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Deutsches Konsortium für Translationale Krebsforschung
Partnerstandort Freiburg

DKTK

Immunmodulation durch SBRT. Ergebnisse der LAPIS Studie

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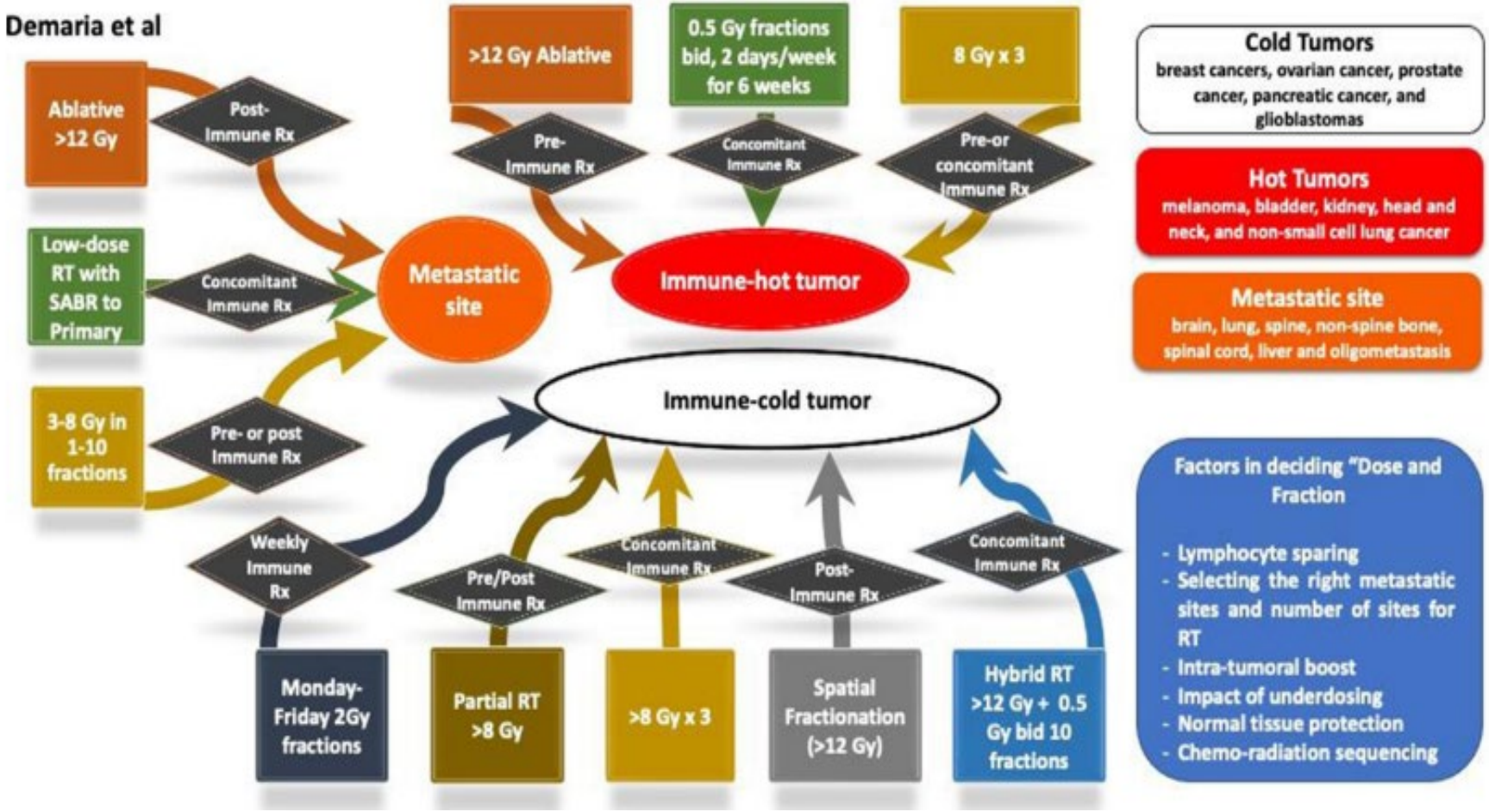
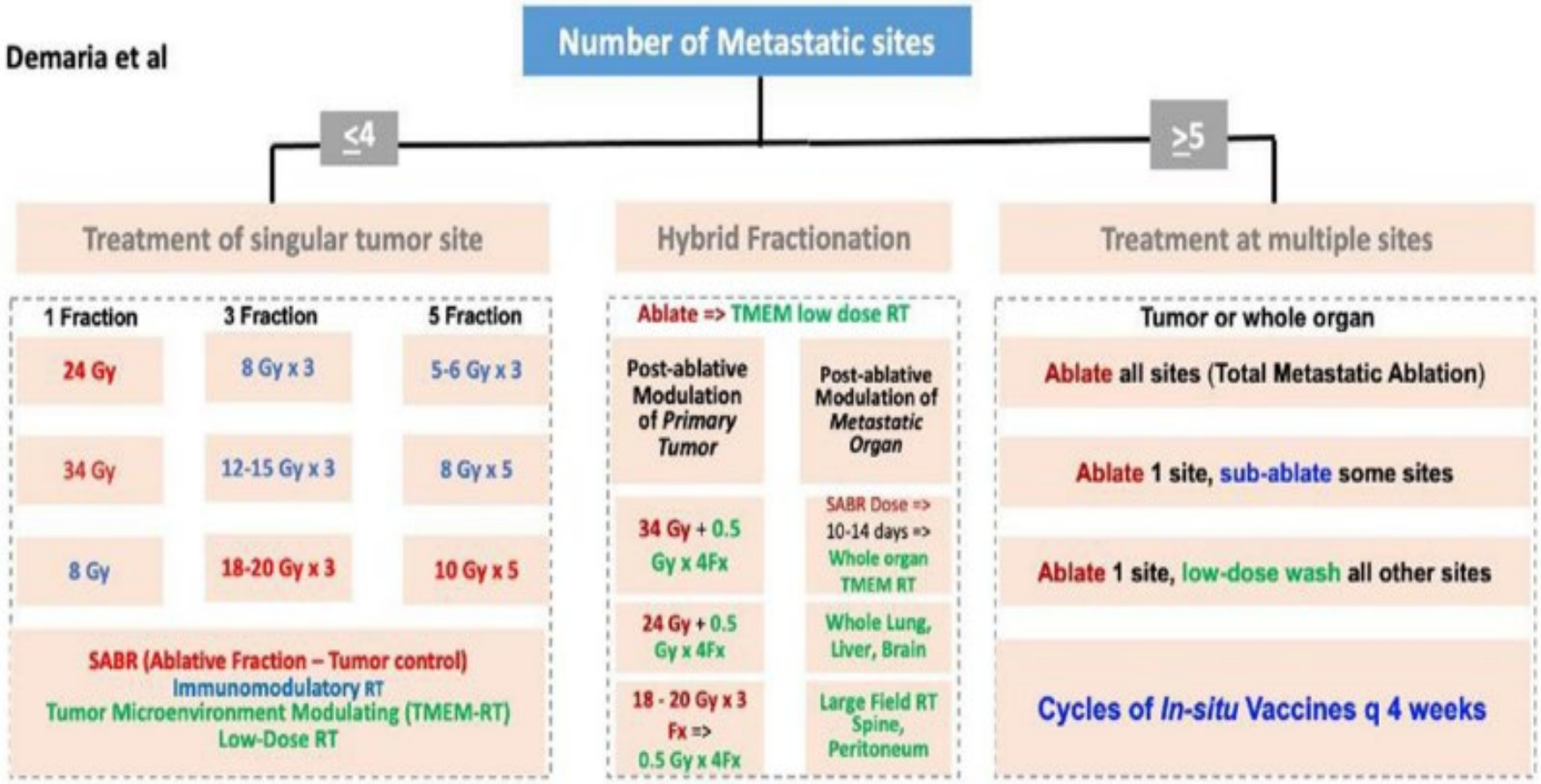
Immunmodulation Dosis und Fraktionierung



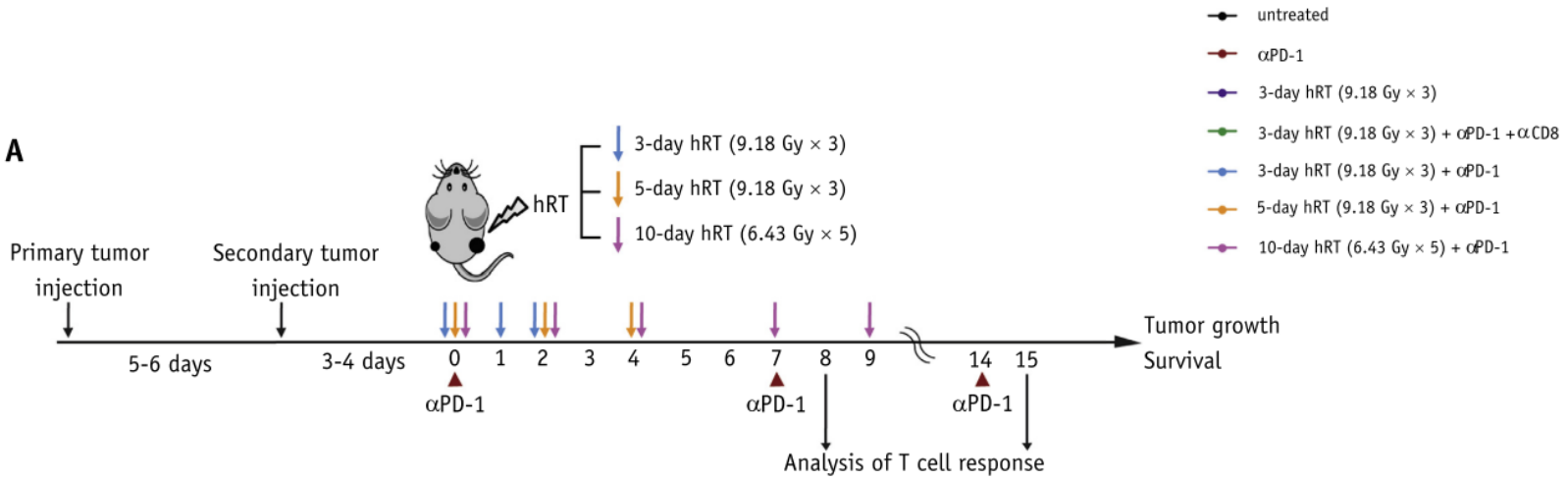
Demaria JITOC 2019

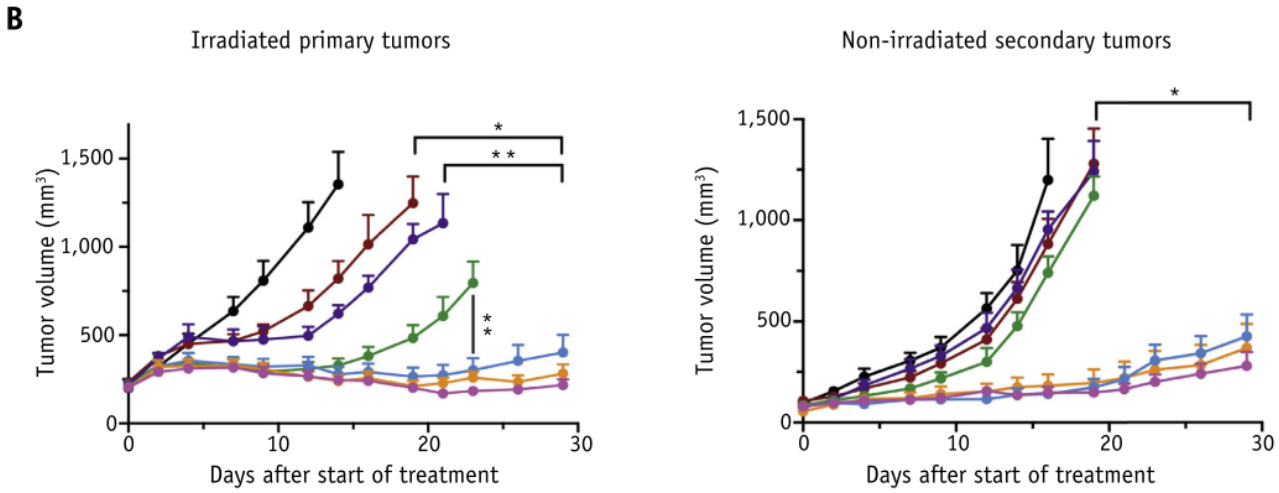
Immunmodulation Dosis und Fraktionierung



Demaria JITOC 2019

Immunmodulation





Zhang Niedermann IJROP 2018

Immunmodulation Dosis und Fraktionierung

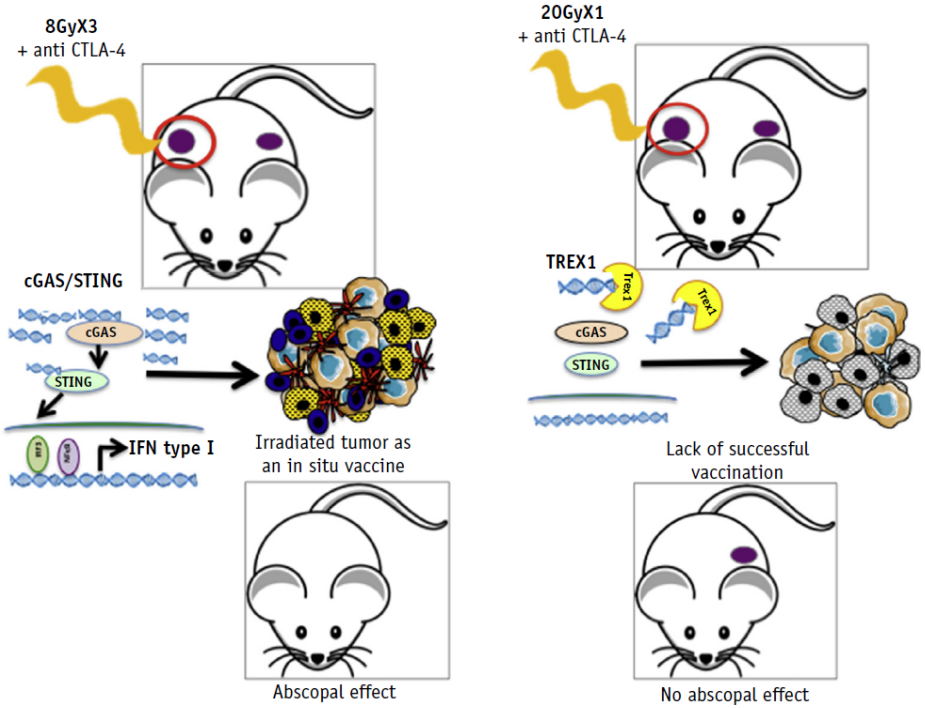


Fig. 1. Role of dose/fraction in inducing abscopal effects. In combination with CTLA-4 blockade, despite comparable in field control of experimental TSA tumors in syngeneic mice, a single dose of 20 or 30 Gy failed to result in abscopal effects, as demonstrated by the response in a synchronous unirradiated tumor. The mechanism was mediated by TREX1 induction, which abrogated interferon-1 signaling (5).

Vanpouille-Box et al. Nat Commun 2017

Immunmodulation PEMBRO RT Studie Oligometastasierung

Table. Response to Treatment

Response	Experimental Arm, No./Total No. (%) (n = 36)[a]	Control Arm, No./Total No. (%) (n = 40)[b]
Best overall response, No.		
Complete response	3	1
Partial response	14	8
Stable disease	9	10
Progressive disease	10	21
Objective response rate at 12 wk		
Overall[c]	13/36 (36)	7/40 (18)
PD-L1 TPS, %		
0	4/18 (22)	1/25 (4)
1-49	3/8 (38)	3/8 (38)
≥50	6/10 (60)	3/5 (60)
Disease control rate at 12 wk[d]	23/36 (64)	16/40 (40)

Abbreviations: PD-L1, programmed death-ligand 1; TPS, tumor proportion score.

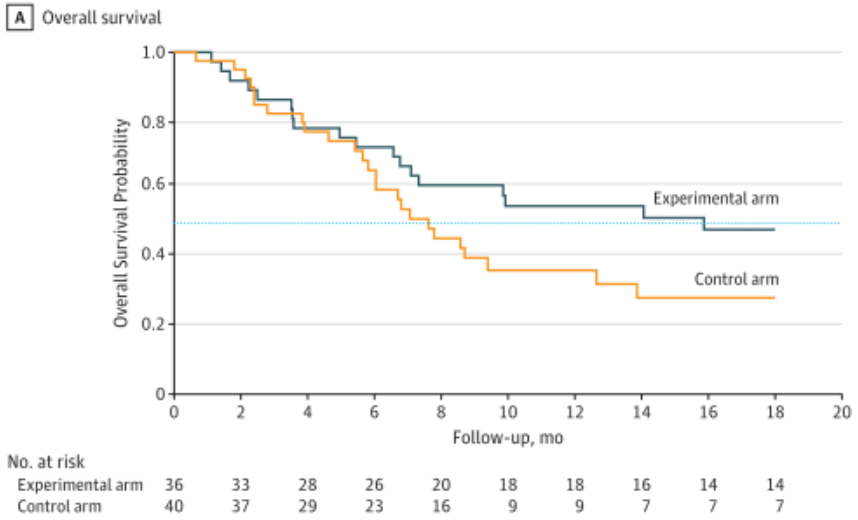
[a] Patients who received pembrolizumab therapy after stereotactic body radiotherapy.

[b] Patients who received pembrolizumab therapy alone.

[c] $P = .07$.

[d] $P = .04$.

Figure 3. Overall Survival in the Intent-to-Treat Population



Theelen JAMA Oncology 2019

Immunmodulation Neoadjuvante „SBRT“ Oligometastasierung

	Major pathological response*	Complete pathological response
Durvalumab monotherapy (n=30)		
IB	1 (3%)	0
IIIA	1 (3%)	0
Durvalumab plus SBRT (n=30)		
IA	1 (3%)	0
IB	0	1 (3%)
IIA	1 (3%)	2 (7%)
IIB	2 (7%)	2 (7%)
IIIA	4 (13%)	3 (10%)

Data are n (%). SBRT=stereotactic body radiotherapy. *Excluding patients with complete pathological response.

Table 2: **Clinical stages in major and complete pathological responders**

	Durvalumab monotherapy		Durvalumab plus SBRT	
	Radiographic response (n=30)	Major pathological response (n=2)	Radiographic response (n=30)	Major pathological response* (n=16)
Stable disease	24 (80%)	1 (50%)	15 (50%)	5 (31%)
Partial response	1 (3%)	1 (50%)	14 (47%)	11 (69%)
Progression	3 (10%)	0	1 (3%)	0
Pseudoprogression	2 (7%)	0	0	0
Complete response	0	0	0	0

Data are n (%). SBRT=stereotactic body radiotherapy. *Including patients with complete pathological response (table 2, figure 2).

Table 3: **Radiographic and major pathological responses**

Single center Ph II Studie

3x8 Gy „SBRT + Durvalumab vs Durvalumab

50% komplette Remission von den Patientnen die eine SBRT + Durvalumab erhalten haben

Altroki Lancet Oncol 2021

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HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

SBRT Immunmodulation
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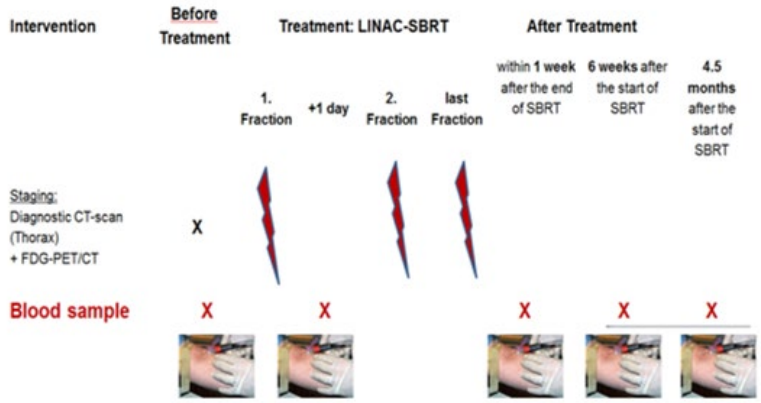
Lung and Liver cancer, Ablative high Precision radiotherapy and the Immune System: Evaluation of immune-modulatory effects of stereotactic body radiation therapy (SBRT)

L_AP_IS -Trial:

Evaluation of immune-modulatory effects of stereotactic body radiation therapy of pulmonary and hepatic malignancies



Changes in number and phenotype of lymphocytes:

- CD8+ T effector cells, stem-like CD8+PD1+ (CD39–CD69–) cells,
- Tregs, memory and Th17 T cells and exhaustion markers – TIM 3, LAG3)
- using as markers CD3, CD4, CD8, CD25, CD127, FoxP3, ICOS, IFN-γ, IL-17A,
- CD45RA, CCR7, Ki67, CD69, CTLA4,, PD-L1,
- especially increase >10% and > 20% of CTL counts and the ratio CTL/Treg
- PMA/Ionomycin stimulation

Changes in number and phenotype of myeloid cells:

- myeloid derived suppressor cells, dendritic cells, etc.,
- using as markers HLA-DR, CD14, CD15, CD11b, CD33, CD3, CD56, CD19, CD11c, CD141, CD123, Clec9A, and PD-L1/PD-1

Significant changes in circulating biomarkers of immune response in the plasma :

- GM-CSF, IFN-γ, IL-1β, IL-10, IL-12 p70, IL-2, IL-6, IL-8, TNF-α, VEGF, PIGF, sVEGFR1, bFGF, VEGF-C, VEGF-D, sTie2, HGF, CCL5, CXCL9, CXCL10, CXCL11, SDF1α/CXCL12, CAIX, TGF-β

Mass cytometry profiling of T cell exhaustion and immune checkpoint expression

- Deep profiling of CD8 T cells in chronic infection and cancer revealed distinct expression of exhaustion and T cell differentiation markers on clusters identified using phenograph

PI Prof Grosu

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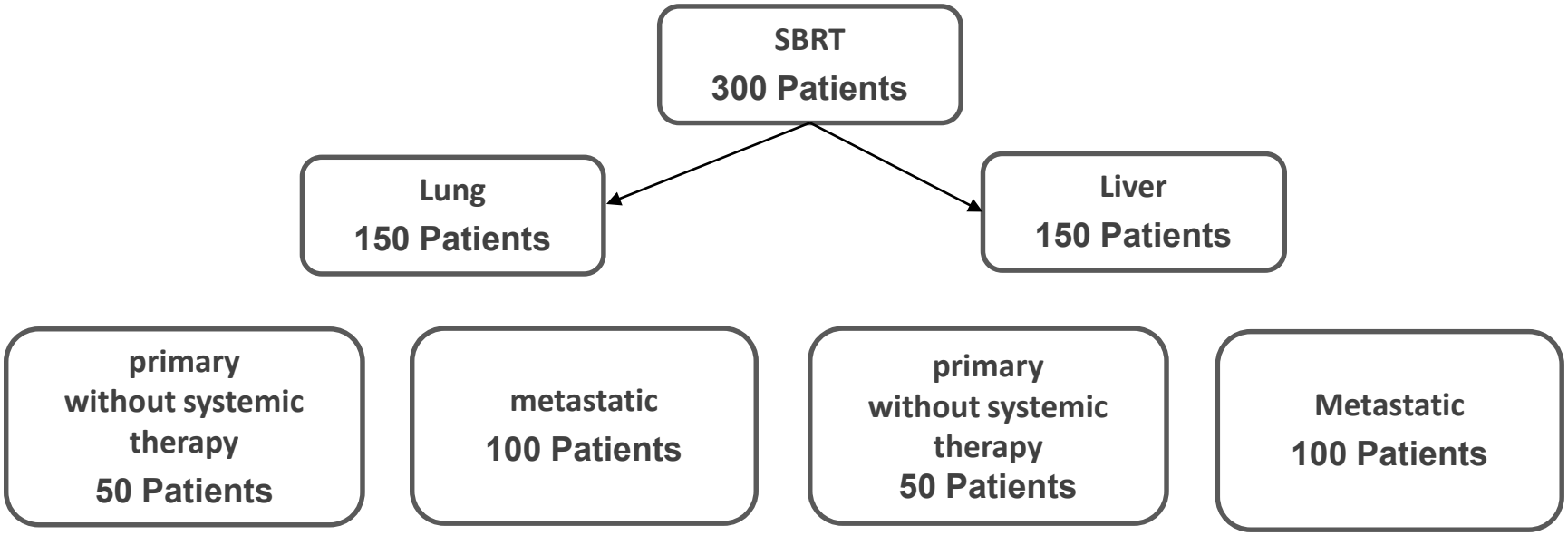

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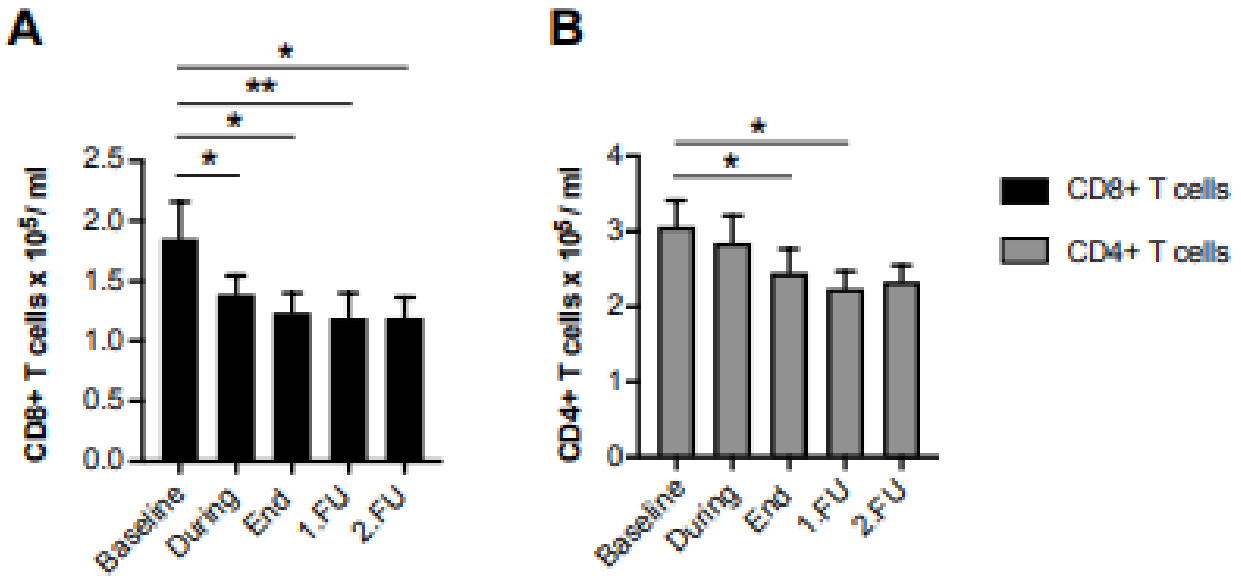
Immunmodulation NSCLC



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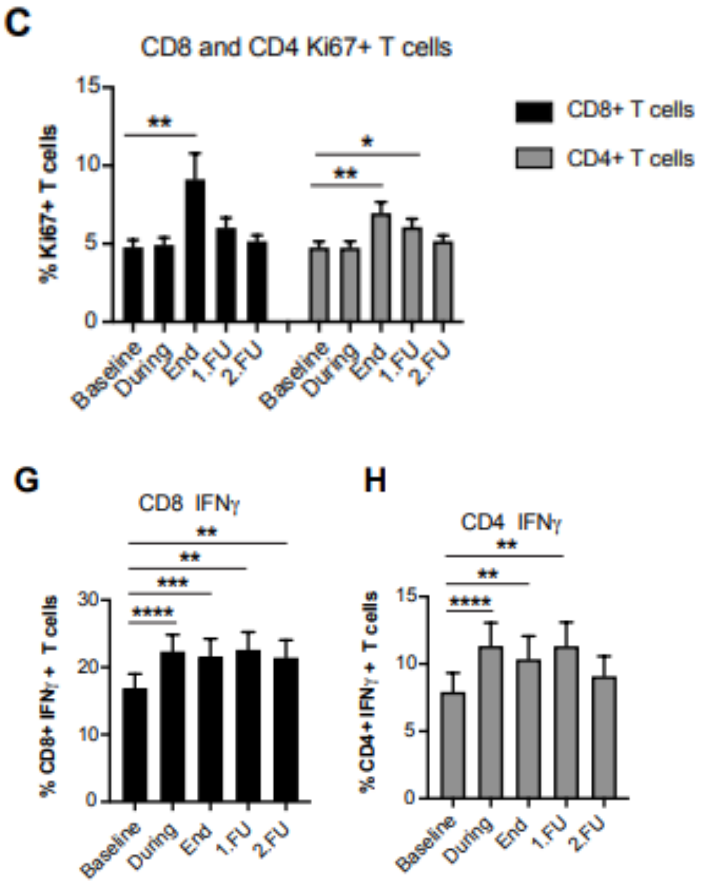
Immunmodulation NSCLC



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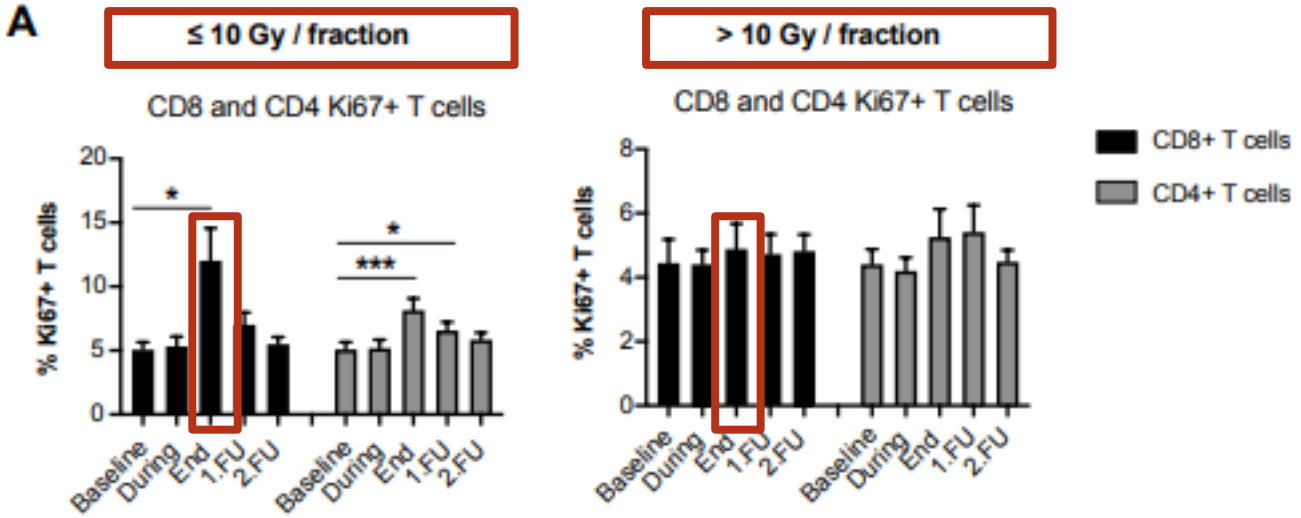
Immunmodulation NSCLC



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SBRT Immunmodulation
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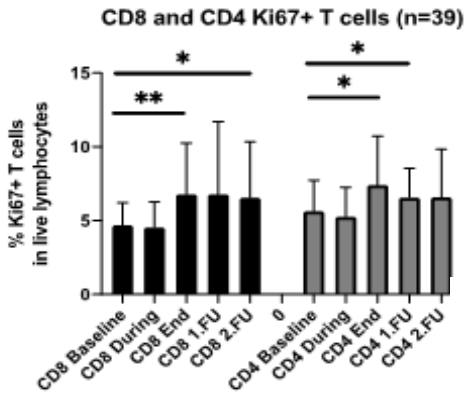
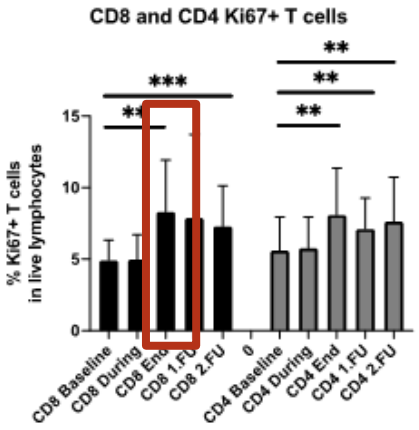
Immunmodulation Oligometastasierung Lunge
Ohne Systemtherapie

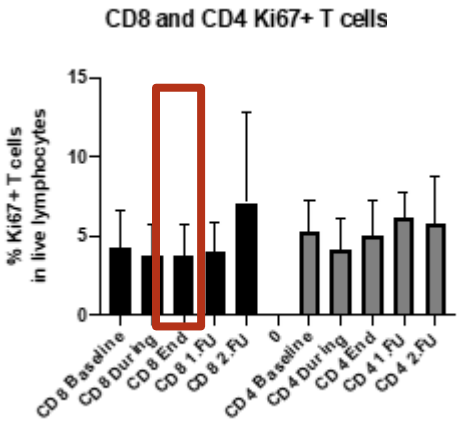
Alle Patienten



≤ 10 Gy



> 10 Gy



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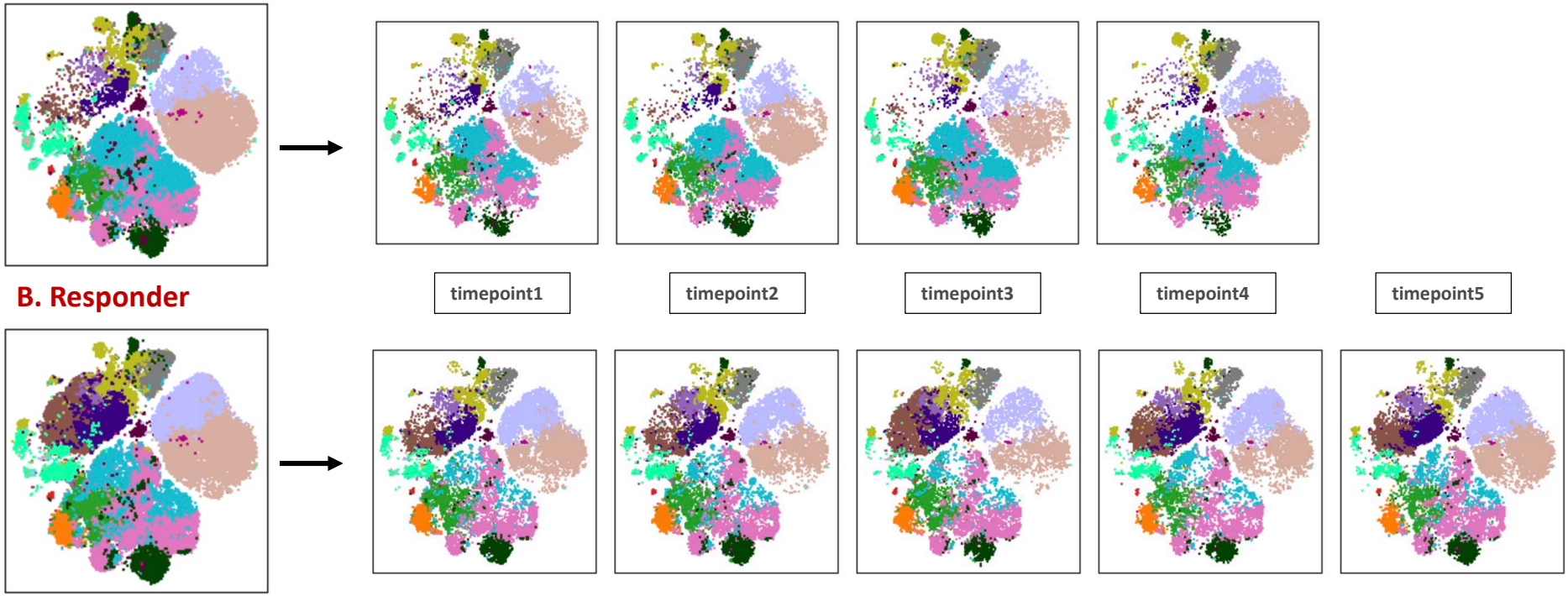
CyTOF

FiTSNE and FSOM

A. Non Responder



B. Responder

E. Gkika

SBRT Immunmodulation Oligometastasierung
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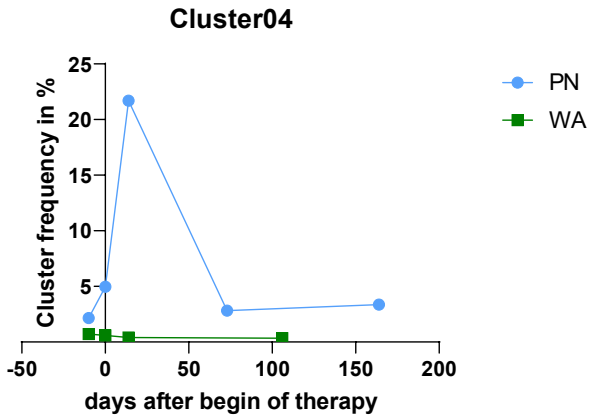
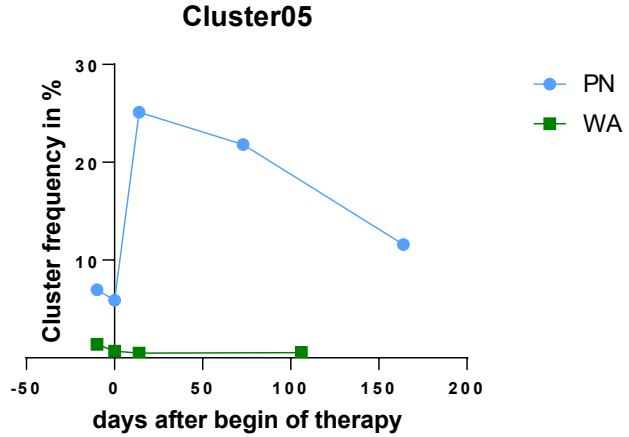
CyTOF





Bei dem Patienten mit dem besseren Therapie-Ansprechen sieht man 2 Wochen nach Therapiebeginn einen starken Anstieg von 2 interessanten CD8 Clustern (PD-1+ CD38 Eomes TOX TIGIT CX3CR1 KLRG1 GzmB) = Cluster 04 und Cluster 05 um das 10 bzw. 4 fache, während der andere Patient keine Reaktion auf Ebene der CD8 Cluster zeigt.

Zusammenfassung

- Signifikanter Anstieg der proliferierenden $CD4^+$ and $CD8^+$ T Zellen, bei der letzten Bestrahlung.
- **10 Gy order weniger pro Fraktion**
- Ablative Gesamtdosen sind immunogen

SBRT Immunmodulation Oligometastasierung
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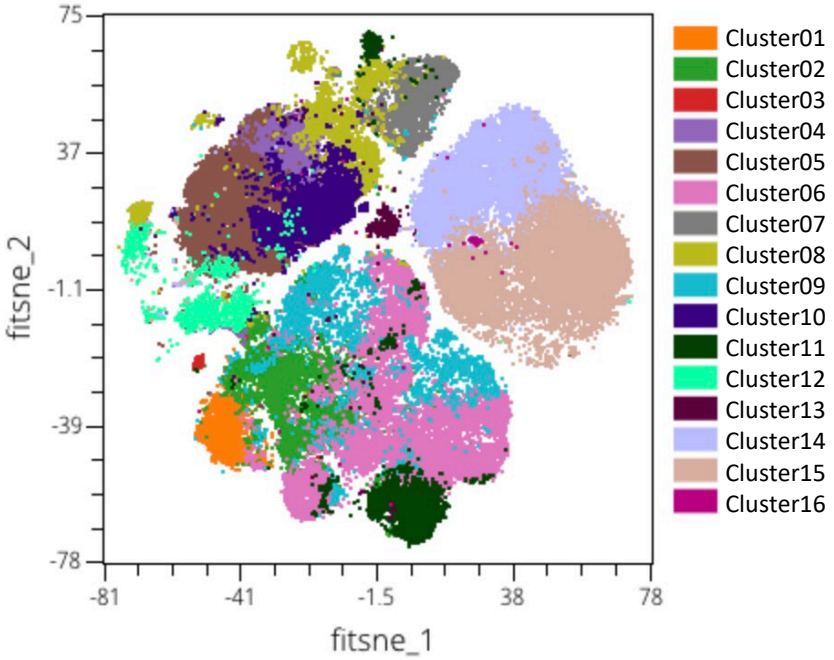
FiTSNE and FSOM



main immune cell populations:

Cluster12: **γδ T cells** (TCRγδ+)
Cluster14: **NK or NKT cells** (CD3+/lowCD56+CD16+)
Cluster15: **NK or NKT cells** (CD3+/lowCD56+CD16+)
Cluster16: **MAIT cells** (TCRVa7.2+ CD161+)

CD8 subsets:

Cluster04
Cluster05
Cluster07
Cluster08
Cluster10

CD4 subsets:

Cluster01
Cluster02
Cluster04
Cluster06
Cluster09
Cluster11
Cluster13

E. Gkika, B. Bengsch