## Disclosure

- Advisory Board Member for:
  - Roche
  - BMS
  - Amgen

# Targeting the immune system

## Situation in Oncology

Research:

- Mechanisms of tumor development and progression better understood
- The gap between advances in basic cancer research and available treatment options in clinical reality is increasing

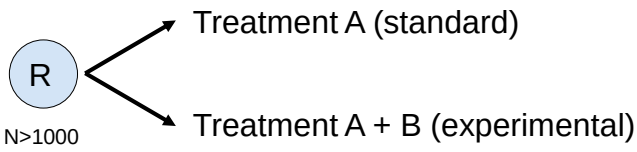
Clinic:

- Most treatment decisions are still based on histomorphological criteria
- Treatments are considered effective when response rates 40-50%
- Adjuvant treatments: about 5-20%of all patients treated benefit
- Only a few predictive markers so far.....

## Situation in Oncology

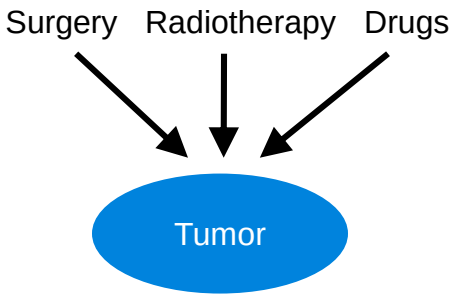
Clinical research:

- Inclusion criterion for most clinical trials is the histomorphological diagnosis, molecular markers rarely addressed
- Classical phase III trial:

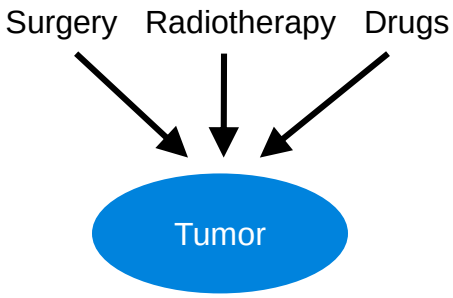



- Approval if A + B show significant benefit (OS)
- Phenomenon `Response´or`non Response´on the molecular level is not understood
- Mechanism of action of many drugs used in oncology is not really understood (including chemotherapy and most targeted drugs)

## Current strategies to individualize cancer treatment

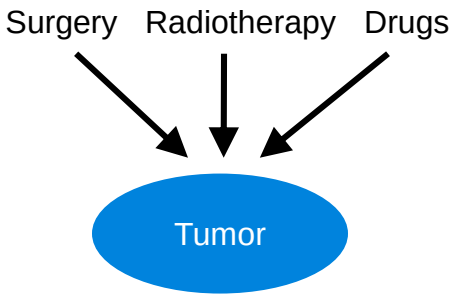



## Current strategies to individualize cancer treatment




Tumor characterization:
-Gene expression
-Genetics
-Epigenetics

## Current strategies to individualize cancer treatment




Tumor characterization:
-Gene expression
-Genetics
-Epigenetics

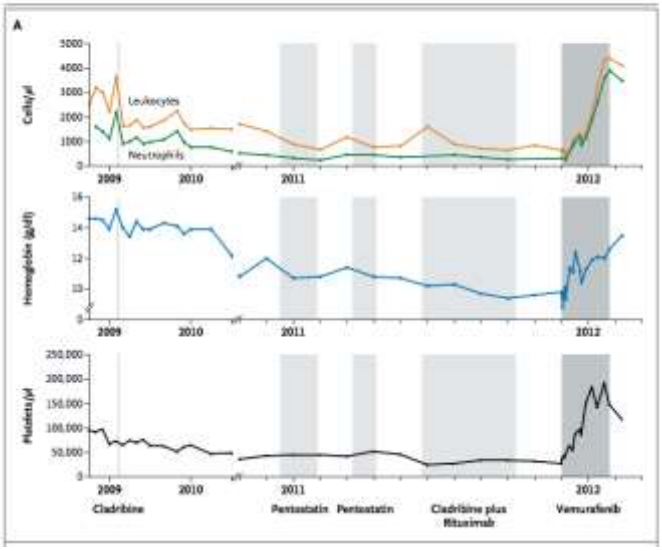
→ Patient selection
Individualized treatment

## Genome in a day.....

## Positive examples.....

### BRAF Inhibition in Refractory Hairy-Cell Leukemia

TO THE EDITOR: Hairy-cell leukemia (HCL) is a mature B-cell lymphoid cancer that is commonly treated with purine analogues.[1] Virtually all patients with HCL carry the BRAF V600E mutation,

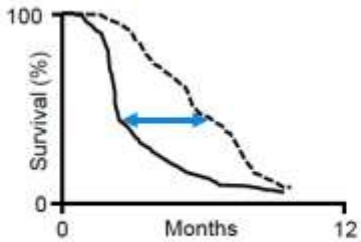




Before BRAFi


After 15 weeks of BRAFi


After 23 weeks of BRAFi




BRAFi=BRAF inhibitor
Wagle N, et al. J Clin Oncol 2011
Adapted from Chapman PB, et al. N Engl J Med 2011

## Prediction of targetable misregulated pathways

The Lancet Oncology, Volume 15, Issue 3, Pages 267 - 274, March 2014
doi:10.1016/S1470-2045(13)70611-9 Cite or Link Using DOI
Published Online: 07 February 2014

< Previous Article | Next Article >



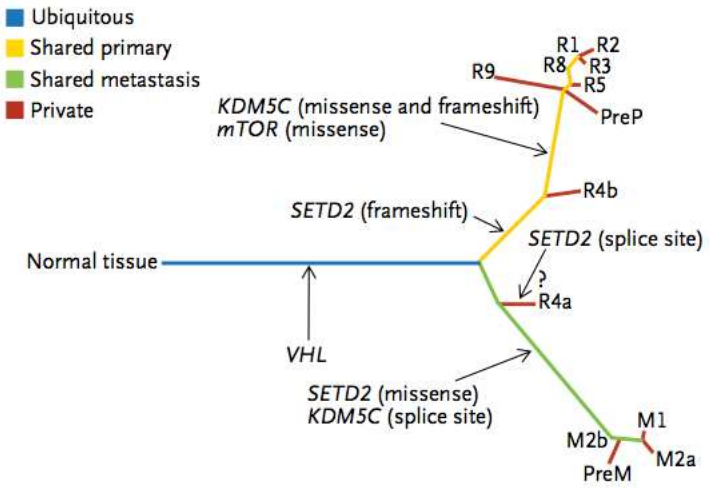
**Comparative genomic hybridisation array and DNA sequencing to direct treatment of metastatic breast cancer: a multicentre, prospective trial (SAFIR01/UNICANCER)**

Prof Fabrice André MD [a b d], Thomas Bachelot MD [e], Frederic Commo MSc [b], Prof Mario Campone MD [f], Monica Arnedos MD [a b], Véronique Dieras MD [g], Magali Lacroix-Triki MD [i], Ludovic Lacroix PharmPhD [c], Pascale Cohen PhD [j k l], David Gentien MSc [h], Jose Adélaide PhD [m], Florence Dalenc MD [n], Anthony Goncalves MD [o], Christelle Levy MD [q], Prof Jean-Marc Ferrero MD [r], Prof Jacques Bonneterre MD [s], Claudia Lefeuvre MD [t], Marta Jimenez MSc [u], Thomas Filleron PhD [p], Prof Hervé Bonnefoi MD [v]

## Prediction of targetable misregulated pathways Negative examples:

- In this prospective clinical trial treatment based on the detection of targetable lesions in patients with advanced breast cancer an individualized treatment (TKI) was compared to a treatment according to physicians choice
- The exome based treatment (targetable misregulated pathway) was not better than treatment according to physicians choice.....

## Tumor Heterogeneity




Gerlinger, NEJM, 2012

## Current strategies to individualize cancer treatment

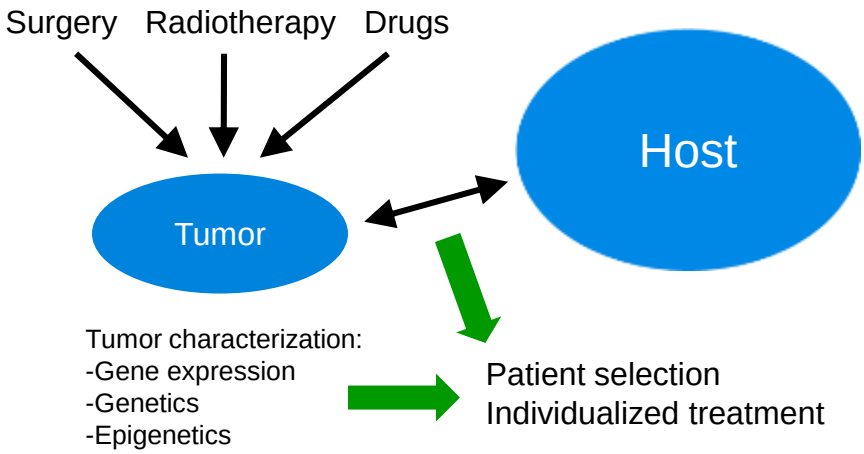
Surgery Radiotherapy Drugs

Tumor

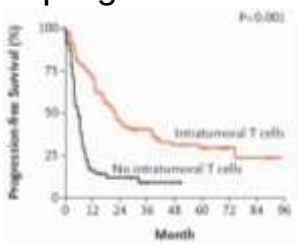
Tumor characterization:
-Gene expression
-Genetics
-Epigenetics

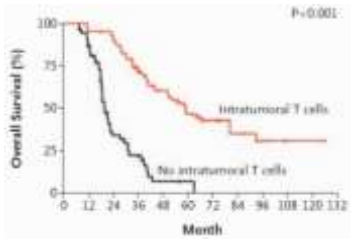
→ Patient selection
Individualized treatment

## Current strategies to individualize cancer treatment




## Infiltrating T cells in ovarian cancer and prognosis



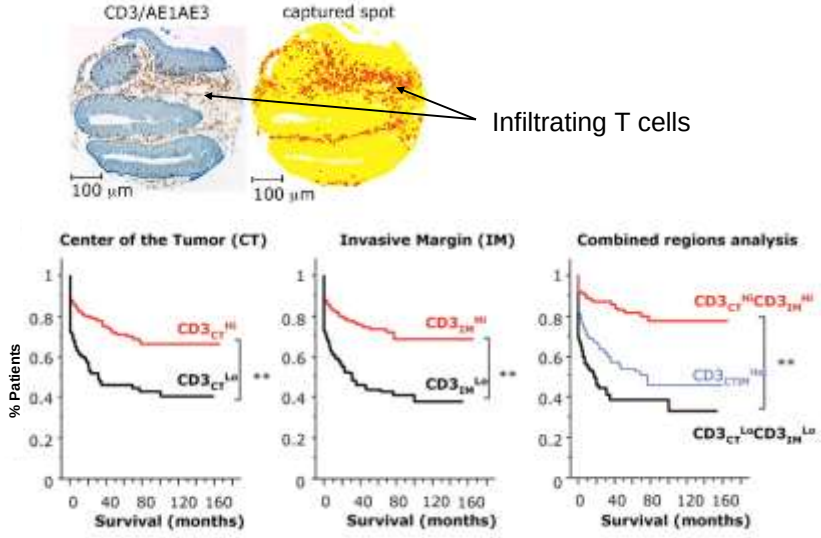




| Intratumoral T Cells | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| At risk | 87 | 63 | 37 | 27 | 19 | 15 | 6 | 4 |
| Events | 24 | 23 | 4 | 6 | 1 | 0 | 1 | 0 |
| Censored data | 0 | 3 | 6 | 2 | 3 | 9 | 1 | 4 |
| **No Intratumoral T Cells** | | | | | | | | |
| At risk | 55 | 8 | 5 | 1 | 1 | | | |
| Events | 44 | 2 | 2 | 0 | 0 | | | |
| Censored data | 3 | 1 | 2 | 0 | 1 | | | |

| Intratumoral T Cells | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| At risk | 102 | 90 | 78 | 57 | 42 | 27 | 17 | 9 | 4 | 1 | 1 |
| Events | 12 | 10 | 16 | 8 | 11 | 2 | 2 | 1 | 0 | 0 | 0 |
| Censored data | 0 | 2 | 5 | 7 | 4 | 8 | 6 | 4 | 3 | 0 | 1 |
| **No Intratumoral T Cells** | | | | | | | | | | | |
| At risk | 72 | 48 | 14 | 8 | 2 | | | | | | |
| Events | 21 | 29 | 5 | 5 | 1 | | | | | | |
| Censored data | 3 | 5 | 1 | 1 | 1 | | | | | | |

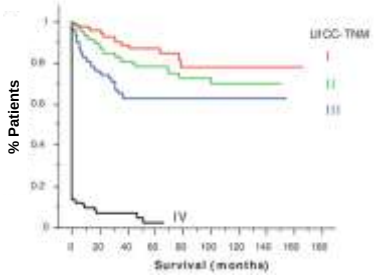
Zhang L, et al. N Engl J Med 2003

## Prognostic significance of infiltrating T cells in CRC



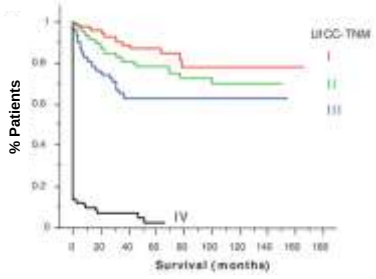

Galon J, et al. Science 2006

## Prognostic significance of infiltrating T cells in CRC

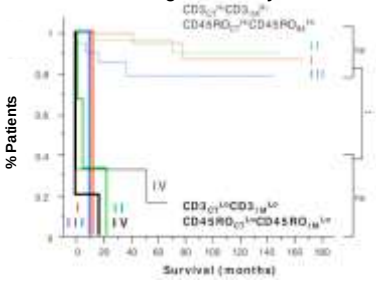



Galon et al., Science, 2006

## Prognostic significance of infiltrating T cells in CRC

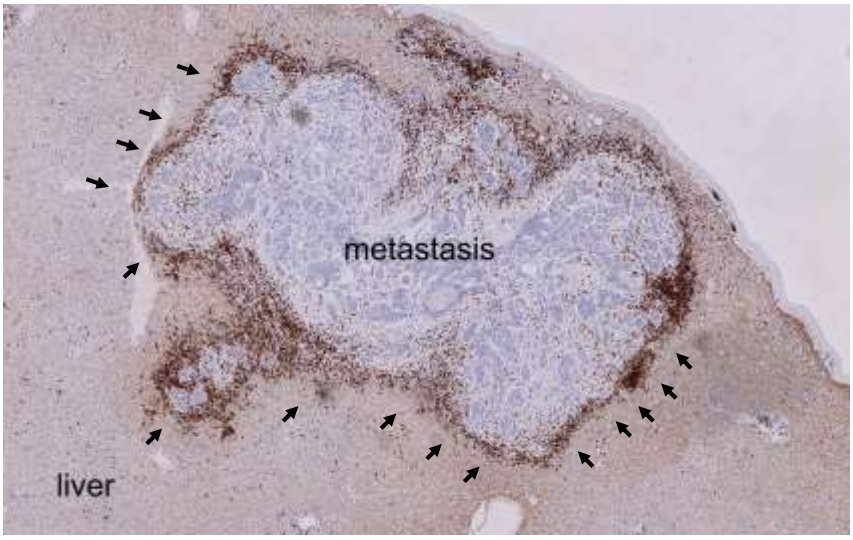


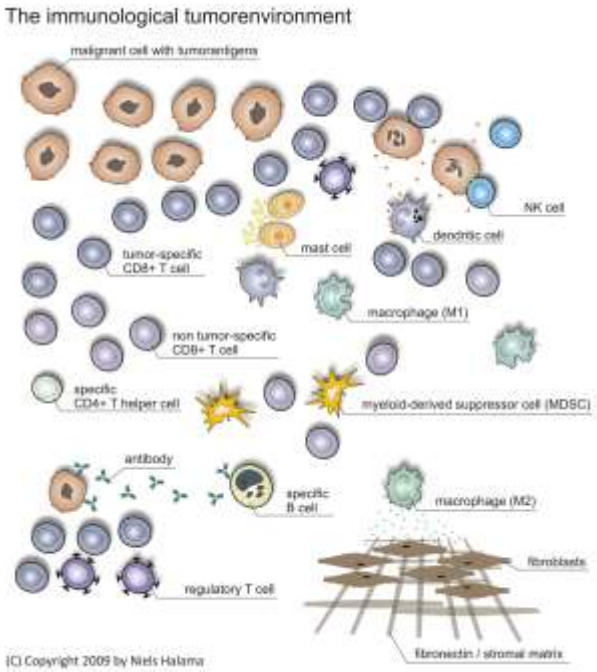

Tumor infiltrating memmory T cells



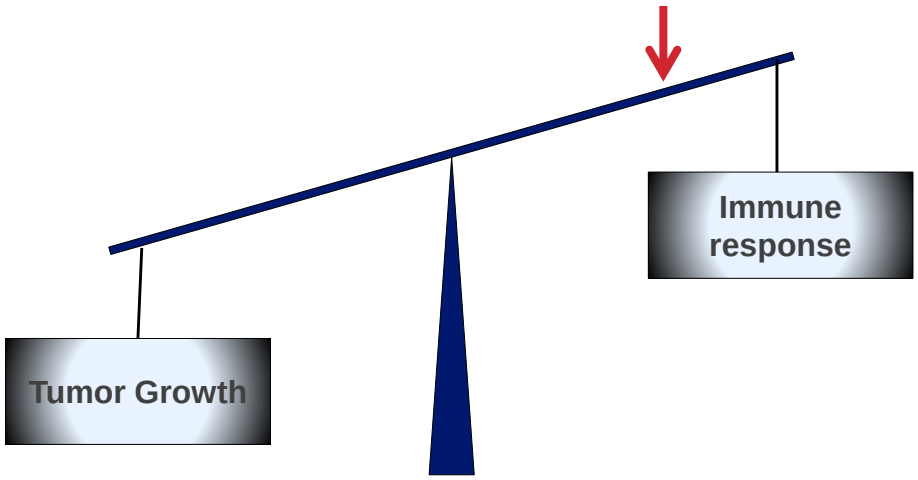

Galon et al., Science, 2006

T cells at the tumor site....

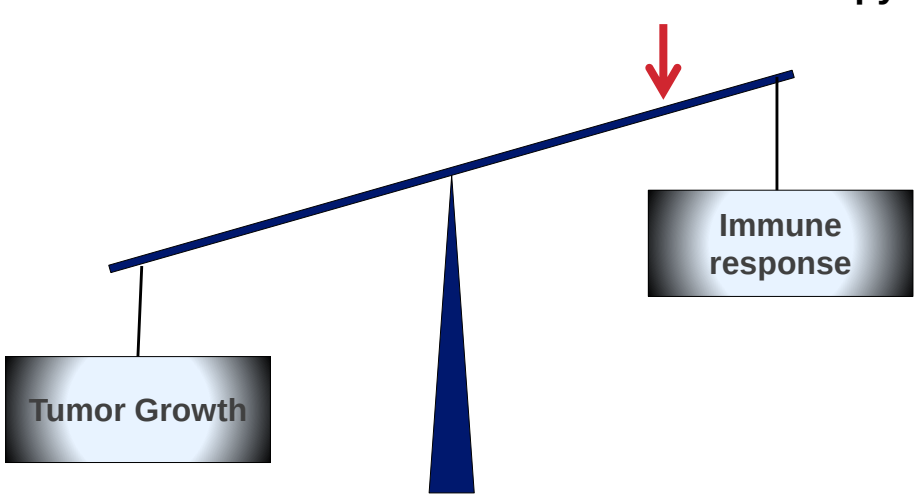




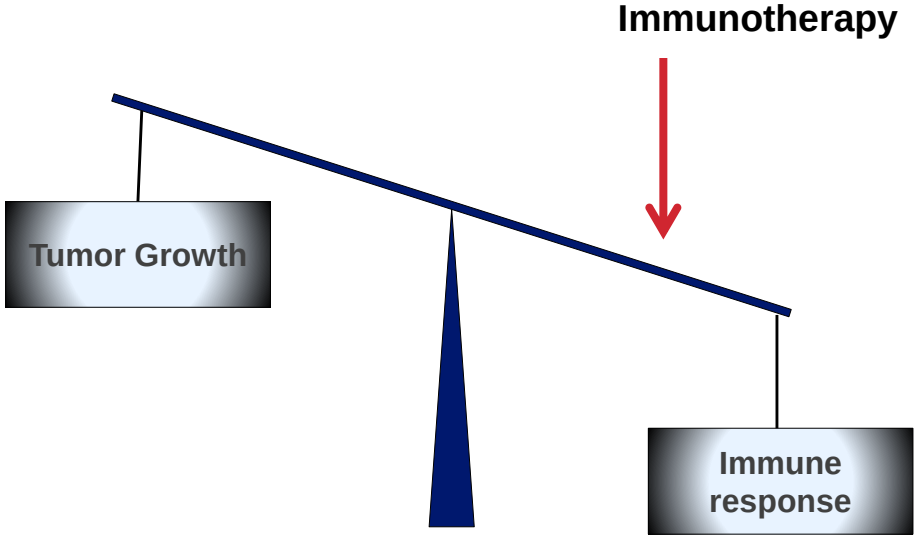

## Immunotherapy



## Immunotherapy




## Immunotherapy



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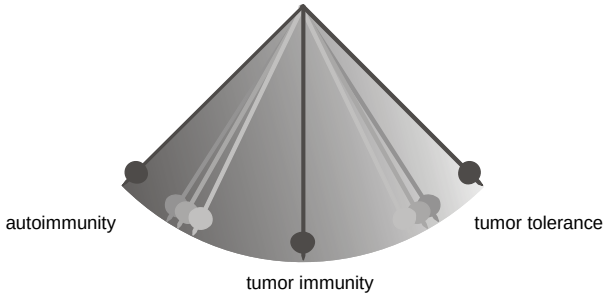
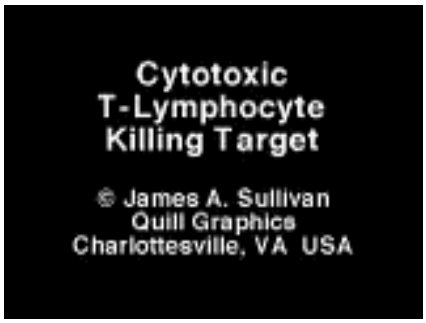
# Inducing tumor immunity without causing autoimmunity....

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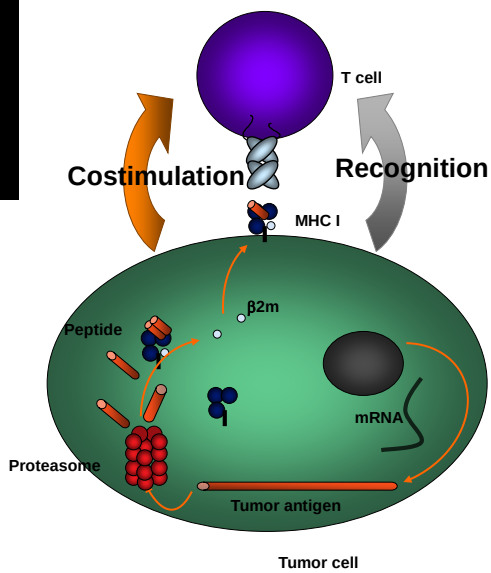
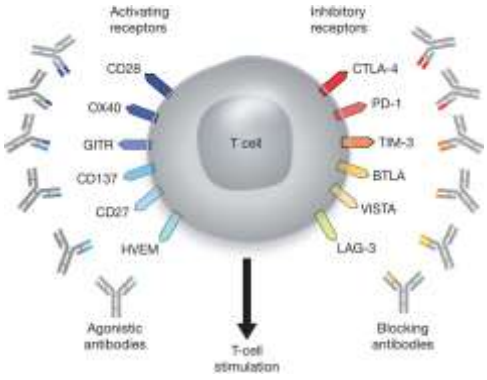
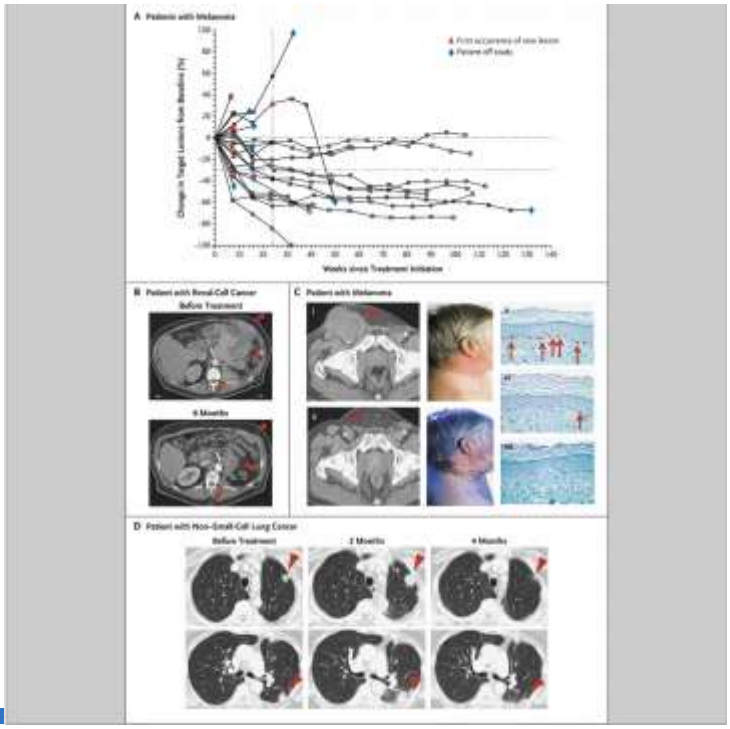


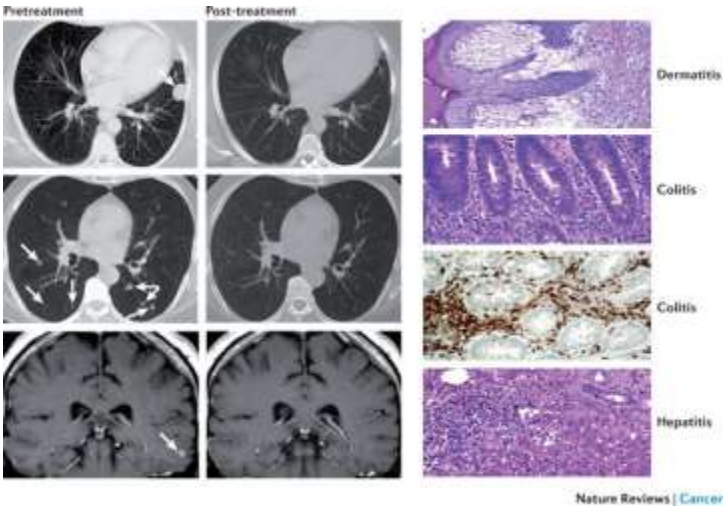
# T cell targets for immunoregulatory antibody therapy.



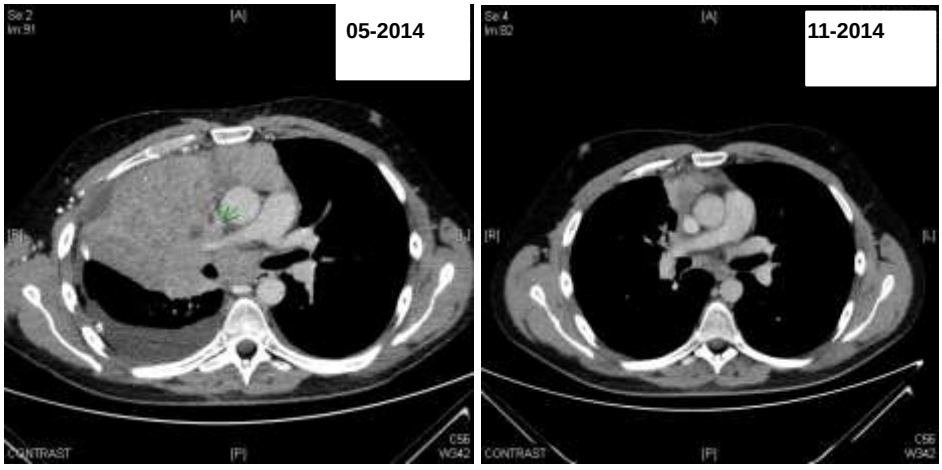

I Mellman *et al. Nature* **480**, 480-489 (2011)



Topalian, N Engl J Med 2012; 366:2443-24540

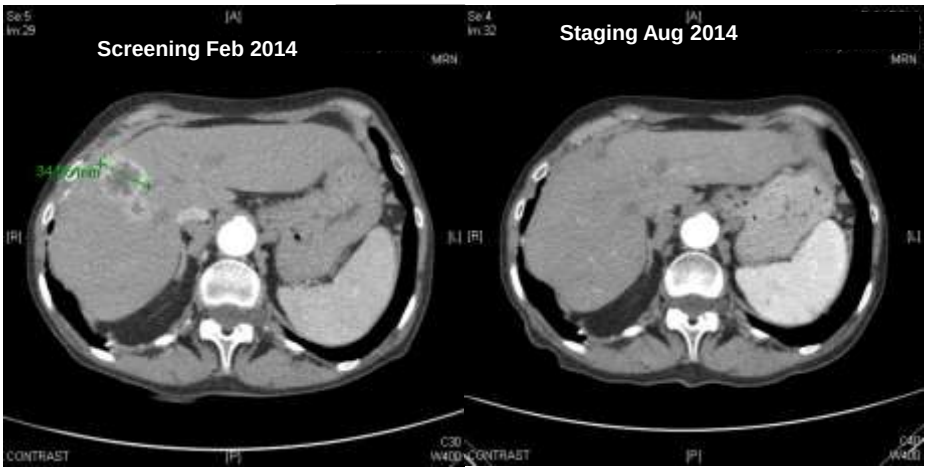



NSCLC, PD under first and second line chemotherapy.....

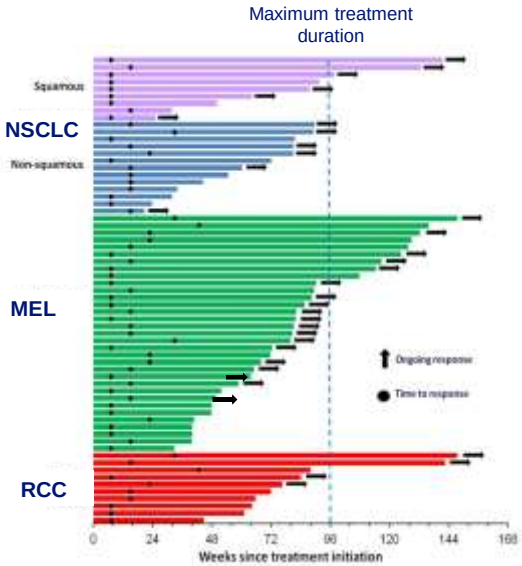



**Very good partial remission, treatment continues for 12 months.....**

## SCLC, extensive disease, 3rd line treatment with PD1 after failing 2 prior chemotherapy regimens



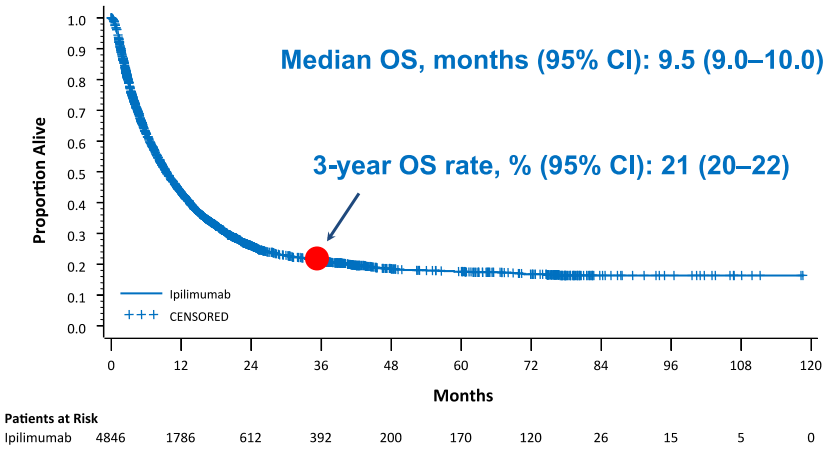

## Durability of Objective Responses Induced by PD1 in Patients with Advanced NSCLC, MEL and RCC




**Sixty-five of 306 patients had ORs (CR/PR):**

- 30 of 65 (**46%**) responses were evident at first tumor evaluation (8 weeks)
- 42 of 65 (**65%**) patients had responses lasting >1 year
- 35 of 65 (**54%**) responses were ongoing at time of data analysis
- Responses persisted off-drug

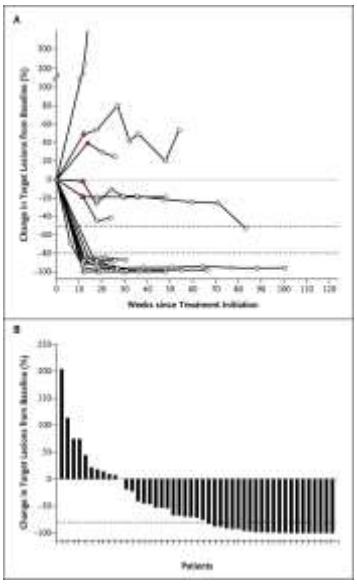
## Ipilimumab in stage IV melanoma




Schadendorf, ECCO 2013

1

## Stage IV melanoma, combination of PD1 + CTLA4 Ab

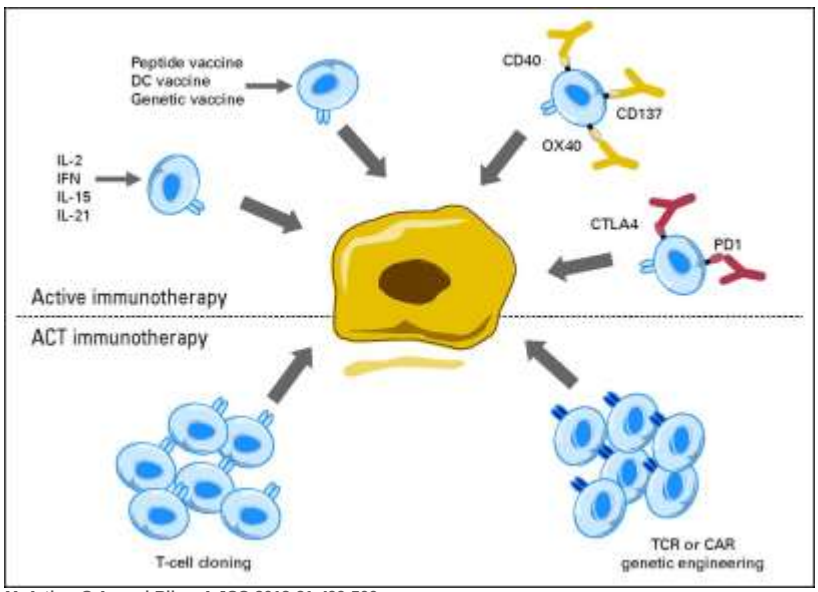


Wolchok JD et al. N Engl J Med 2013;369:122-133.

## Checkpoint Inhibition

- High response rates in different tumor entities like NSCLC, bladder cancer, melanoma, renal cancer and others....
- Low response rates in GI cancers
- Ongoing complete remissions in some patients
- Moderate toxicity

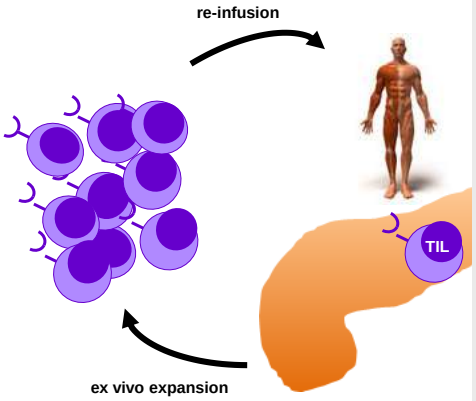
## Strategies Immunotherapy




McArthur G A , and Ribas A JCO 2013;31:499-506

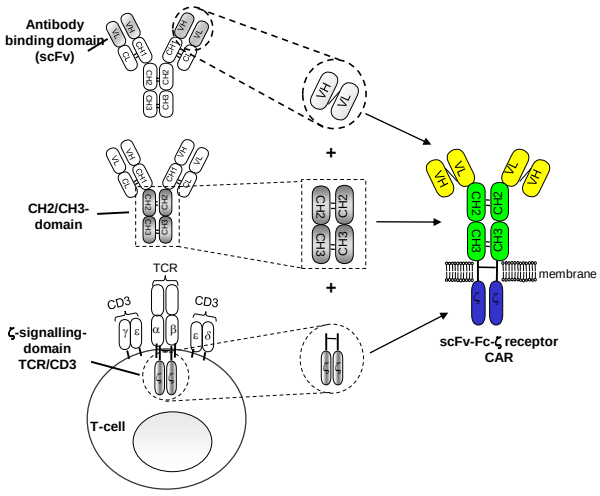
# Adoptive T cell transfer

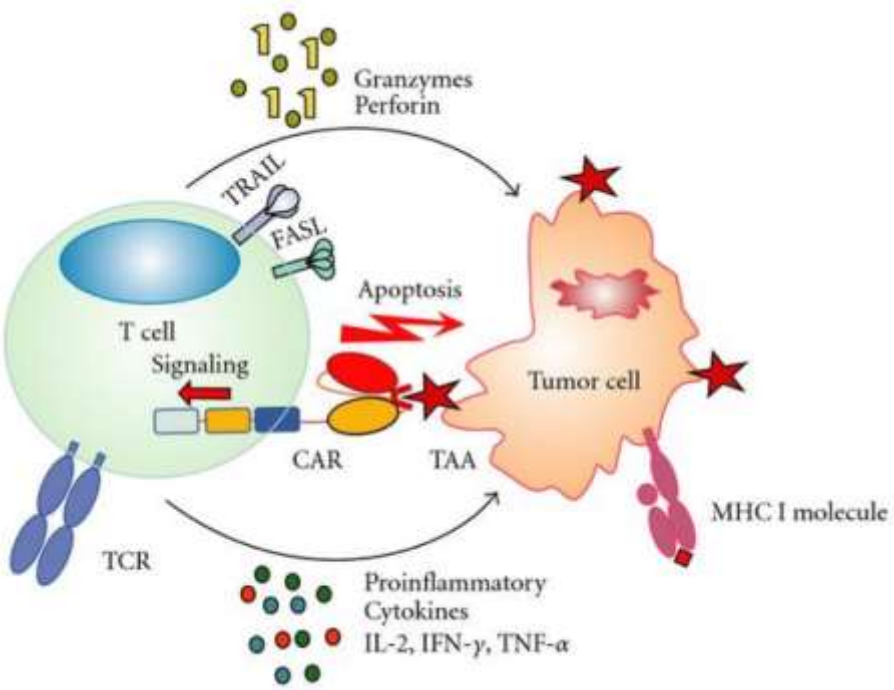
## TIL Therapie





# CARs (chimeric antigen receptor transduced T cells)





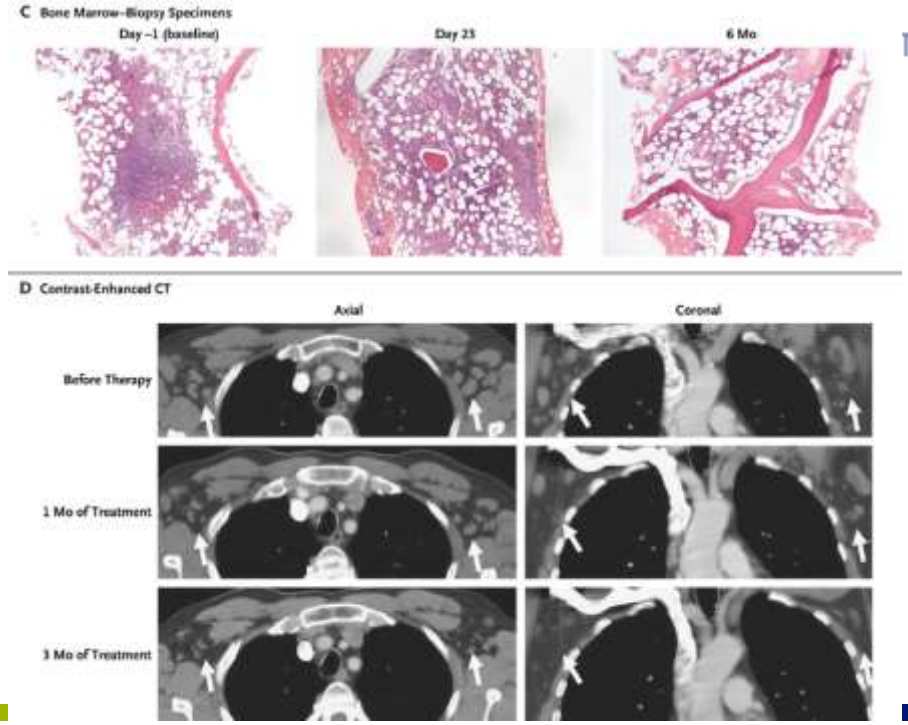

NCT

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

# Chimeric Antigen Receptor–Modified T Cells in Chronic Lymphoid Leukemia

David L. Porter, M.D., Bruce L. Levine, Ph.D., Michael Kalos, Ph.D., Adam Bagg, M.D., and Carl H. June, M.D.




JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

# Chemotherapy-Refractory Diffuse Large B-Cell Lymphoma and Indolent B-Cell Malignancies Can Be Effectively Treated With Autologous T Cells Expressing an Anti-CD19 Chimeric Antigen Receptor

*James N. Kochenderfer, Mark E. Dudley, Sadik H. Kassim, Robert P.T. Somerville, Robert O. Carpenter, Maryalice Stetler-Stevenson, James C. Yang, Giao Q. Phan, Marybeth S. Hughes, Richard M. Sherry, Mark Raffeld, Steven Feldman, Lily Lu, Yong F. Li, Lien T. Ngo, Andre Goy, Tatyana Feldman, David E. Spaner, Michael L. Wang, Clara C. Chen, Sarah M. Kranick, Avindra Nath, Debbie-Ann N. Nathan, Kathleen E. Morton, Mary Ann Toomey, and Steven A. Rosenberg*

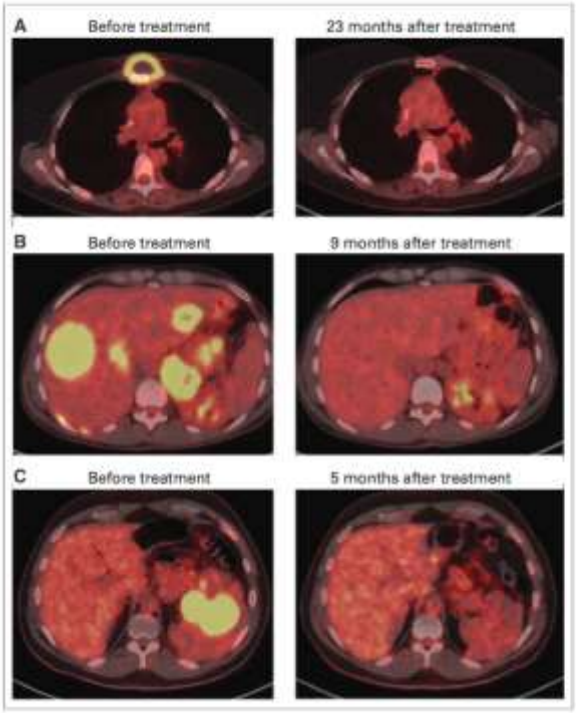
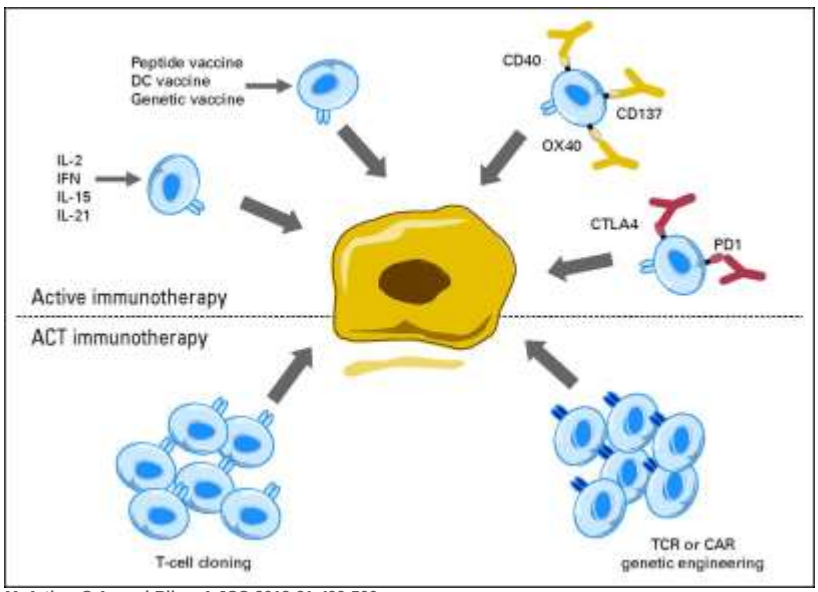
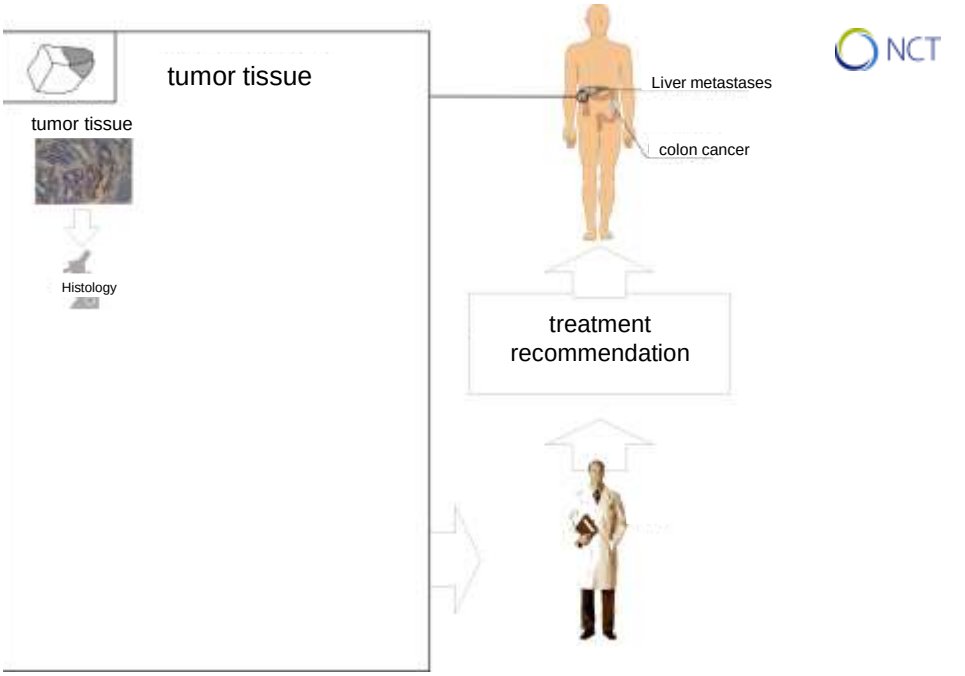


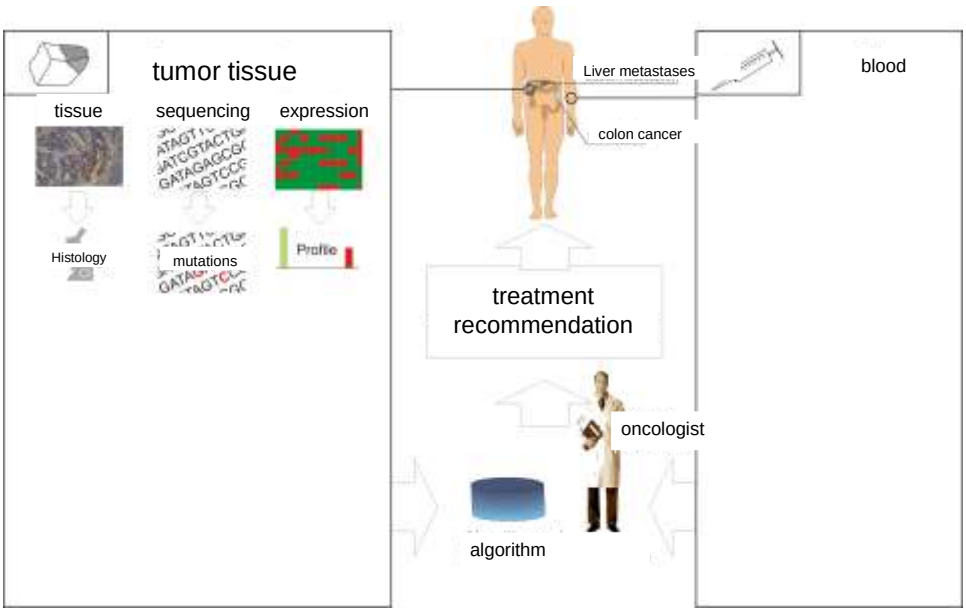

Fig 2. Complete remissions (CRs) of chemotherapy-refractory large-cell lymphomas in patients receiving anti-CD19 chimeric antigen receptor T cells. (A) Positron emission tomography (PET)/computed tomography (CT) scans show CR of chemotherapy-refractory primary mediastinal B-cell lymphoma (PMBCL) in patient No. 2. (B) PET/CT scans demonstrate CR of lymphoma in patient No. 8 who had chemotherapy-refractory PMBCL with extensive liver involvement. (C) PET/CT images show CR of diffuse large B-cell lymphoma, not otherwise specified, in patient No. 14, who had extensive splenic lymphoma.

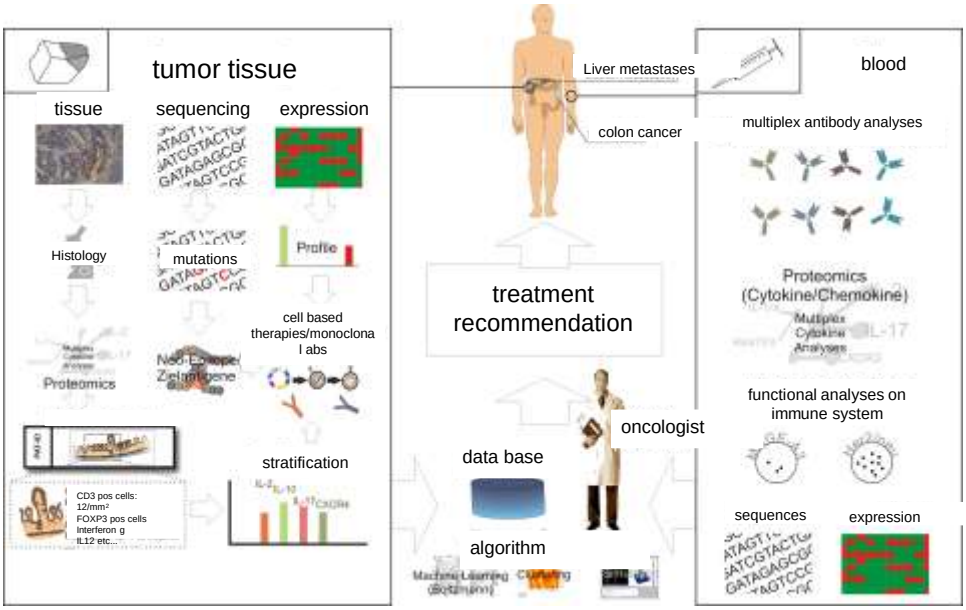
## Strategies Immunotherapy




McArthur G A , and Ribas A JCO 2013;31:499-506


tumor tissue
tumor tissue
Histology
Liver metastases
colon cancer
treatment recommendation
NCT


tumor tissue
tissue
sequencing
expression
Histology
mutations
Profile
Liver metastases
colon cancer
blood
treatment recommendation
oncologist
algorithm




NCT

## Precision oncology

- Molecular diagnostics of individual diseases including genetics, epigenetics, immunology
- Integration of all molecular and immunological data in a model of the individual cancer disease
- Based on those data design of an individual optimal treatment combination:
  - Targeted Drugs (TKI etc)
  - Immunmodulation
  - Individualized vaccine
  - Cell based treatments (adoptive transfer with modified or unmodified T cells)
  - Intelligent combinations
- Treatment includes monitoring of treatment effects in tumor lesions (need for sequential biopsies)
- All data are used to optimize modeling algorithms...

# Jäger Lab
## Medical Oncology
## CCU Applied Tumor Immunity DKFZ

University Medical Center Heidelberg
Dr. Niels Halama
Dr. Inka Zörnig
Dr. Patrick Schmidt
Rodrigo Moraleda
Julia Bitzer
Sophia Keim
Sampada Hundekari
Jin Ho Lee
Jutta Funk
Isabella Gosch
Claudia Ziegelmeier
Claudia Luckner-Minden
Iris Kaiser
Petra Narrog
Max Langknecht

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Zeynep Kosaloglu
Anna Spille
Tina Lerchl
Rosa Eurich