Individualizing Immunotherapy

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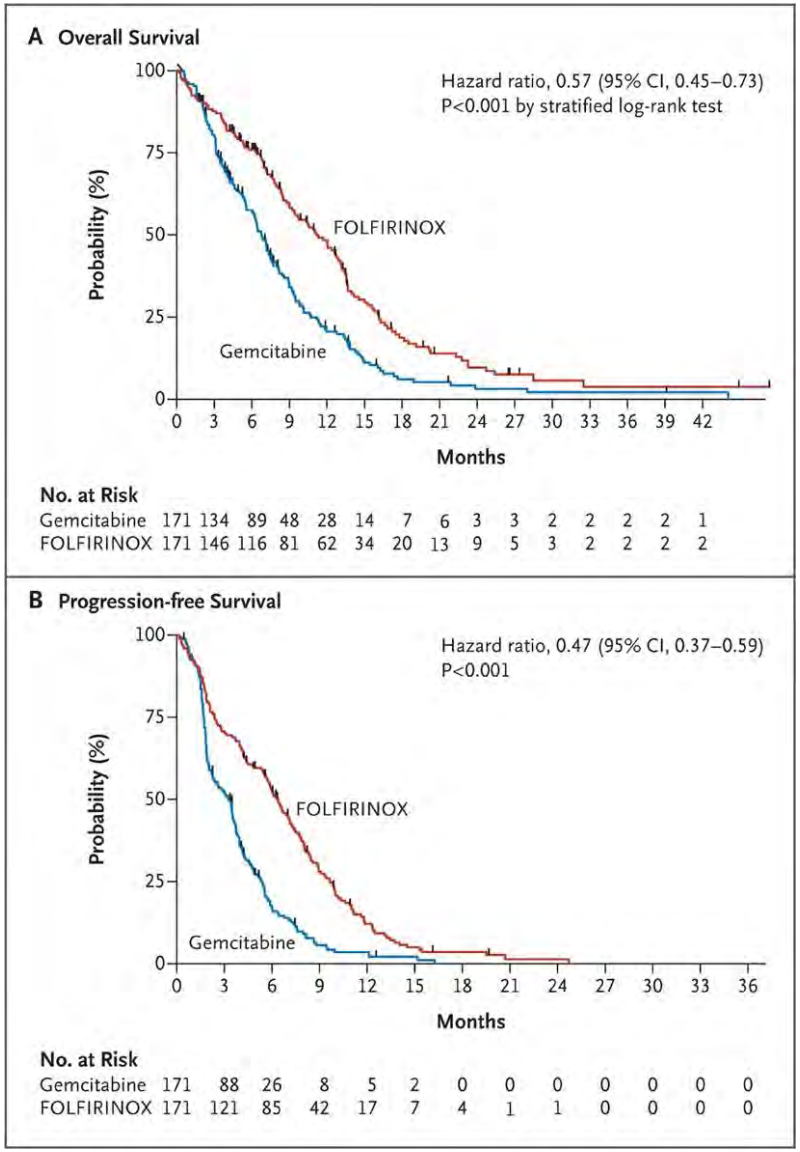
Routine diagnostics

- Routine:
  - Morphological description of microscopic images (histology)
  - Several markers IHC
  - A few molecular markers (mutations)
- In scientific programs:
  - DNA/RNA Sequencing (specific mutations, mutational burden)
- Single centers:
  - Proteomics, Environment, host response, etc….

Treatment indication

Is based on statistical outcomes of a specific treatment in prospective trials….

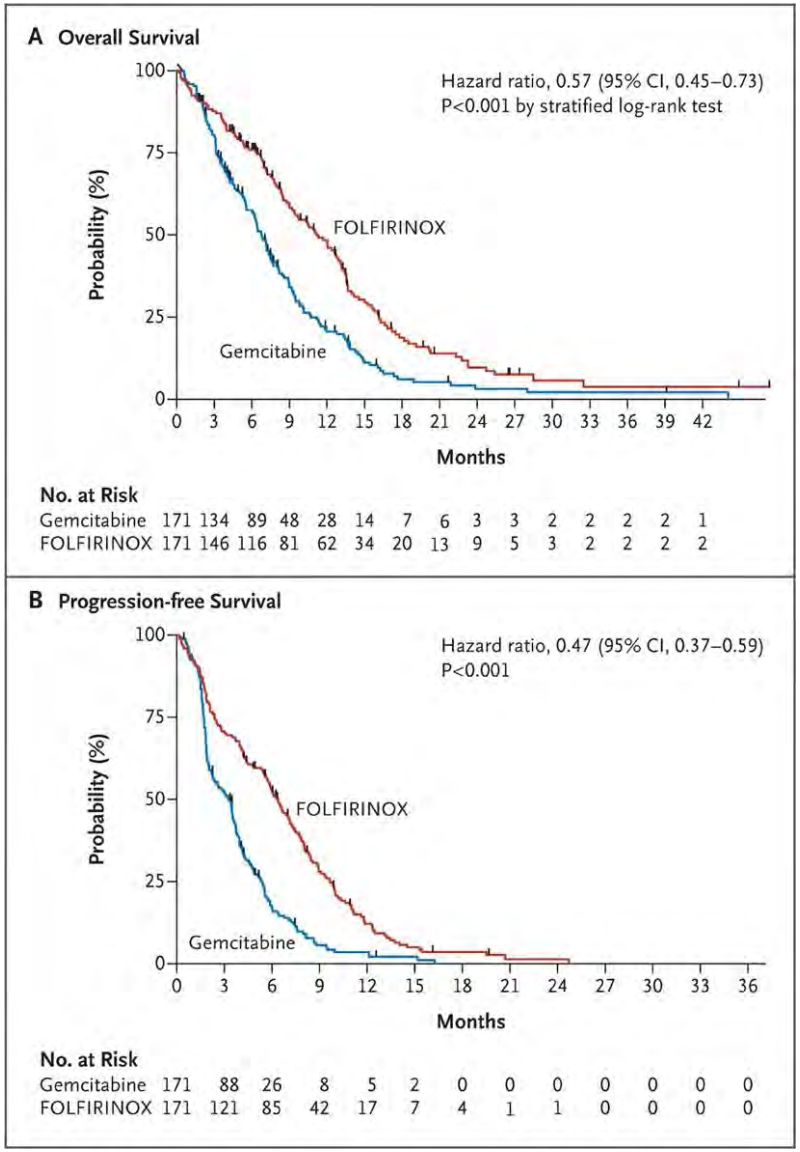


Conroy T et al. N Engl J Med 2011;364:1817-1825.

Treatment indication

Is based on statistical outcome of a specific treatment in prospective trials….

And we treat the statistical patient….



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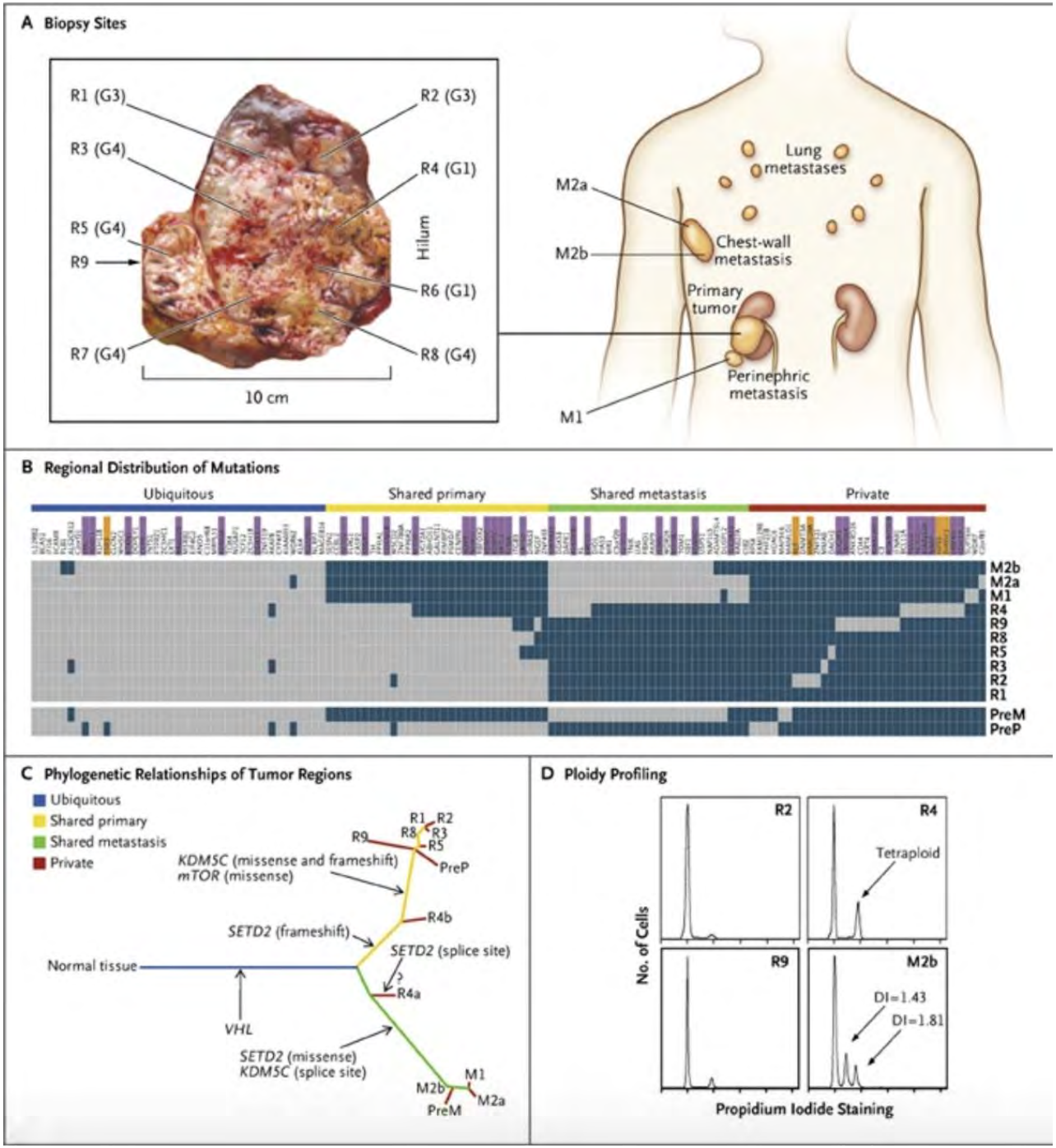
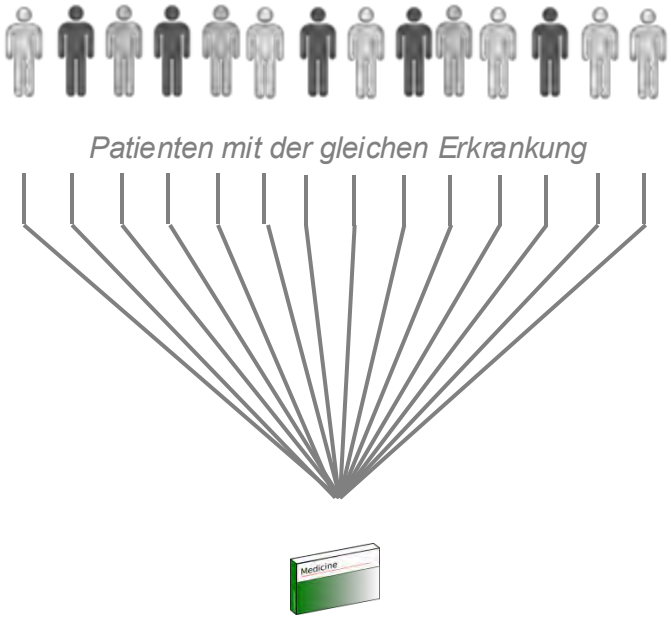


Gerlinger et al., N Engl J Med 2012

Oncology today – Standard Treatment

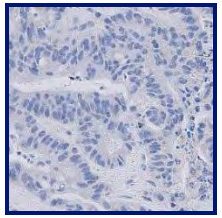
Standard Treatment means,
Same treatment for all patients with specific disease

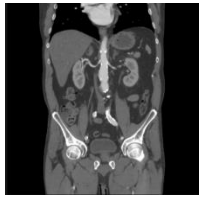


Background

Oncologists indicate treatments based on minimal information…

- *Histology (morphological description of a microscopic image)*
- *Information from Imaging (CT, MRI, PET-CT, Ultrasound)*

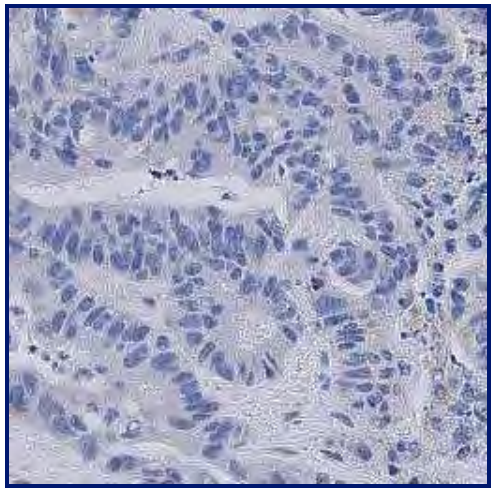


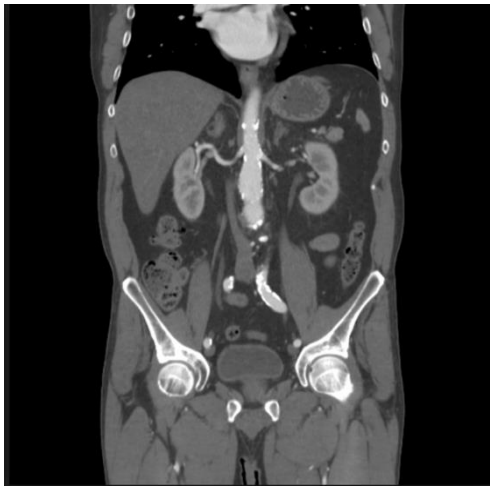


Example

- Resected colon cancer
- Histology: moderate differentiated adeno carcinoma, 2 positive LK

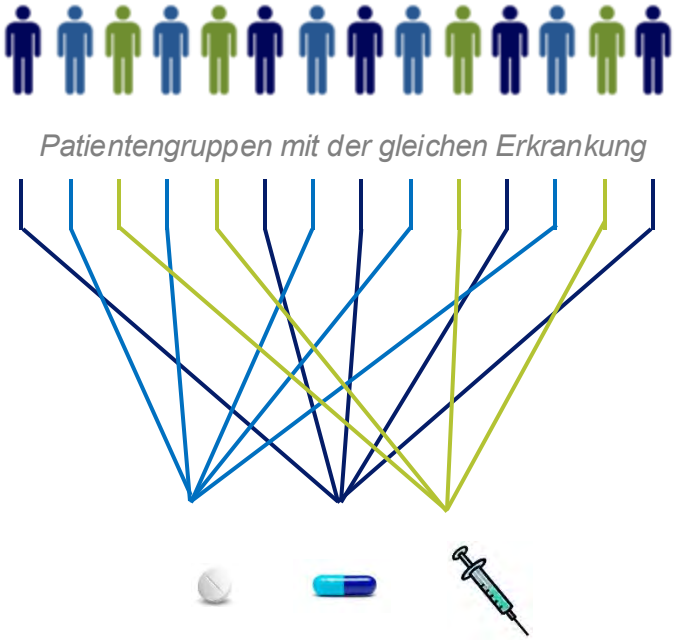
  Imaging: no distant disease
- Recommendation: adjuvant chemotherapy FOLFOX over 6 months
- 15-17% of all treated patients benefit…





Personalized treatments

Personalized treatments means,
The right treatment for the right subgroup at the right time



Aim

- *Characterization of several disease subgroups*
- *Ultimately, we need to define every individual disease as its own tumor entity*

Current situation

- We don`t understand why an individual patient is responding
- We don`t understand why an individual patient is not responding
- We assess response and non response 2-3 months under treatment using CT or MRI imaging
- We don`t understand what mechanisms or what sequence of different mechanisms led to the result
- NGS does not help to assess or understand such mechanisms
- We assess effects of novel treatments statistically in the overall trial population, we don`t assess treatment effects in the individual patient

Understanding the individual patient

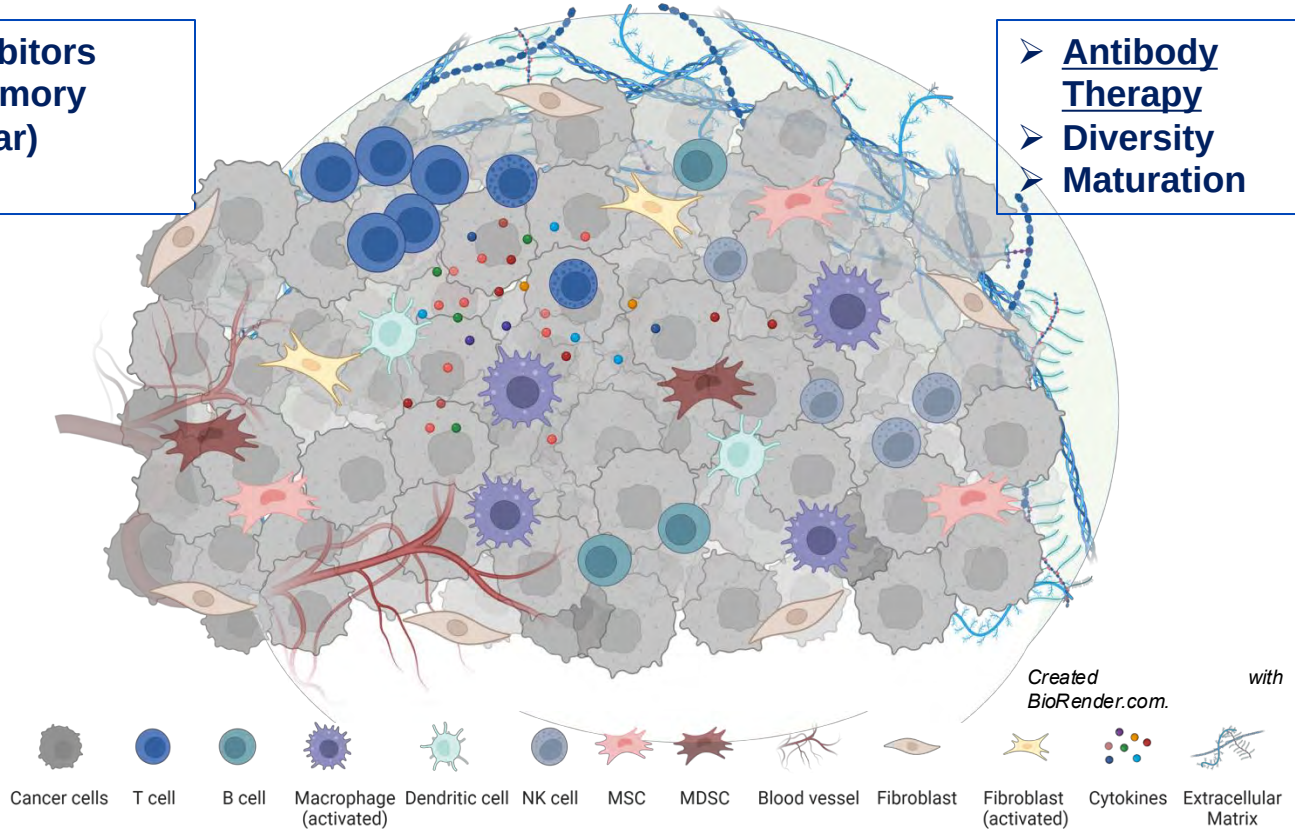
- Is based on the characterization of the highly complex interplay of tumor cells, stroma cells, immune cell subpopulations, bacteria, etc…in the tumor
- We should assess the effects of a treatment on this complex system, assess how this system reacts to the treatment
- We need models/systems that reflect/simulate the complexity of an individual tumor and recognizes the uniqueness of each tumor
- We have to understand what mechanisms tumors use to escape treatment effects

Challenges in Immunotherapy

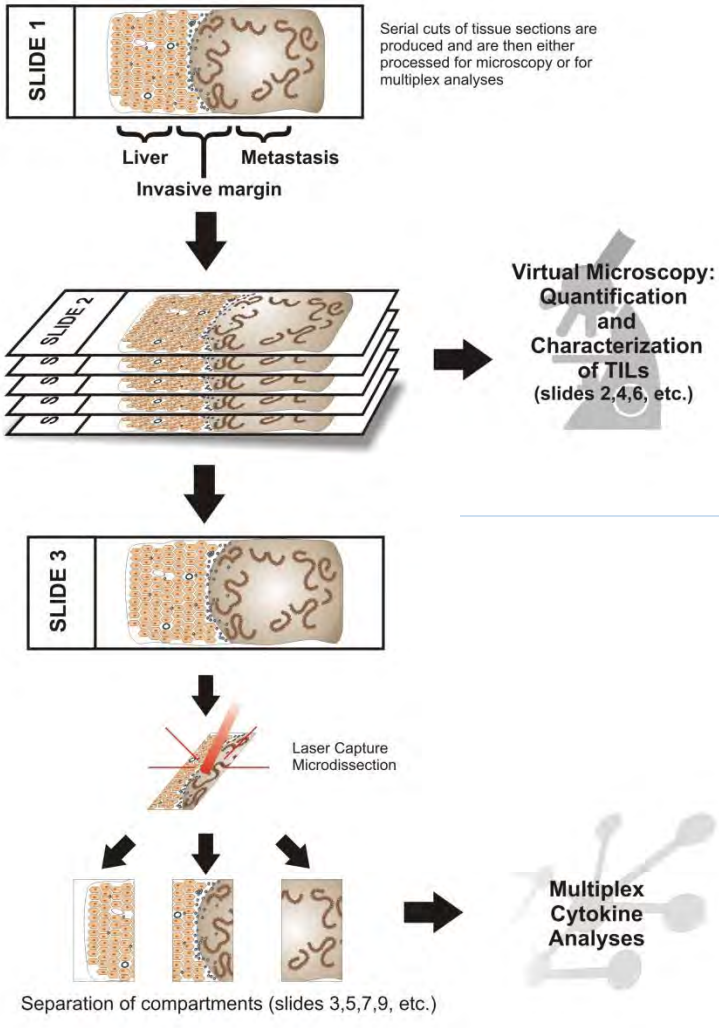
Immune Checkpoint Inhibitors
- T cell exhaustion / memory
- Additional (intracellular) checkpoints

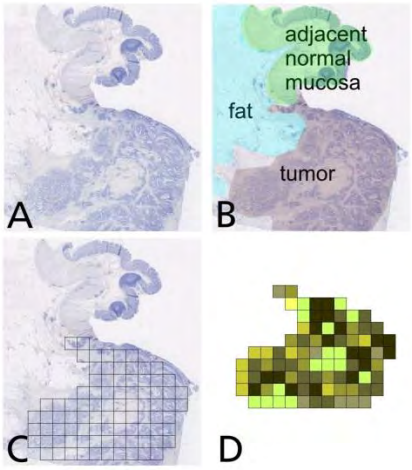
- **Antibody Therapy**
- Diversity
- Maturation

- **Adoptive Cell Therapy**
- T cell homing
- T cell persistence
- Metabolic fitness



Immunological characterization of the tumor environment

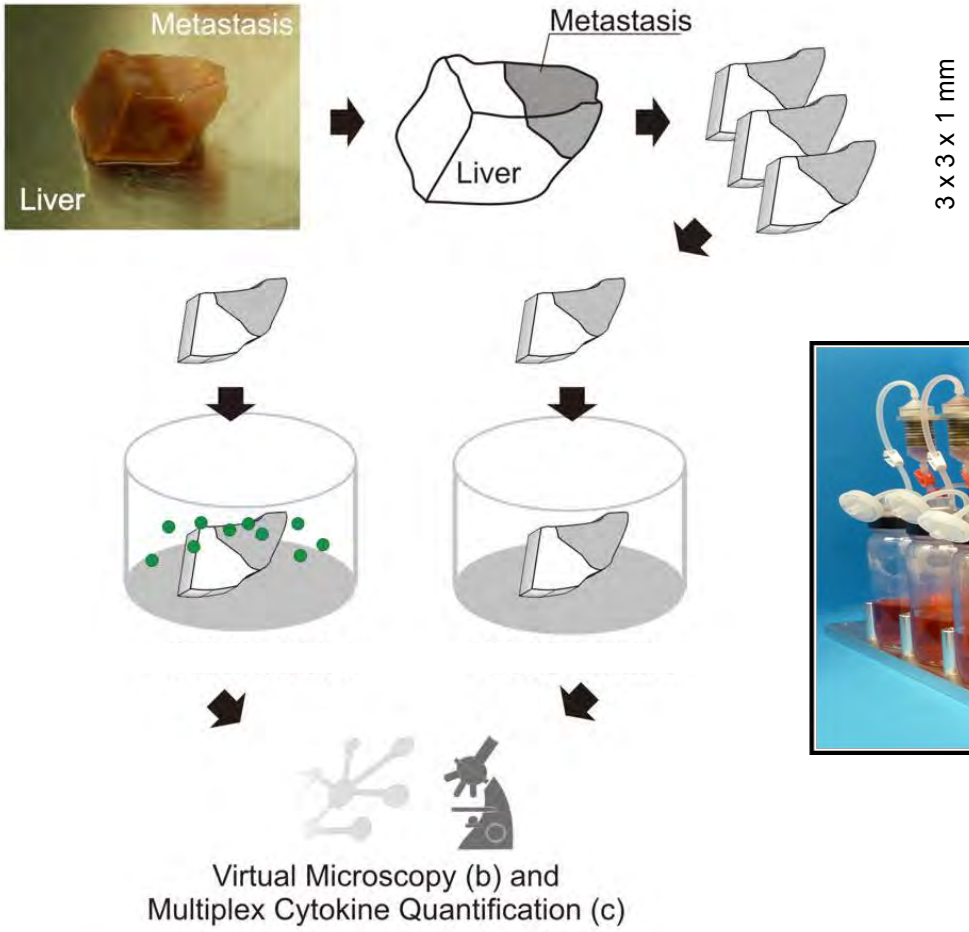


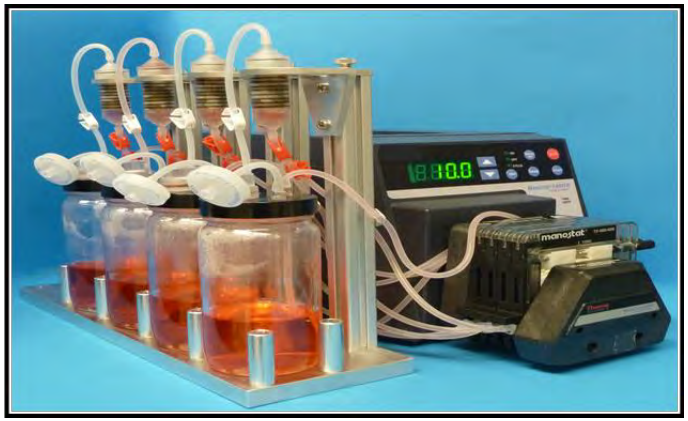


Surface markers analyzed:
CD3, CD4, CD8, CD68, CD163, NKp46, FOXP3, CD56, LCK, Arginase, iNOS, iCAM, VCAM, Ki67, CCR5, CCL5, PD-1, PD-L1, PD-L2, CD44, CD74, CCR1, CXCL9, CXCL10, CD11b, CD11c, CD14, CCR3, TUNEL, CD20, CD21, CD33, CD105, Beta-tubulin, SNAIL, SLUG, IL-1alpha, CK10, CK14, CK16, CK17, IFNalpha2, 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.

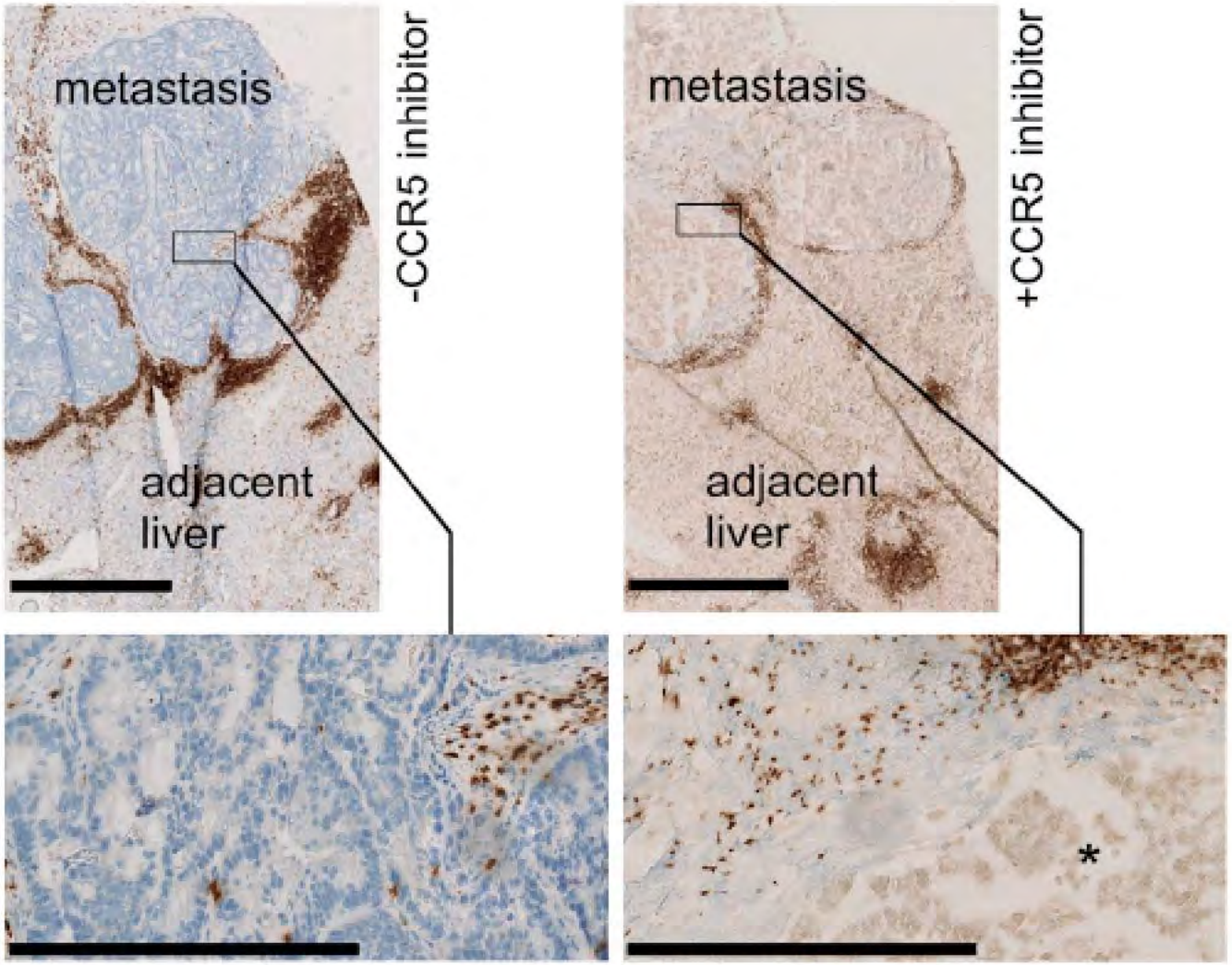
Human Tumor Explant Model (organotypic)





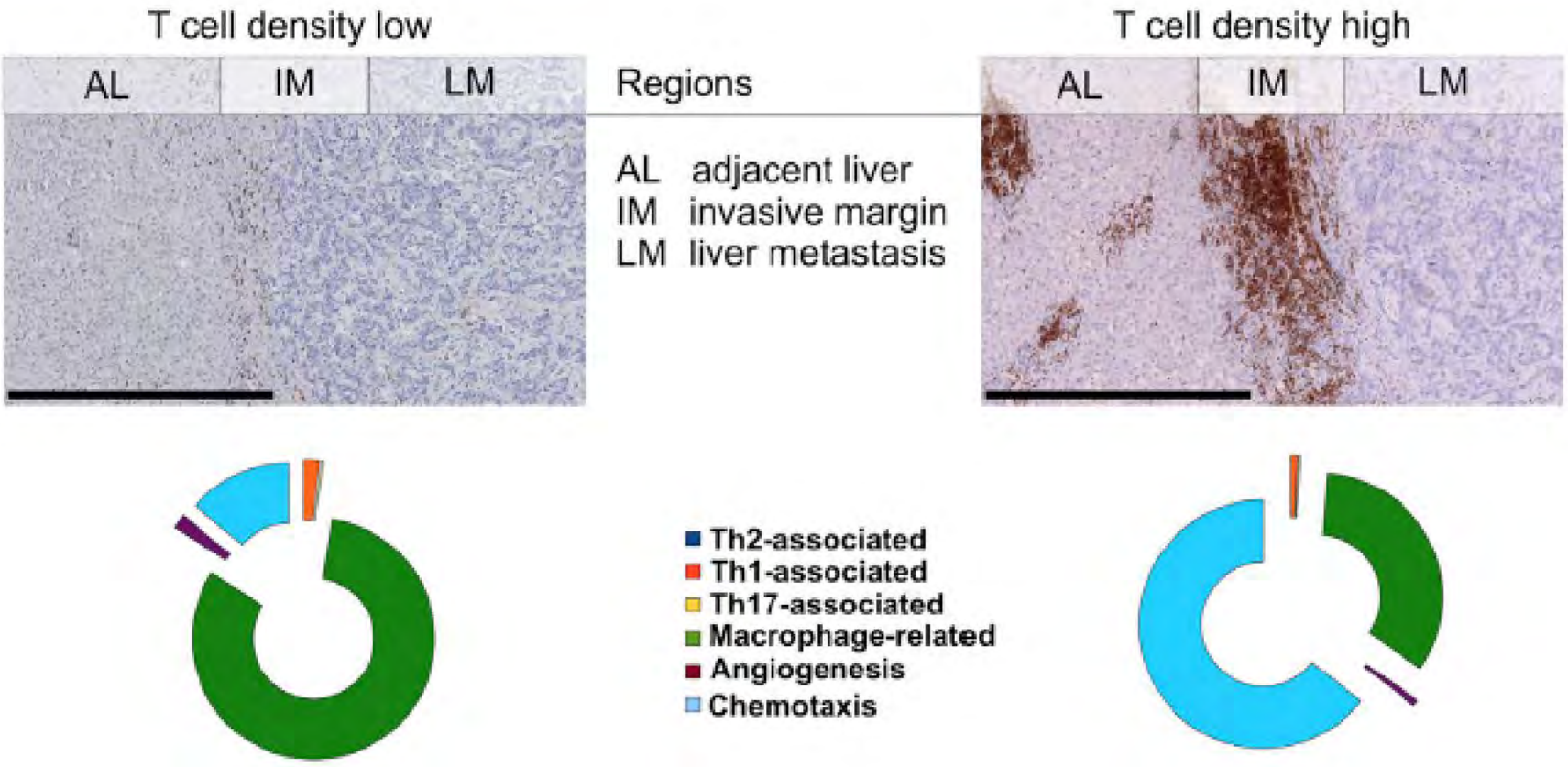
Human tumor explant model

- Fully human, fully immunocompetent patient specific model
  - Test experimental drugs
  - Understand mechanisms of response and resistance
  - Identify novel targets
  - Test effects of novel compounds targeting such targets
  - Validate patient specific explants in early phase clinical trials where we treat explant and patient in parallel and compare on treatment biopsy with explant data



Halama N., Cancer Cell 2016

Cytokine patterns in CRC



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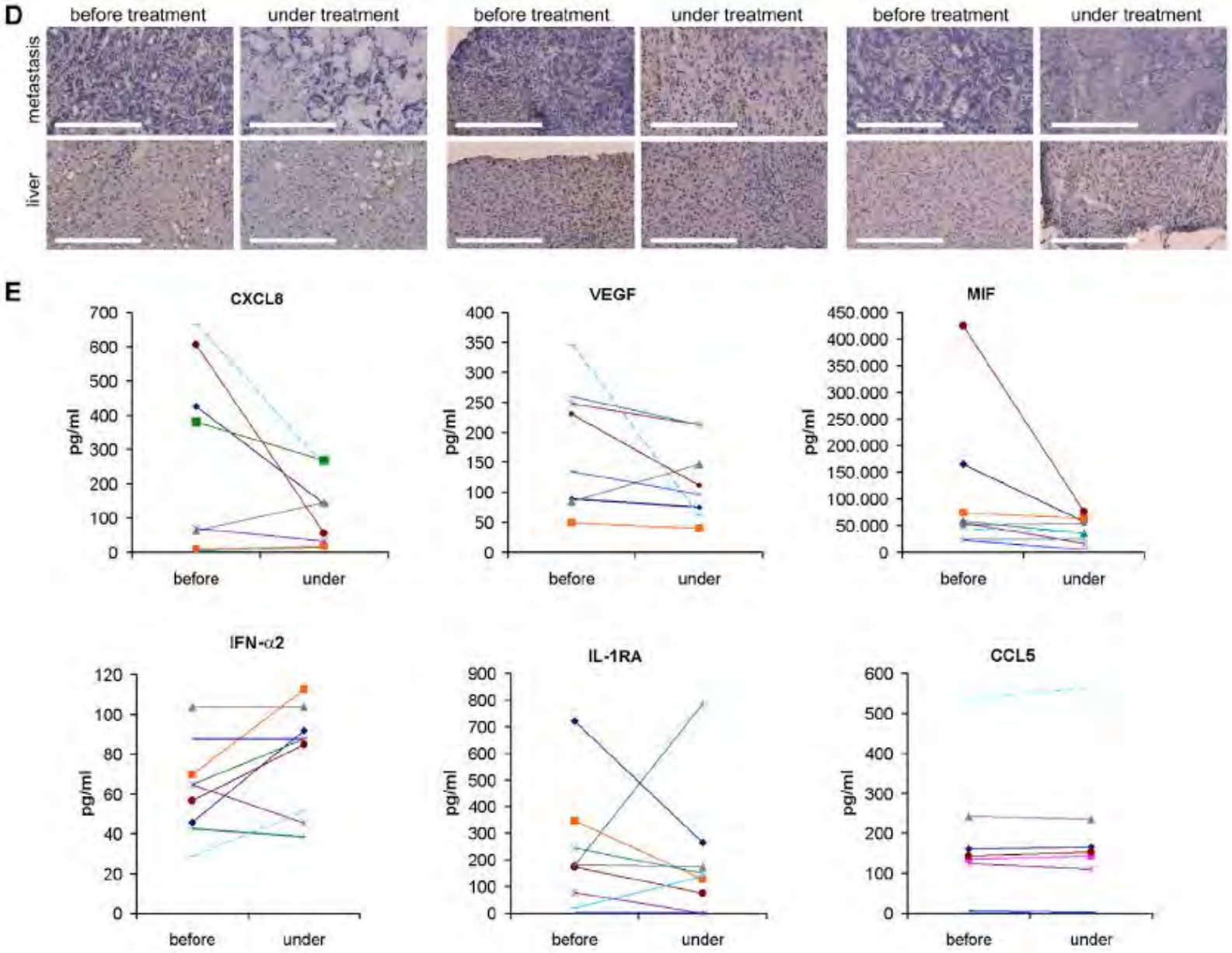
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before treatment
under treatment
before treatment
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before treatment
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metastasis
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MIF
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IFN-α2
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IL-1RA
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300
200
100
0
before
under
CCL5
pg/ml
600
500
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300
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100
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before
under

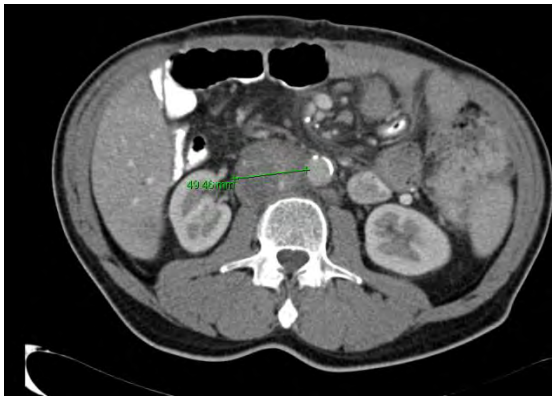
Metastatic CRC MSS

Baseline-CT

3 cycles PD1 + CCR5-inhibitor

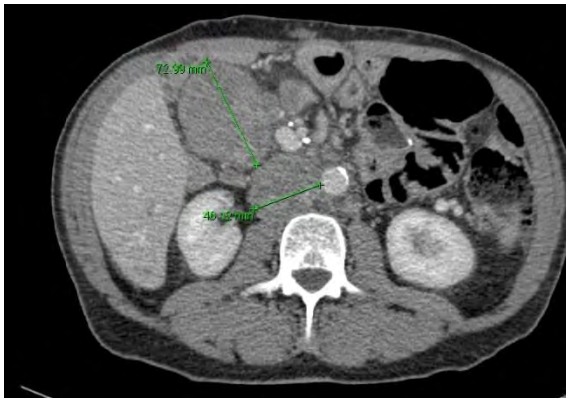
6 cycles PD1 + CCR5-inhibitor

CT Abd 10.09.2014



LN-Bulk 49,46 mm

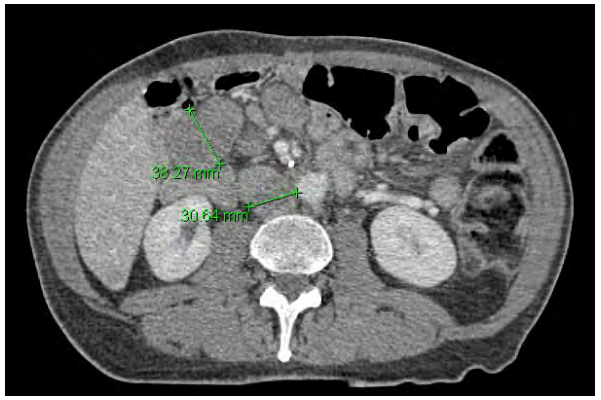
CT Abd 20.01.2015



LN-Bulk 46,12 mm

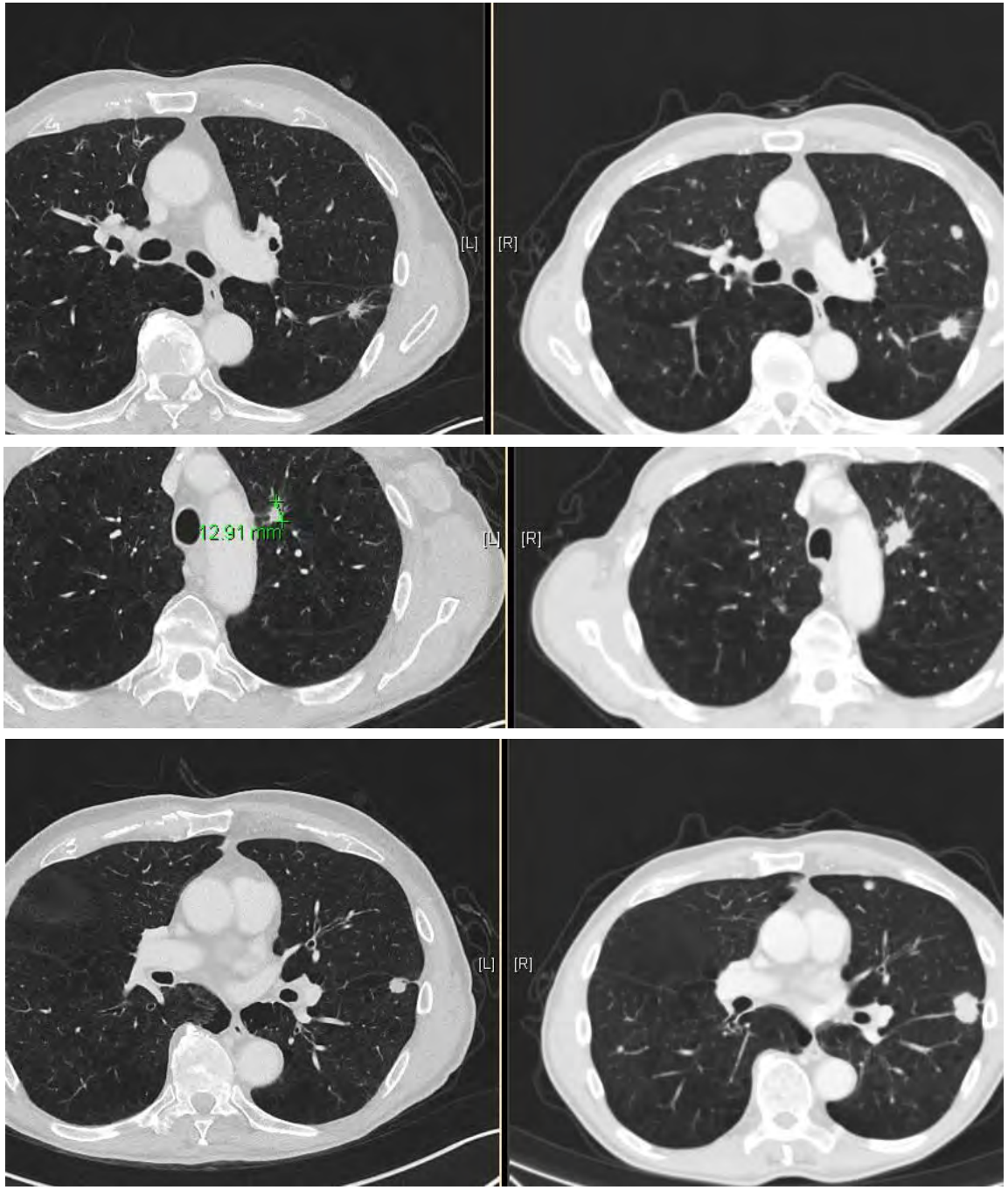
newLN-Bulk 72,99 mm

CT Abd 20.03.2015

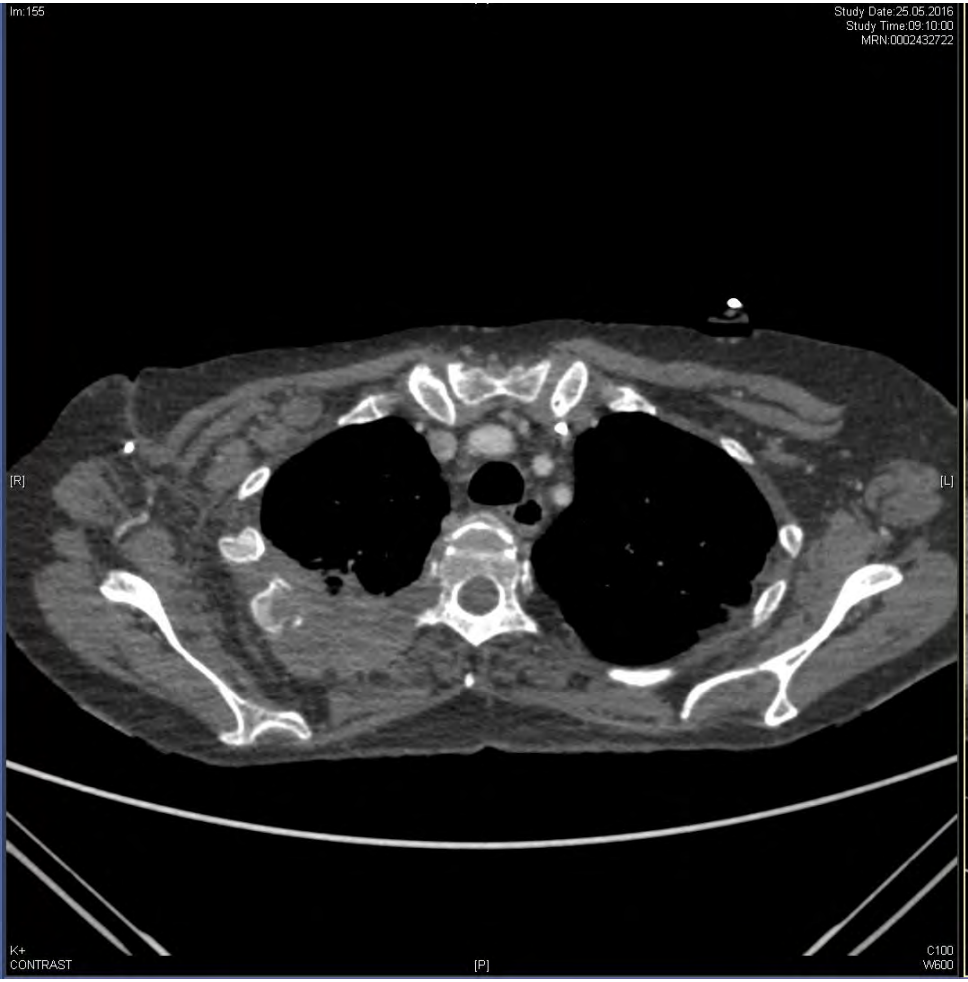


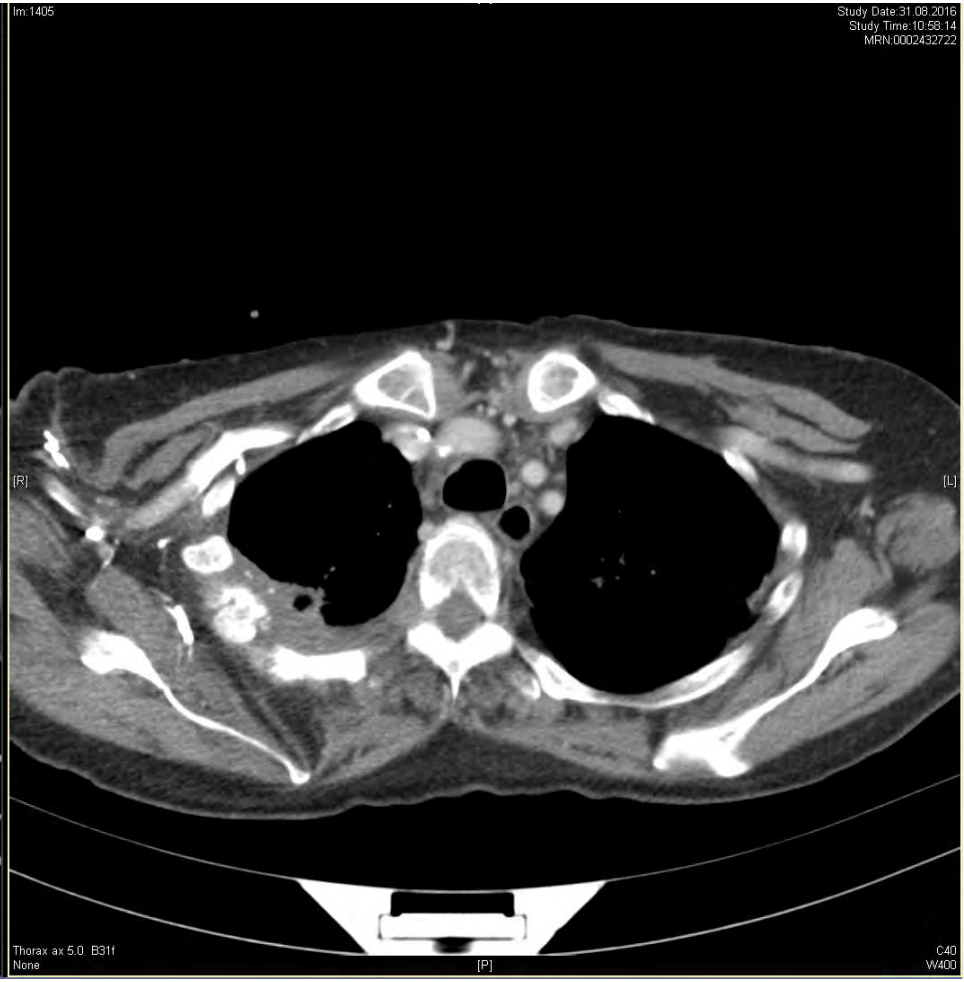
LN-Bulk 30,64 mm

newLN-Bulk 38,27 mm

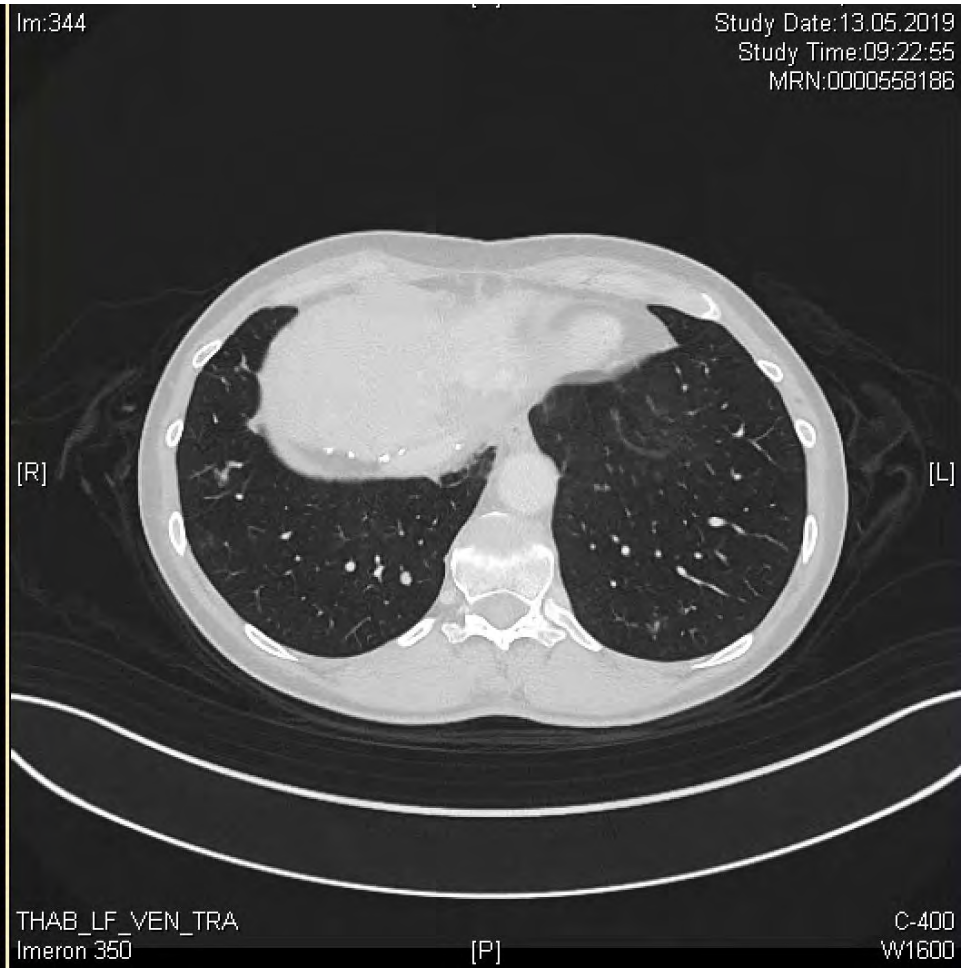

[L]
[R]
12.91 mm
[L]
[R]
[L]
[R]

PDAC Nivo+Ipi+Maraviroc in 7th line

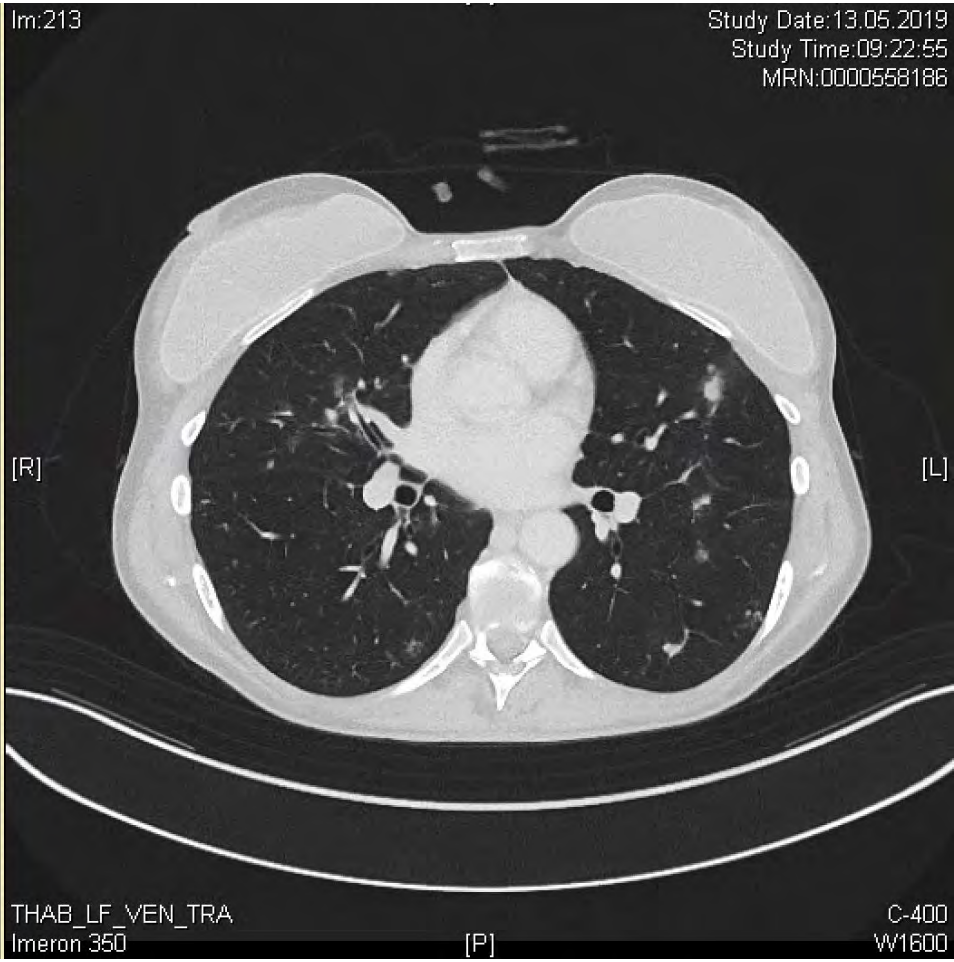




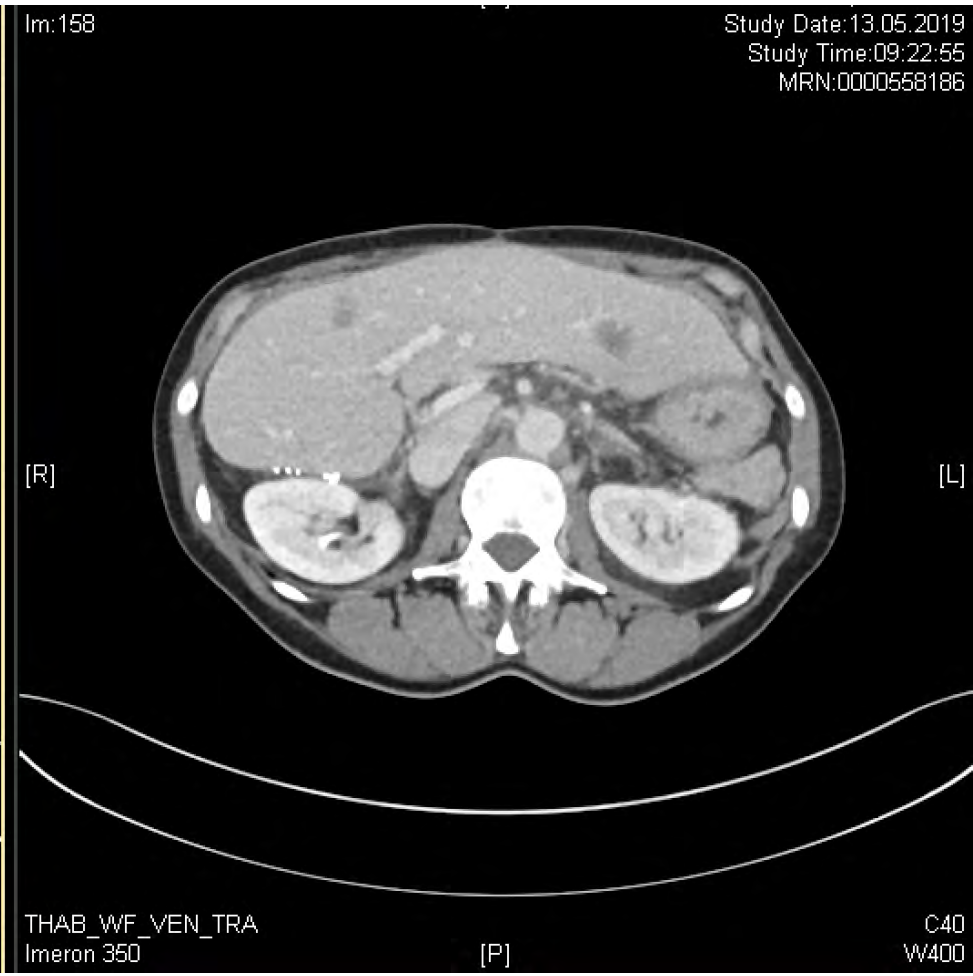
Last line setting CRC, MSS
Ipi+nivo+maraviroc



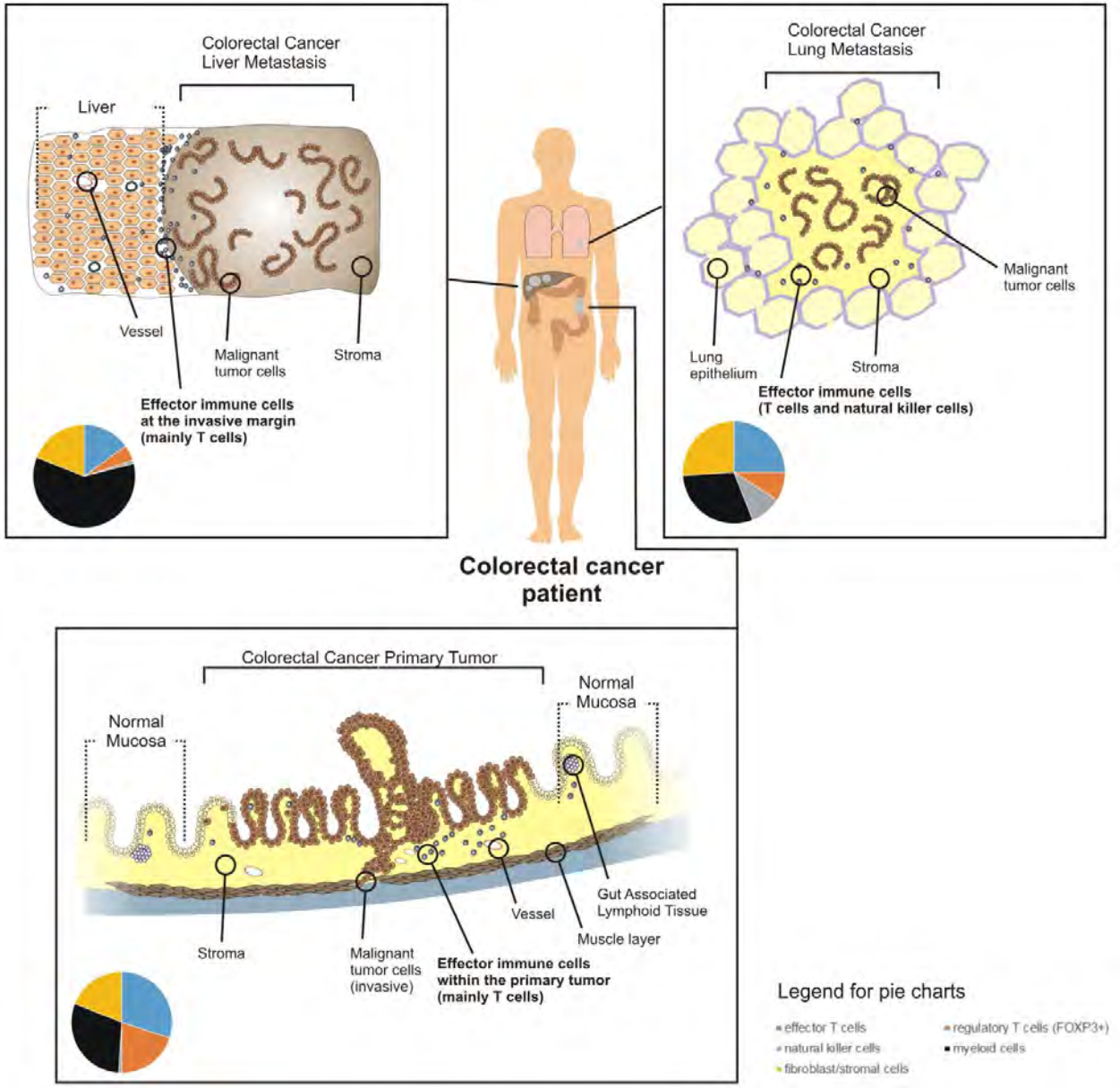
Last line setting CRC, MSS
Ipi+nivo+maraviroc



Last line setting CRC, MSS
Ipi+nivo+maraviroc



Immunologic landscape of metastatic colorectal cancer



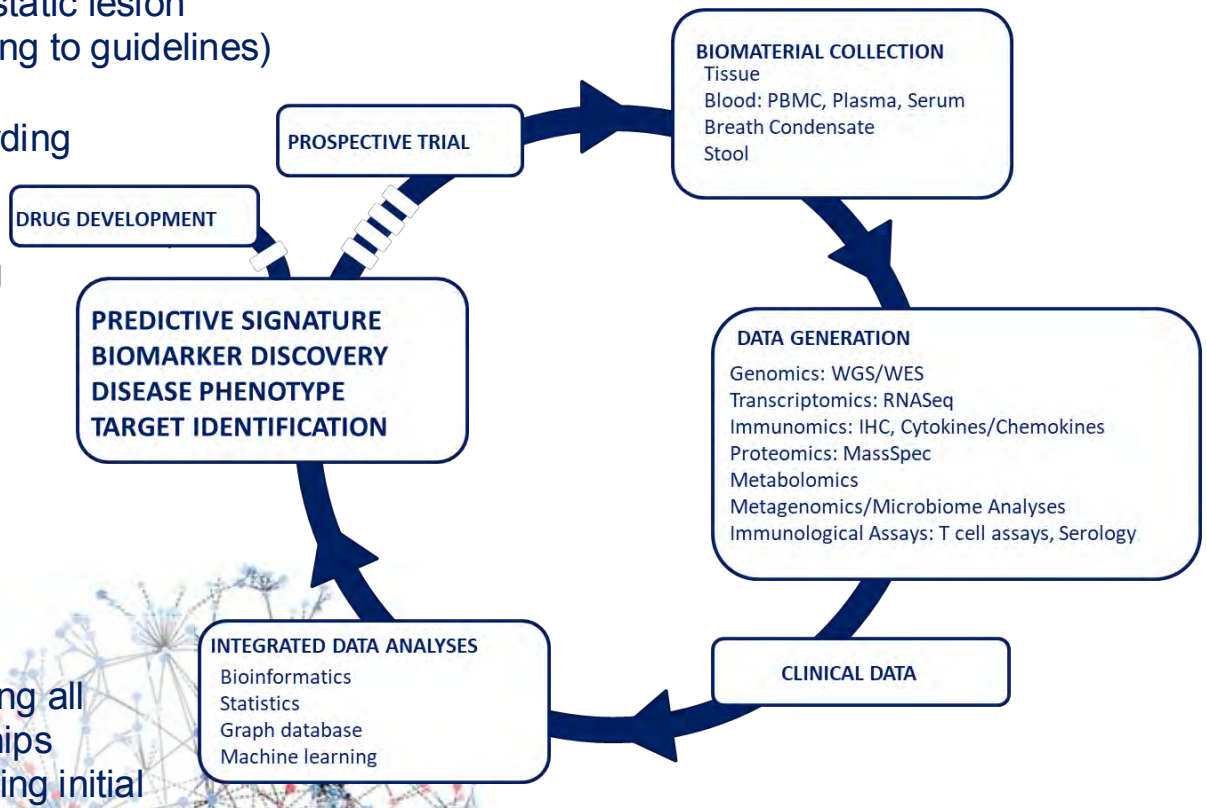
Oncoimmunology 2012; Oncoimmunology 2013; Cancer Immunol Immunotherapy 2017

PROMISE

Predictive Immunological Signatures in Lung Cancer

- Including 150 patients with newly diagnosed NSCLC
- Open biopsy/resection of a metastatic lesion
- Start standard treatment (according to guidelines)
- Rebiopsy at time of progression
- Start second line treatment according to guidelines
- Initiation in 2018, patient recruitment and analysis ongoing

Goal: Identification of biomarker signature that predict response/resistance



Graph database

- Graph can be built without knowing all entities, attributes, and relationships
- A graph can be traversed specifying initial and end entities (nodes) without need to specify a path
- Large repertoire of graph algorithms that can be applied
- Allows to discover new knowledge about not just its attributes, but also relationships

Funded by Dietmar Hopp Stiftung

Immunological Analyses

Tumor microenvironment characterization

Computer-based algorithms and Integrated data analysis

- Biopsies (cryo tissue)
  - Genome sequencing
  - Transcriptome sequencing
  - Immunhistochemistry
  - Cytokine/Chemokine
  - Proteomics
  - Metabolomics
  - Metagenome analysis
  - Microbiome analysis
- „Buffy Coat“/PBMC
  - Genome sequencing
  - Transcriptome sequencing
- Cell-free plasma
  - Exome sequencing
- Stool
  - Metagenome analysis
  - Microbiome analysis
- Serum
  - Cytokine/chemokine
  - Auto-antibody analysis
  - Metabolomics
- Blood/PBMC
  - Functional analysis
  - Pharmacological analysis
- Breath condensate
  - Proteomics

Kather et al. PLOS Med 2019
Kather and Halama. Br J Cancer 2019

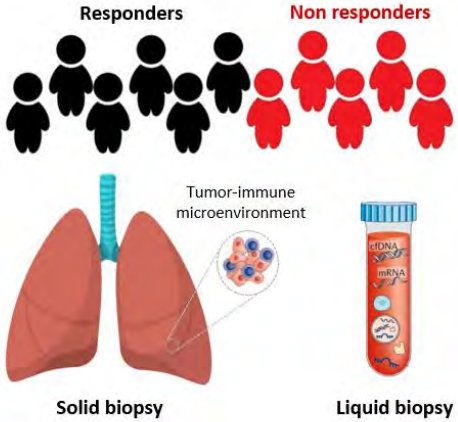
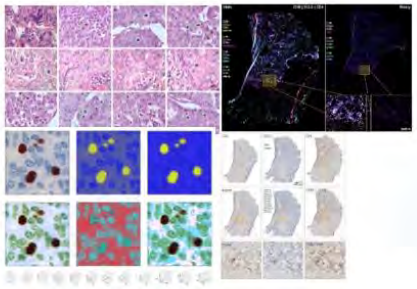
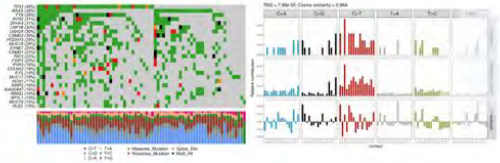
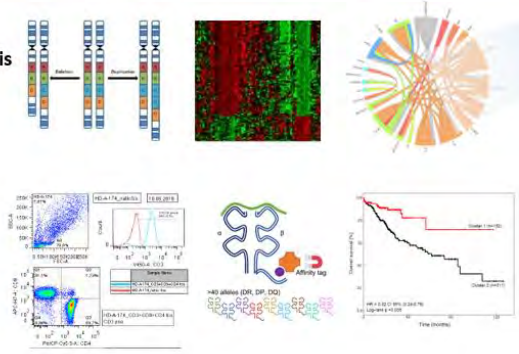


Image analysis



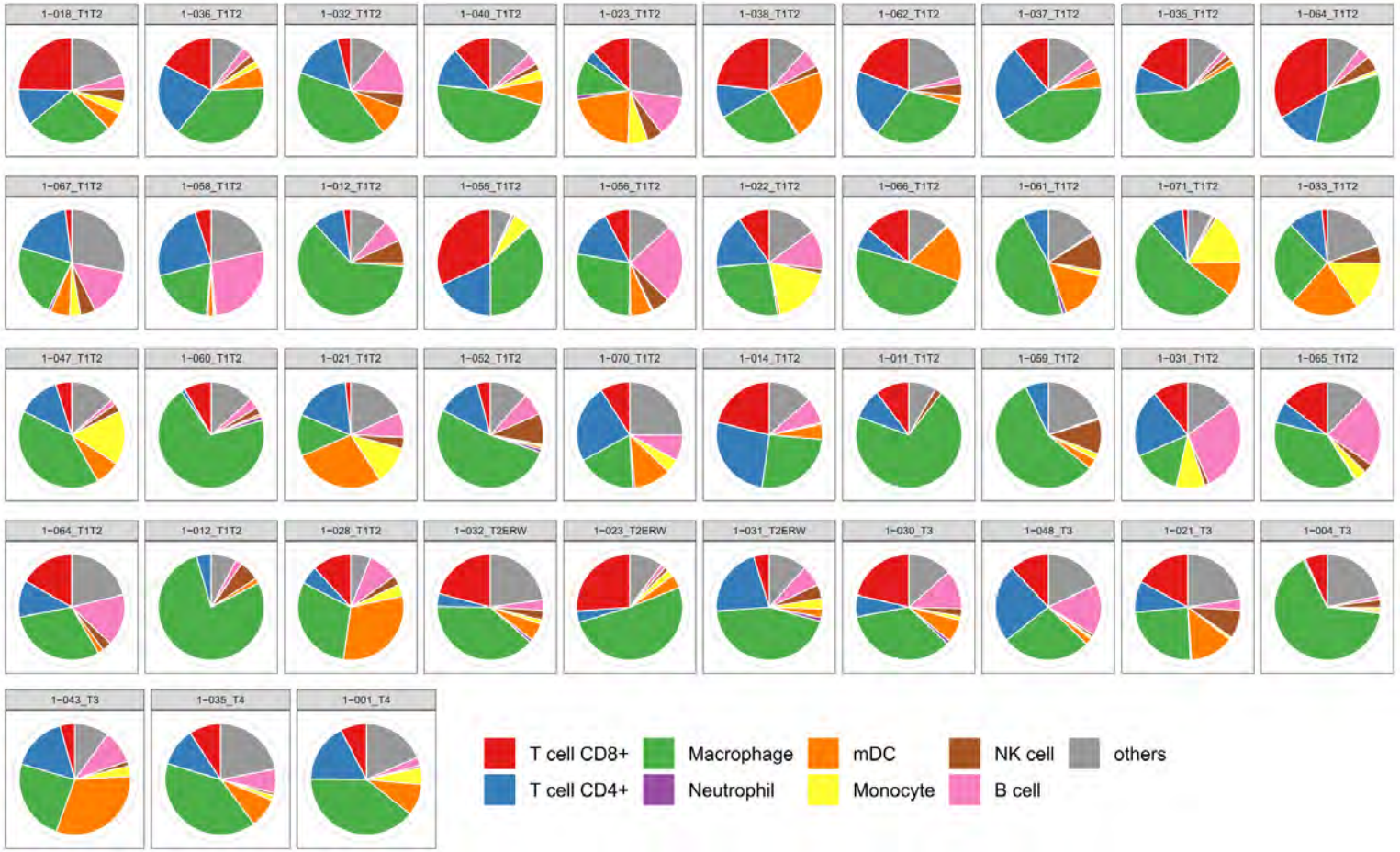


Multi-omics analysis



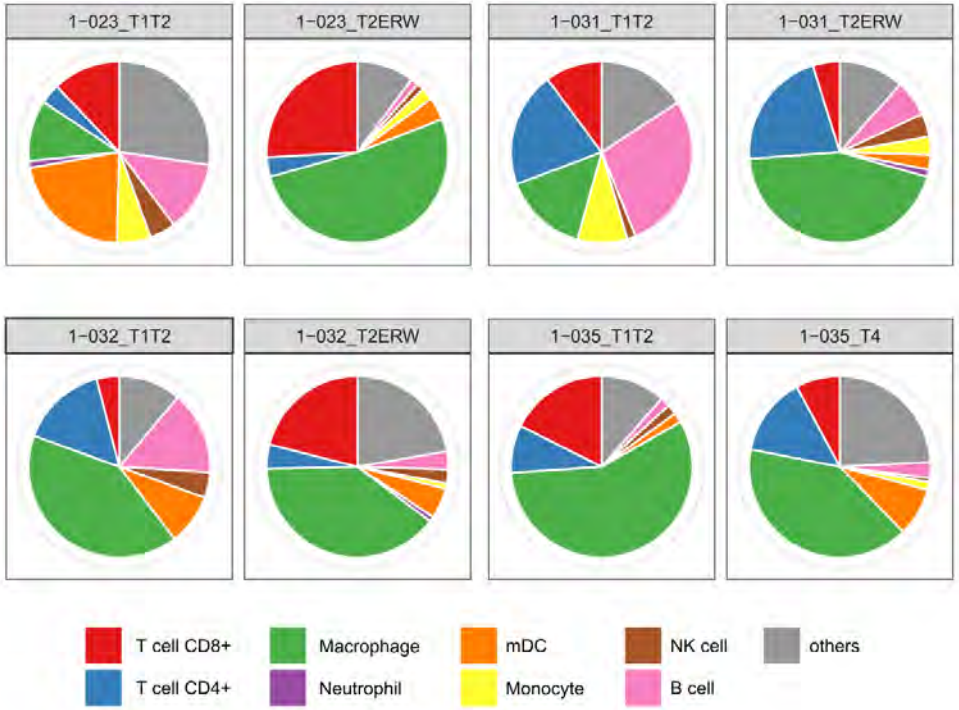
Graph Convolutional Networks

Immune infiltration estimation (RNAseq, n=43)



Immune infiltration

Estimation at baseline and post-treatment



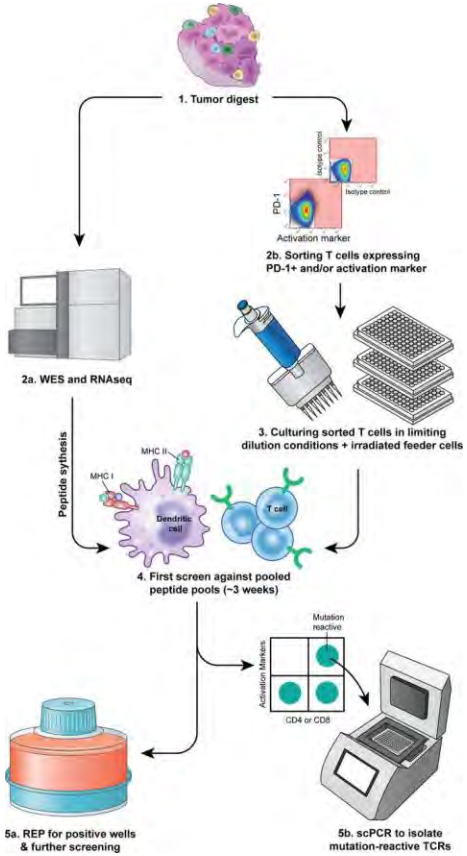
IREP trial

- Neoadjuvant trial with atezolizumab + carboplatinum + taxane in NSCLC
- We assess treatment effects in patients and in patient specific explant models in parallel
- We test if patient specific explant models are predictive
- We hope to identify predictive biomarker signatures

Immunotherapy

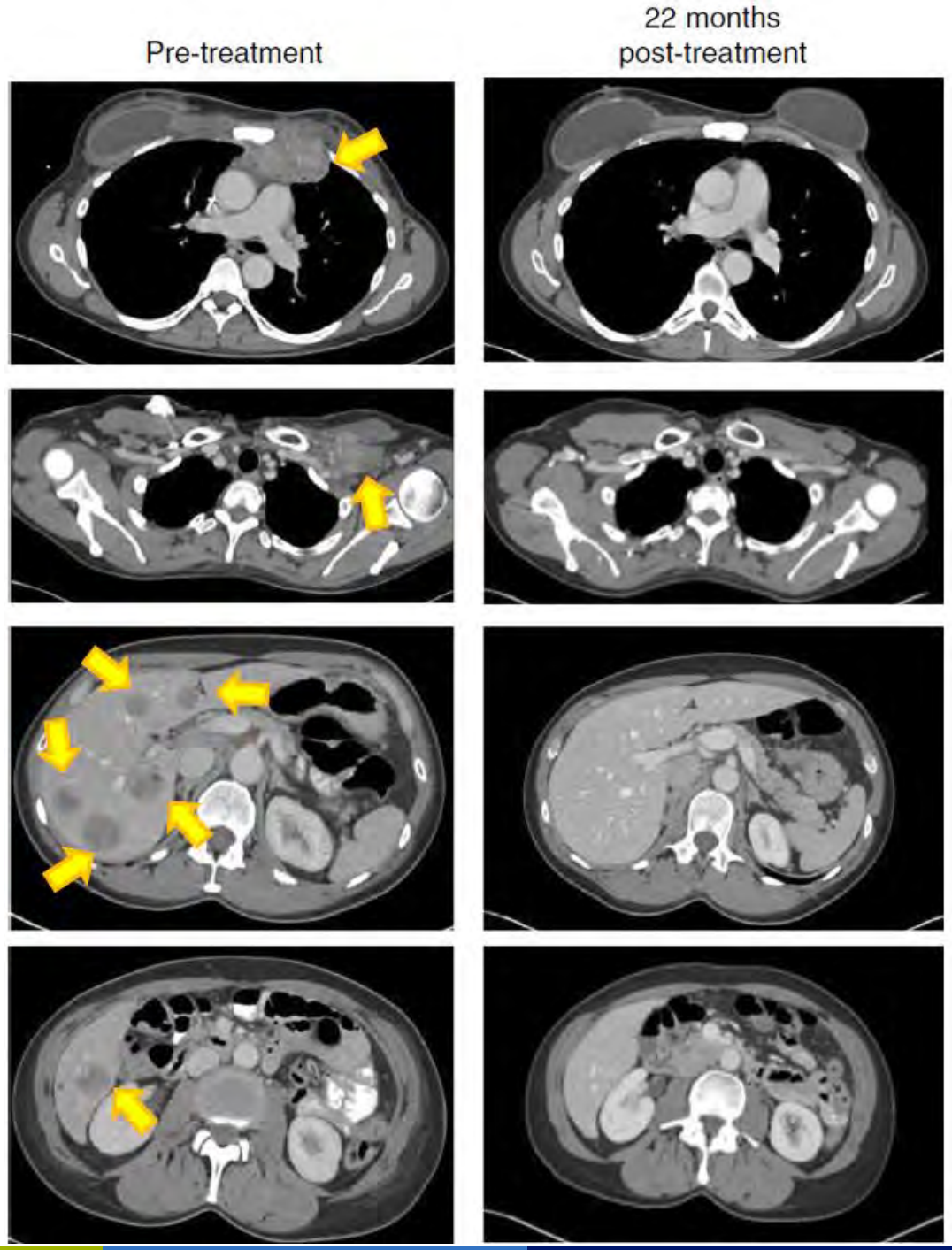
- CPI work in situations where there is sufficient preexisting immunity
- Low/no preexisting immunity? Suppressive environment?
- Infuse potent tumor immunity (CAR-T, TIL, TCR-T, …)

Identification of neoantigen-reactive T cells for highly personalized treatments using mutation specific TCR transduced T cells



1. WGS Tumor
2. Expression of predicted neoepitopes
3. Identification of reactive T cells
4. TCR cloning
5. Retroviral gene transfer in autologous T cells
6. Testing of TCR transduced T cells against tumor

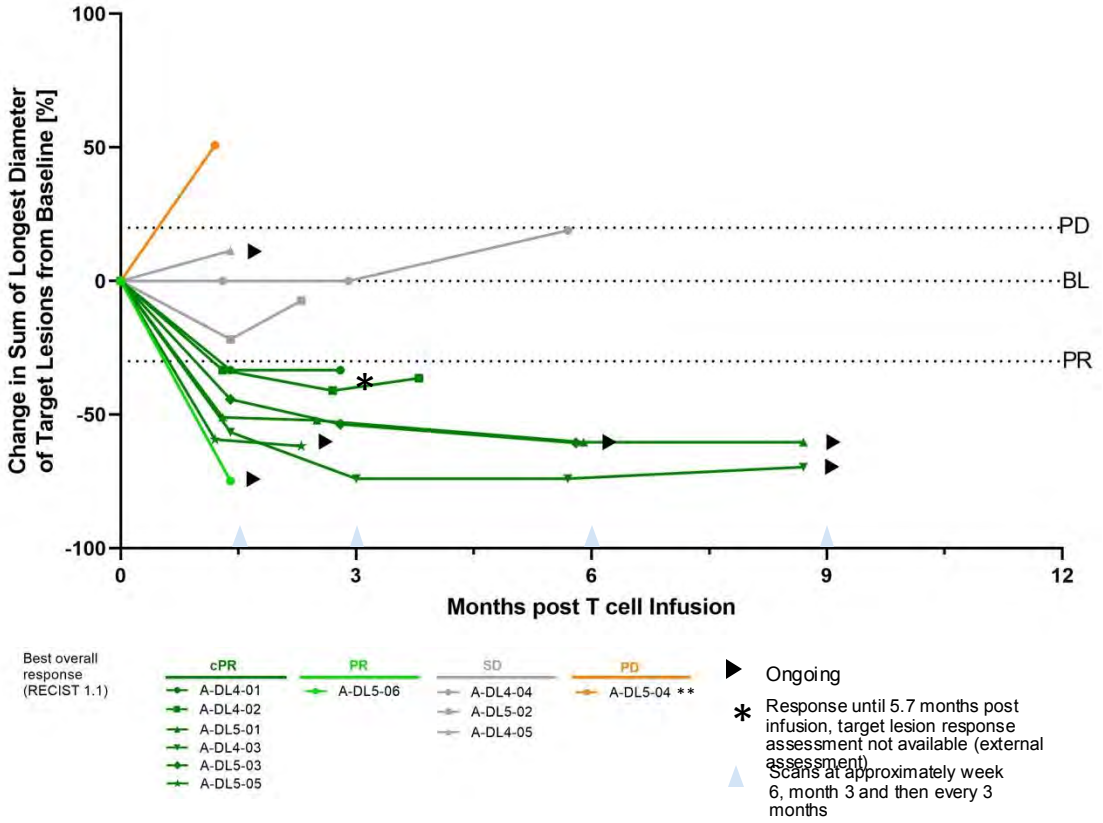
JCI Insight DOI: 10.1172/jci.insight.122467



Nikolaos Zacharakis et al
nature medicine 2018

Response over Time – Phase 1b Cohort A

Durable Partial Responses 9+ Months after IMA203 TCR-T Treatment



Median DOR[1], min, max DOR	**Not reached, 1.3+, 8.8+ months**
Median Follow-up[2]	**8.5 months**

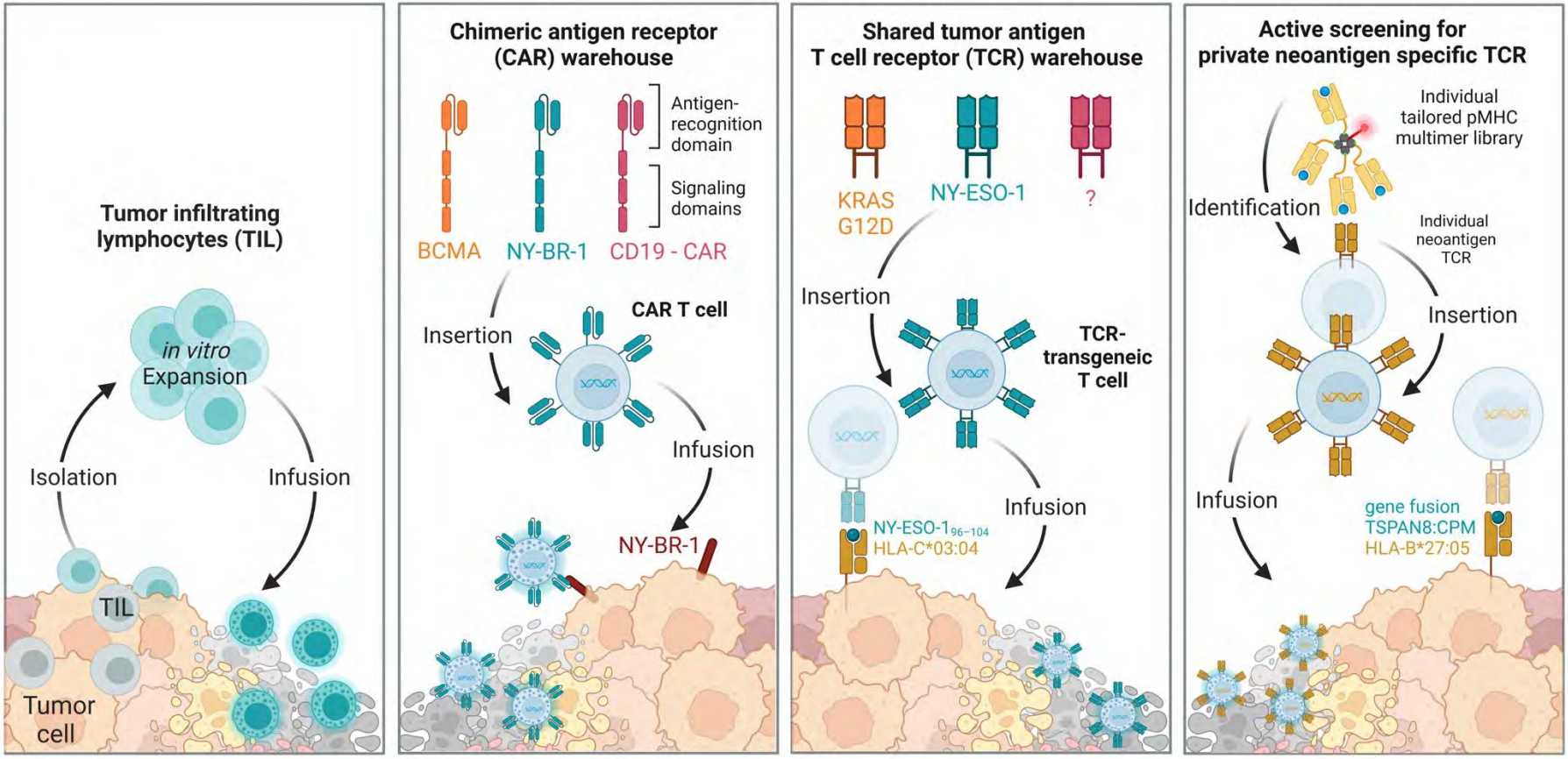
Median time from IMA203 TCR-T infusion to onset of response was 1.4 months

Ongoing responses in 5 of 7 responders:

- 2 cPRs (cut. & uveal melanoma) ongoing at 9+ months
- 1 cPR (cut. melanoma) ongoing at 6+ months
- 1 cPR (ovarian cancer) ongoing at ~3 months
- 1 PR (synovial sarcoma) ongoing at 6+ weeks

**Ovarian cancer patient A-DL5-04 erroneously received one dose of nivolumab and is part of intent-to-treat population (shown here) but not per-protocol population; [1] Duration of response (DOR) in confirmed responders is defined as time from first documented response until disease progression/death. Patients with ongoing response will be censored at date of data cut-off. Median DOR is analyzed by using the Kaplan-Meier method; [2] Median Follow-up is analyzed by using the reverse Kaplan-Meier method; PD: Progressive Disease; SD: Stable Disease; PR: Partial Response; cPR: Confirmed Partial Response; BL: Baseline

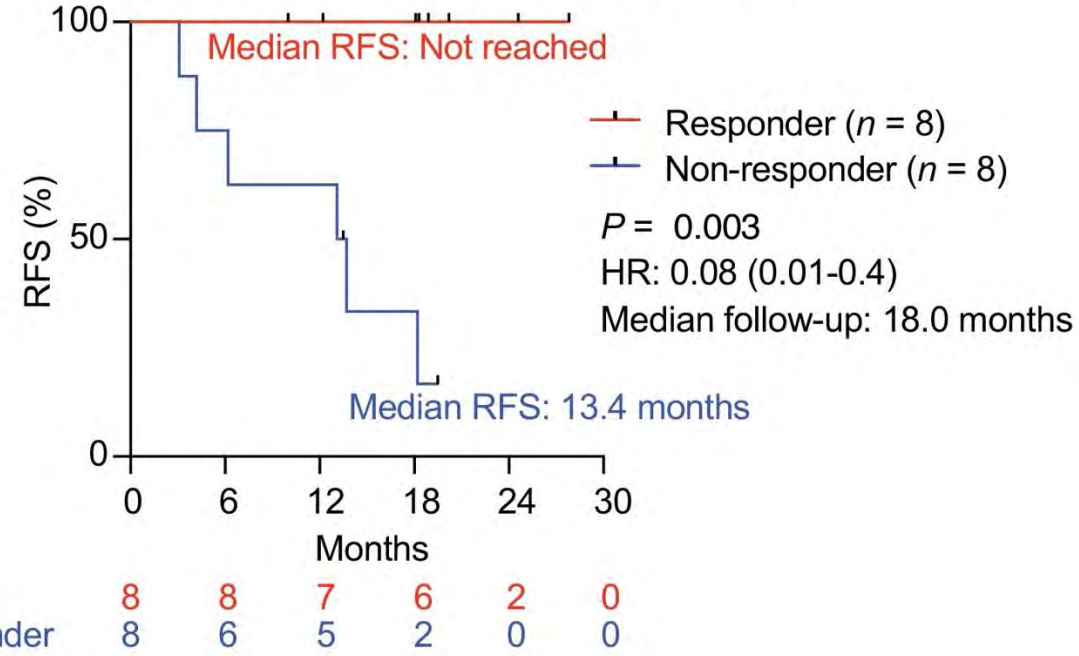
CIT T cell Therapy Portfolio



Vaccine-induced T cell immunity correlates with delayed recurrence

RFS

Recurrence-free survival from resection



At risk						
Responder	8	8	7	6	2	0
Non-responder	8	6	5	2	0	0

Memorial Sloan Kettering Cancer Center

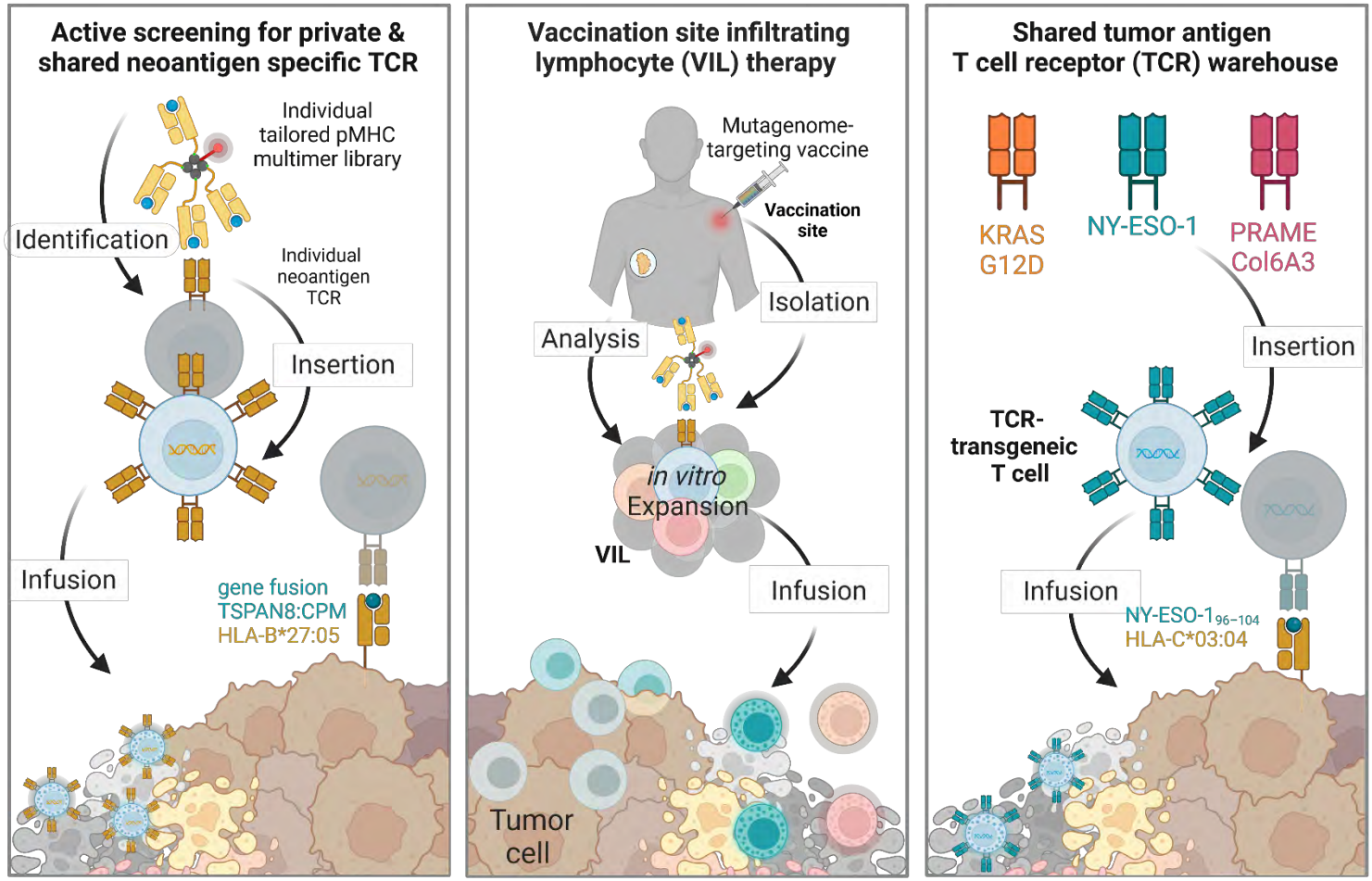
Presenter: Vinod P. Balachandran
ASCO Annual Meeting, 2022
Poster No. 2516

Our tumor (neo)antigen-specific TCR autologous adoptive T cell therapy portfolio

D120 (NCT 3.0 TCR POC) & UKHD (PIKT 2.0)

D120 & UKHD (PIKT 2.0) & D210 (AG Eichmüller)

D120 (PROMISE) & UKHD & Thorax clinic



> 6 months	< 6 months	< 2-3 months

Duration from tumor mutanome analysis until ACT infusion

Dr. Marten Meyer, TCR Discovery
DKFZ, D120 & UKHD, Med. Onco.
AG Jäger

Vaccine site reaction

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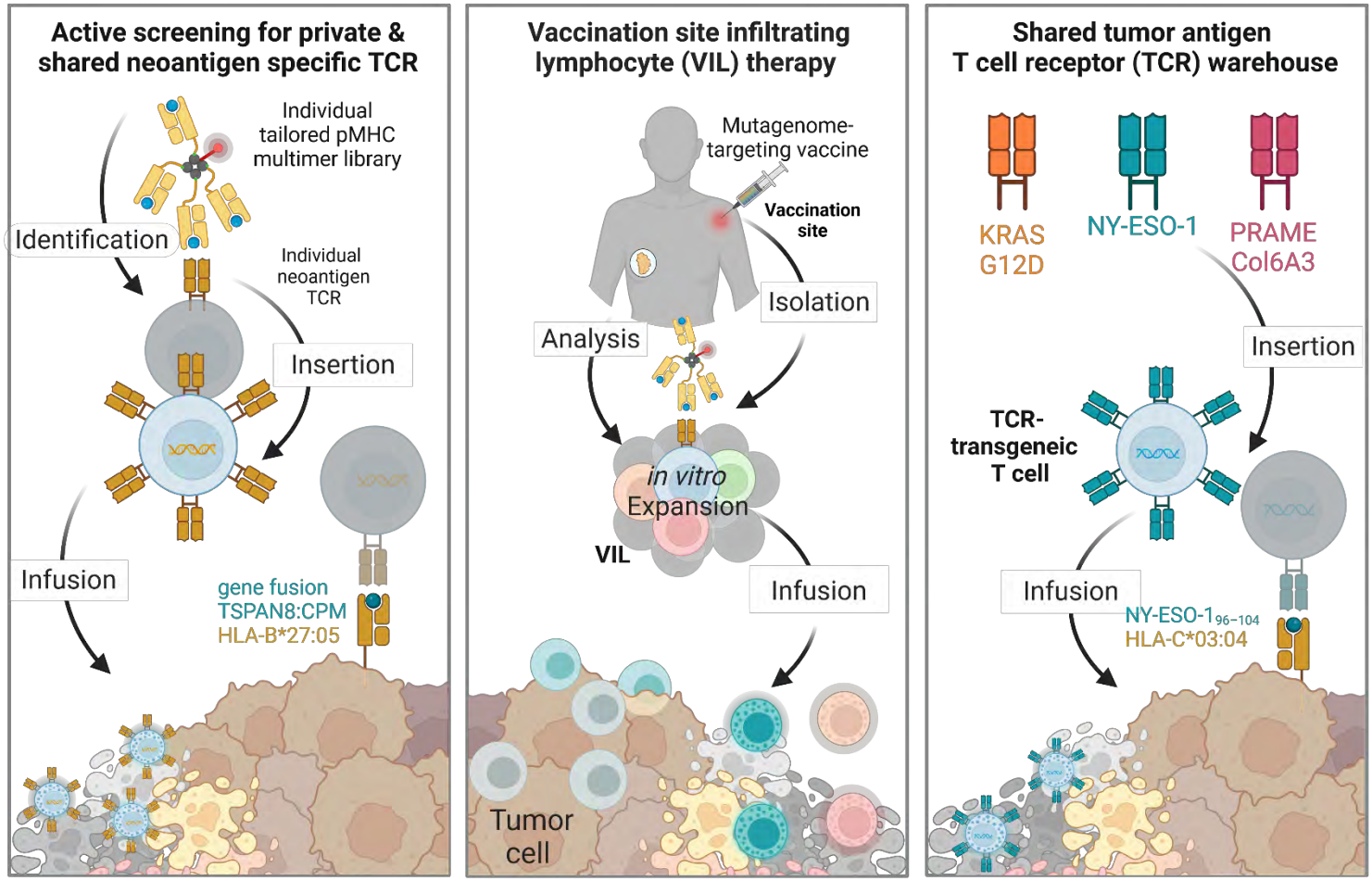

> 6 months	< 6 months	< 2-3 months

Duration from tumor mutanome analysis until ACT infusion

Dr. Marten Meyer, TCR Discovery
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Clinical translational strategies:

- High risk adjuvant situations:
  - Oligometastatic PDAC:
    - Neoadjuvant FOLFIRINOX + mutanome vaccine
    - VIL expansion and testing
    - Resection of primary and metastases
    - VIL infusion post op followed by CPI
  - Oligometastatic NSCLC:
    - Neoadjuvant CTX + PD1 + mutanome vaccine
    - VIL expansion and testing
    - Resection of primary and metastases
    - VIL infusion post op followed by CPI

Center for individualized treatments (CIT)

- Cooperation between DKFZ, UKHD, University and D. Hopp foundation
- GMP Unit to produce cells (modified and unmodified) and peptides
- Capacity for 250 cell treatments p.a.


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