Using the patients immune system to treat tumors

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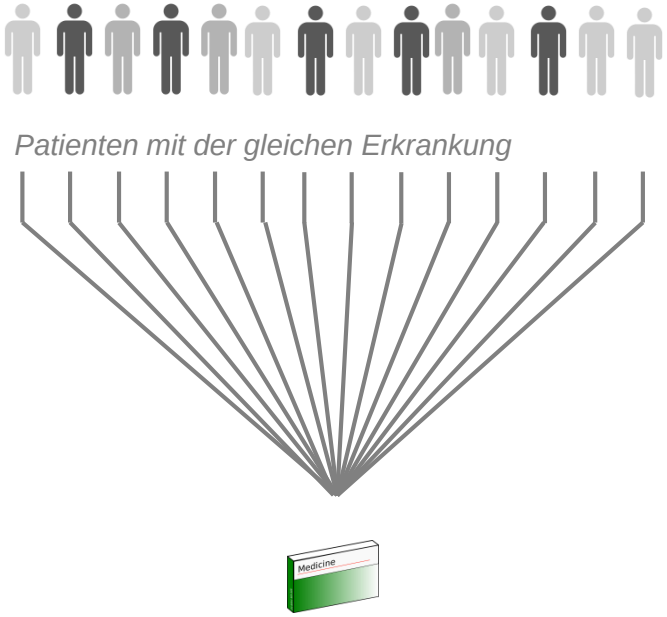
Oncology today

- Most treatment decisions are based on very limited information:
  - morphological description of a microscopical image
  - information from imaging (staging)
  - some situations molecular markers
- Standard recommendations:
  - are based on statistical outcome of randomized trials
  - no deep information available from patients
  - individual patient situation is not reflected
  - adjuvant treatments help the minority of patients treated
  - metastatic disease: 50% chance to benefit for CRC

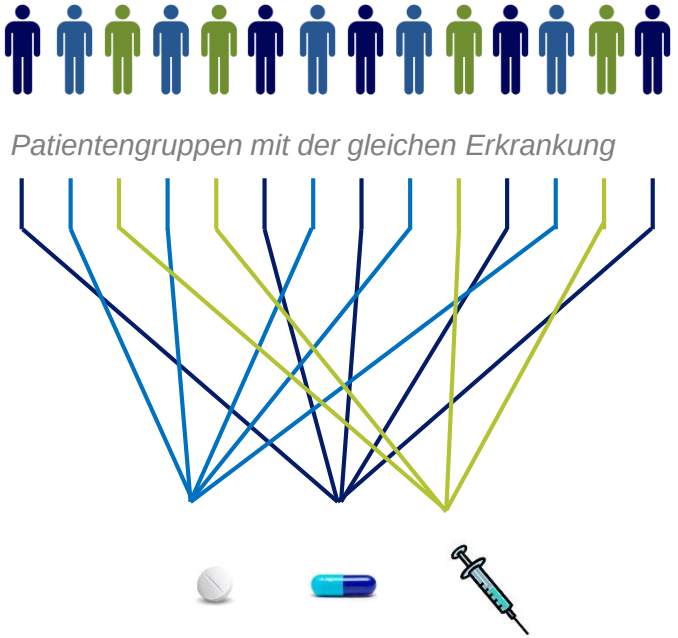
Personalized oncology

Standard treatment:
same disease, same treatment



One treatment for all (standard)

Personalized:
the right treatment for the right subgroup at the right time



Targeted treatments

Genetic profiling (NGS)

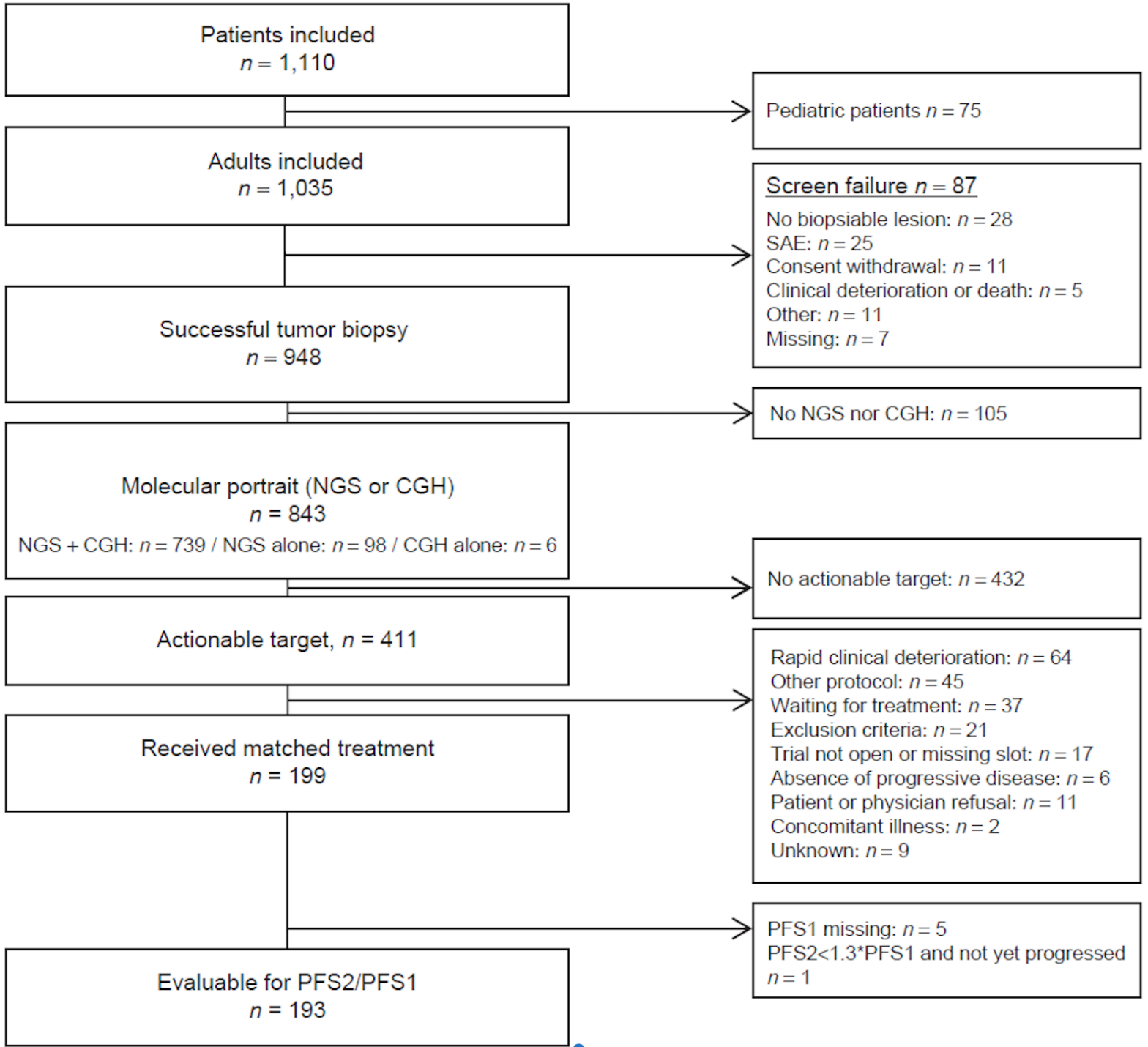
CANCER DISCOVERY

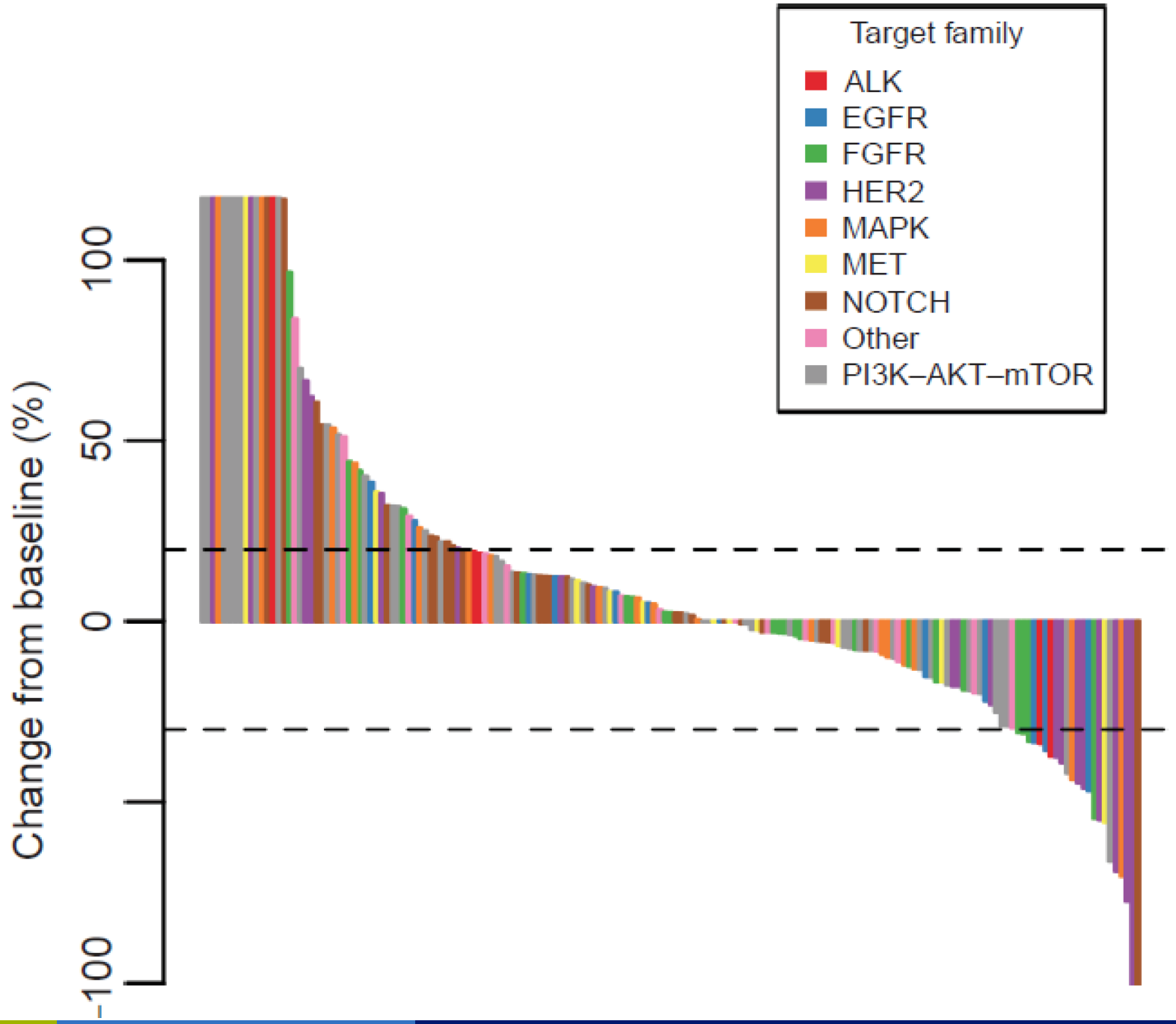
Research Articles

High-Throughput Genomics and Clinical Outcome in Hard-to-Treat Advanced Cancers: Results of the MOSCATO 01 Trial

Christophe Massard, Stefan Michiels, Charles Ferté, Marie-Cécile Le Deley, Ludovic Lacroix, Antoine Hollebecque, Loic Verlingue, Ecaterina Ileana, Silvia Rosellini, Samy Ammari, Maud Ngo-Camus, Rastislav Bahleda, Anas Gazzah, Andrea Varga, Sophie Postel-Vinay, Yohann Loriot, Caroline Even, Ingrid Breuskin, Nathalie Auger, Bastien Job, Thierry De Baere, Frederic Deschamps, Philippe Vielh, Jean-Yves Scoazec, Vladimir Lazar, Catherine Richon, Vincent Ribrag, Eric Deutsch, Eric Angevin, Gilles Vassal, Alexander Eggermont, Fabrice André, and Jean-Charles Soria

DOI: 10.1158/2159-8290.CD-16-1396 Published April 2017

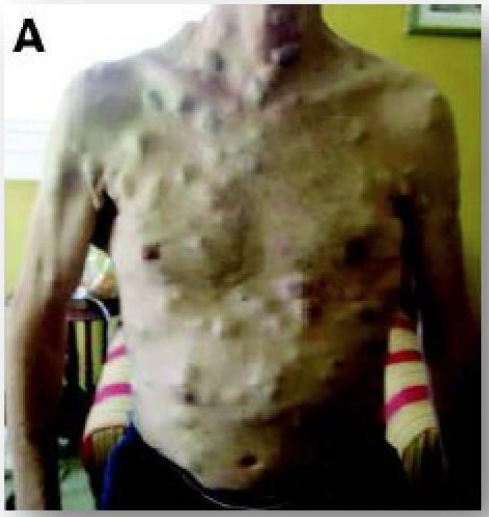

Patients included
n = 1,110
Pediatric patients n = 75
Adults included
n = 1,035
Screen failure n = 87
No biopsiable lesion: n = 28
SAE: n = 25
Consent withdrawal: n = 11
Clinical deterioration or death: n = 5
Other: n = 11
Missing: n = 7
Successful tumor biopsy
n = 948
No NGS nor CGH: n = 105
Molecular portrait (NGS or CGH)
n = 843
NGS + CGH: n = 739 / NGS alone: n = 98 / CGH alone: n = 6
No actionable target: n = 432
Actionable target, n = 411
Rapid clinical deterioration: n = 64
Other protocol: n = 45
Waiting for treatment: n = 37
Exclusion criteria: n = 21
Trial not open or missing slot: n = 17
Absence of progressive disease: n = 6
Patient or physician refusal: n = 11
Concomitant illness: n = 2
Unknown: n = 9
Received matched treatment
n = 199
PFS1 missing: n = 5
PFS2<1.3*PFS1 and not yet progressed
n = 1
Evaluable for PFS2/PFS1
n = 193


Target family
ALK
EGFR
FGFR
HER2
MAPK
MET
NOTCH
Other
PI3K–AKT–mTOR
Change from baseline (%)
100
50
0
−100

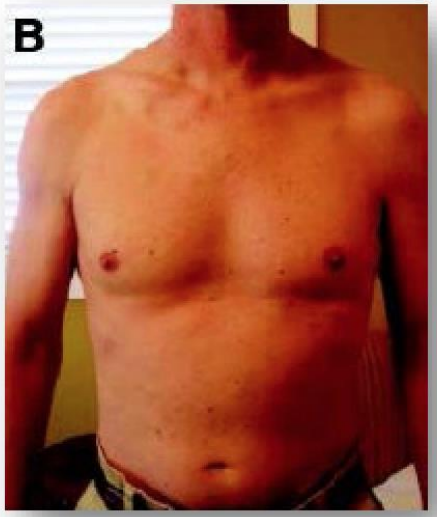
Summary MOSCATO 001

- 1,035 adult patients were included, biopsy was performed in 948.
- An actionable molecular alteration was identified in 411 of 843
- A total of 199 patients were treated with a targeted therapy matched to a genomic alteration
- The PFS2/PFS1 ratio was >1.3 in 33% of the patients (63/193). Objective responses were observed in 22 of 194 patients (11%; 95% CI, 7%–17%), and median overall survival was 11.9 months (95% CI, 9.5–14.3 months).
- **SIGNIFICANCE:** This study suggests that high-throughput genomics could improve outcomes in a subset of patients with hard-to-treat cancers. Although these results are encouraging, **only 7%** of the successfully screened patients benefited from this approach.

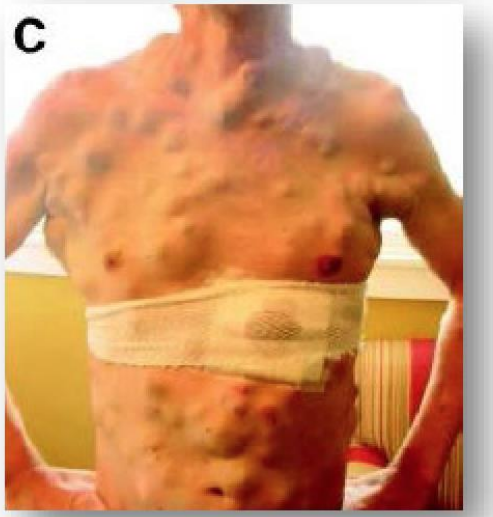
Cancer Discov; 7(6); 1–10. ©2017 AACR



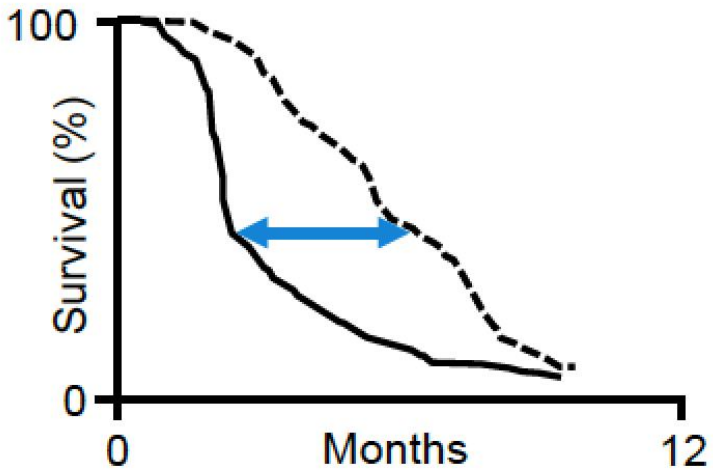
Before BRAFi



After 15 weeks of BRAFi



After 23 weeks of BRAFi

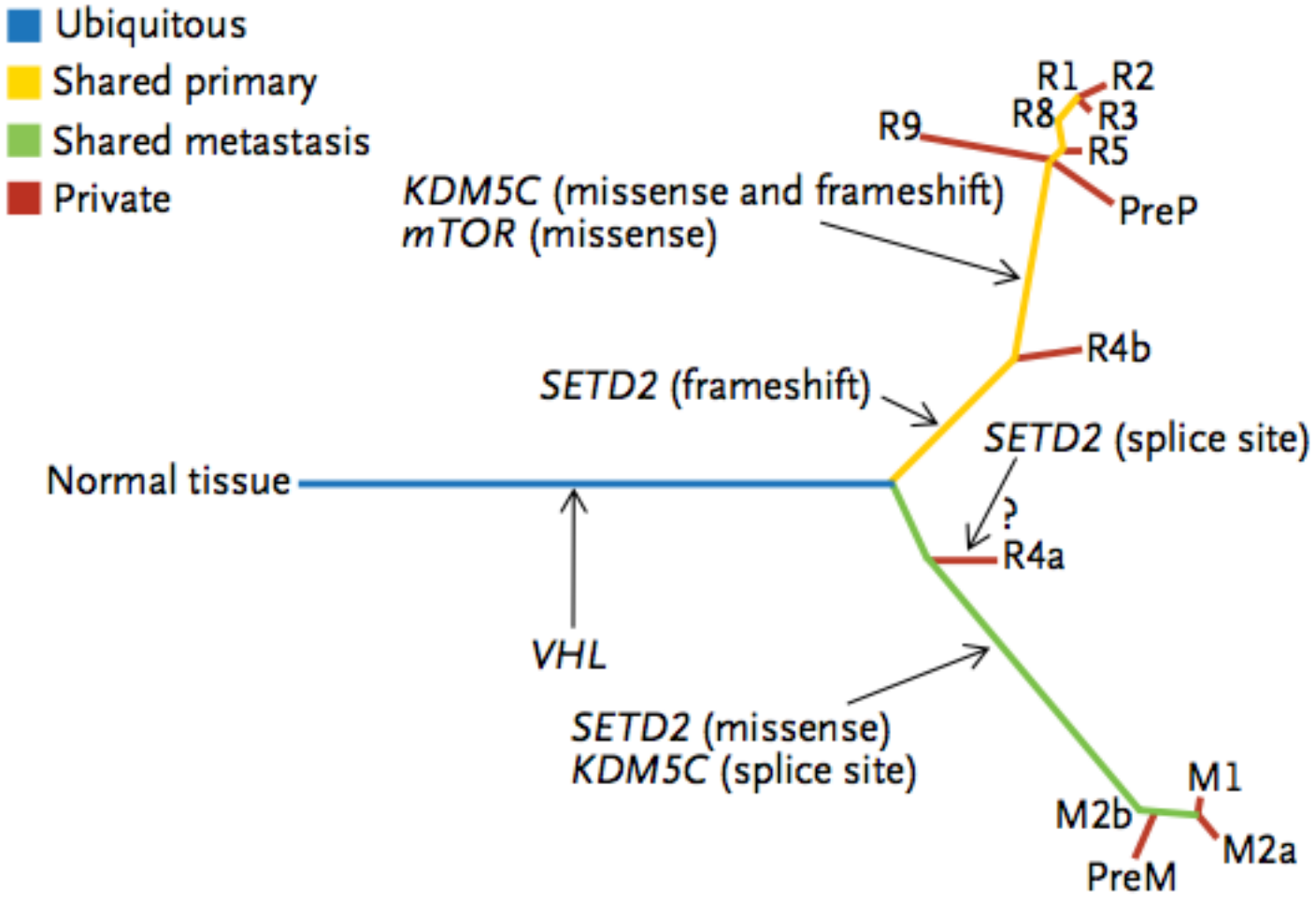


BRAFi=BRAF inhibitor

Wagle N, et al. J Clin Oncol 2011

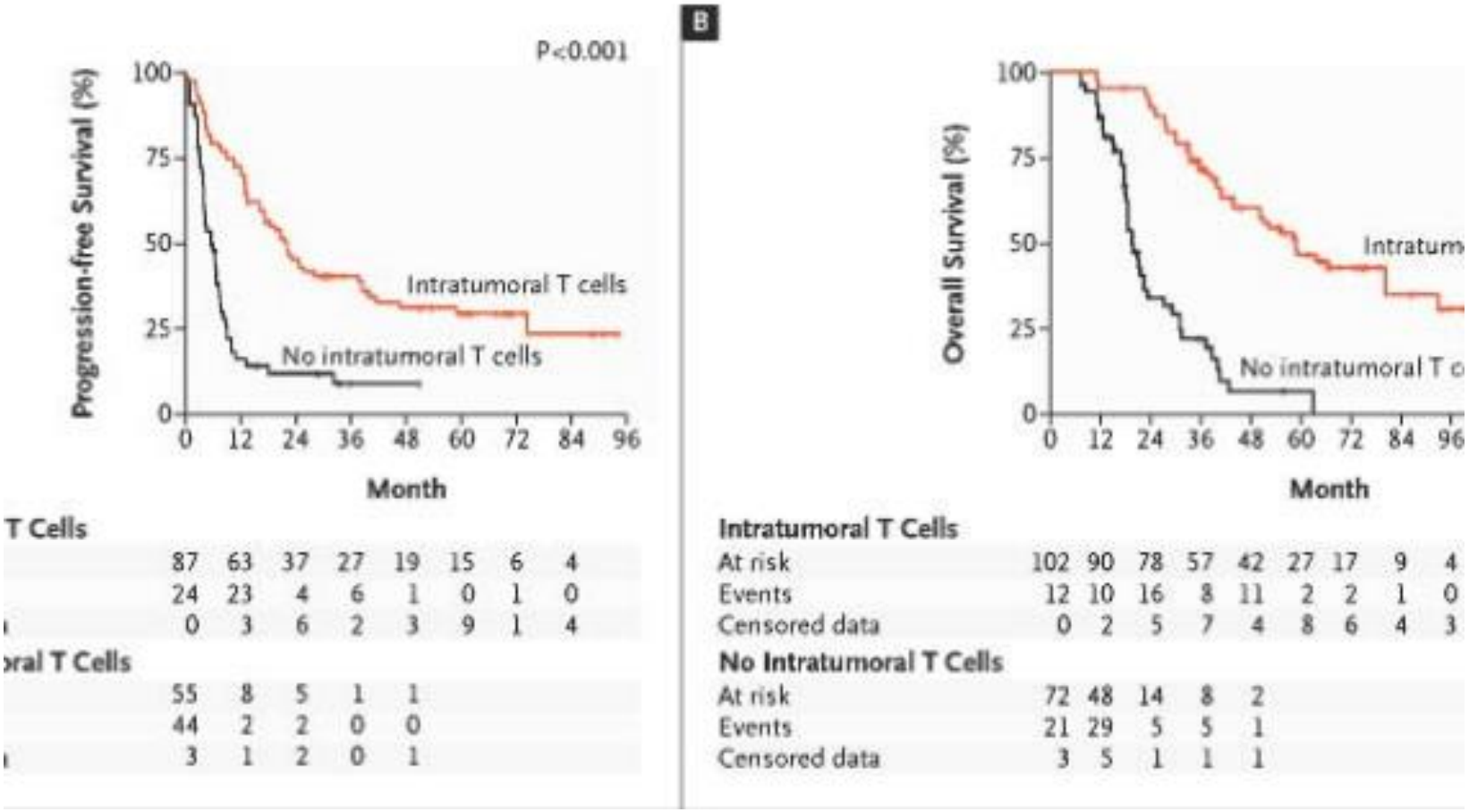
Adapted from Chapman PB, et al. N Engl J Med 2011

Tumor Heterogeneity



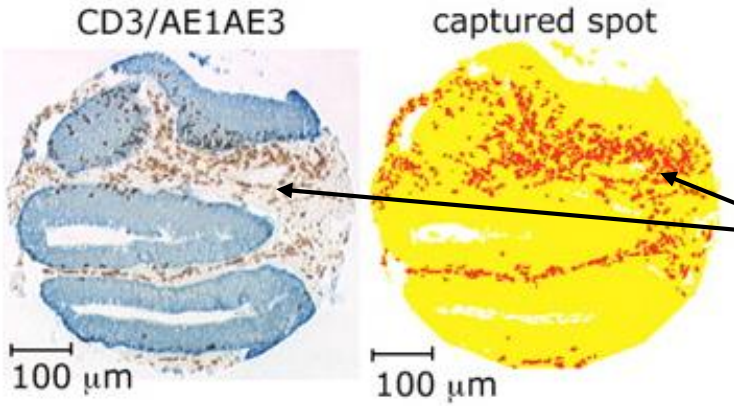
Gerlinger, NEJM, 2012

Infiltrating T cells in ovarian cancer

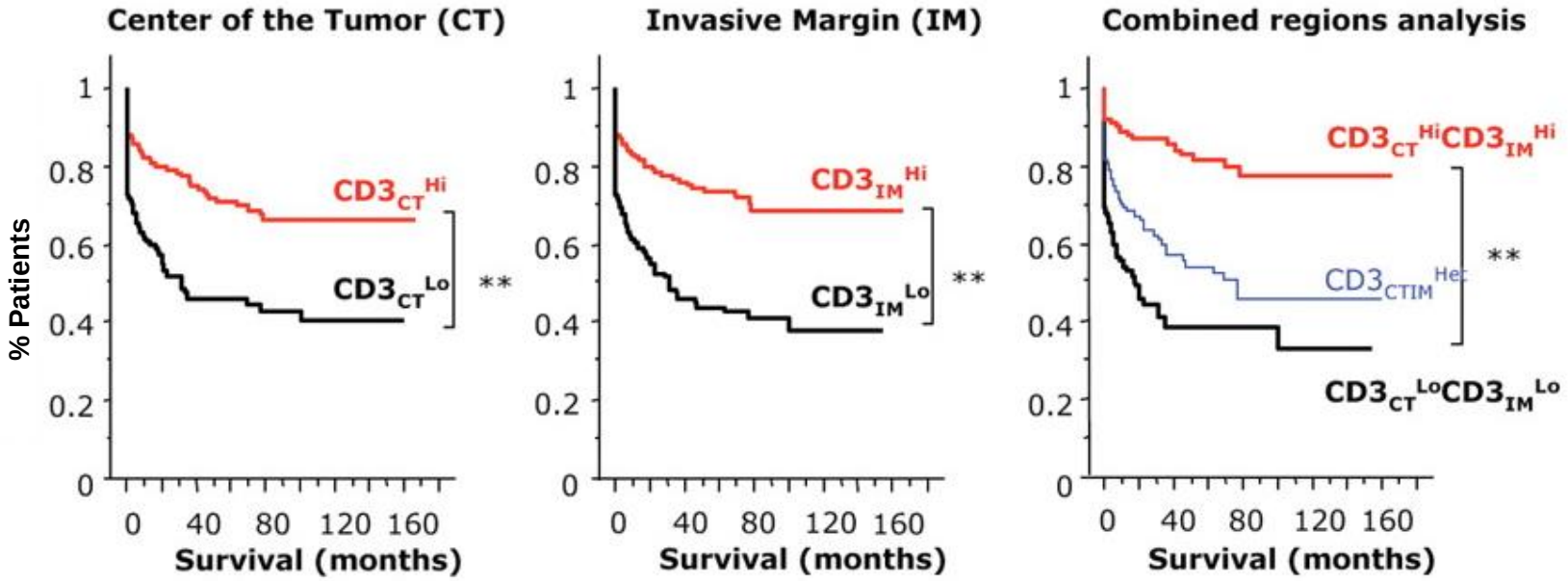


Zhang, N Engl J Med 2003;

Prognostic significance of infiltrating T cells in CRC

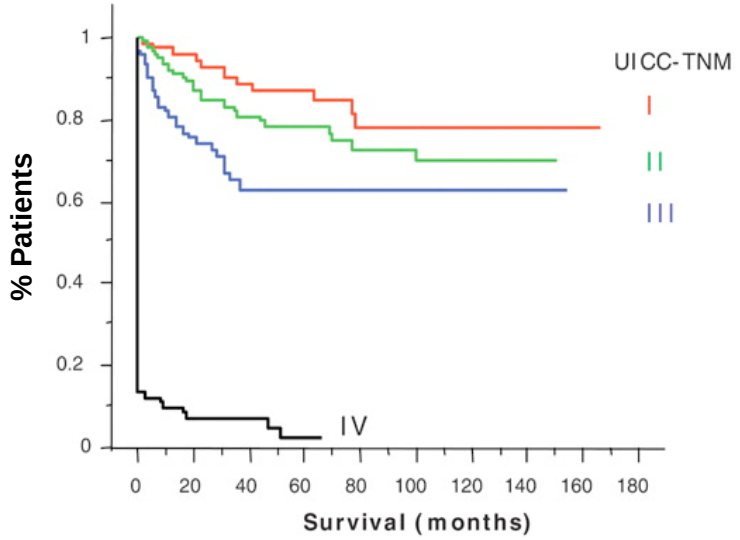


Infiltrating T cells

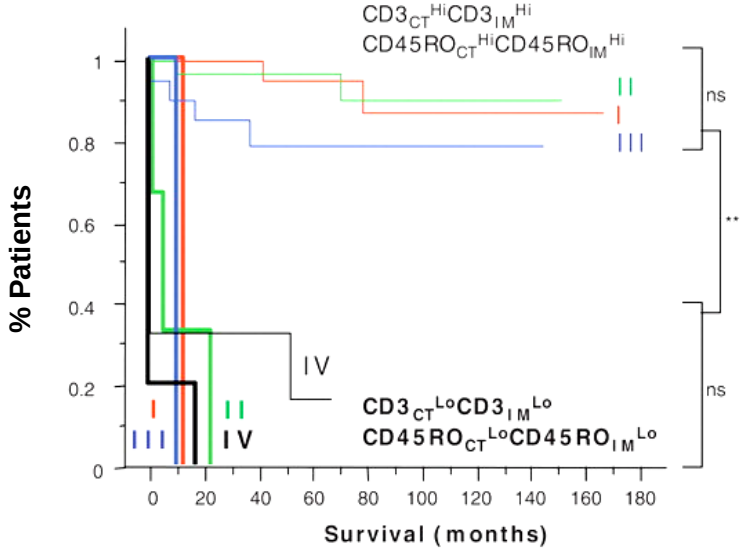


Galon J, et al. Science 2006

Prognostic significance of infiltrating T cells in CRC

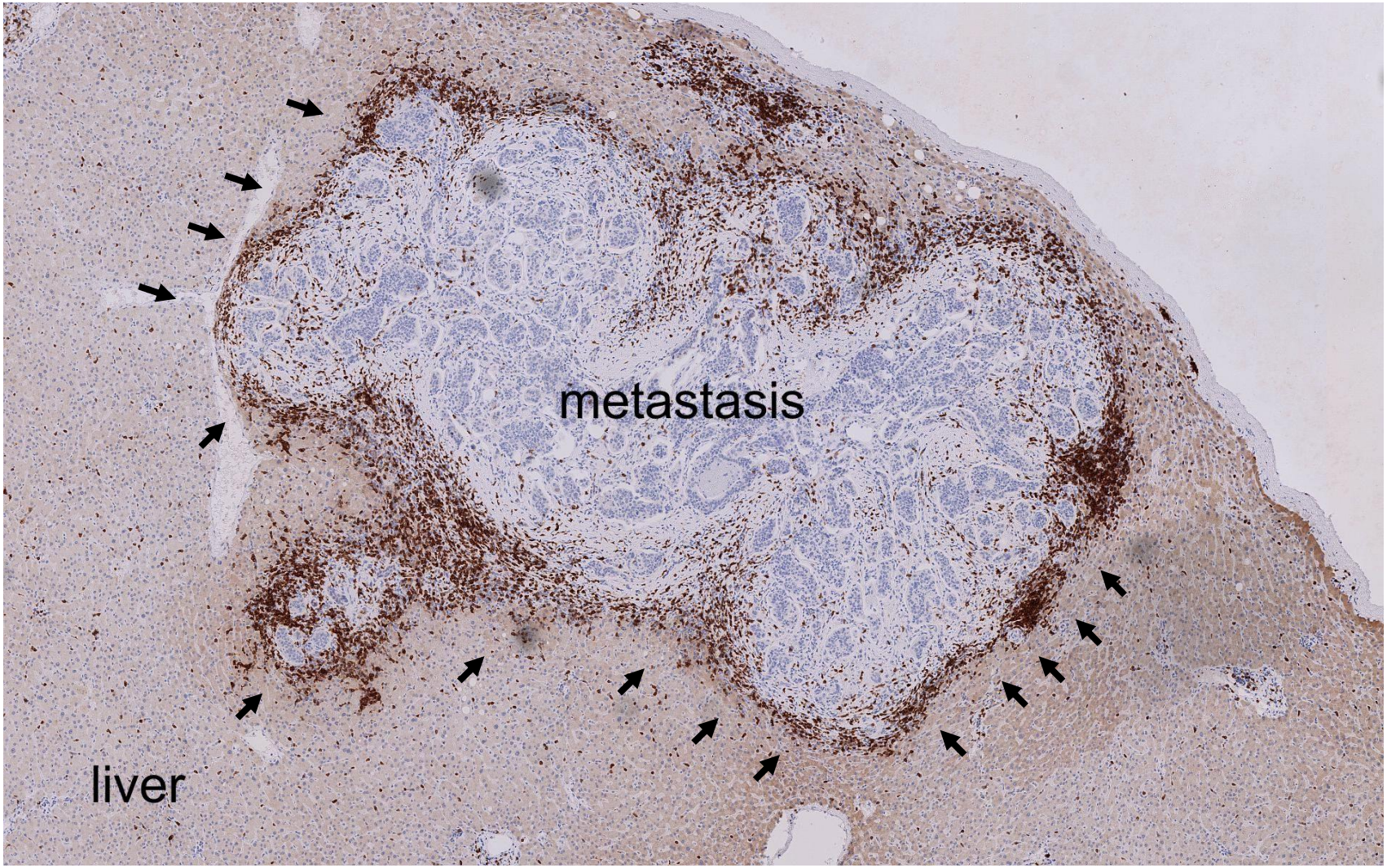


Tumor infiltrating memmory T cells

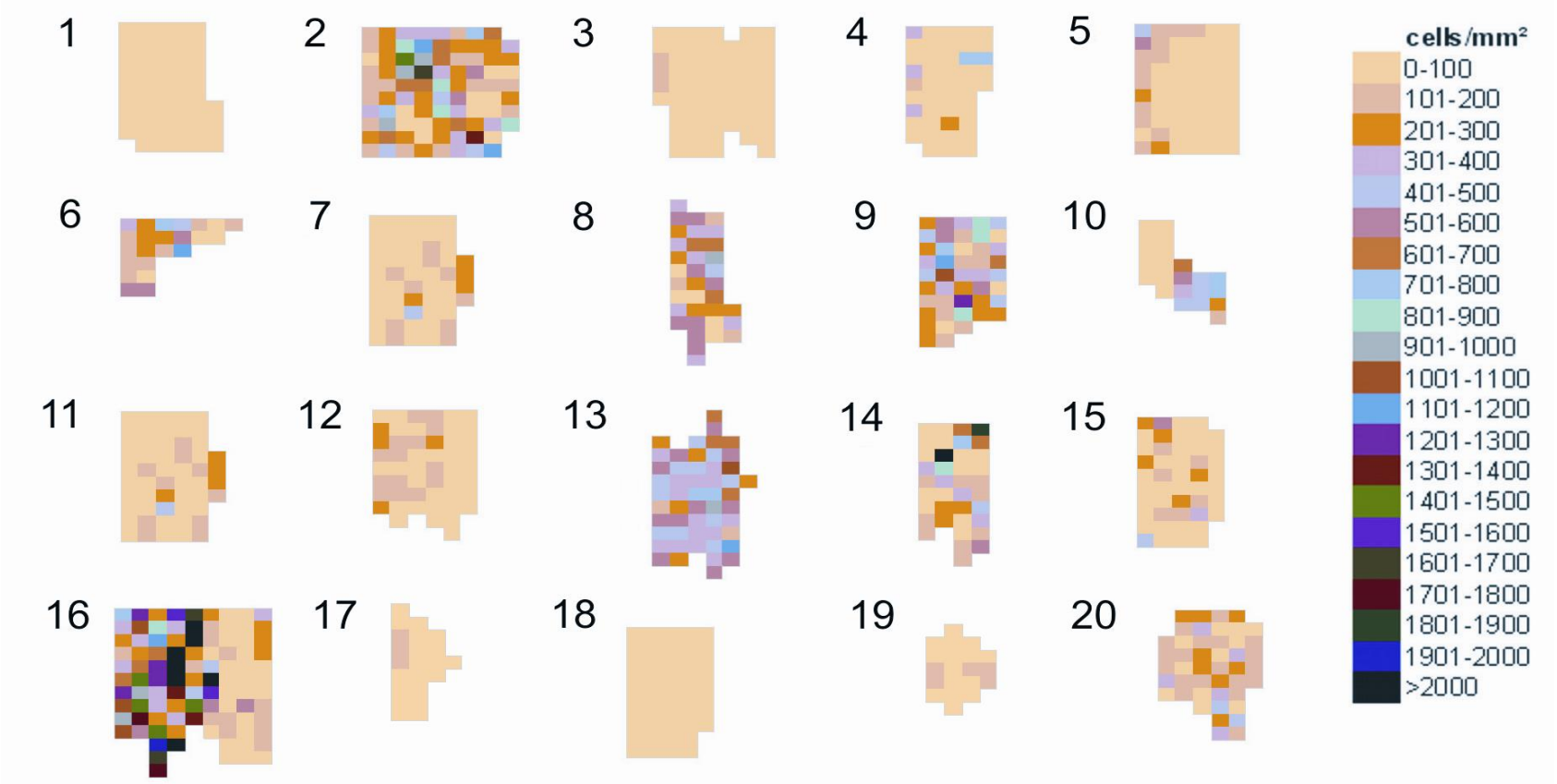


Galon et al., Science, 2006

T cells at the metastatic tumor site (CRC, MSS)



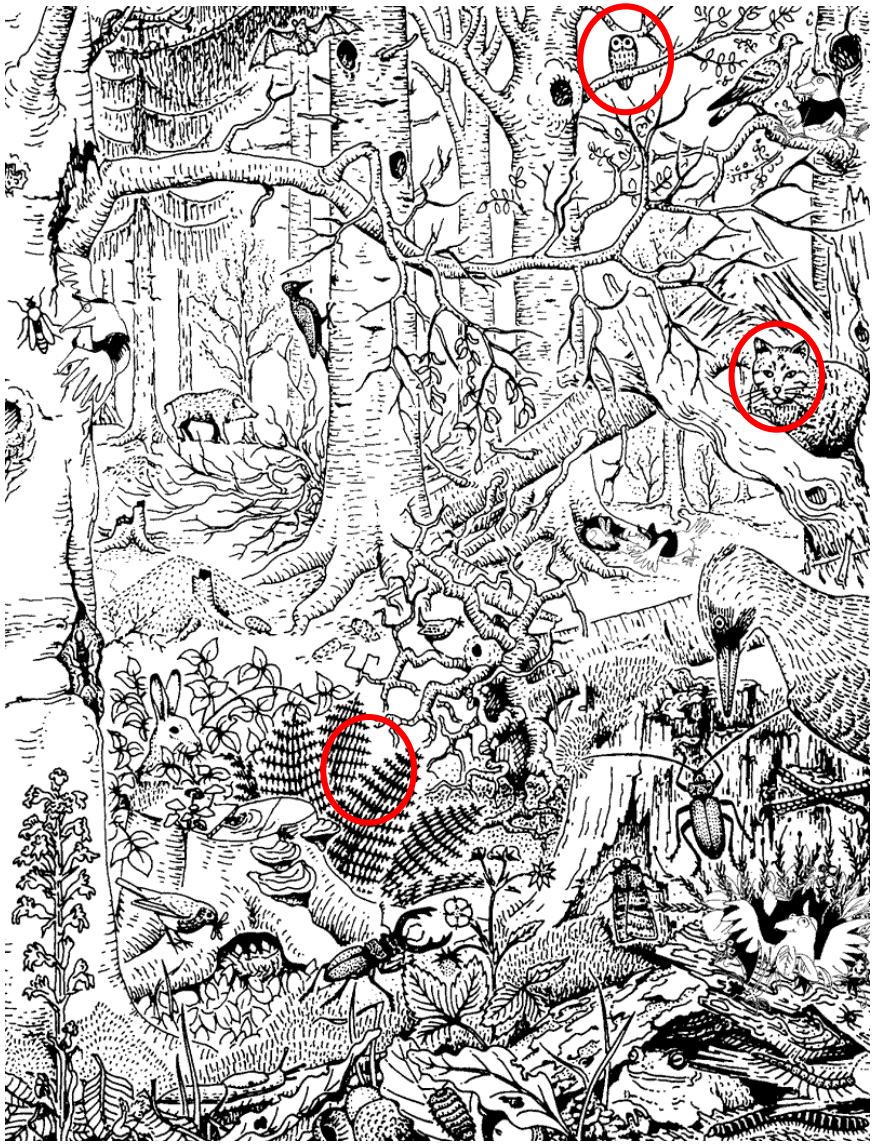
Immunological tumor maps



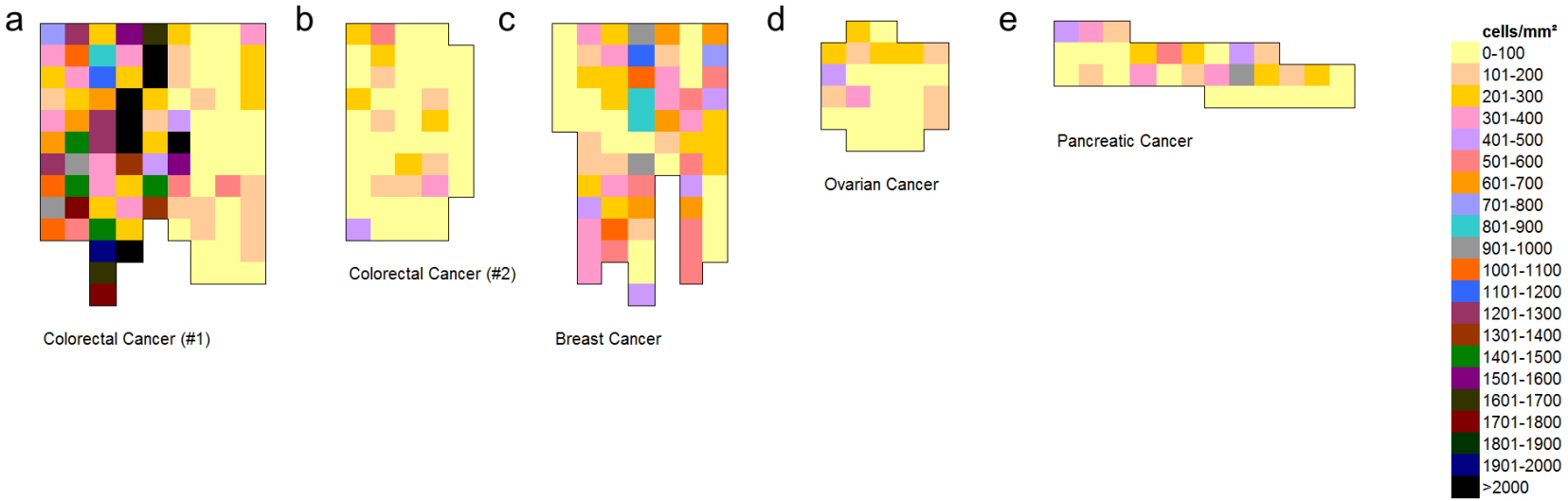
Primary CRC, no MSI

Halama N, Zoernig I, Michel S, Kloor M, Grauling-Halama S, Schirmacher P, Jäger D, Grabe N.
Tumor Maps: Quantification of Prognostic Immune Cell Markers in Colorectal Cancer Using Whole Slide Imaging, *Analytical and Quantitative Cytology and Histology*, 2010

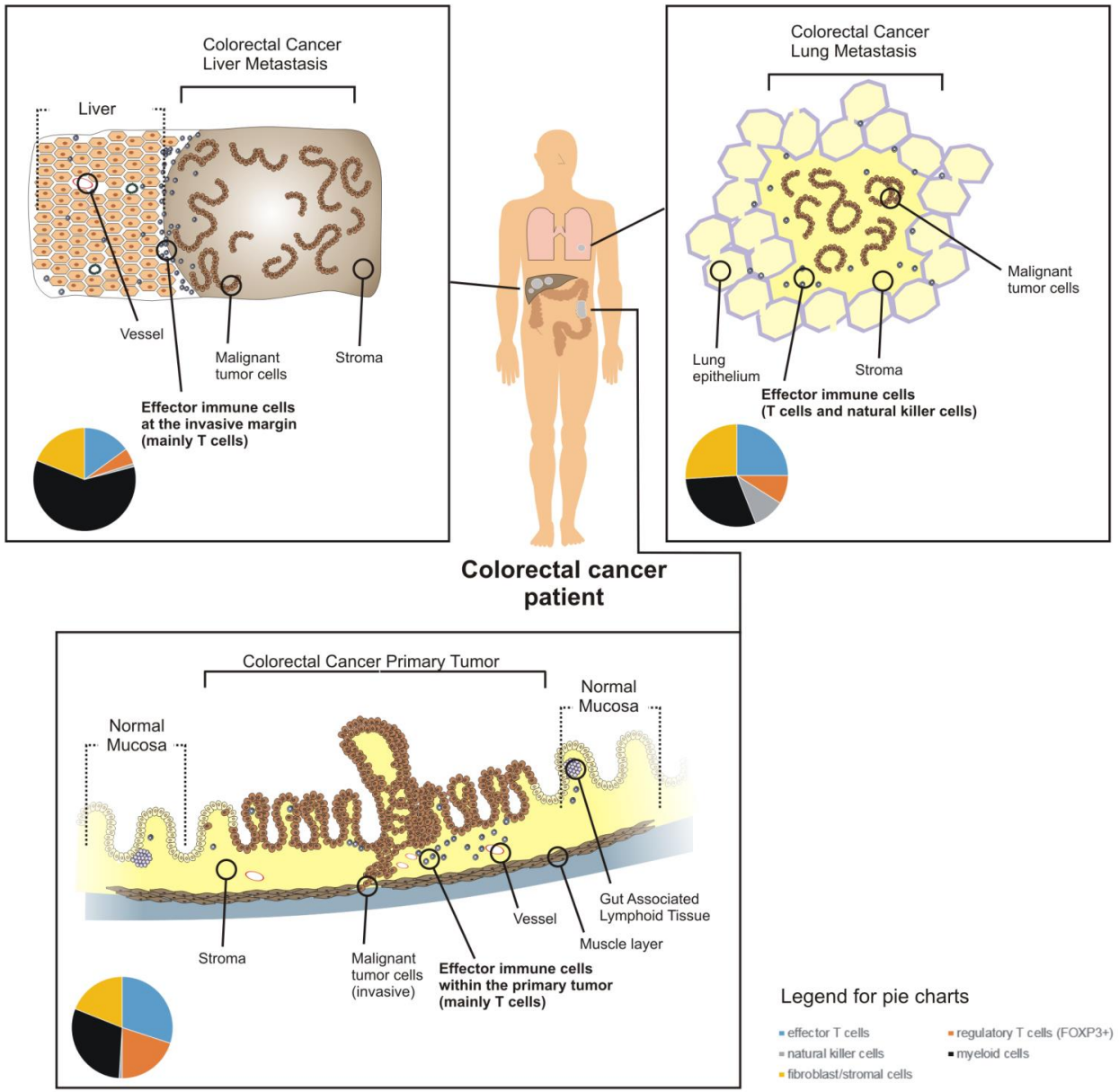
Selecting a representative region…?



Immunological tumor maps: Differences between different entities

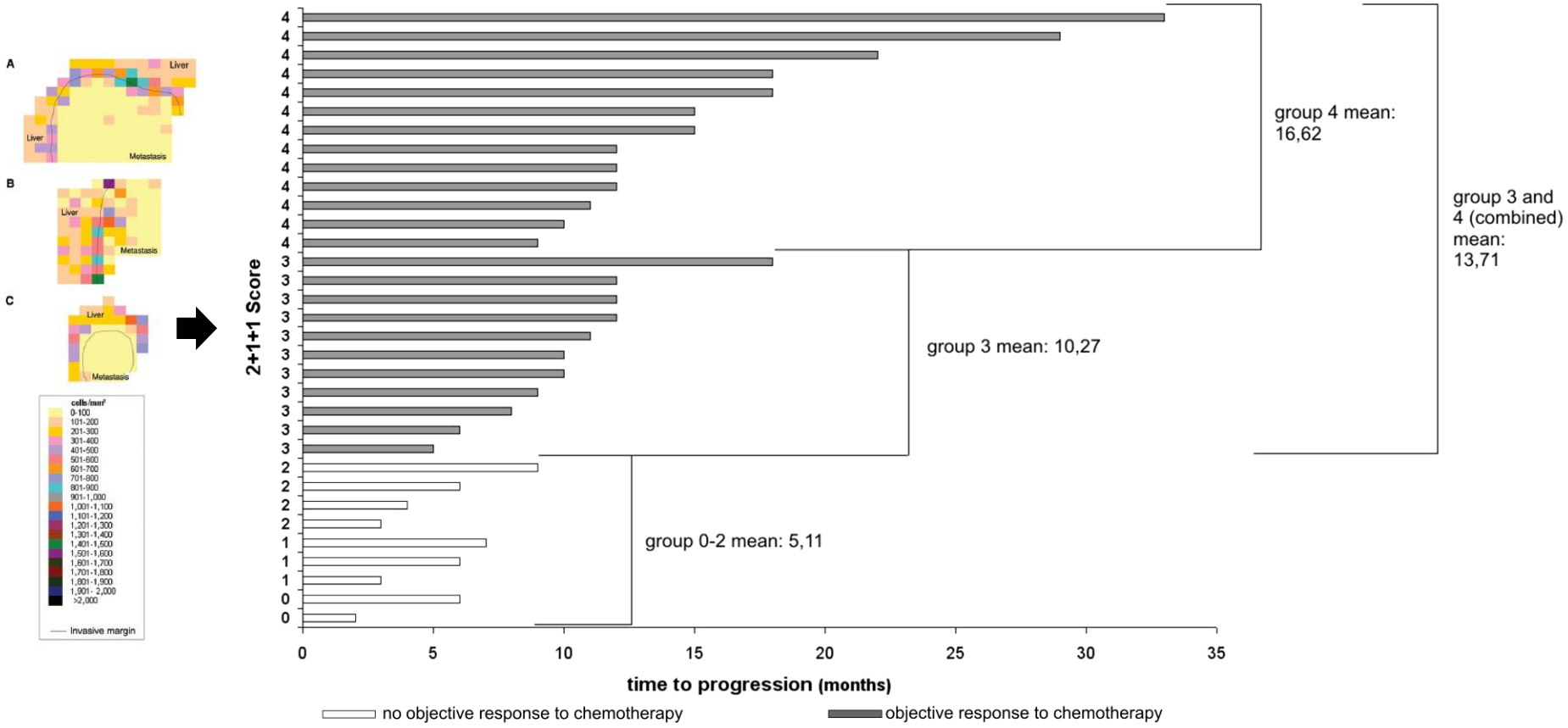


Immunologic landscape of metastatic colorectal cancer



Halama et al. Oncoimmunology 2012
Keim et al. Oncoimmunology 2013
Halama et al. Cancer Immunol Immunotherapy, in revision

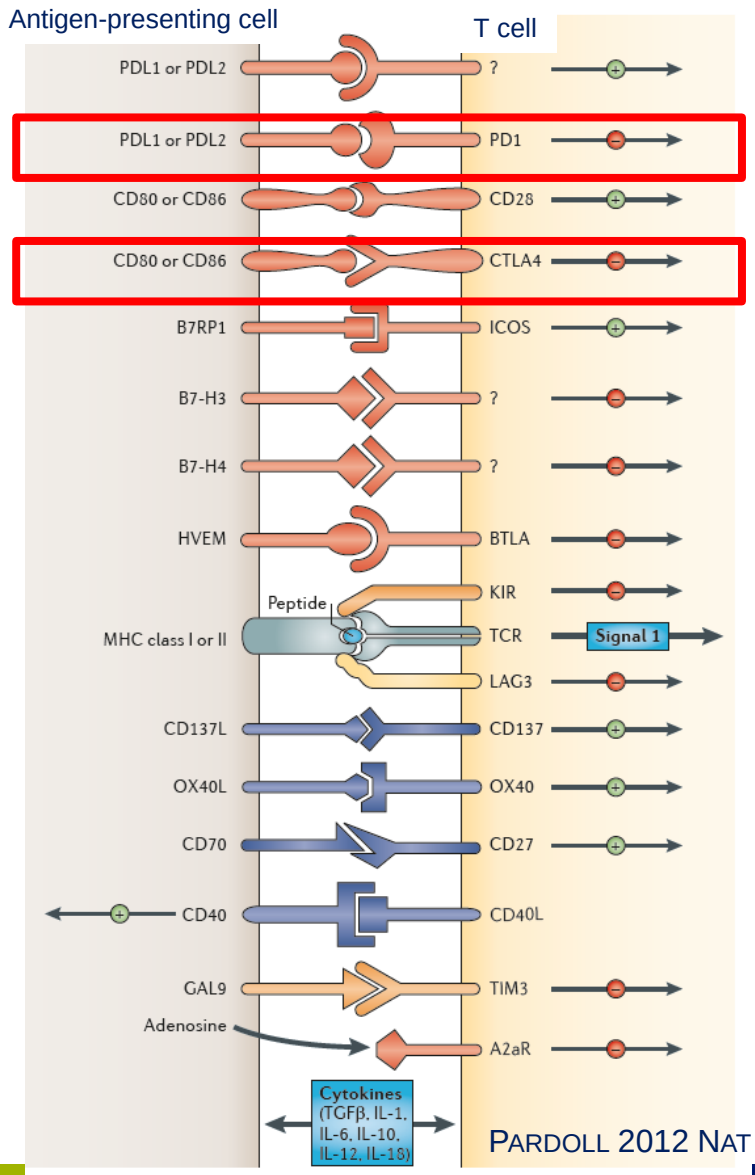
T cell density and response to chemotherapy



Validation cohort
101 pts from multicenter trial (CELIM)
Prediction:
Objective response to chemotherapy
Sensitivity: 79%
Specificity: 100%

Halama et al. Cancer Research 2011

Regulation of T cell responses by co-stimulation and co-inhibition



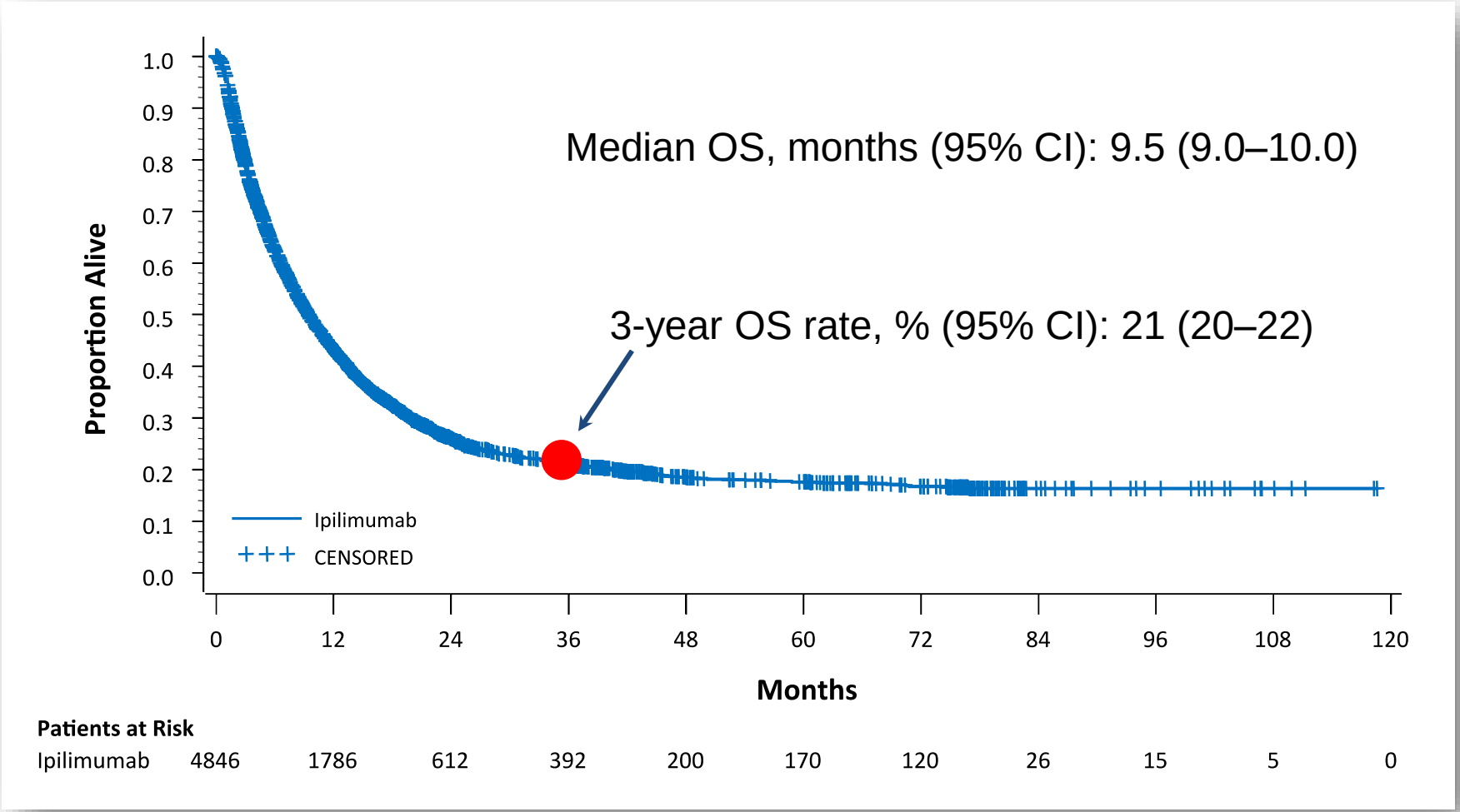
Anti-CTLA-4 antibodies:
Ipilimumab (Yervoy , Bristol- Myers Squibb)

Anti-PD-1 antibodies:
Nivolumab (Opdivo, Brristol.Myers Squibb)
Pembrolizumab (Keytruda, Merck)

Anti-PD-L1 Antikörper
Atezolizumab (Genentech/Roche)
Durvalumab (MSD)

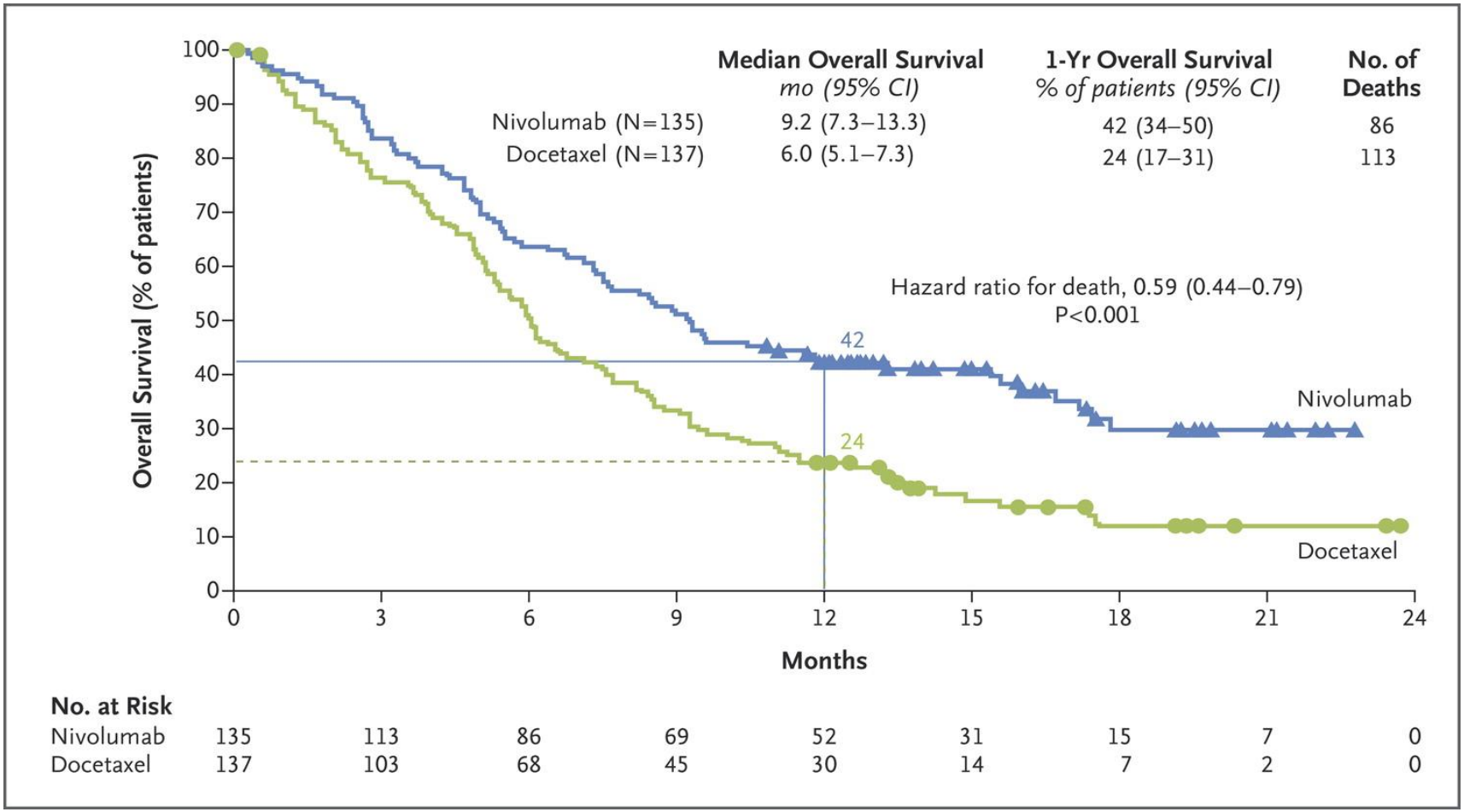
PARDOLL 2012 NAT REV CANCER

Ipilimumab in stage IV melanoma



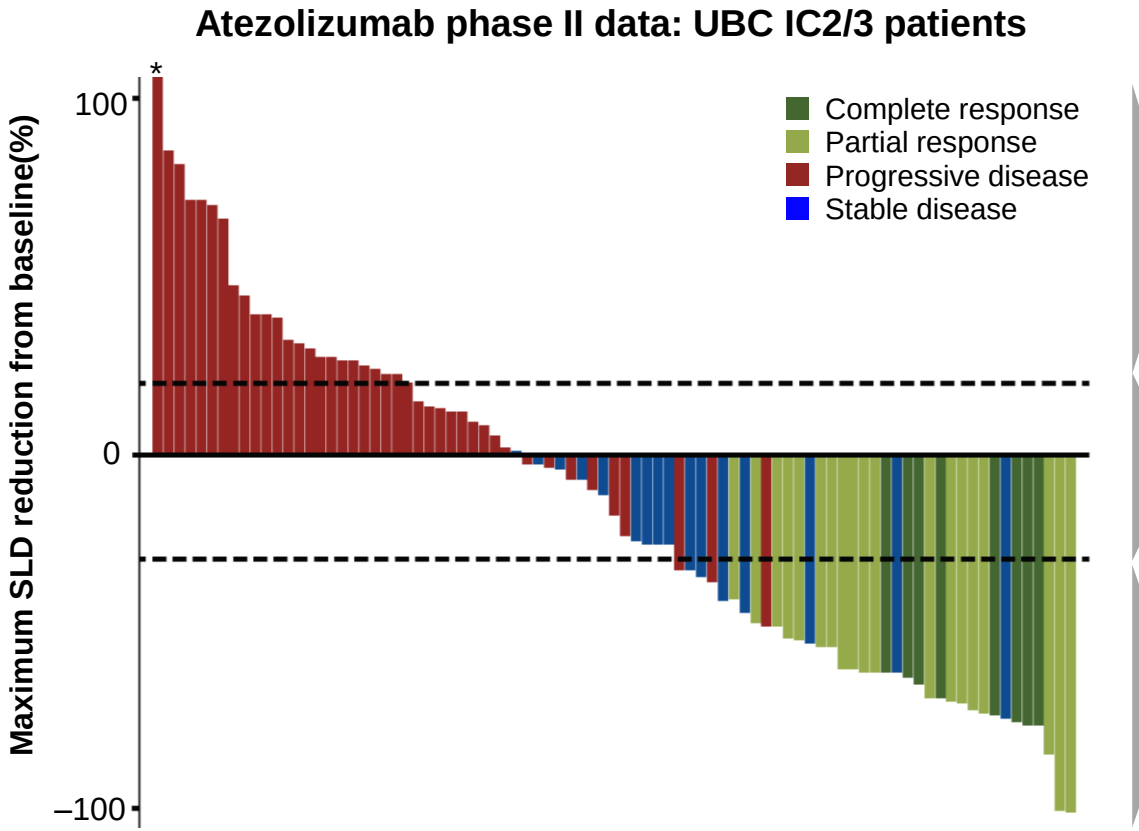
Schadendorf, et al. J Clin Oncol 2015

Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer



Brahmer J et al. N Engl J Med 2015;373:123-135.

Why do some patients not respond?



Progressive disease (PD)
- *No pre-existing immunity?*

Stable disease (SD)
- *Insufficient T cell immunity?*
- *Multiple negative regulators?*

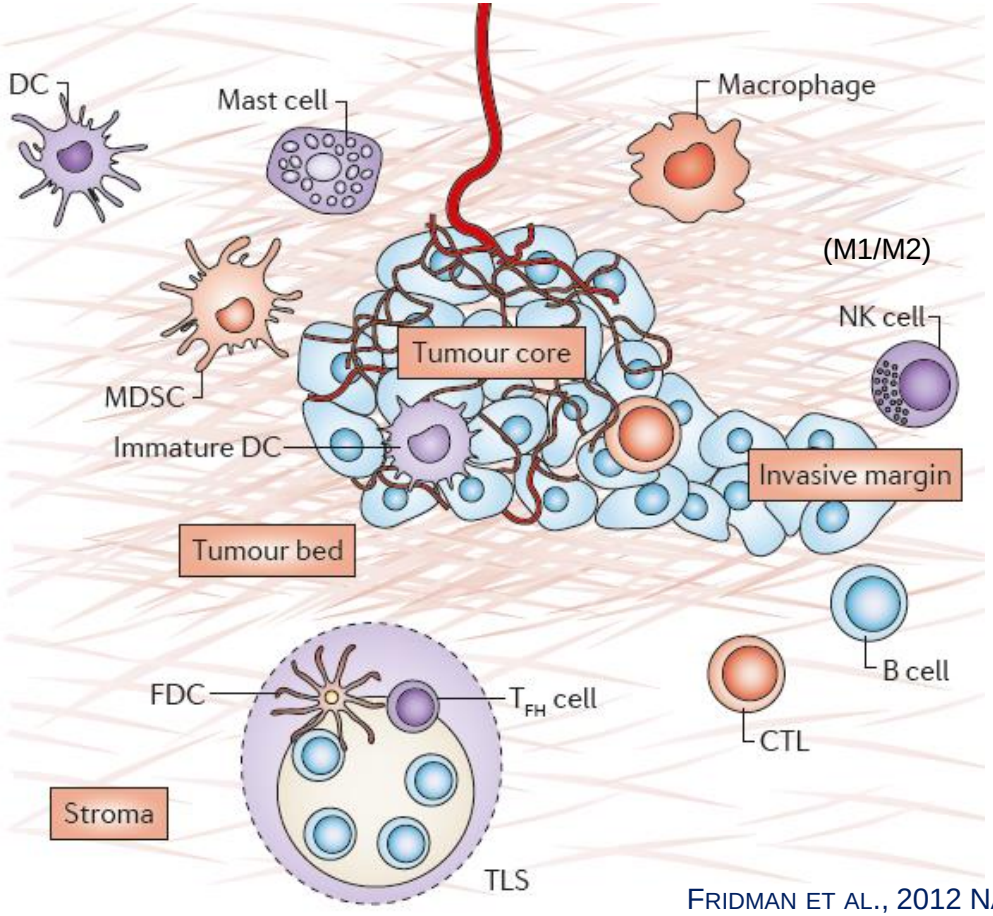
Monotherapy durable responses (PR/CR)
- *Insufficient T cell immunity?*
- *Multiple negative regulators?*

SLD, sum of longest diameters. *>100% increase.

Per RECIST v1.1 (independent review). Data cutoff May 5, 2015. Follow up ≥24 weeks. Patients without post-baseline tumour assessments not included. Several patients with CR had <100% reduction due to lymph node target lesions. All lymph nodes returned to normal size per RECIST v1.1.

Rosenberg, et al. ECC 2015

Tumor micromileu

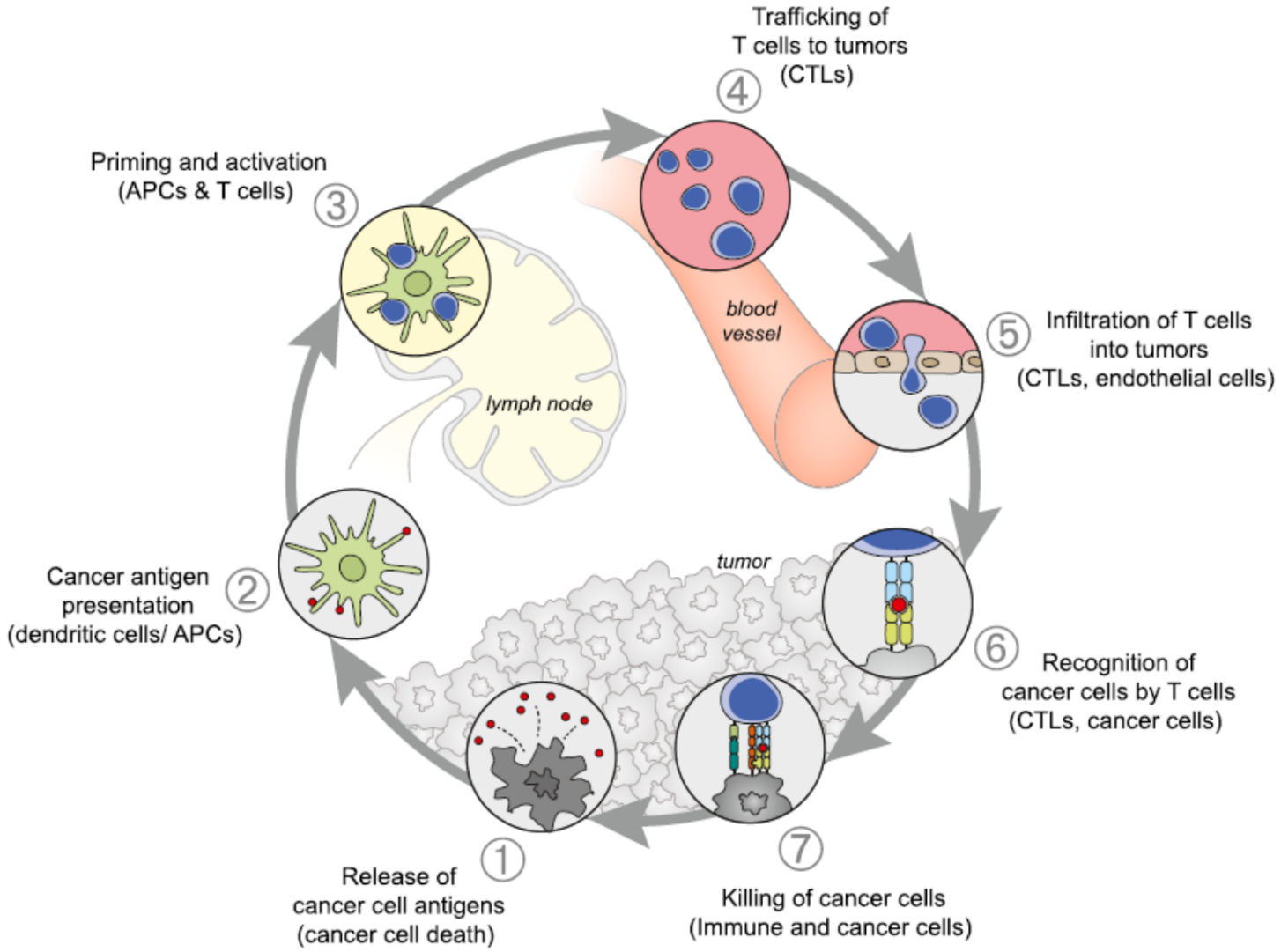


FRIDMAN ET AL., 2012 NAT REV CANCER

Tumor infiltrating T cells (TIL) are prognostic and predictive

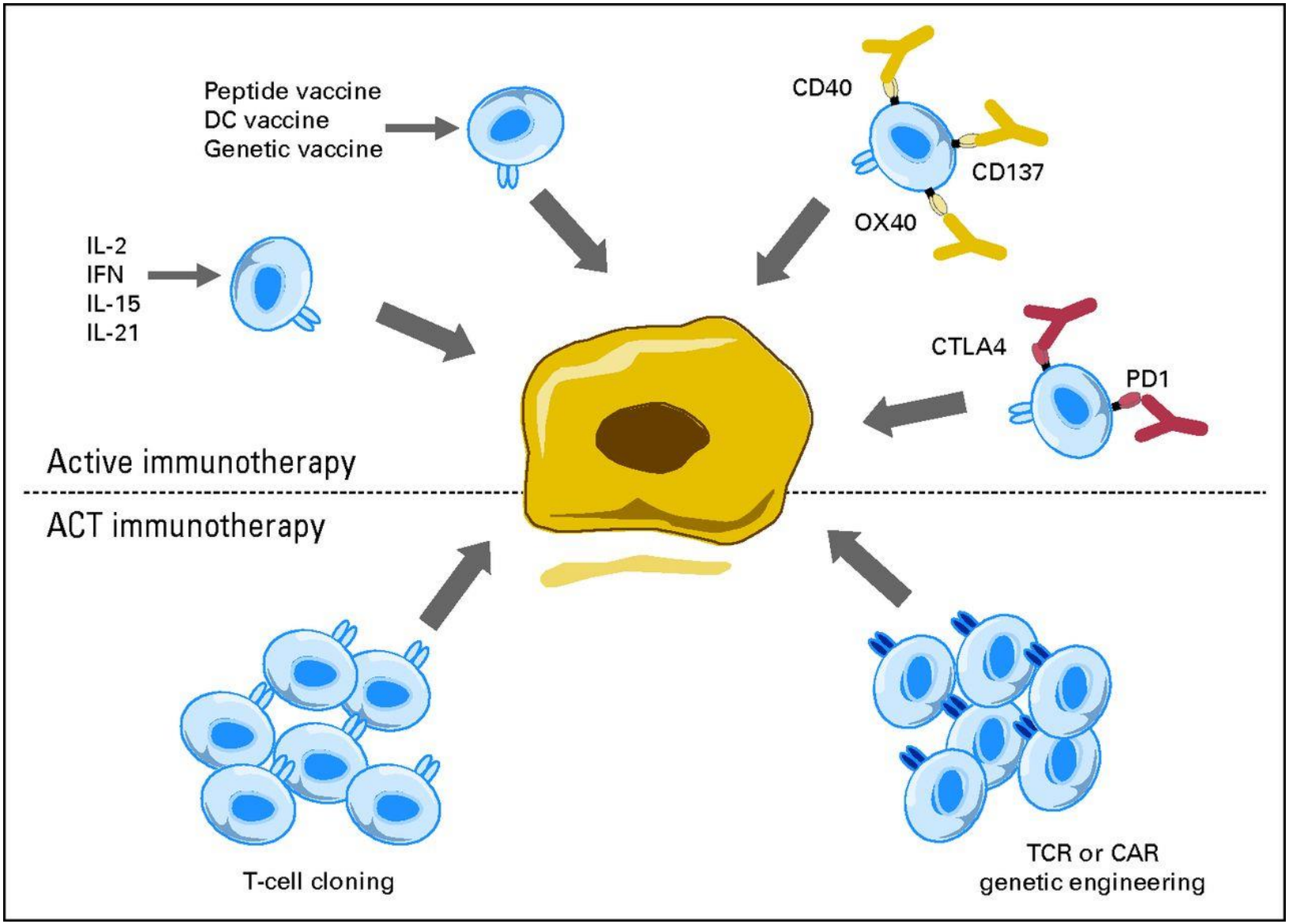
- ADAMS ET AL., 2014 J CLIN ONCOL
- DENKERT ET AL., 2010 J CLIN ONCOL
- DENKERT ET AL., 2014 J CLIN ONCOL
- LOI ET AL., 2013 J CLIN ONCOL
- WEST ET AL., 2011 BREAST CANCER RES
- MAHMOUD ET AL., 2011 J CLIN ONCOL
- MARROGI ET AL., 1997 INT J CANCER
- MENEGAZ ET AL., 2008 EUR J GYNAECOL ONCOL

Complexity of tumor host interaction



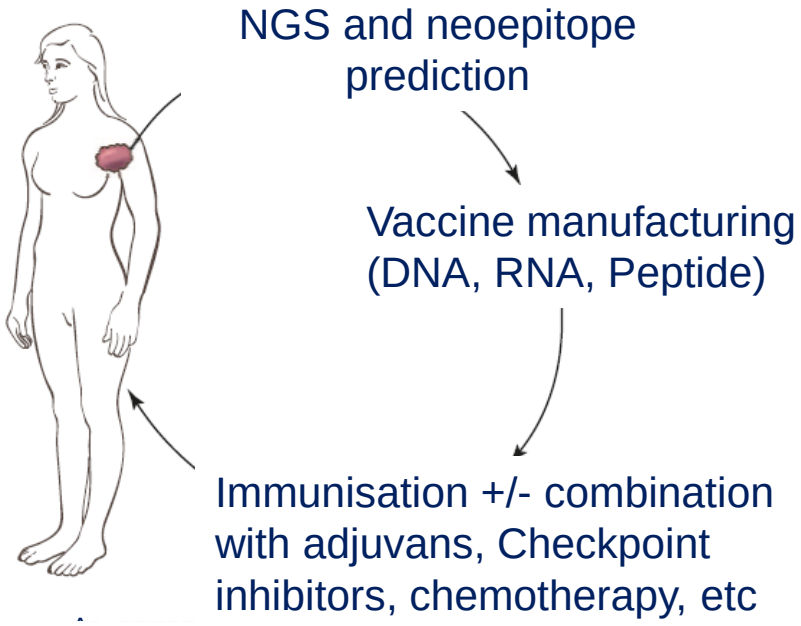
APC = antigen presenting cell
Chen DS & Mellman I. Immunity 2013

Strategies Immunotherapy



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

Individualized vaccine strategies

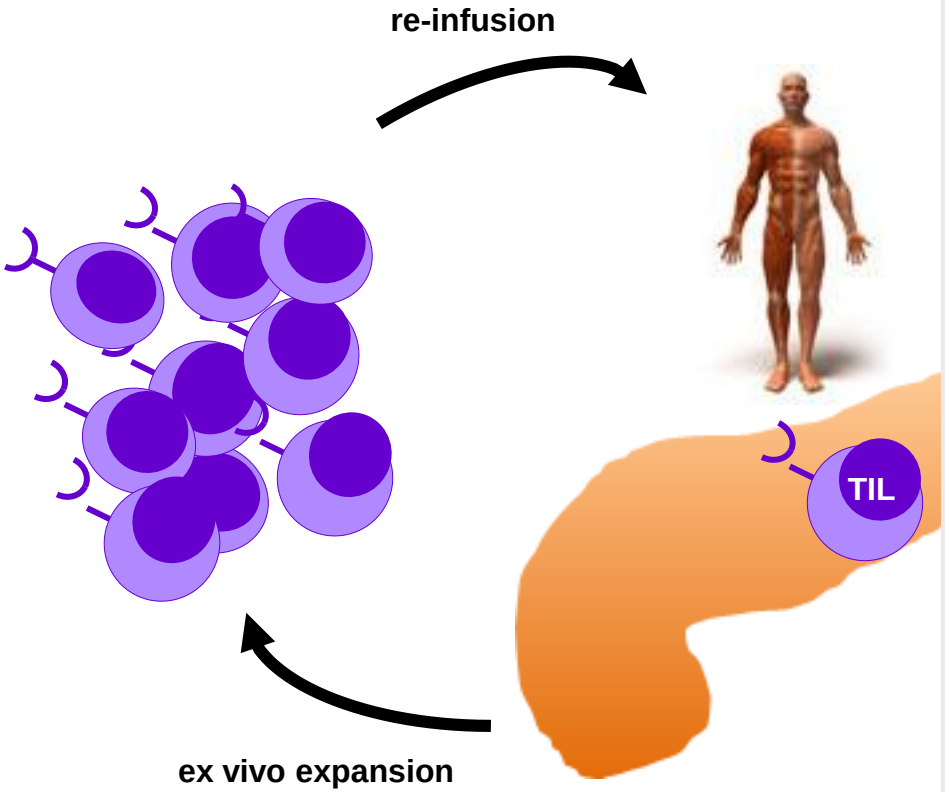


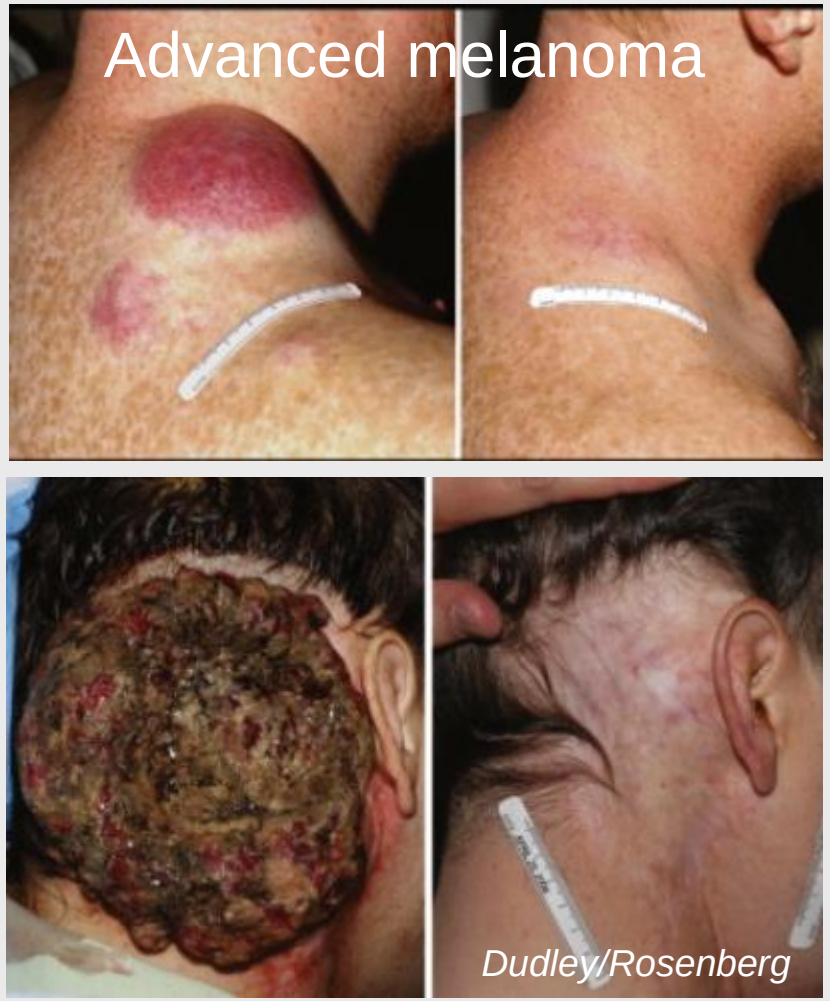
Projected trials at NCT :

- Mutanome based vaccine in advanced solid tumors
- Mutanome based vaccine in TNBC
- Mutanome based vaccine in adjuvant TNBC
- Mutanome based vaccine + PDL1 in different metastatic tumors

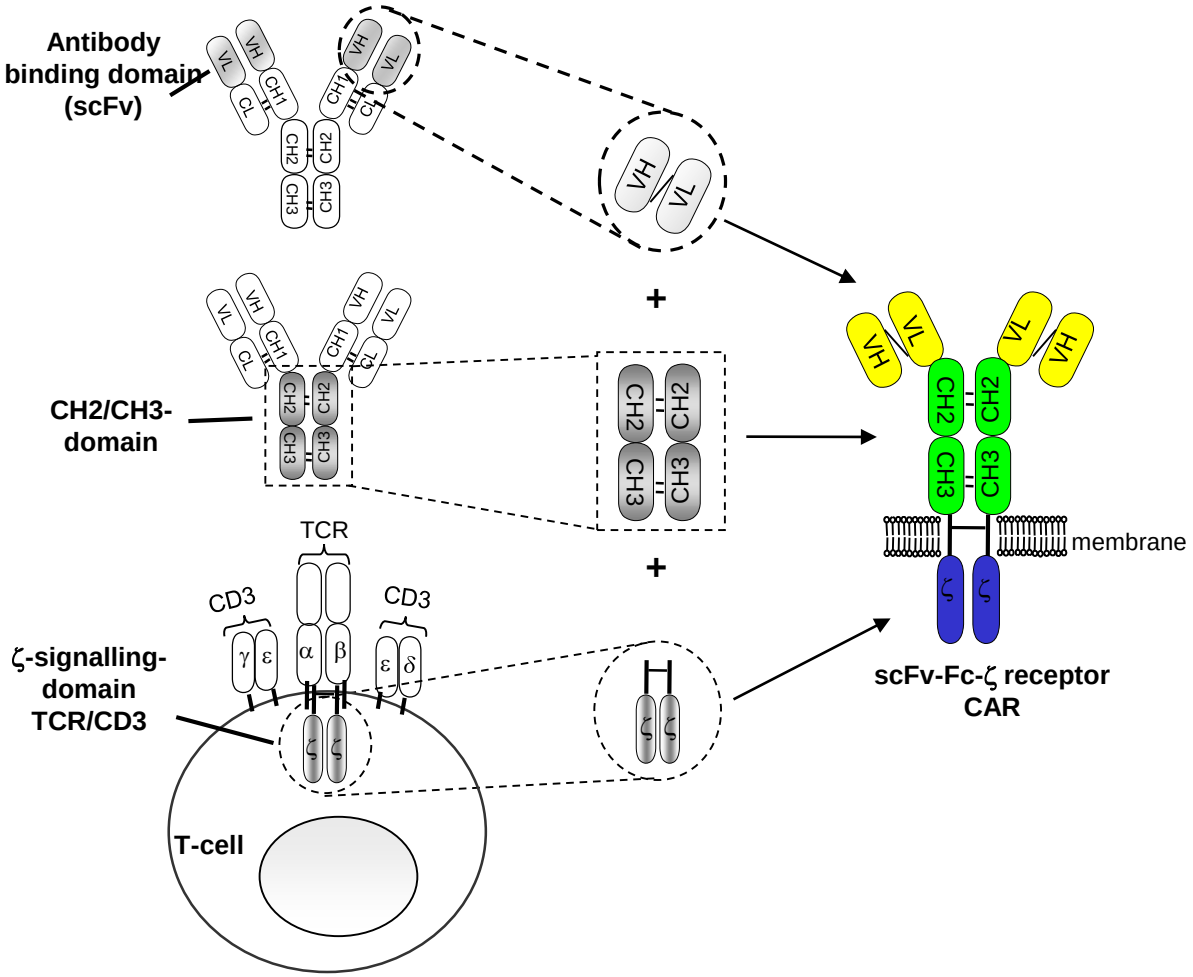
Adoptive T cell transfer

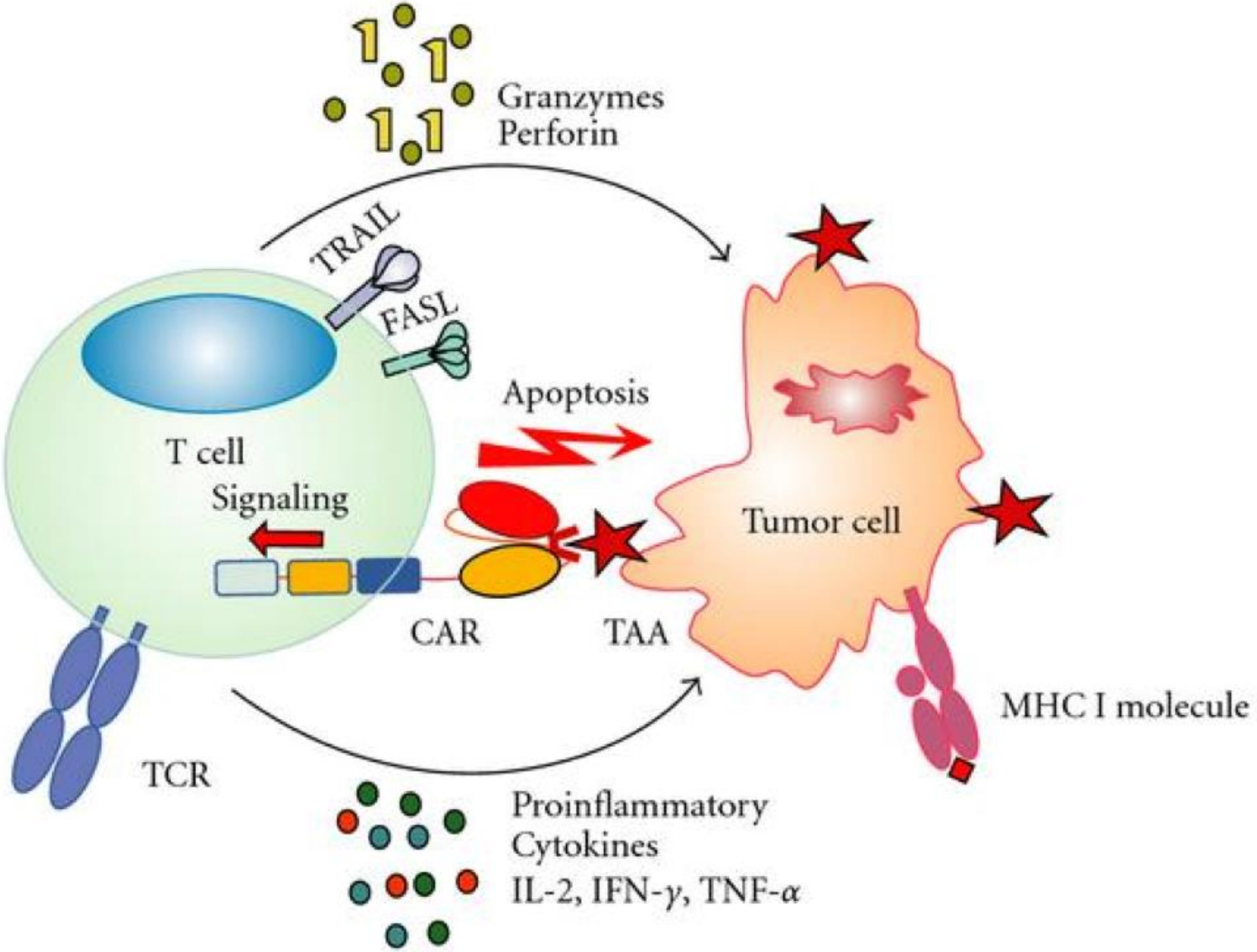
TIL Therapie





CARs (chimeric antigen receptor transduced T cells)



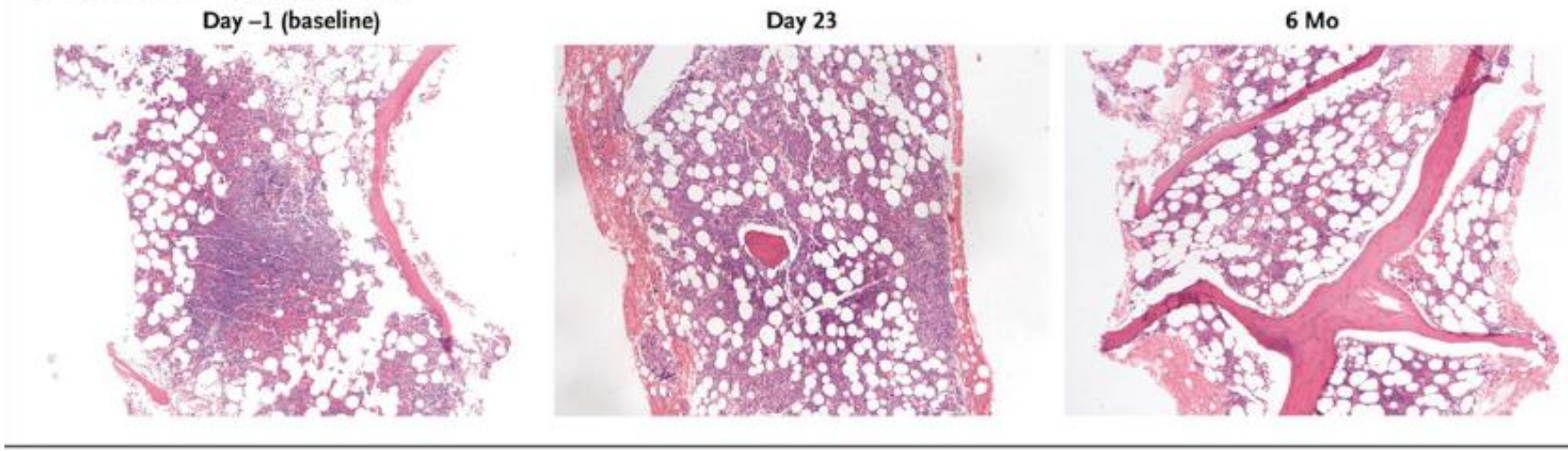

Granzymes
Perforin
TRAIL
FASL
Apoptosis
T cell
Signaling
Tumor cell
CAR
TAA
MHC I molecule
TCR
Proinflammatory
Cytokines
IL-2, IFN-γ, TNF-α

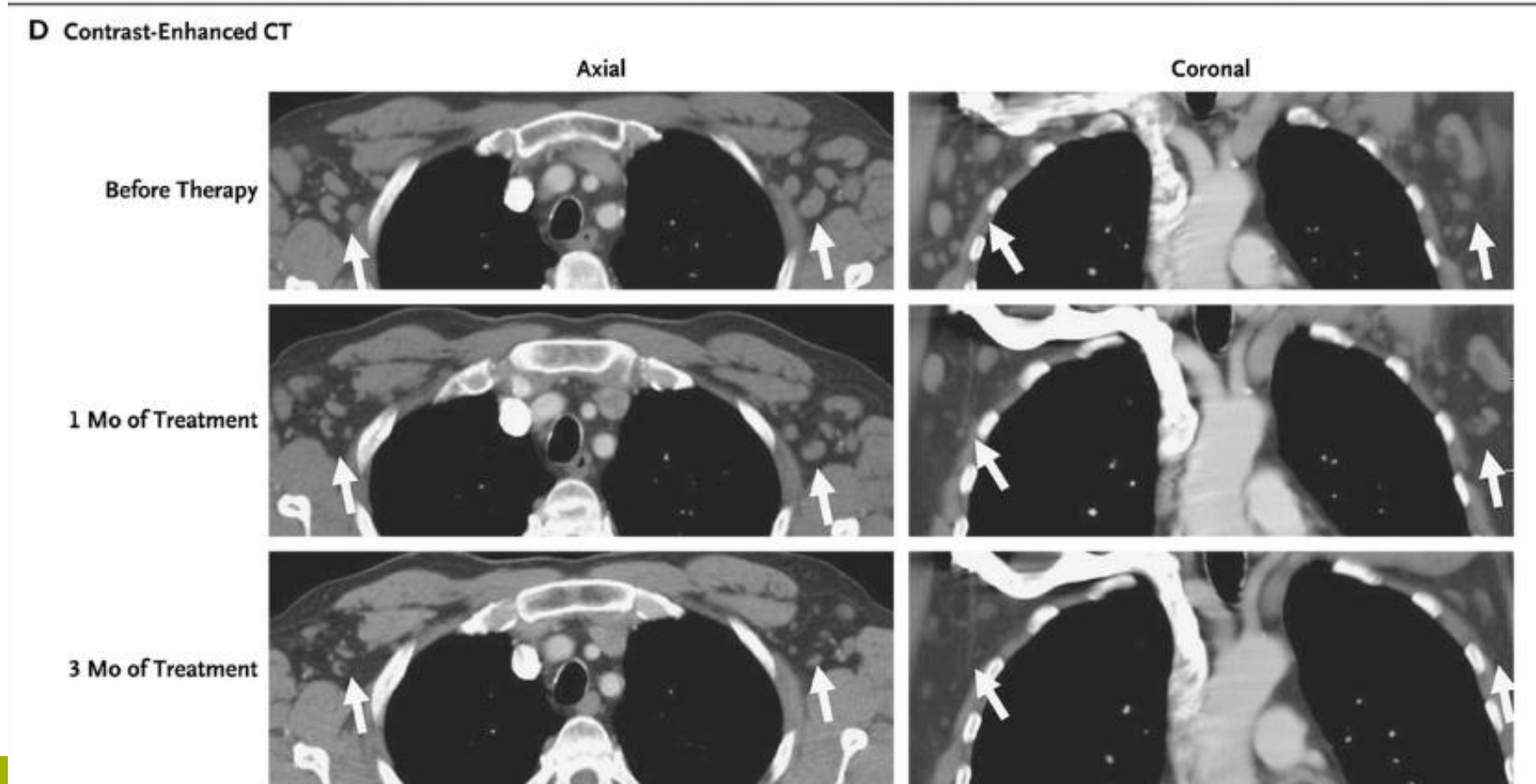
The NEW ENGLAND JOURNAL of MEDICINE

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.


C Bone Marrow–Biopsy Specimens
Day –1 (baseline)
Day 23
6 Mo


D Contrast-Enhanced CT
Axial
Coronal
Before Therapy
1 Mo of Treatment
3 Mo of Treatment

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

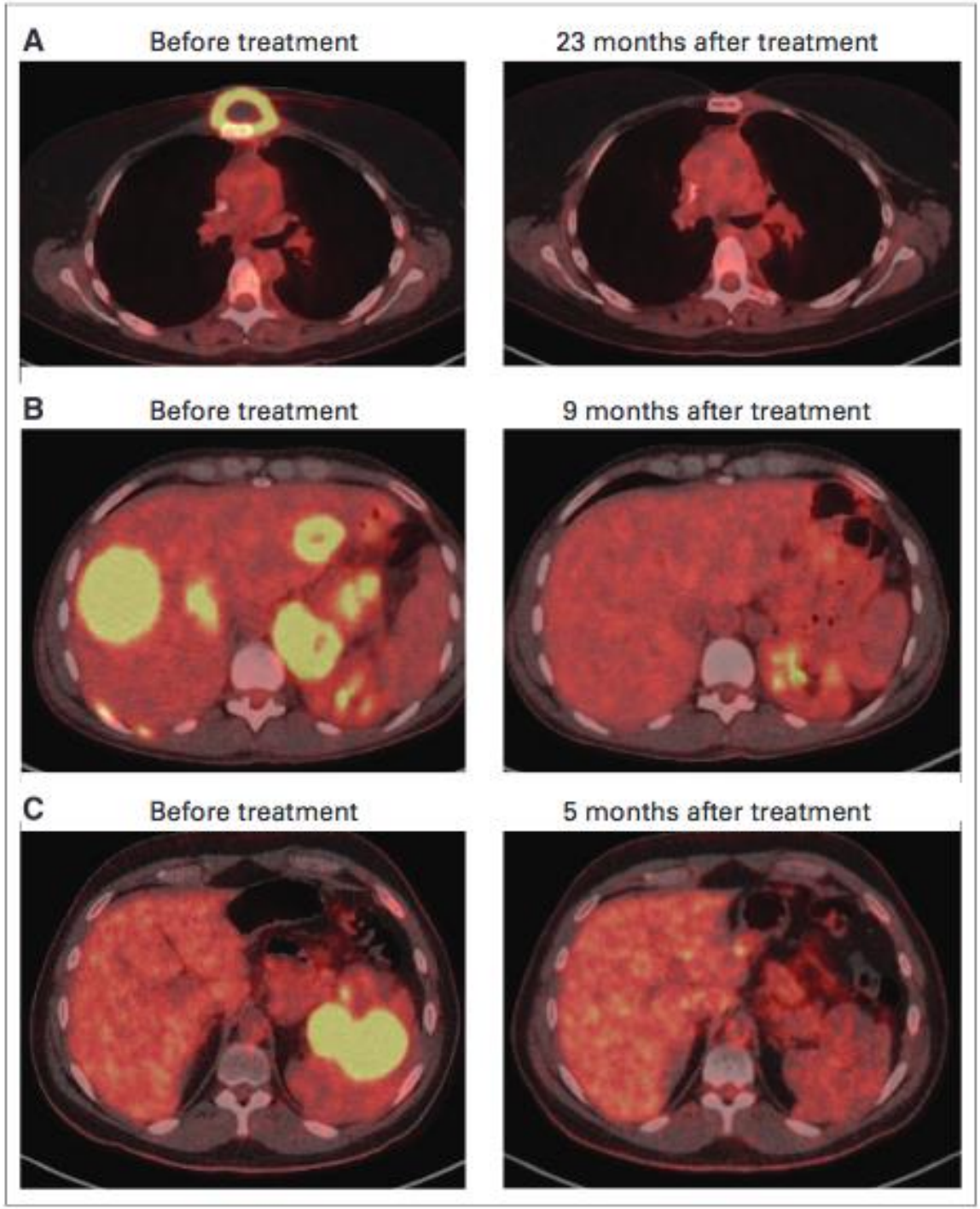
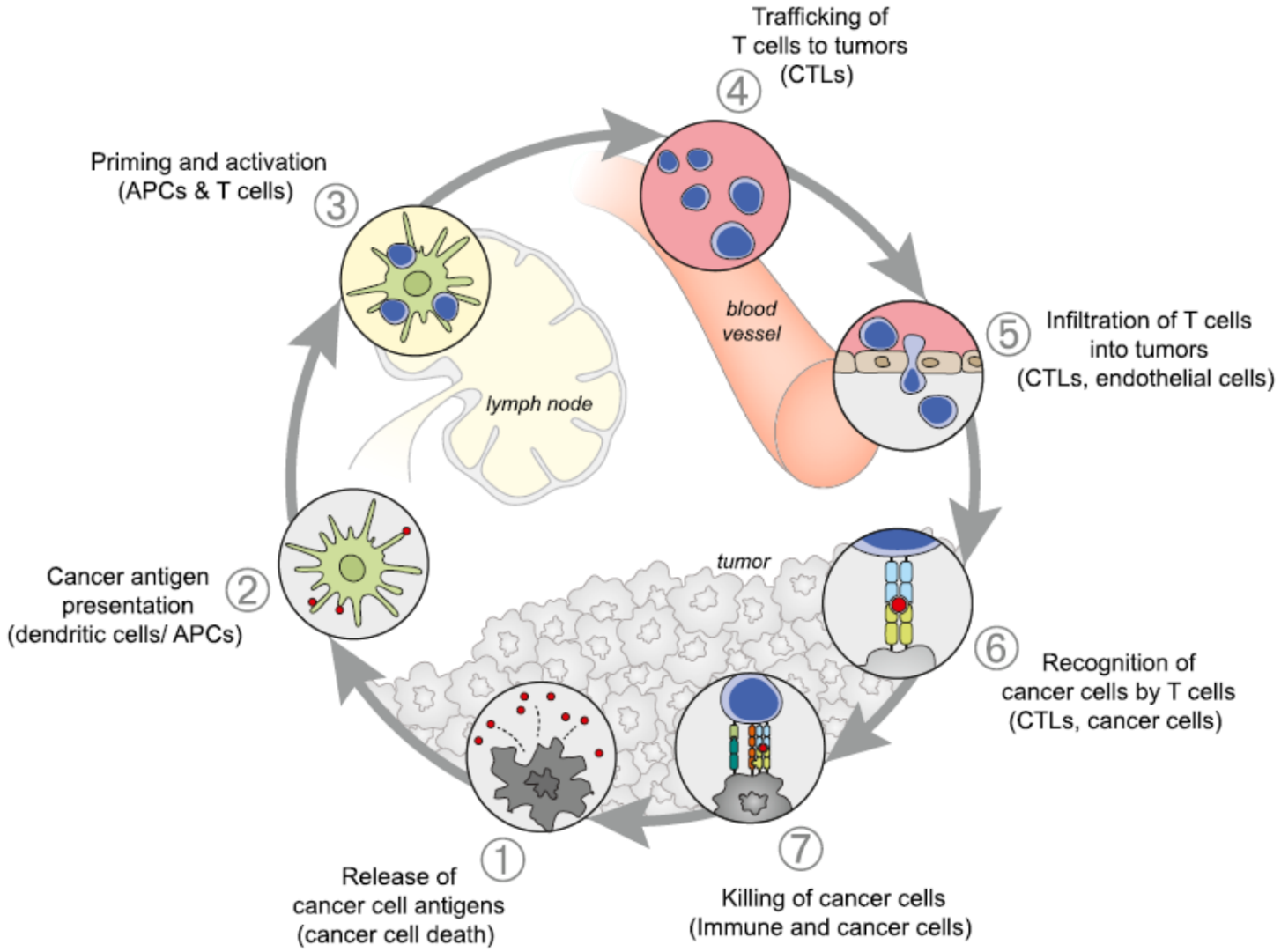


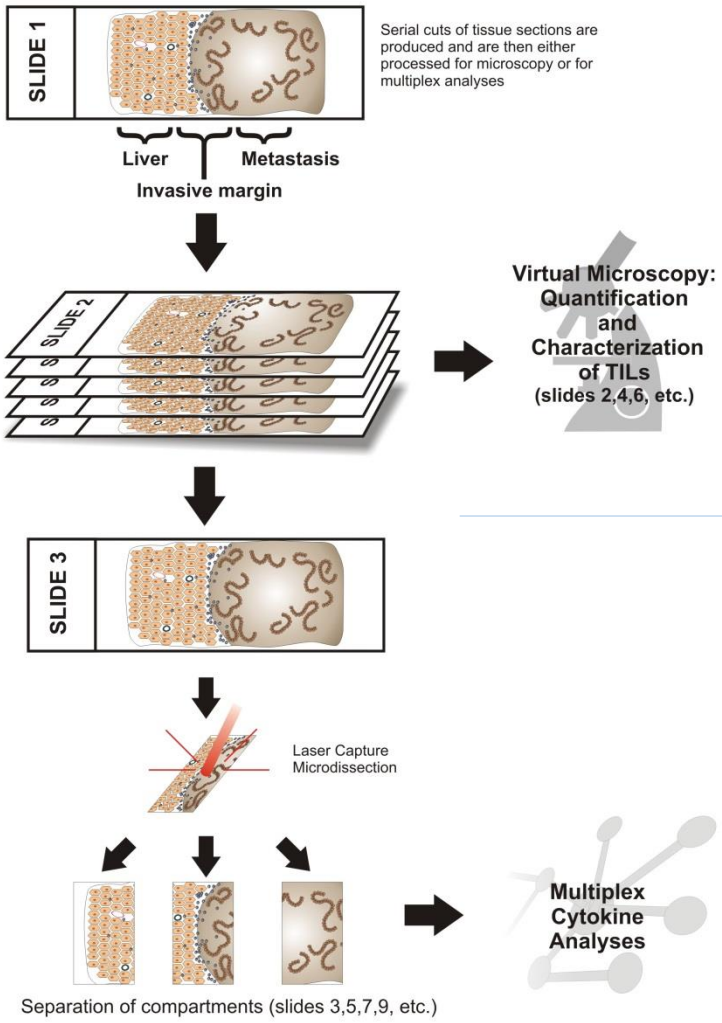
Fig 2. Complete remissions (CRs) of chemotherapy-refractory large-cell lymphomas in patients receiving anti-CD19 chimeric antigen receptor T cells. (A) Positron emission tomography (PET)/computed tomography (CT) scans show CR of chemotherapy-refractory primary mediastinal B-cell lymphoma (PMBCL) in patient 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.

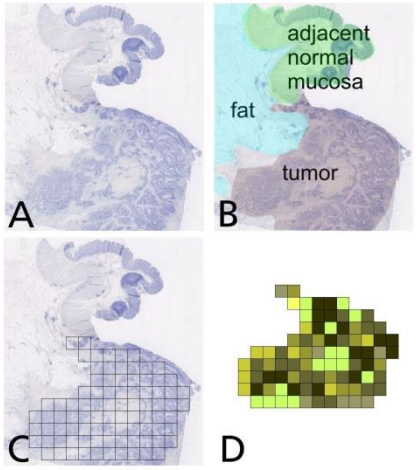
Complexity of tumor host interaction



APC = antigen presenting cell
Chen DS & Mellman I. Immunity 2013

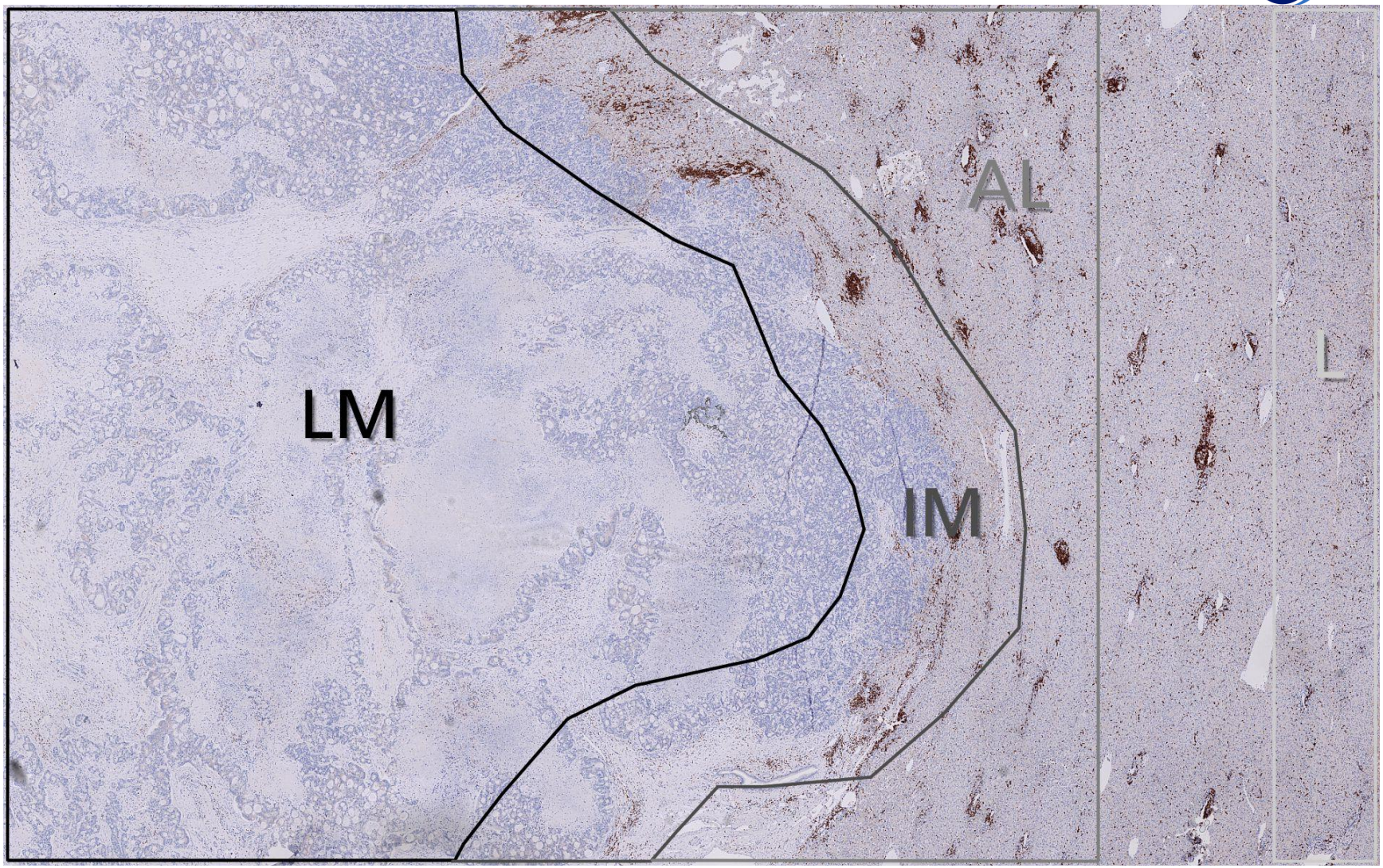
Immunological characterization of the tumor environment



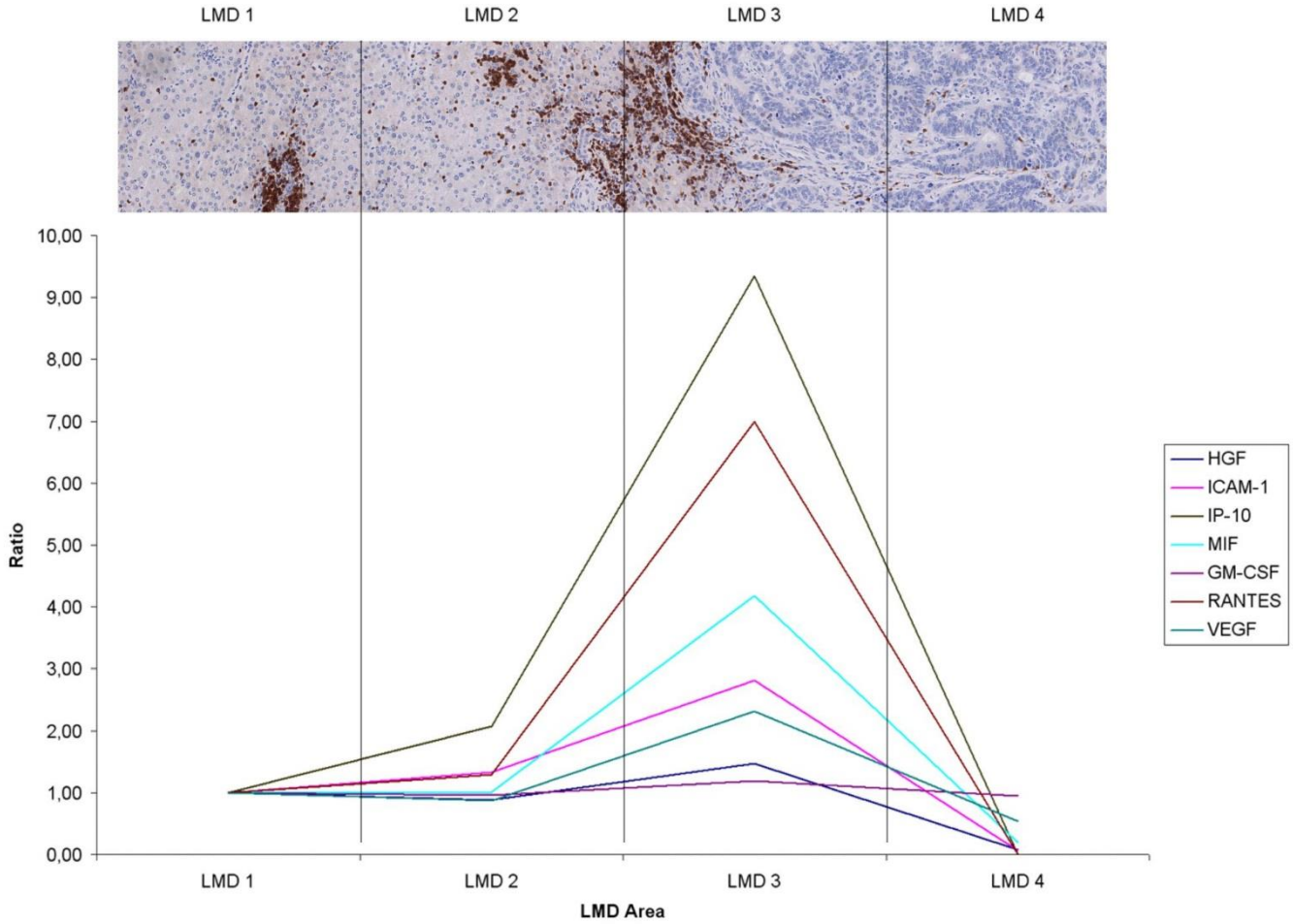


Surface markers analyzed:
CD3, CD4, CD8, CD68, CD163, NKp46, FOXP3, CD56, LCK, Arginase, iNOS, iCAM, VCAM, Ki67, CCR5, CCL5, PD-1, PD-L1, PD-L2, CD44, CD74, CCR1, CXCL9, CXCL10, CD11b, CD11c, CD14, CCR3, TUNEL, CD20, CD21, CD33, CD105, Beta-tubulin, SNAIL, SLUG, IL-1alpha, CK10, CK14, CK16, CK17, IFNalpha2, IFNgamma, HLA class I, HLA class II, HER2/neu, CEA, CA19-9, CD31, FAPalpha, MIF, Annexin V, CD133, CD208, CD45RO, CD6, Chymase, DKK3, Follistatin, Tryptase, CD107a, B7-H4, pEGFR, TNFalpha, CEACAM5, CD19, CA125, ALDH1, CD24, CTLA-4, etc.

Cytokines analyzed:
IL-1b, IL-1RA ,IL-2 ,IL-4 ,IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12(p70),IL-13, IL-15, IL-17, Eotaxin,FGF basic, G-CSF,GM-CSF,IFN-g,IP-10,MCP-1(MCAF),MIP-1a, MIP-1b, PDGF-bb, RANTES, TNF-a, VEGF, IL-1a,IL-2Ra,IL-3,IL-12 (p40),IL-16,IL-18, LIF, MCP-3,M-CSF,MIF,MIG,b-NGF,SCF,SCGF-b,SDF-1a, TNF-b,TRAIL, HGF, CTACK, GRO-a,IFN-a2, TNFSF13, TNFSF13B, TNFRSF8, sCD163, Chitinase-3-like 1, sIL-6Rβ, IFN-α2, IFN-β, sIL-6Rα, IL-11, IL-19, IL-20, IL-22, IL-26, IL-27 (p28), IFN-λ2, IFN-λ1, IL-32, IL-34, IL-35, TNFSF14, MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-10, MMP-12, MMP-13, Osteocalcin, Osteopontin, Pentraxin-3, sTNF-R1, sTNF-R2, TSLP, TNFSF12, CCL21, CXCL13, CXCL5, CCL11, CCL24, CCL26, CX3CL1, CXCL6, CCL1, CXCL11, CCL8, CCL7, CCL13, CCL22, CCL3, CCL15, CCL20, CCL19, CCL23, CXCL16, CCL17, CCL25, Bad, Bax/Bcl-2 dimer, Bcl-xL, Bim, Mcl-1, etc.

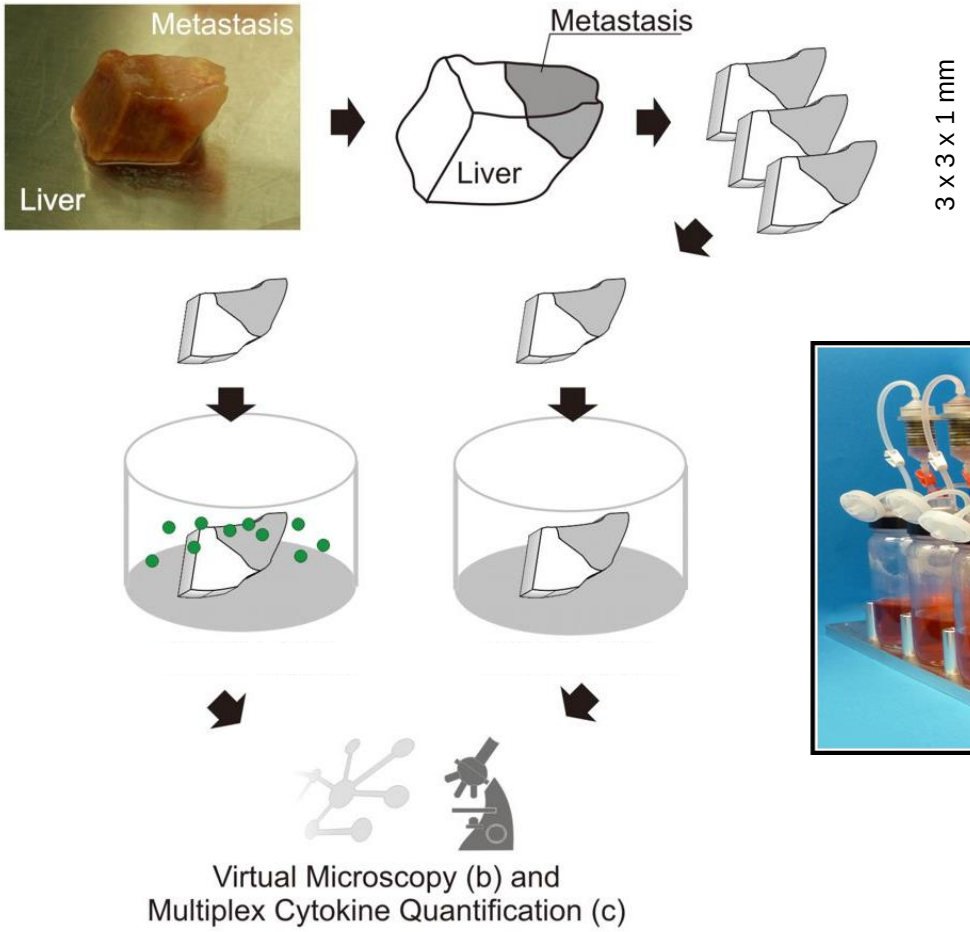

AL
LM
IM
L

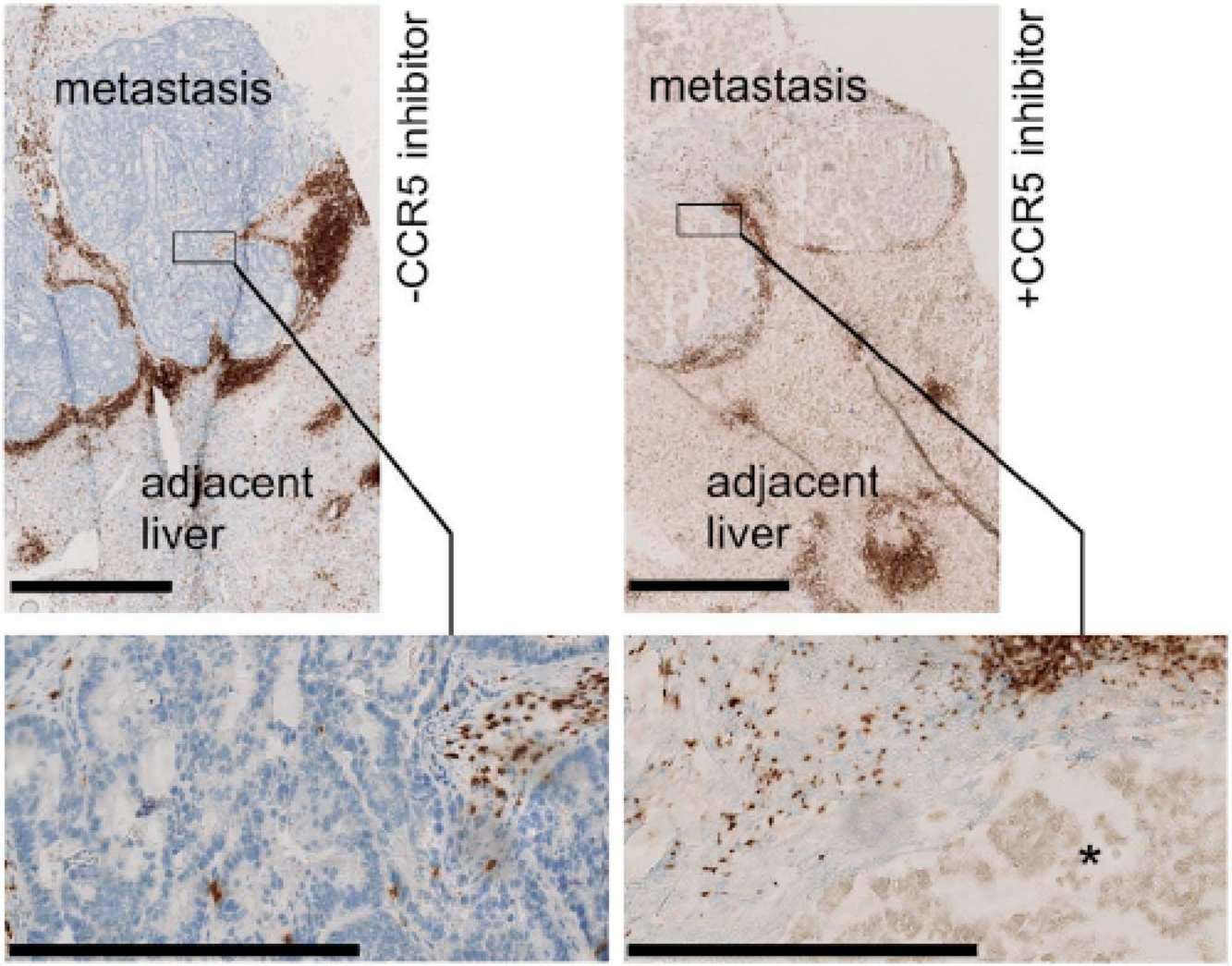
Laser microdissektion (LMD) across different areas



Protein concentrations measured in pg/ml from each LMD region. AL is used as reference (1).

Human tumor explant models (organotypic)





Cancer Cell 2016

Precision oncology

- Molecular diagnosis 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 vaccines
  - 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...

Implications

- In the future, a diagnosis like breast or colon cancer is not sufficient to characterize an individual disease
- Information on the molecular make up and the tumor-host interaction is needed
- Complex data sets are currently used
- Not easy to translate in a content that can be deposited in a registry
- Cancer registries will have to deal with much larger data sets
- Interpretation of registry data much more complicated

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