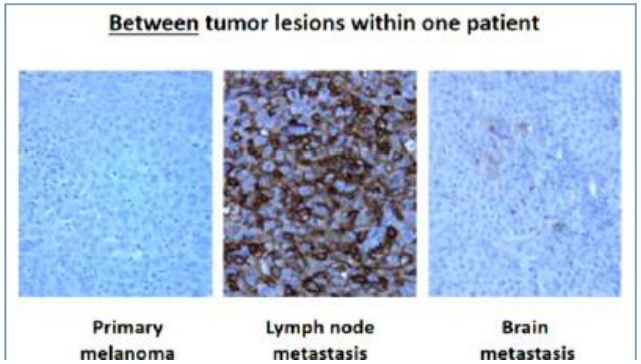
**Προκλήσεις:**

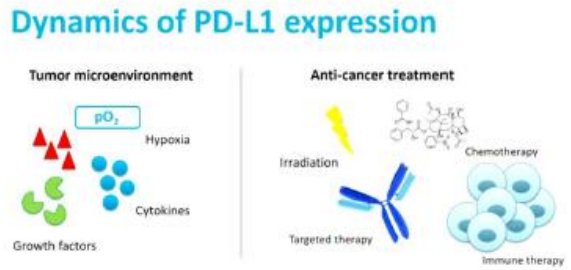
->Σωστή επιλογή των ασθενών που θα λάβουν ICIs

**Heterogeneous PD-L1 expression**




-> Απεικονιστική εκτίμηση της ανταπόκρισης.

## CME 7 Session - EANM'19

EANM Meeting Barcelona 2019 - Imaging immune therapy

**Imaging of Immunological targets**

Wolfgang Weber, MD
Technical University Munich
School of Medicine
Department of Nuclear Medicine

### Imaging Immune Therapy

**Lecture 1**

Wolfgang Weber (Munich, Germany): Imaging of Immunological Targets

**Lecture 2**

Caroline Bodet-Milin (Nantes, France): Current State of Imaging in Assessment of Immunotherapy

**Lecture 3**

Margret Schottelius (Garching, Germany): Emerging Imaging Concepts in Immuno-Oncology

Current state of PET imaging for the assessment of check-points inhibitors therapy

Caroline Bodet-Milin, Nantes, France

Emerging Imaging Concepts in Immuno-Oncology

Margret Schottelius

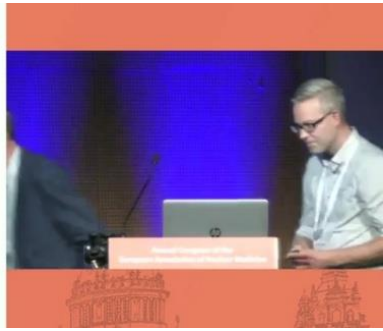
Translational Radiopharmaceutical Sciences
Department of Nuclear Medicine and Molecular Imaging (CHUV) and Department of Oncology (UNIL)
Centre Hospitalier Universitaire Vaudois and University of Lausanne, Switzerland


## Teaching Session 2 - EANM'19

### Imaging of Immune Cells

**Introduction**

Peter Laverman (Nijmegen, Netherlands)

**Lecture 1**

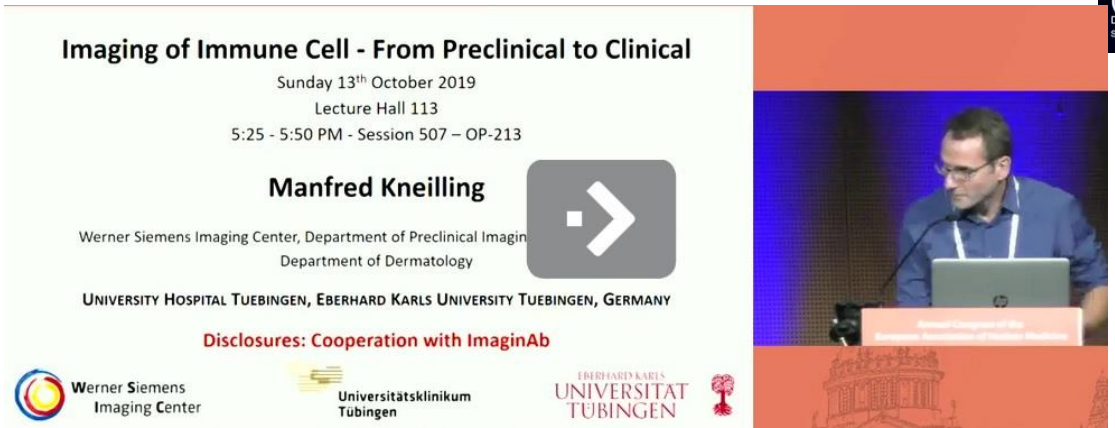
Erik Aarntzen (Nijmegen, Netherlands): Basics of Immune Cells – Expression, Role and Targeting Possibilities

**Lecture 2**

Rafael Torres Martin De Rosales (London, United Kingdom): Methods for Immune Cell Radiolabeling


**Lecture 3**

Manfred Kneilling (Tübingen, Germany): Imaging of Immune Cell - From Preclinical to Clinical

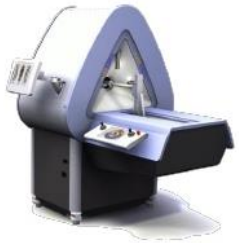


# Εξελίξεις στην απεικόνιση με PET & SPECT στην Ανοσοθεραπεία του καρκίνου

Pre-clinical

**microPET/CT and microSPECT/CT**
(Nuclear Medicine)

microPET/CT



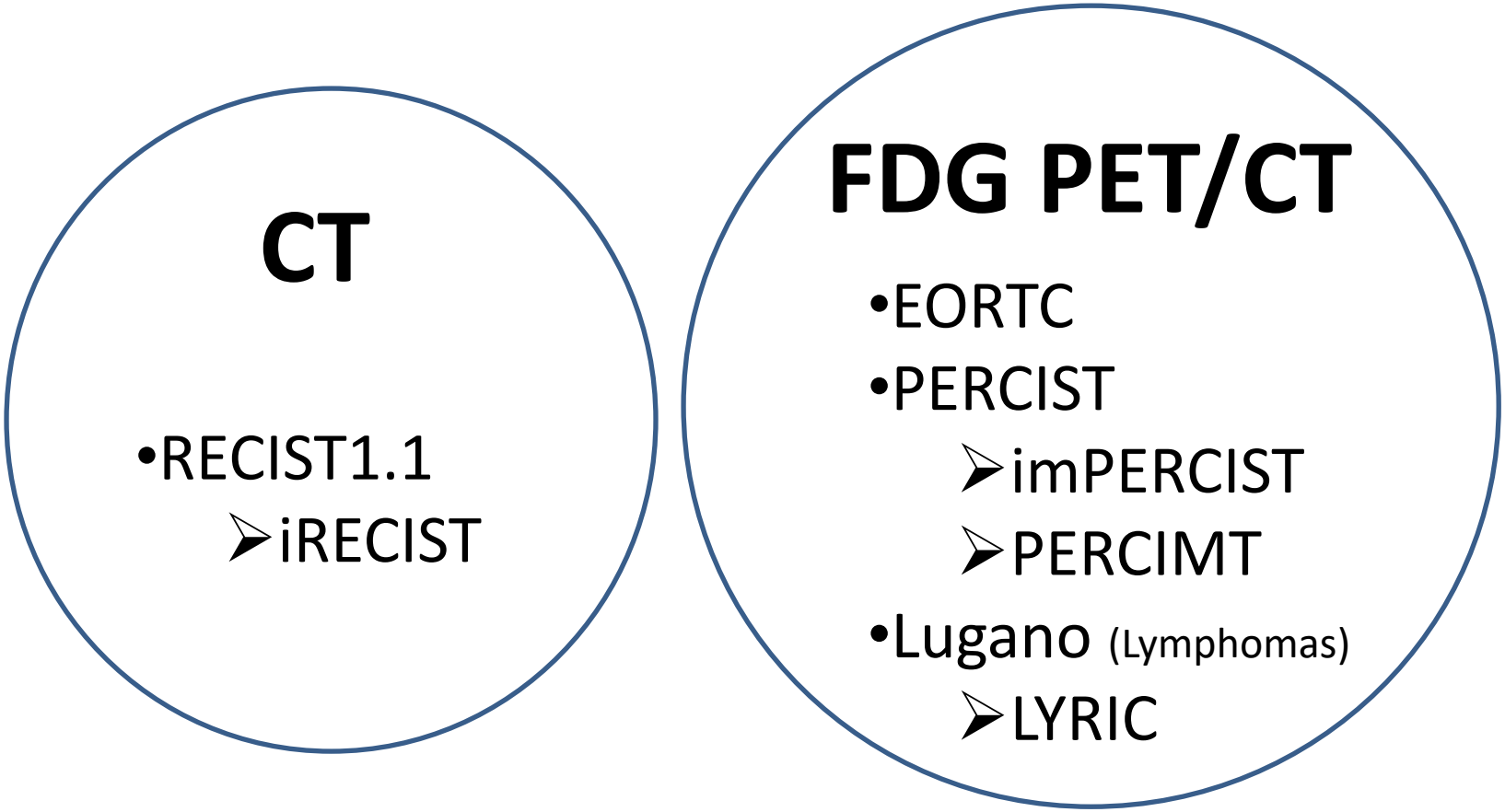
microSPET/CT

Clinical Translation

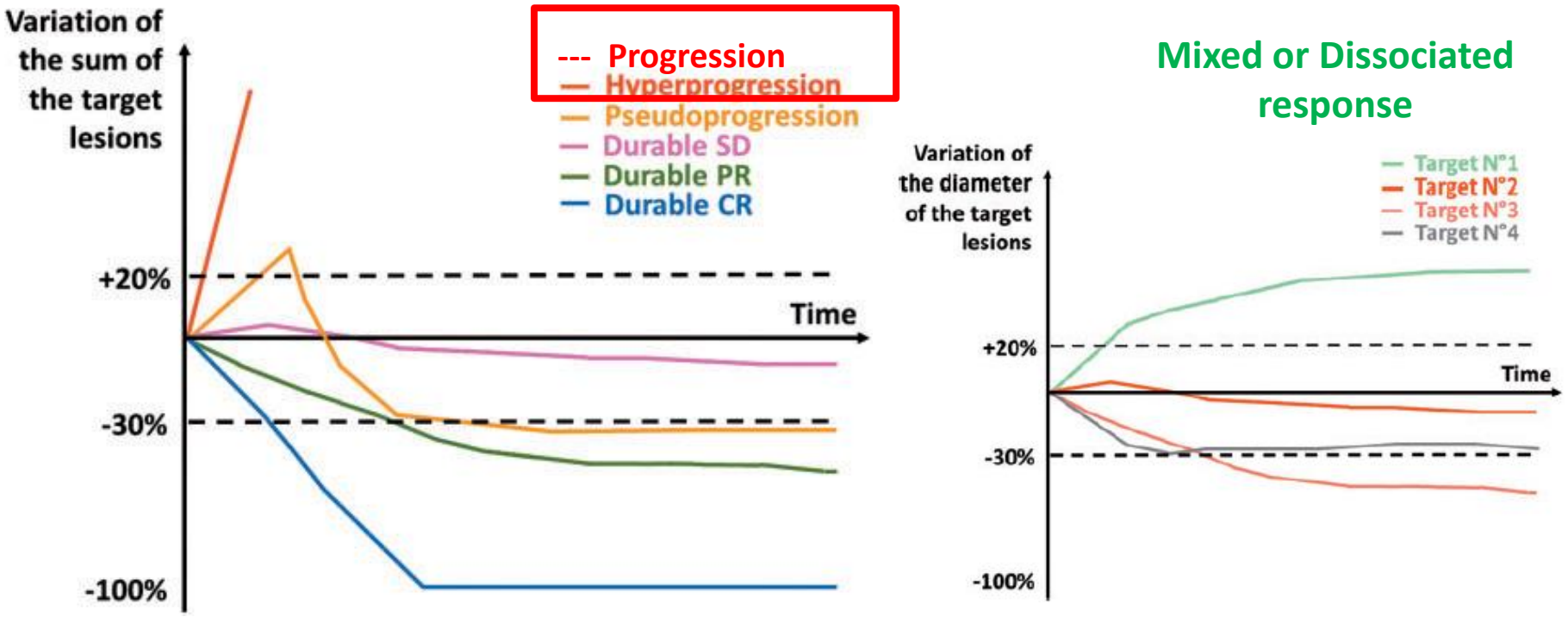
Clinical

# Clinical data

✓Απεικονιστικά κριτήρια εκτίμησης ανταπόκρισης στην Ανοσοθεραπεία



# Novel patterns of response under ICIs




*Annals of Oncology* 0: 1–12, 2019
doi:10.1093/annonc/mdz003
Published online 18 January 2019

FEATURED ARTICLE OF THE MONTH

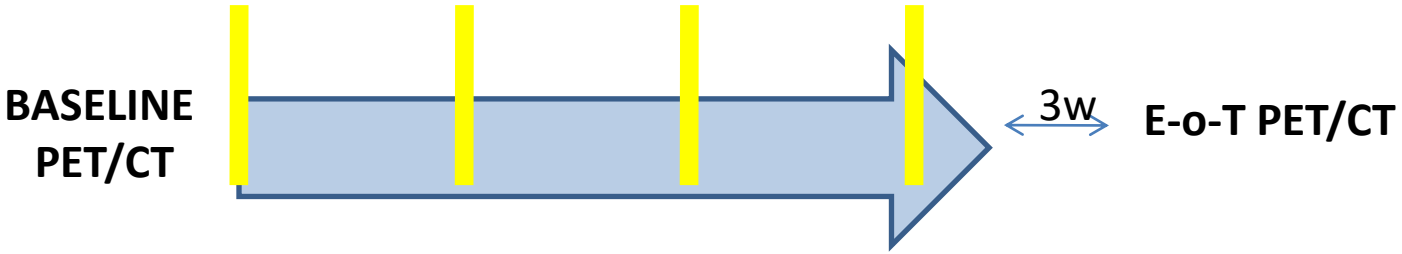
# $^{18}$F-FDG PET/CT for Monitoring of Ipilimumab Therapy in Patients with Metastatic Melanoma

IPILIMUMAB RESPONSE USING IMPERCIST • Ito et al.

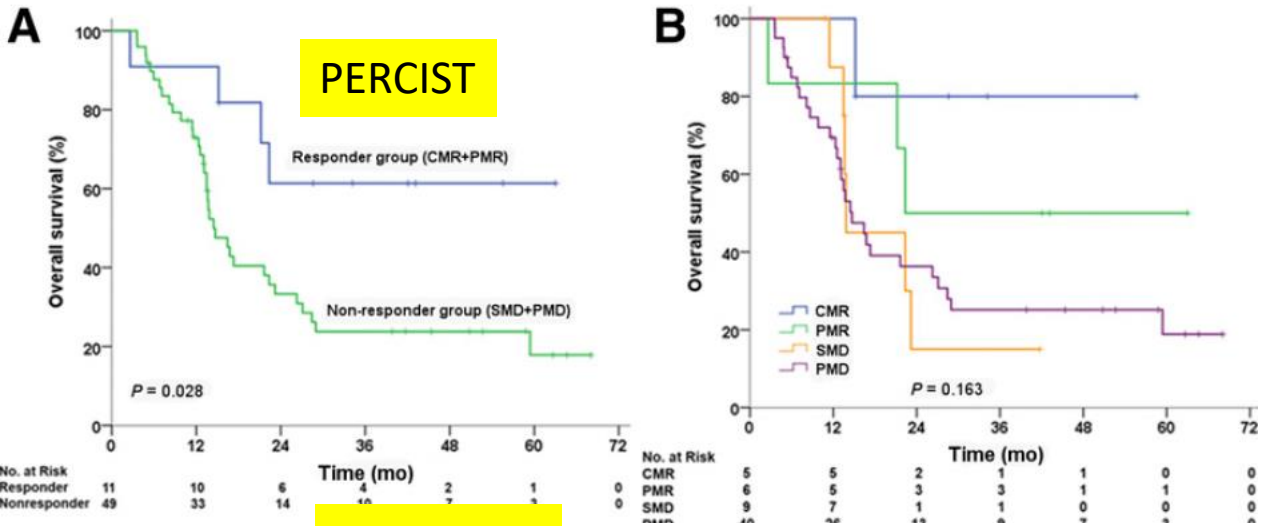
*Memorial Sloan Kettering Cancer Center, New York,*

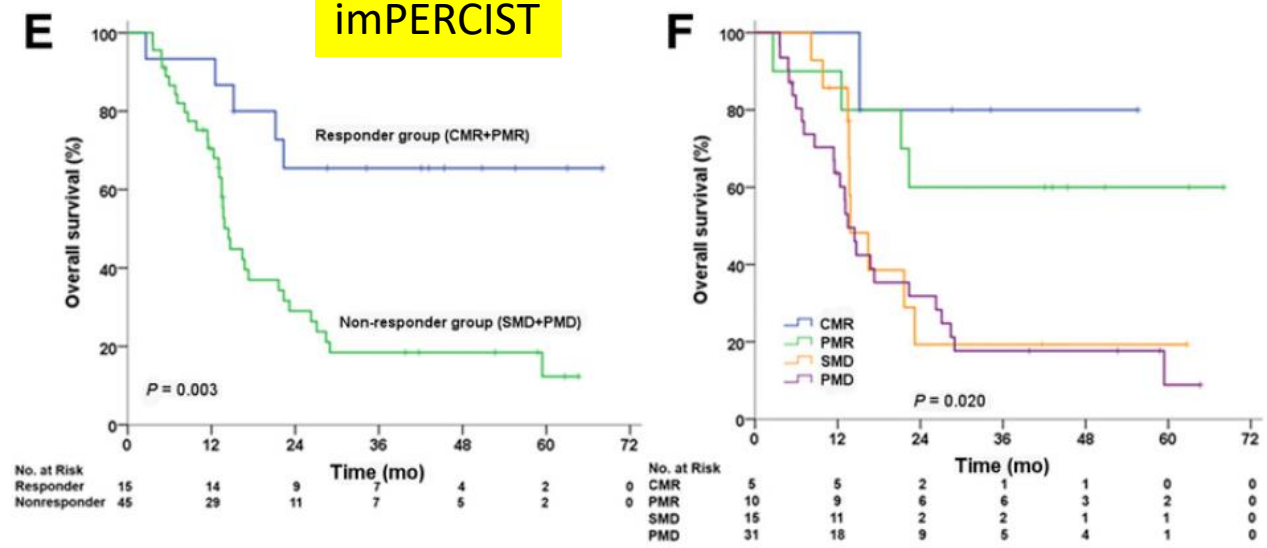
J Nucl Med 2019; 60:335–341

✓60 patients with metastatic melanoma treated with ipilimumab




| | PERCIST | imPERCIST |
|---|---|---|
| PMD | sum of SULpeak5 >30% **or** new lesions | sum of SULpeak5 >30% |




✓Pseudoprogression ~2%

✓In most patients, the appearance of new lesions was associated with progression and poor prognosis.

PET/CT is a good method for immune therapy response assessment

Eur J Nucl Med Mol Imaging (2018) 45:376–383
https://doi.org/10.1007/s00259-017-3870-6

ORIGINAL ARTICLE

# Absolute number of new lesions on $^{18}$F-FDG PET/CT is more predictive of clinical response than SUV changes in metastatic melanoma patients receiving ipilimumab

Hoda Anwar[1] · Christos Sachpekidis[1] · Julia Winkler[2] · Annette Kopp-Schneider[3] · Uwe Haberkorn[1,4] · Jessica C. Hassel[2] · Antonia Dimitrakopoulou-Strauss[1]

## Melanoma - Ipilimumab

**PE**T **R**esponse Evaluation **C**riteria for **IM**muno**T**herapy

| | EORTC | PERCIMT |
|---|---|---|
| CMR | Complete resolution of $^{18}$F-FDG uptake within the tumor volume | Complete resolution of all pre-existing $^{18}$F-FDG avid lesions. No new, $^{18}$F-FDG avid lesions. |
| PMR | Decrease in tumor SUV>25% after more than 1 therapeutic cycle | Complete resolution of some pre-existing $^{18}$F-FDG avid lesions. No new, $^{18}$F-FDG avid lesions. |
| SMD | Increase in tumor SUV<25% or decrease in SUV<15% | Neither PMD nor PMR/CMR |
| PMD | Increase in tumor SUV>25% or appearance of new lesions | **≥ 4 new lesions of less than 1 cm in functional diameter or ≥ 3 new lesions of more than 1.0 cm in functional diameter or ≥ 2 new lesions of more than 1.5 cm in functional diameter** |

ORIGINAL ARTICLE

European Journal of Nuclear Medicine and Molecular Imaging (2019) 46:930–939

# Prognostic value of baseline metabolic tumor volume measured on $^{18}$F-fluorodeoxyglucose positron emission tomography/computed tomography in melanoma patients treated with ipilimumab therapy

Kimiteru Ito[1,2] · Heiko Schöder[1] · Rebecca Teng[1] · John L. Humm[3] · Ai Ni[4] · Jedd D. Wolchok[5] · Wolfgang A. Weber[1,6]

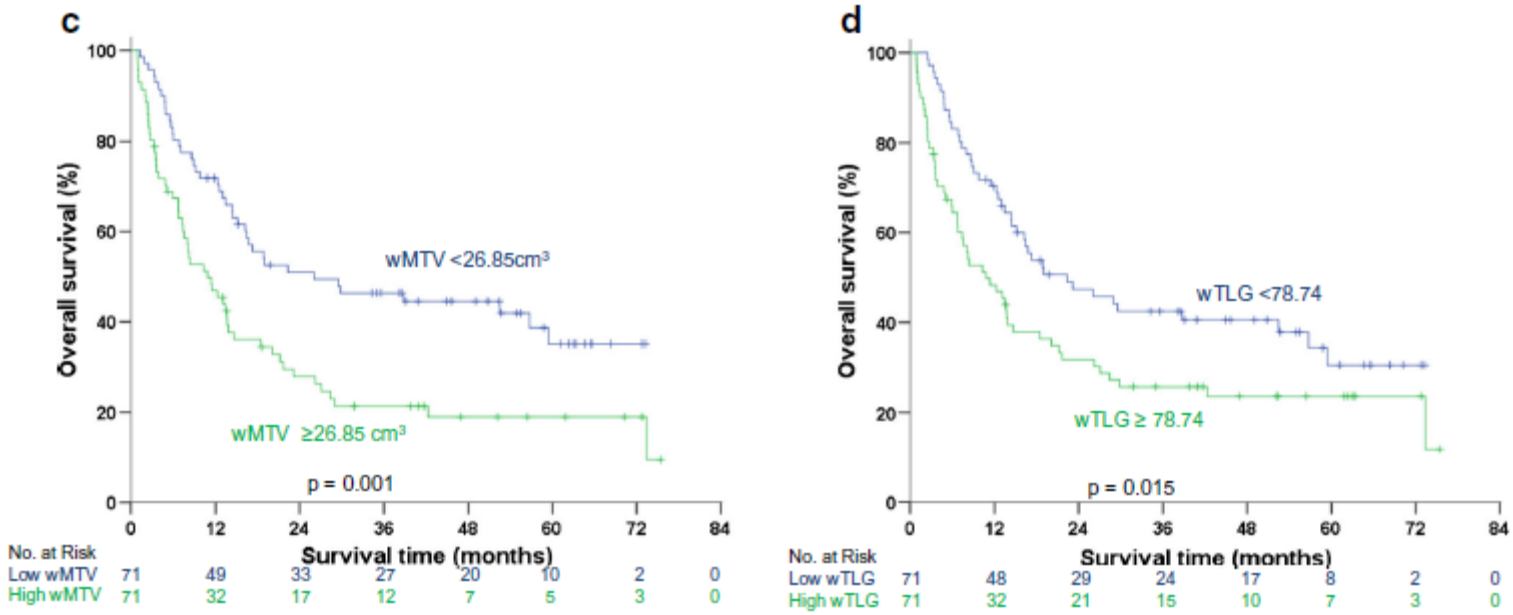



**Fig. 2** Kaplan-Meier curves for overall survival in relation to **a** SULmax, **b** sum of SULpeak in five highest uptake lesions, **c** wMTV, and **d** wTLG

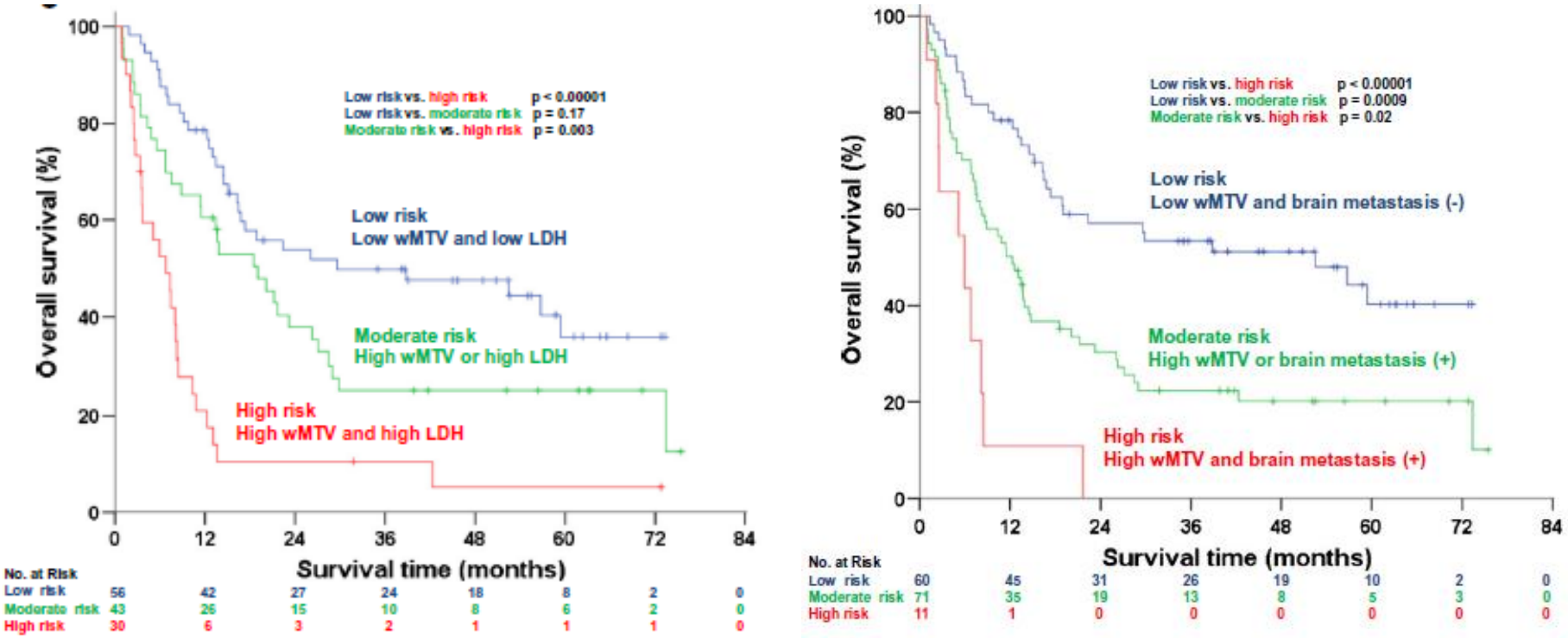



**Fig. 4** Kaplan-Meier curves for overall survival in three risk groups stratified according to wMTV combined with the four independent prognostic factors in relation to **a** presence of brain metastases, **b** age, **c** LDH level, and **d** number of lines prior chemotherapy

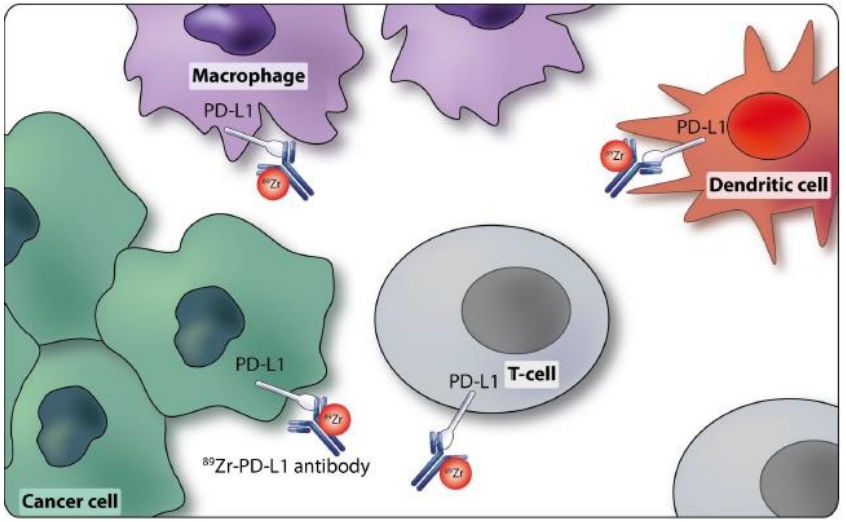
# Clinical Translation

- Απεικόνιση των PD1/PD-L1 -> επιλογή των ασθενών

- Ιχνηλάτηση των T cell για την παρακολούθηση της ανοσιακής απόκρισης.

**ImmunoPET**

| Radio-nuclide | $T_{1/2}$ (h) |
|---|---|
| $^{68}Ga$ | 1.1 |
| $^{18}F$ | 1.8 |
| $^{64}Cu$ | 12.7 |
| $^{86}Y$ | 14.7 |
| $^{76}Br$ | 16.2 |
| $^{89}Zr$ | 78.5 |
| $^{124}I$ | 100.3 |



nature medicine

LETTERS

https://doi.org/10.1038/s41591-018-0255-8

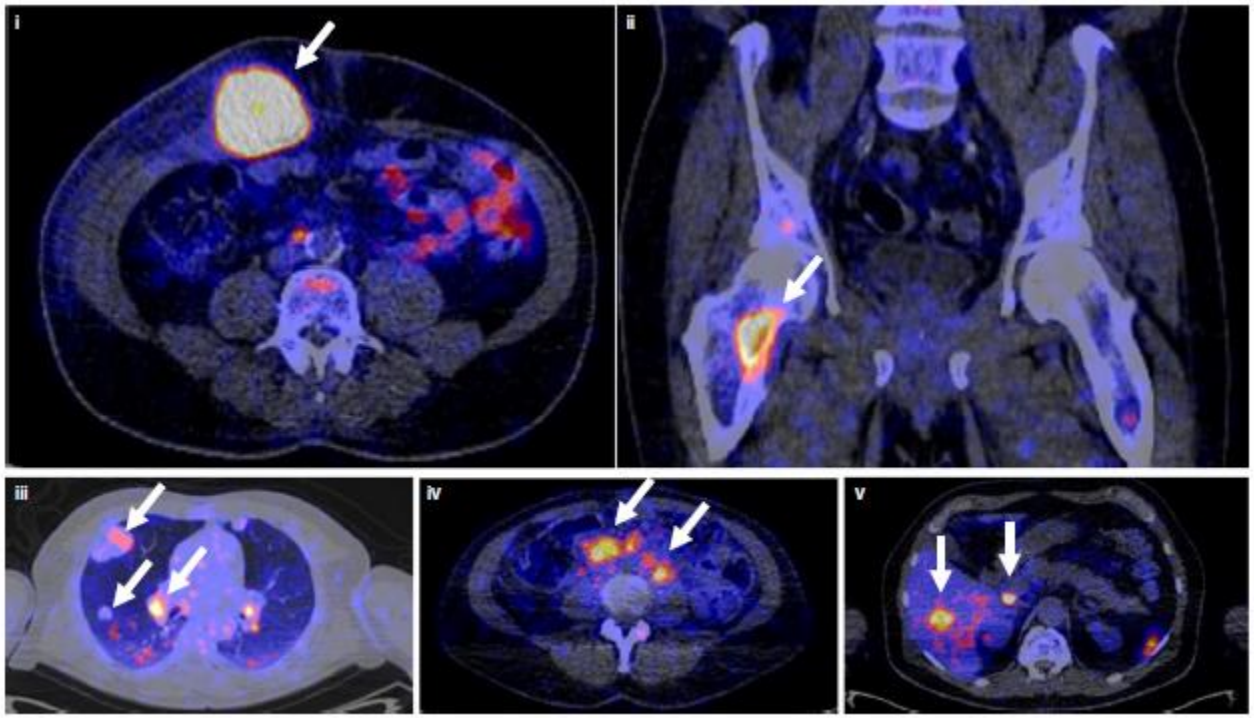
# $^{89}$Zr-atezolizumab imaging as a non-invasive approach to assess clinical response to PD-L1 blockade in cancer

Frederike Bensch[1], Elly L. van der Veen[1], Marjolijn N. Lub-de Hooge[2,3], Annelies Jorritsma-Smit[2], Ronald Boellaard[3], Iris C. Kok[1], Sjoukje F. Oosting[1], Carolina P. Schröder[1], T. Jeroen N. Hiltermann[4], Anthonie J. van der Wekken[4], Harry J. M. Groen[4], Thomas C. Kwee[3], Sjoerd G. Elias[5], Jourik A. Gietema[1], Sandra Sanabria Bohorquez[6], Alex de Crespigny[6], Simon-Peter Williams[6], Christoph Mancao[7], Adrienne H. Brouwers[3], Bernard M. Fine[6] and Elisabeth G. E. de Vries[1*]

**First in human PET/CT 89Zr - atezolizumab (anti-PD-L1)**

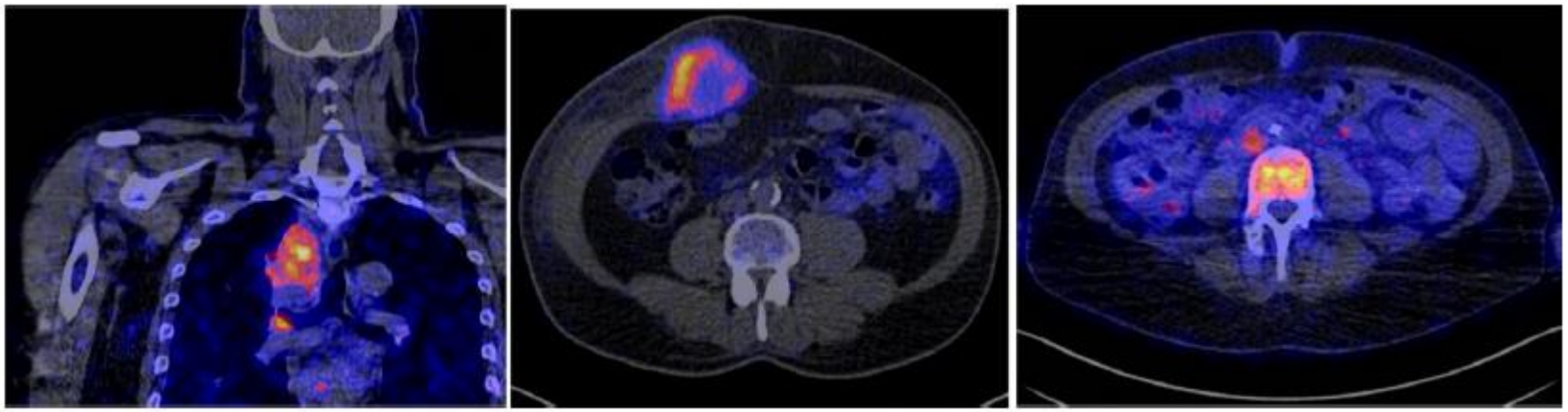
**22 patients with three tumor types (bladder, NSCLC, TNBC) before the start of atezolizumab therapy**

89Zr-atezolizumab **PET/CT** on day 7 post-injection




✓Feasibility and safety

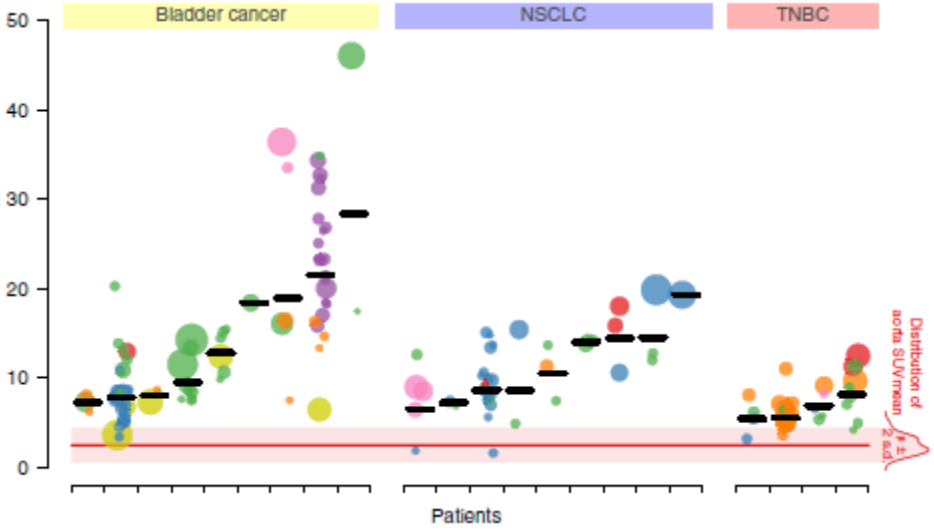
➢ The **anti-PD-L1** PET signal was generally **high** but **heterogeneous,** varying within and among lesions and tumor types.



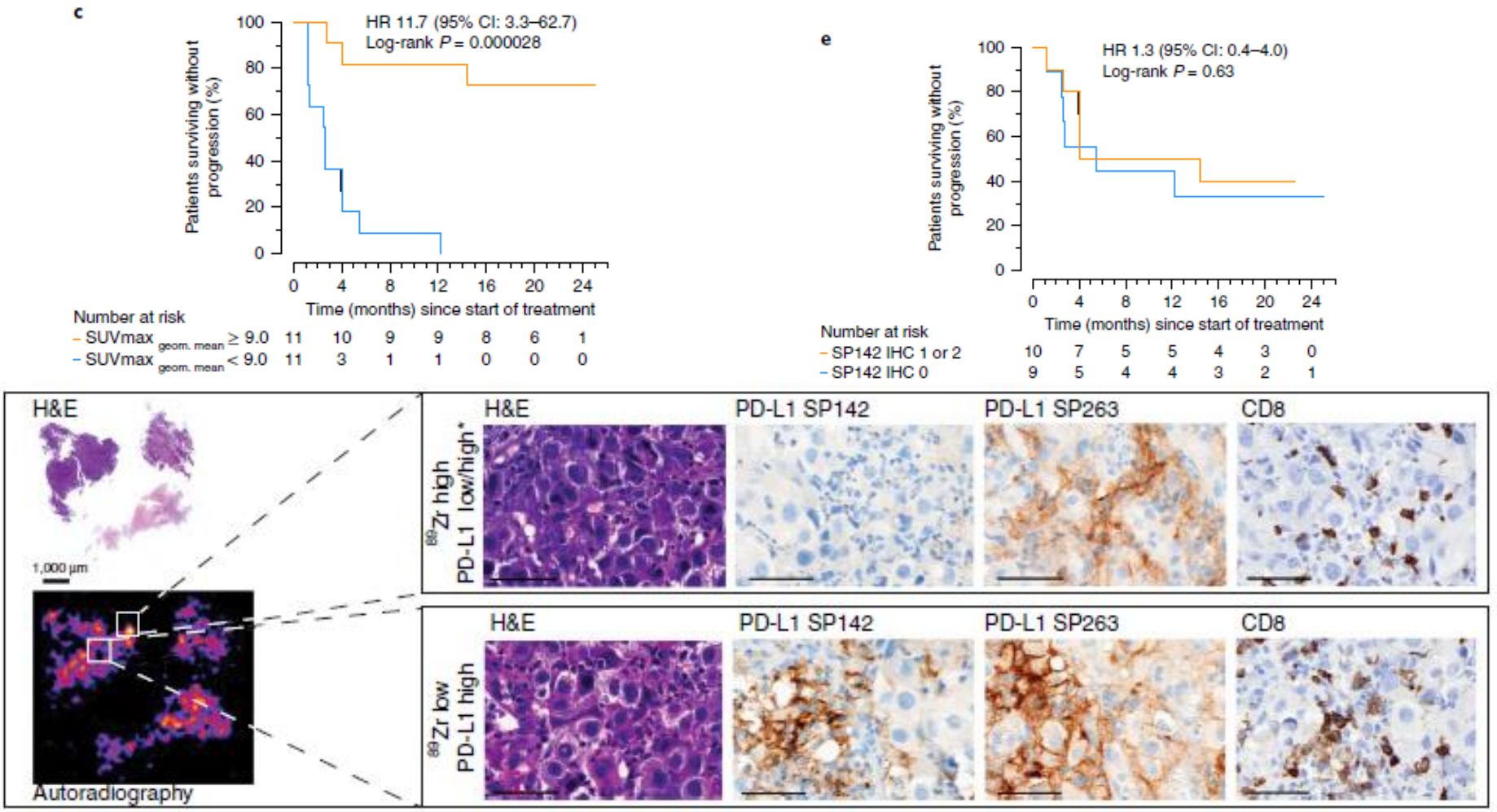
Mediastinal lesion of a NSCLC patient (SUVmax 19.9)

abdominal wall metastases of a bladder cancer patient (SUVmax

bone metastasis of a TNBC patient (SUVmax 7.1)



➢ **Clinical responses were better correlated with pretreatment PET signal than with immunohistochemistry- or RNA-sequencing based predictive biomarkers, encouraging further development of molecular PET imaging for assessment of PD-L1 status and clinical response prediction.**



ARTICLE

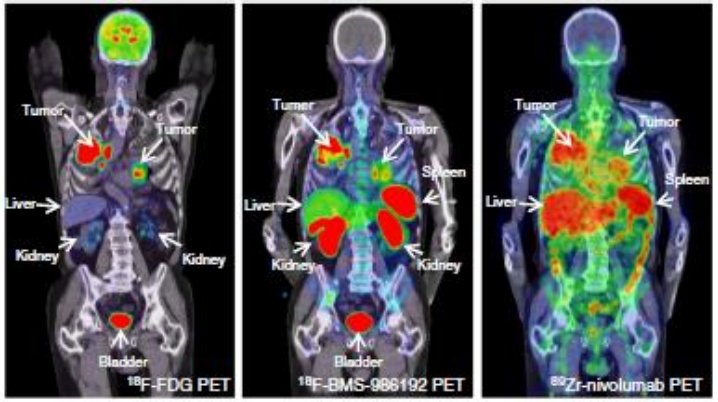
DOI: 10.1038/s41467-018-07131-y OPEN

nature COMMUNICATIONS

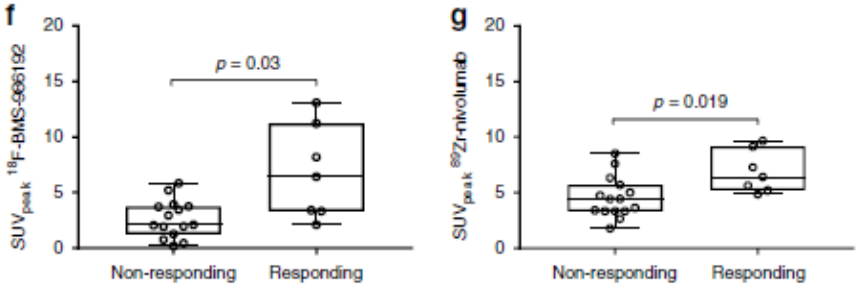
# Whole body PD-1 and PD-L1 positron emission tomography in patients with non-small-cell lung cancer

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]

**First-in-human study** results of whole body PET imaging with **18F-BMS-986192** (anti-PD-l1) and **89Zr-Nivolumab** (anti-PD1) in 13 patients with advanced NSCLC, prior to treatment with nivolumab.




- safety
- Heterogeneous radiotracer uptake.




- Radiotracer uptake is related to response.

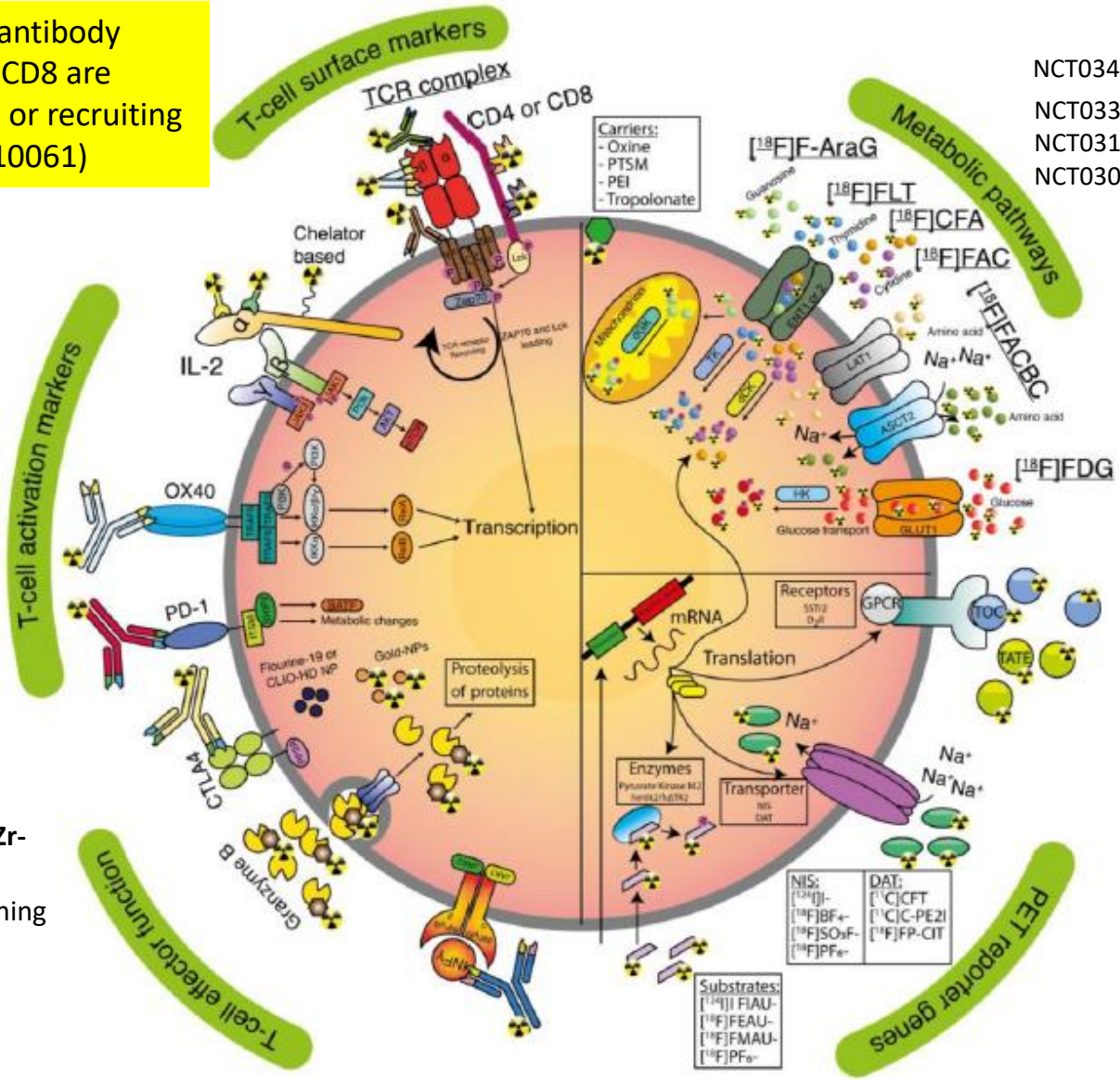
# Pre-Clinical setting →Clinical Translation

Clinical studies using engineered antibody fragments (minibodies) targeting CD8 are either completed (NCT03107663) or recruiting patients (NCT03802123, NCT03610061)

humanised OX40 agonist monoclonal antibodies are currently being introduced in early phase clinical trials for various cancer types (*e.g.* NCT02318394).

Two studies on **[89Zr]Zr-DFO-pembrolizumab** imaging are currently open for locally advanced or metastatic melanoma or non-small cell lung cancer (NCT03065764, NCT02760225).

A phase 2 clinical trial with **[89Zr]Zr-DFO-ipilimumab** in metastatic melanoma patients is currently running (NCT03313323).




NCT03409419
NCT03311672
NCT03142204
NCT03007719

# Tracking T cells

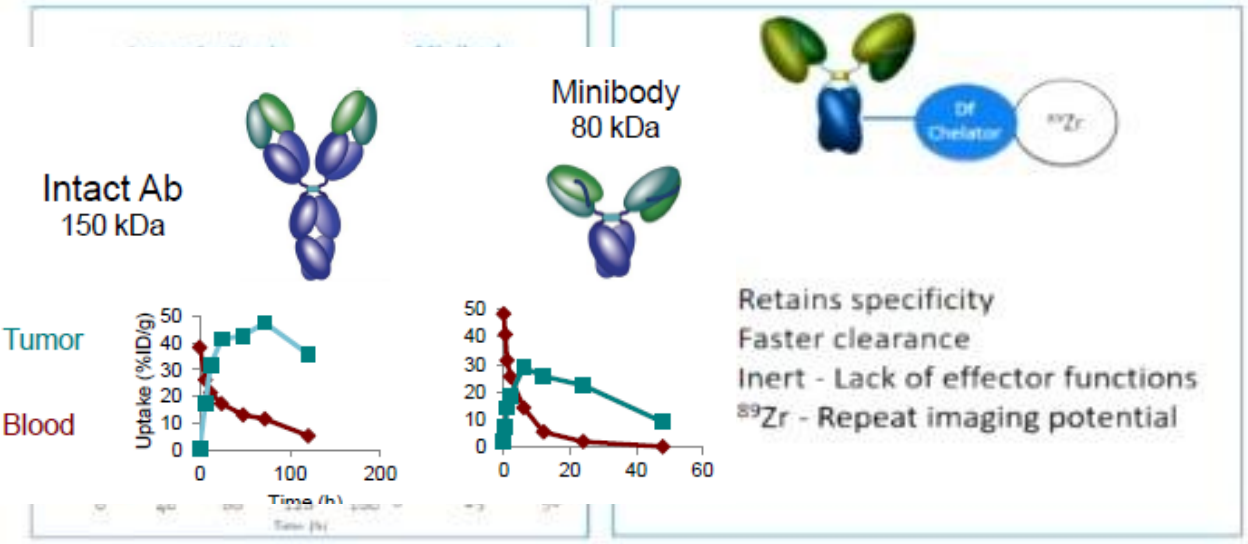
## First in Human Trial of $^{89}$Zr-Df-IAB22M2C anti-CD8 minibody in patients with Solid tumors


Neeta Pandit-Taskar[1], Micheal Postow[1], Joseph A. O'Donoghue[1], James J. Harding[1], Martha Ziolkowska[1], Serge K. Lyashchenko[1], Jason S. Lewis[1], Anna M. Wu[2], William Le[3], Jean Gudas, PhD[3], Ronald L. Korn[4], Michael Torgov[3], Jedd Wolchok[1], Wolfgang A. Weber[1,5]

[1]Memorial Sloan Kettering Cancer Center, New York, NY,
[2]University of California, Los Angeles
[3]ImaginAb, Inc., Inglewood, CA
[4]Imaging Endpoints, Scottsdale, AZ
Technical University Munich, Germany


HONORHEALTH Penn ImaginAb

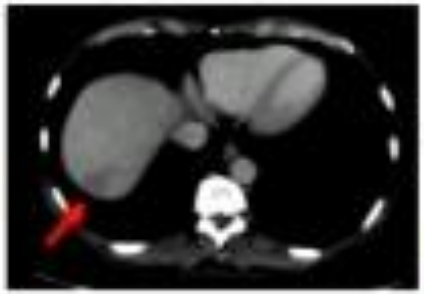
### CD8 T-cell imaging

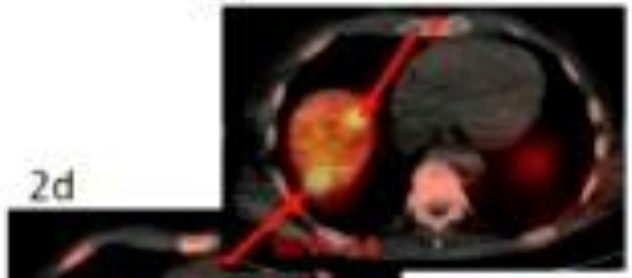


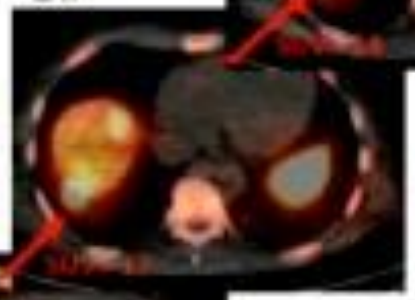

->Παρακολούθηση της ανοσιακής απόκρισης στην χορήγηση ICIs
->Πρόβλεψη irAEs ?
->διάκριση της Ψευδοπροόδου από την Αληθή Πρόοδο νόσου?

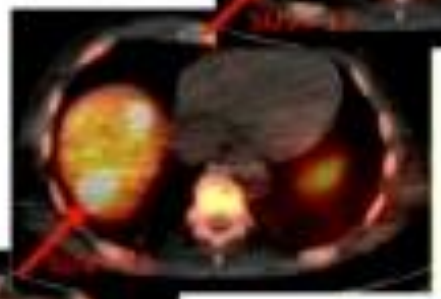
**Patient 2 - Subject**: 64 years old, male Metastatic hepatocellular carcinoma, diagnosed 26-May-2017
**Treatment history:** Nivolumab: Ongoing CPI treatment for 2 weeks prior to scan

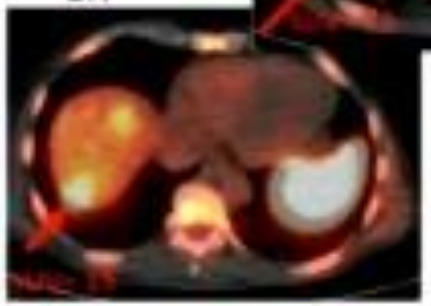
Note: All images are $^{89}$Zr-IAB22M2C, except CT in left hand corner



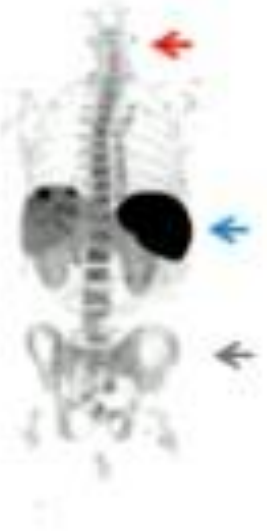




Day1: 6 h



Day 6

LN
Sp
BM

- Localization $^{89}$Zr-Df-IAB22M2C in known area of tumor with high uptake, increase lesion detection
- Activity is stable and can be easily quantitative
- Same day imaging possible

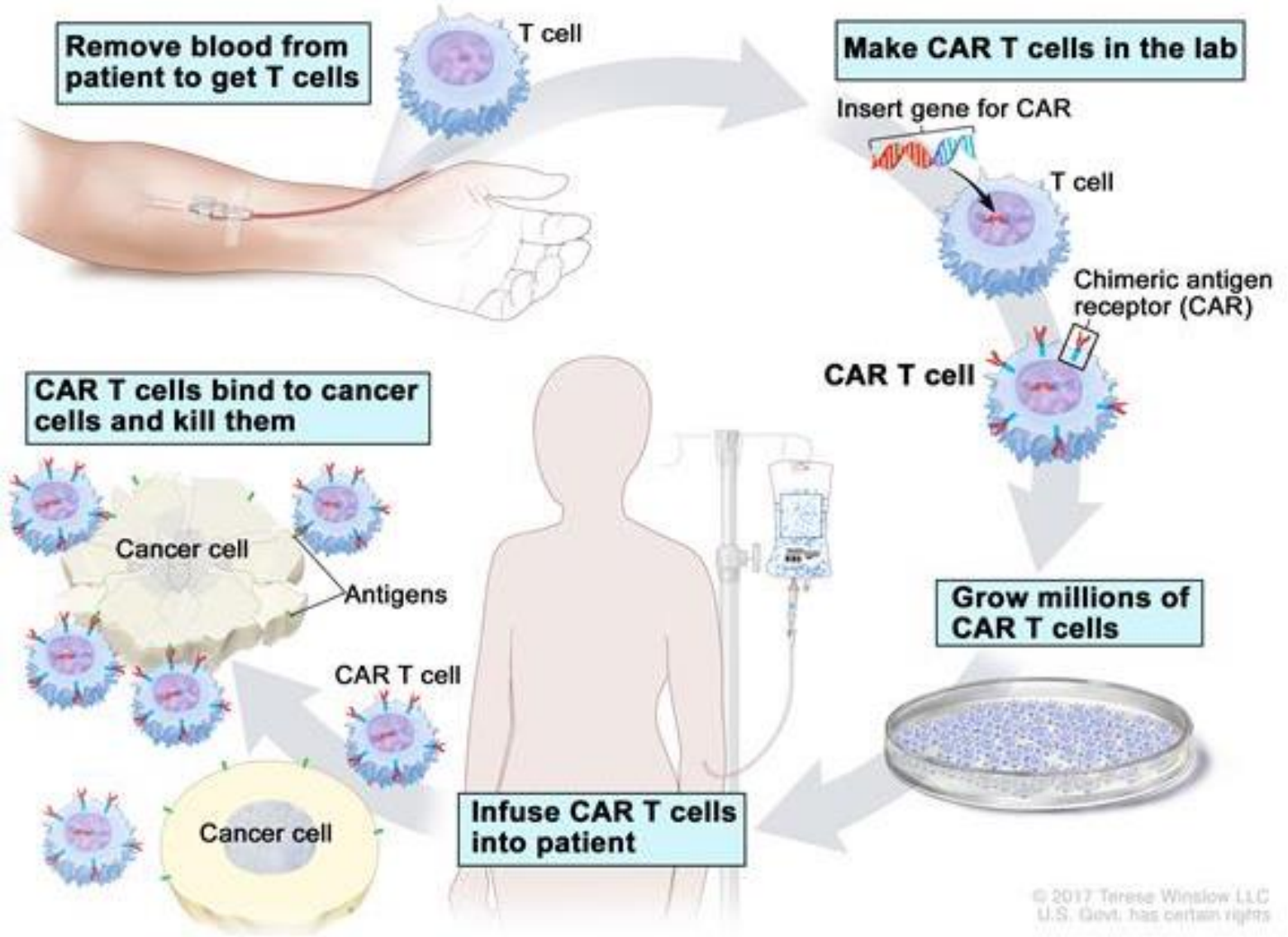
HONORHEALTH

Penn

ImaginAb


2010
2011
2012
2013
2014
2015
2016
2017
03/04/2017: avelumab approved for Merckel cell carcinoma
2011
First ICI approved by FDA
2013-CAR T cell therapy achieves 89% response rate in ALL and complete responses in B-ALL
03/04/15: nivolumab approved for squamous NSCLC after
chemotherapy
09/30/15: ipilimumab+nivolumab approved for BRAF V600
melanoma
10/02/15: pembroliuzmab approved for PD-L1+NSCLC aft
therapy targeting EGFR or ALK mutations with companion
10/09/15: nivolumab approved for nonsquamous NSCLC a
chemotherapy
10/27/15: T-VEC approved for locally recurrent malignant n
10/28/15: ipilimumab approved for adjuvant therapy of Sta
11/23/15: nivolumab approved for metastatic RCC after pr
11/24/15: nivolumab approved for first line therapy of meta
mutation status
11/21/15: daratumumab approved for multiple myeloma
11/30/15: elotuzumab approved for multiple myeloma
12/18/15: pembrolizumab approved for first line therapy of metastatic melanoma regardless of
BRAF mutation status
2017
FDA approval of CD19 CAR therapy for pediatric ALL and NHL

# CAR T cell Therapies



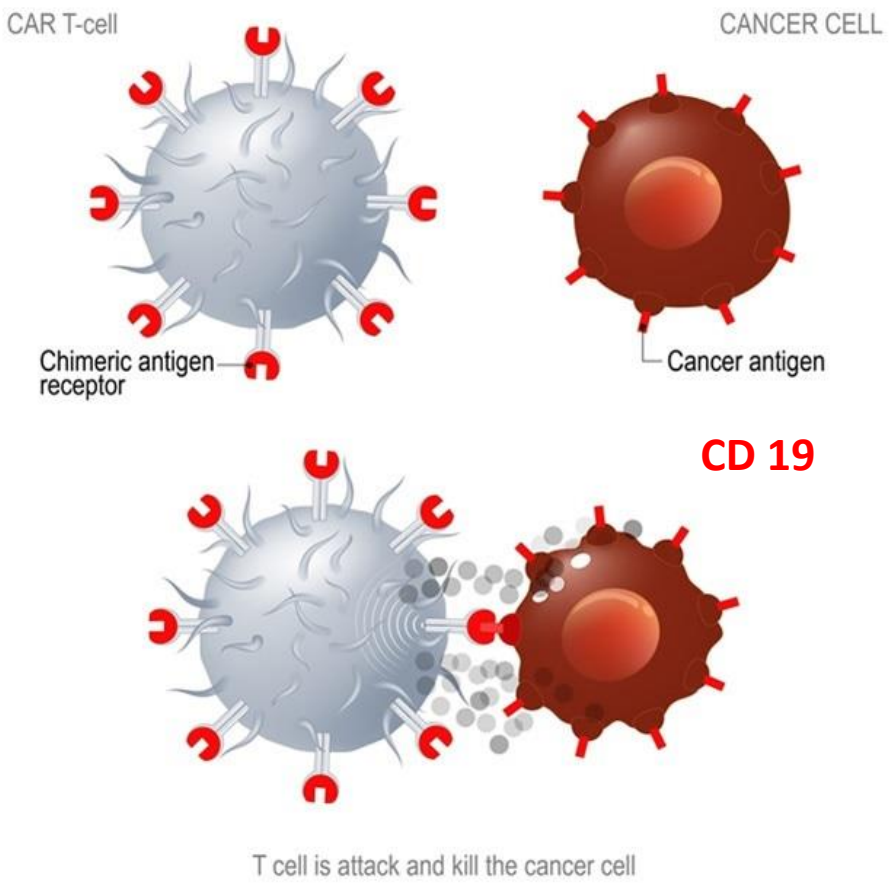
# CAR T cell Therapies

**FDA approval 2017**
**EMA approval 2018**

**->** Relapsed or refractory diffuse large B-cell lymphoma (DLBCL)

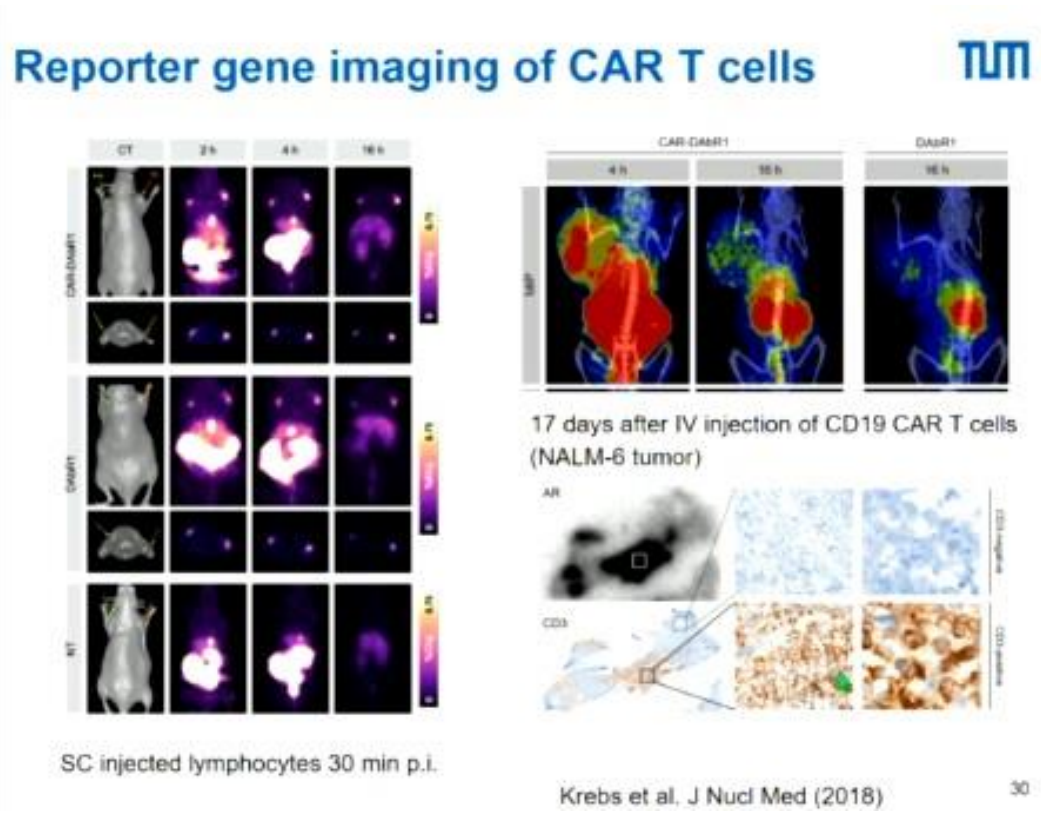
**->** Relapsed or refractory acute lymphoblastic leukemia (ALL)

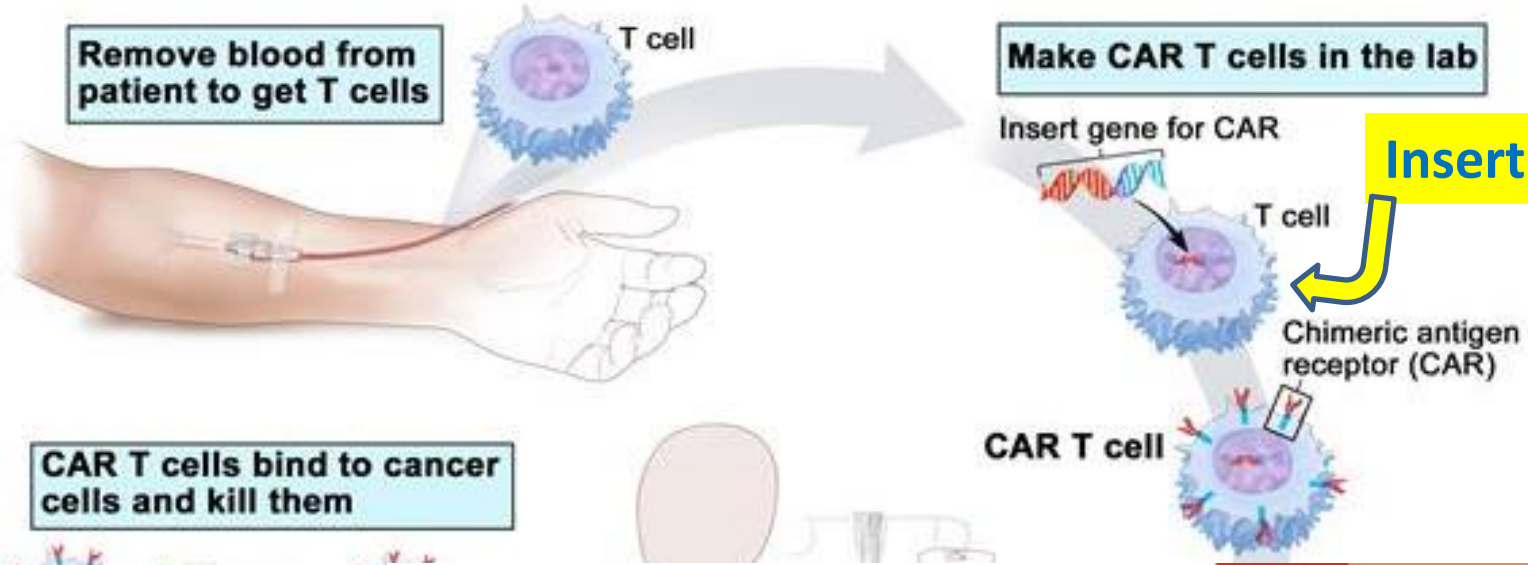
Cost ~400,000 €



# Why do we need CAR T cell tracking?

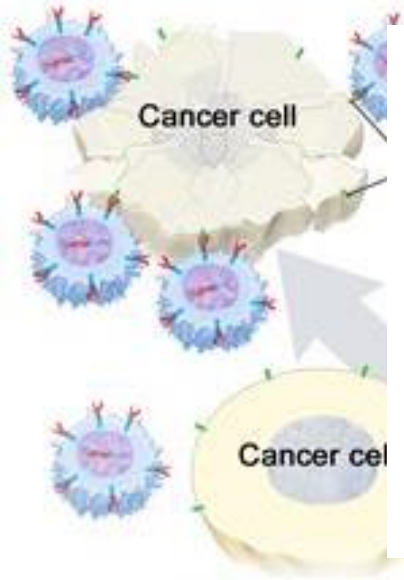
-> Να δειχθεί η ακριβής στόχευση της θεραπείας.




Insert reporter gene

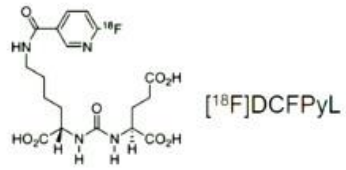
CAR T cells bind to cancer cells and kill them




## Indirect radiolabelling – PSMA reporter gene

KING'S College LONDON

Επανεκκίνηση και επανα



[$^{18}$F]DCFPyL

CAR T-cells
CD19-tPSMA$^{(N9del)}$

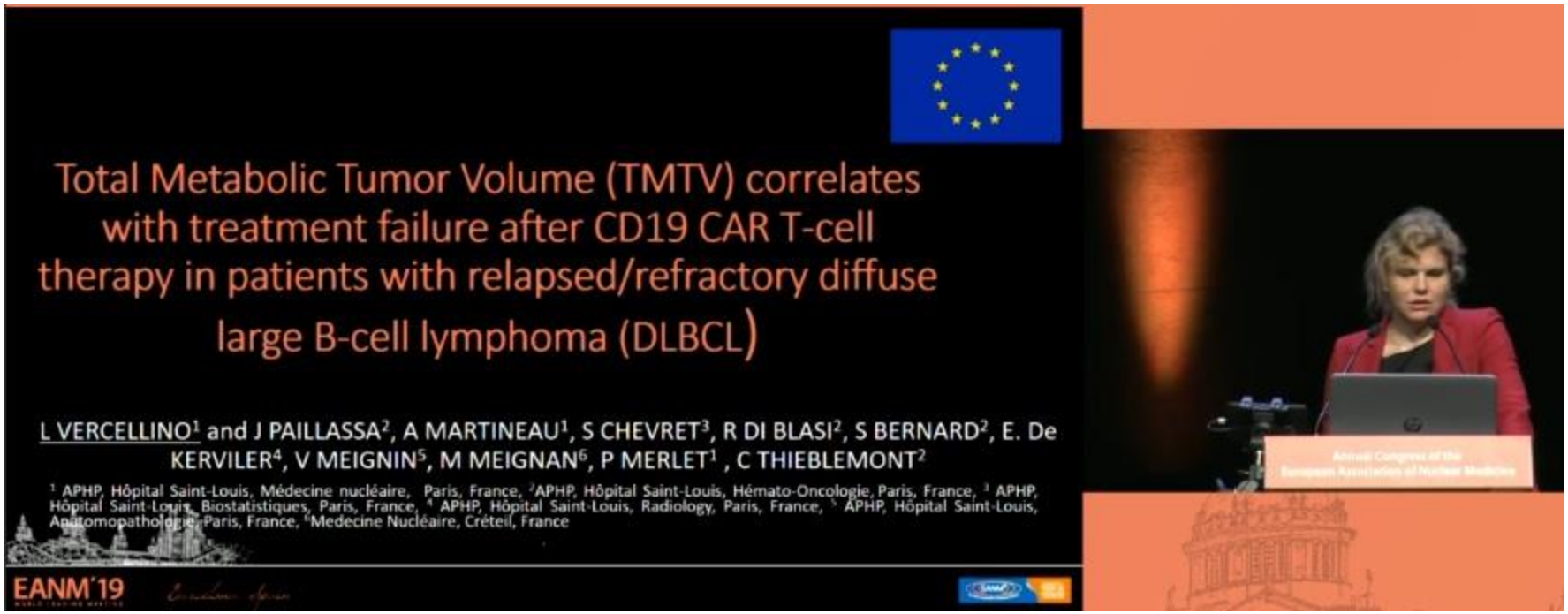
CD19 → surface marker of B cell malignancies → CAR T cell therapy

Anti-CD19 CAR T cells engineered for PSMA reporter gene expression

Why? PSMA has restricted normal tissue expression and a variety of radiotracers available (many in clinical trials e.g. [$^{18}$F]DCFPyL)

Nor PSMA reporter gene, nor [$^{18}$F]DCFPyL binding affect function

Minn et al. Science Advances, **2019**, DOI: 10.1126/sciadv.aaw5096



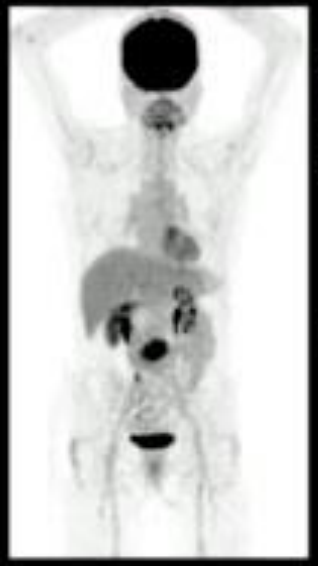

*L. S. Vercellino*[1], *J. Paillassa*[1], *A. Martineau*[1], *S. Chevret*[1], *R. Di Blasi*[1], *S. Bernard*[1], *E. De Kerviler*[1], *V. Meignin*[1], *M. Meignan*[2], *P. Merlet*[1], *C. Thieblemont*[1];

[1]*Hôpital Saint Louis, Paris, FRANCE,* [2]*LYSA Imaging Henri Mondor University Hospitals, Créteil, FRANCE.*

**Background** Despite significant clinical benefit in relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL), patients treated with autologous anti-CD19 chimeric antigen receptor (CD19 CAR) T-cells may experience early relapse/progression within the first 90 days after infusion

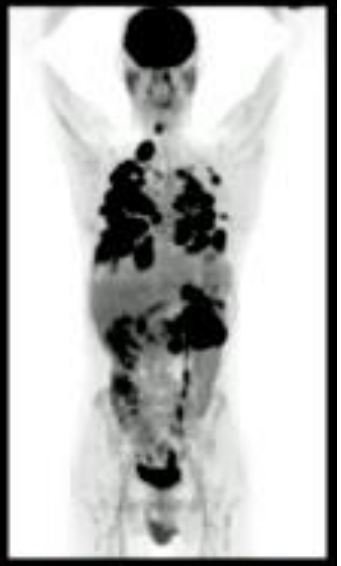
The **aim of our study** was to evaluate if **high TMTV** measured immediately before infusion was associated with treatment failure in patients with R/R DLBCL receiving CAR T-cells

We conducted the analysis on **31 patients** who received CD19 CAR T-cells at our center Median $TMTV_{41\%}$ was 37.9 $cm^3$ (range: 1.44-630.9) and median TMTV4 was 48 $cm^3$ (range: 0-940). Median TLG41% was 294.3 g (range: 2.43-6685.2) and median TLGSUV4 was 379.5 g (range: 0-781.839). Treatment failure occurred in 11 patients, with a median time of 18 days (range: 4-119).



Left:
TMTV: 33 cm3
CMR at 3 mo post infusion

Right:
TMTV: 770 cm3
Progression at 1 mo post infusion



After multivariate analysis and model selection, only the number of previous lines (HR 1.66, CI95% [1.10;2.52], p 0.016), and $TLG_{41\%}$ (HR 4.46, CI95% [1.58-12.6], p 0.005) were predictive of relapse. Similar results were reached with $TMTV_{SUV4}$ (HR 4.91, CI95% [1.47-16.5], p 0.010).

**Conclusion In our cohort, high baseline TMTV and TLG were correlated to treatment failure in patients with R/R DLBCL treated with CAR T-cells**

# Συμπερασματικά

ImmunoPET ?

FDG PET/CT

-Response assessment

-Prognostic index

Pre-clinical


Clinical Translation

Clinical

# holla