

Immun- und Systemtherapie nach Metastasenresektion beim metastasierten Nierenzellkarzinom Ergebnisse einer Phase I/II Studie



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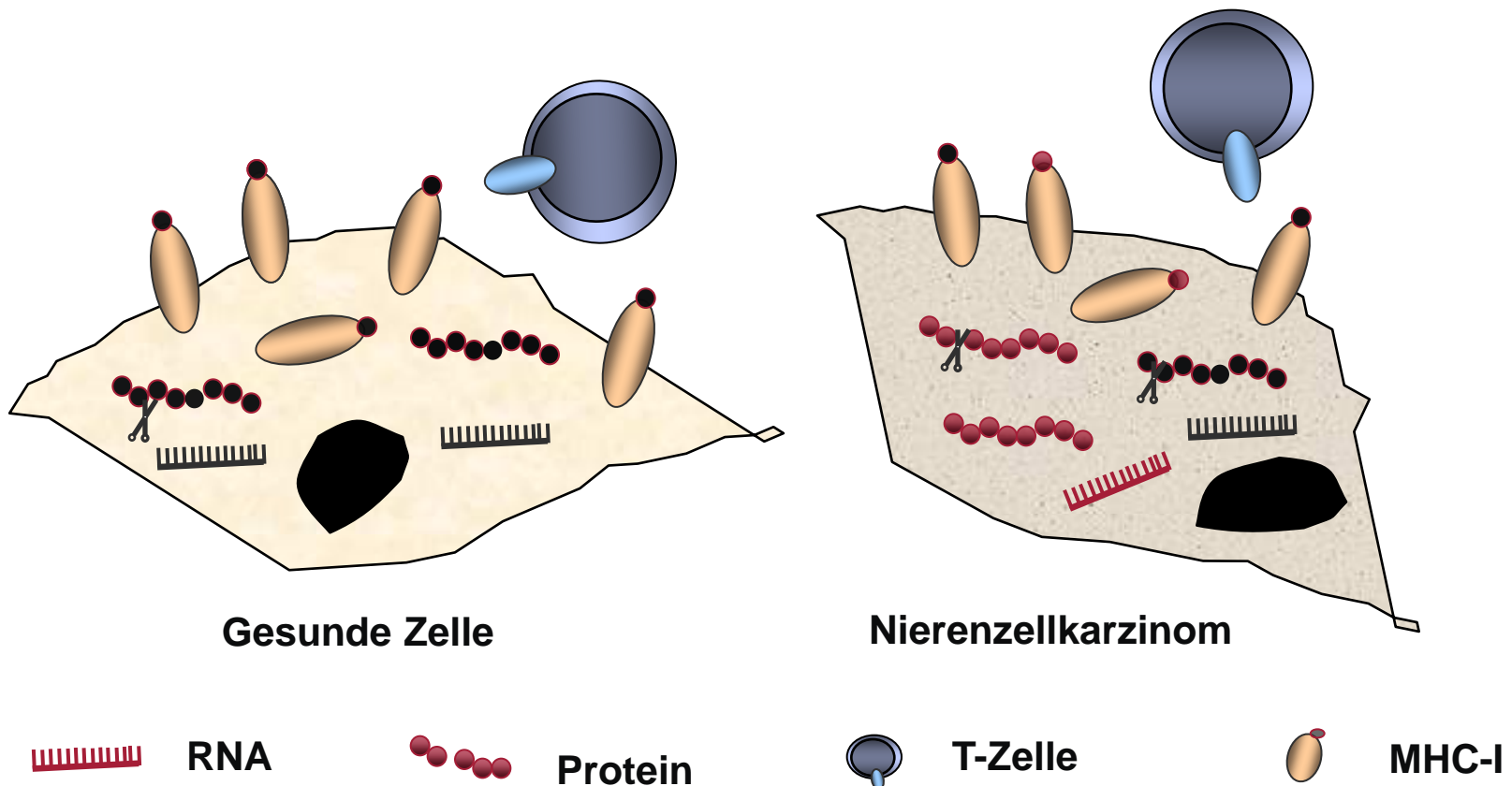


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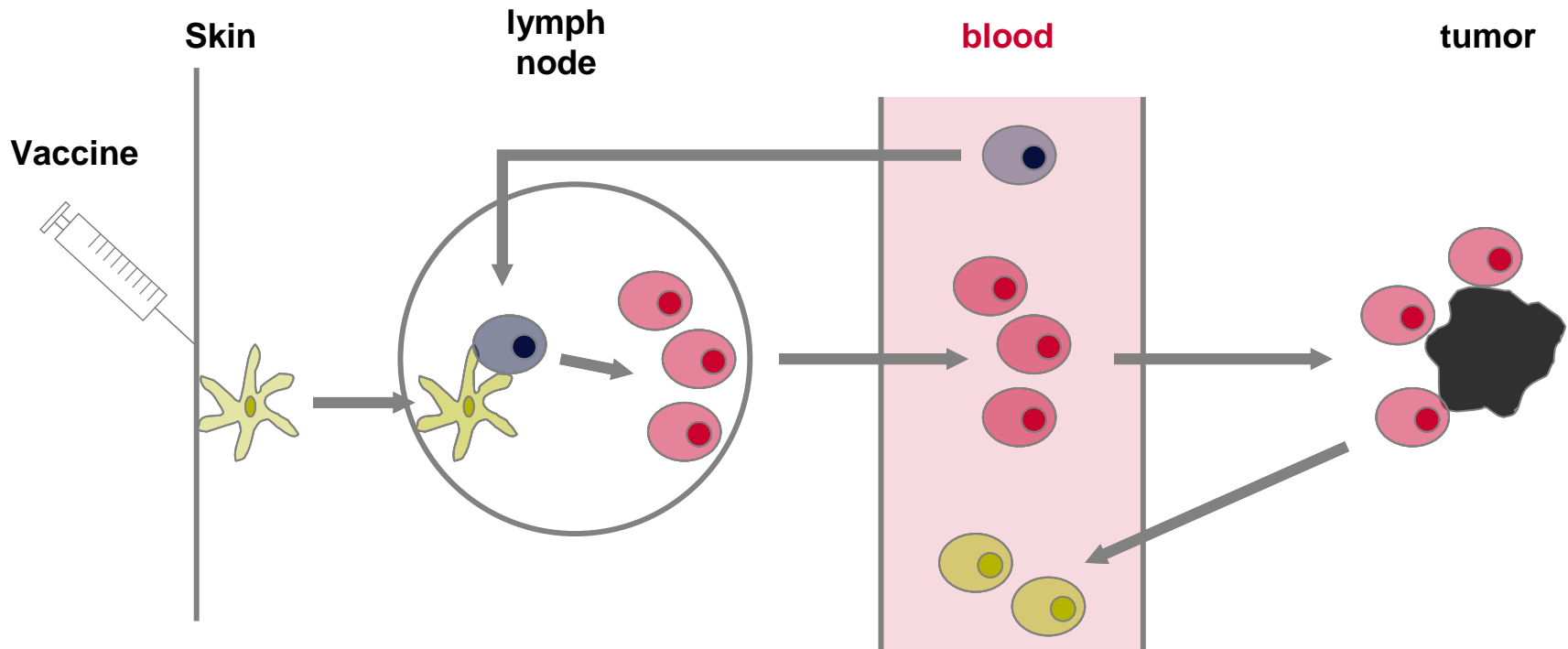
Spezifische T-Zellaktivierung

Tumor-assoziierte Antigene (TAA)

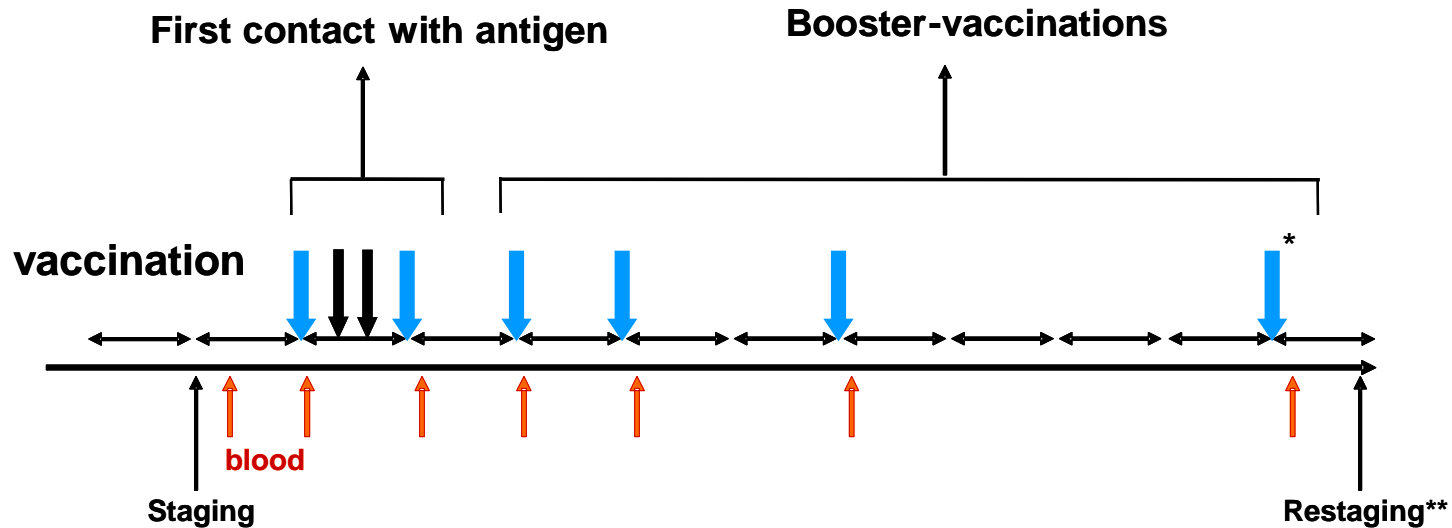




Spezifische T-Zellaktivierung



Vaccination schedule



↔ 7 d

↓ Montanide: depot effect

↓ / ↓ GM-CSF: repetitive local activation of antigen-presenting cells

* further vaccinations every month up to 18 applications or until progression

** clinical restaging every 3 months

300 µg peptide in Montanide or GM-CSF (75µg)



Peptide Cocktail – MHC class I

Source of peptide	Gene ID	Sequence	Position	HLA ligand	T-cell epitope
Apolipoprotein L1	APOL-1	FLGENISNFL	242-251	Flad (1998)	
Apolipoprotein L1	APOL-2	ALADGVQKV	176-184	Weinschenk (2002)	
	KIAA0367	ALFDGDPHL	1-9	Weinschenk (2002)	
Guanylate cyclase 1	GUCY1A3	SVFAGVVG	581-589	Weinschenk (2002)	
Integrin alpha-3	ITGA3	LLYPTTEITV	798-806	Krüger (2005)	
Mucin	MUC-1	STAPPVHNV	950-958		Brossart (1999)
Adipophilin	ADFP	SVASTITGV	129-137	Weinschenk (2002)	Schmidt (2004)
MET protooncogene	MET	YVDPVITSI	654-662	Weinschenk (2002)	Schag (2004)
Regulator of G protein signalling 5	RGS5	LAALPHSCL	5-13	Krüger (2005)	Boß/Brossart (2007)
Cyclin D1	CCND1	LLGATCMFV	101-109		Sadoynikoya (1998)
Influenza A virus	IMP	GILGFVFTL	58-66		Falk (1991)
HBV core antigen	HBV	FLPSDFFPSV	18-27		Bertoletti (1993)

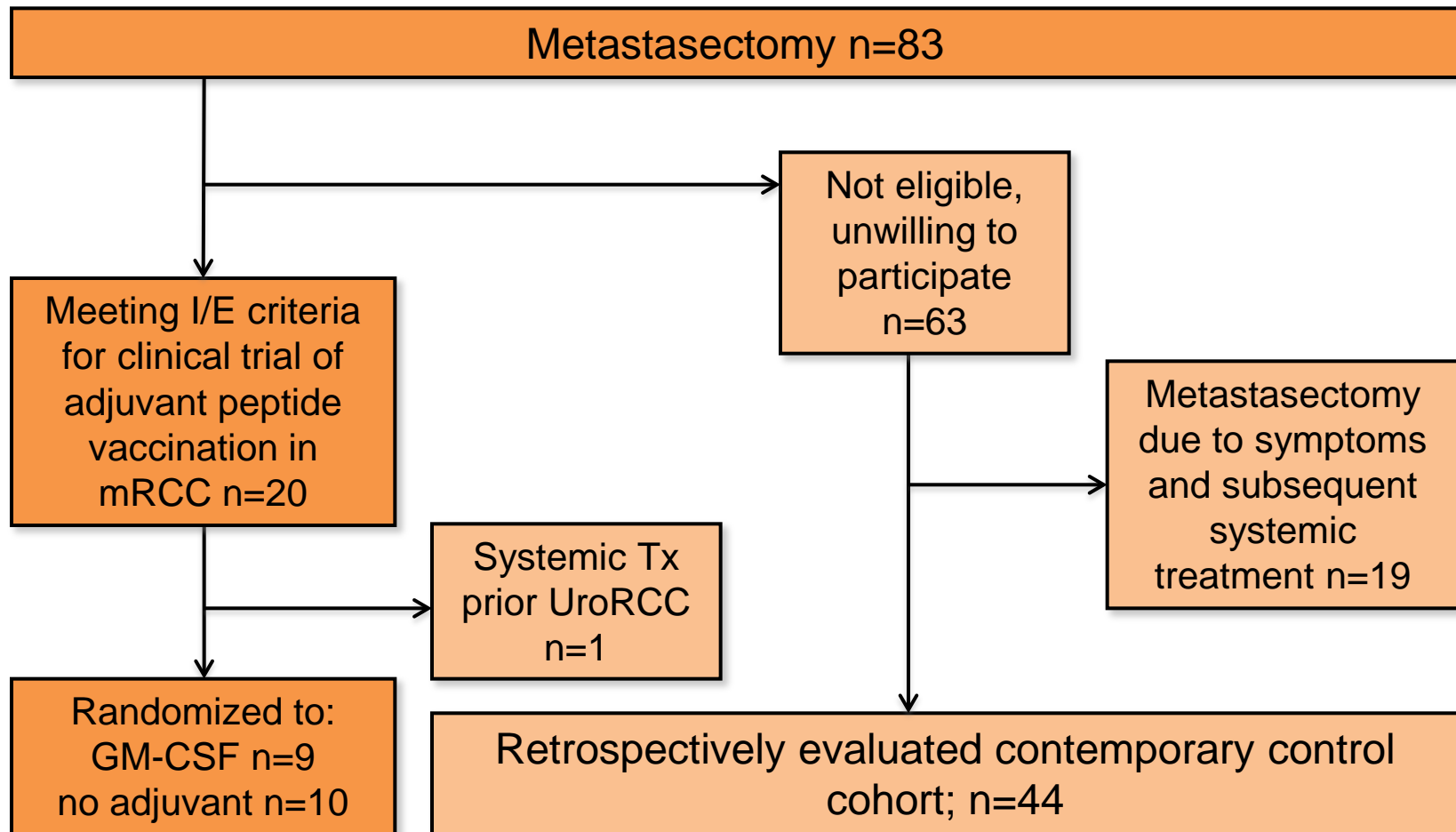


Peptide Cocktail – MHC class II

Source of peptide	Gene ID	Sequence	Position	T-cell epitope
Cyclin D1	CCND1	NPPSMVAAGSVVAAV	198-212	DRB1*0401, Dengjel (2004)
Insulin-like growth factor binding protein 3	IGFBP3	HSKIIIIKKGHAKDSQ	142-157	DRB1*11, Dengjel (2006)
Matrix metalloproteinase 7	MMP7	SQDDIKGIQKLYGKRS	153-168	DRB1*11, Dengjel (2006)
Carbonic anhydrase 9	G250	EIHVVHLSTAFARVDEALGR	212-231	DR4, (HLA-A2) Vissers (2002)



CONSORT Diagramm





Klinische Parameter

Covariate	Metastasectomy	Metastasectomy + UroRCC	p-Wert
Geschlecht (m/w)	34/10	15/4	0,58
Alter	64,5	54,4	0,07
Knochenmetastasen	6/44	4/19	0,35
Lebermetastasen	4/44	1/19	0,52
Lungenmetastasen	11/44	5/19	0,57
Zerebrale Metastasen	2/44	0/19	0,48
LK Metastasen	8/44	1/19	0,17
Anderer Metastasenort	11/44	10/19	0,03

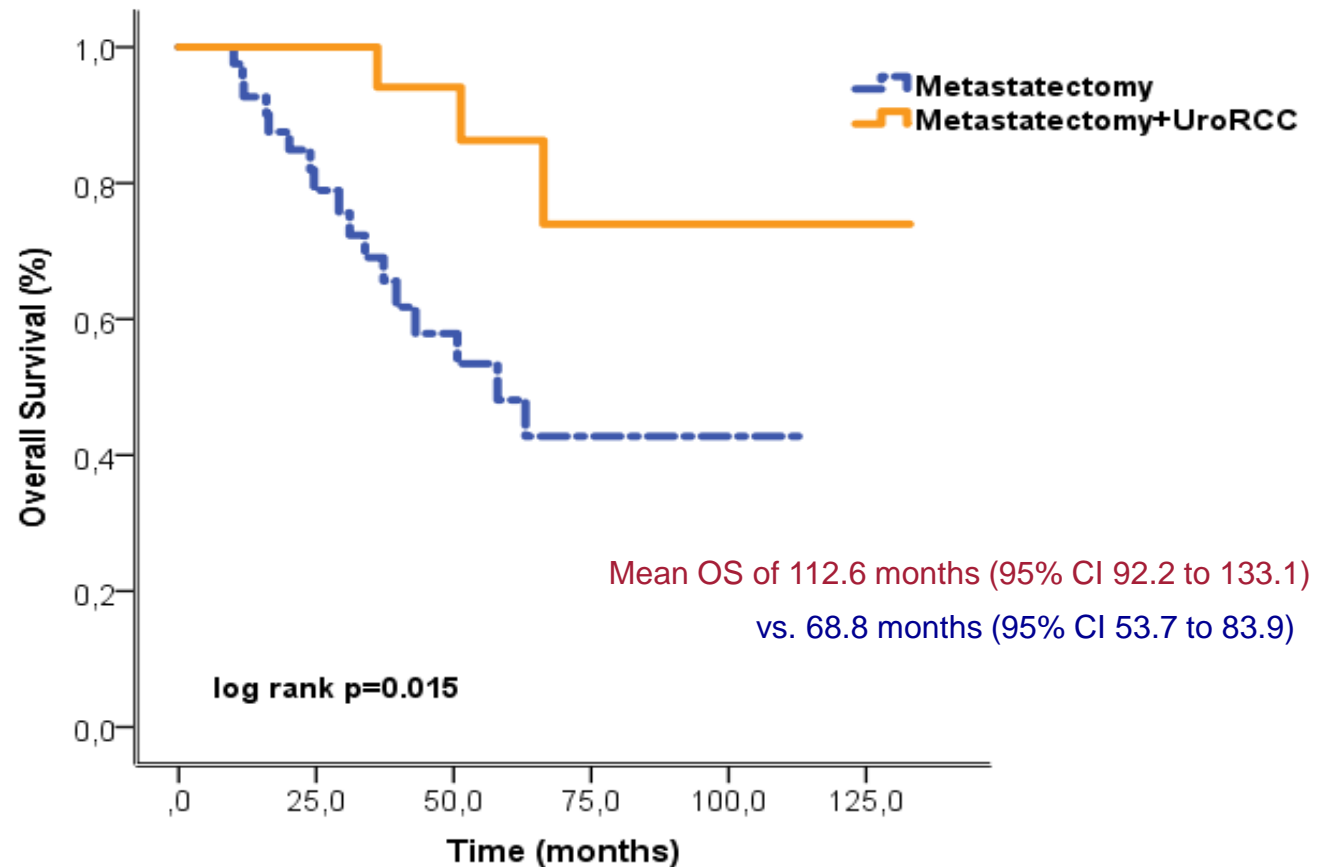


Nebenwirkungen – IIT population

Category	Adverse Event	Grade I°	Grade II°	Grade III°	Grade IV°
Musculoskeletal and connective tissue disorders	Arthralgia	1/20			
Nervous system disorders	Dizziness	1/20			
	Headache	1/20			
Skin and subcutaneous tissue disorders	Skin induration	11/20			
Vascular disorders	Lymphedema	1/20			
Gastrointestinal disorders	Nausea	1/20			
General disorders and administration site conditions	Fatigue	1/20			
	Injection site reaction (redness)	5/20		1/20 (redness with necrosis)	
Immune system disorders	Activated sarcoidosis		1/20		
Infections and infestations	Skin infection (injection site)	2/20			



Overall Survival – Kaplan Meier Analysis



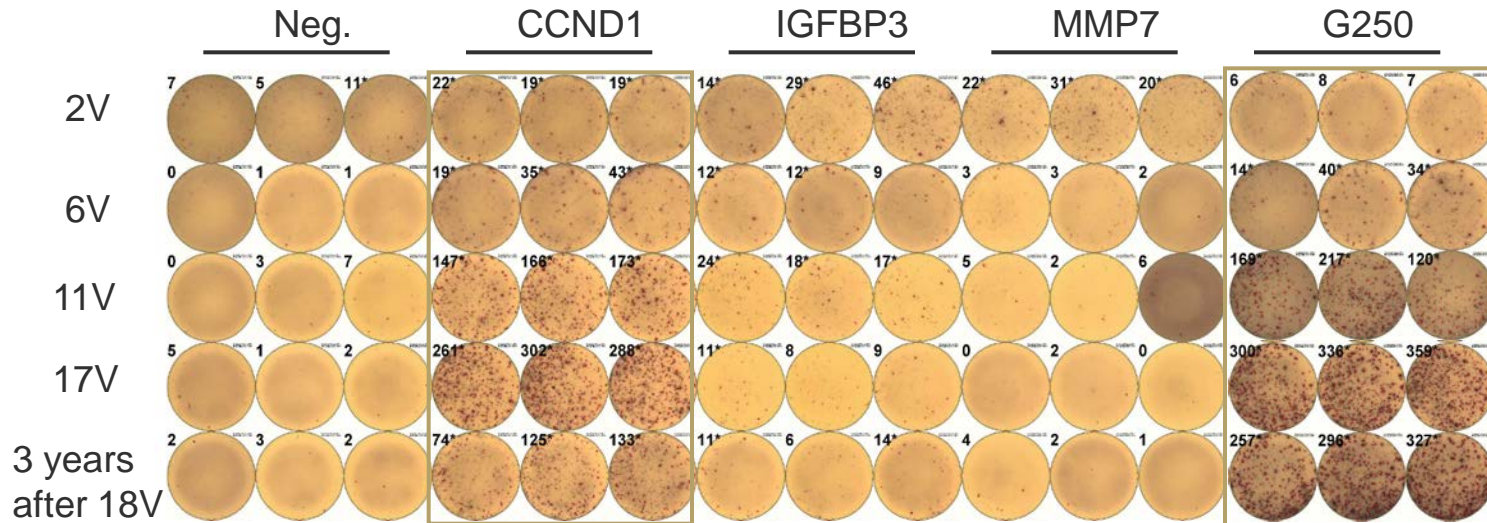


Multivariates Modell

Covariate	HR	(95% CI)	p-Wert
Alter	1,03	0,96 – 1,12	0,40
Knochenmetastasen	1,37	0,37 – 5,07	0,64
Lebermetastasen	1,48	0,26 – 8,29	0,66
Lungenmetastasen	4,90	0,78 – 30,83	0,90
Cerebrale Metastasen	2,84	0,61 – 13,21	0,18
Lymphknotenmetastase	1,39	0,30 – 6,44	0,67
Lokalrezidiv	1,10	0,28 – 4,24	0,89
Anderer Metastasenort	1,56	0,49 – 4,91	0,44
MSKCC Risikogruppe	10,65	1,71 – 66,15	0,011
Behandlung mit UroRCC	0,19	0,05 – 0,69	0,012

- multivariable Cox regression model with a backward selection criteria

Immune response

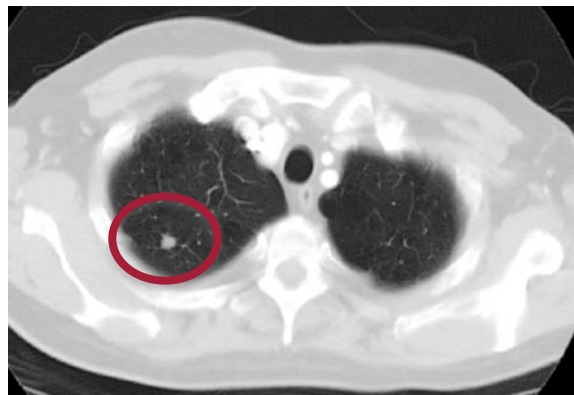


- HLA class I: 4/14 (29%)
- HLA class II: 15/16 (94%)



Zusammenfassung

- Metastasenresektion beim metastasierten RCC:
Erste Therapieoption auch im Zeitalter TKI/mTOR
- Bei Resektion: Ziel der R0-Situation
- Zusätzliche Immuntherapie durch Peptidvakzinierung verlängert das Overall Survival
- Haben wir eine (adjuvante) Therapielücke nach Metastasenresektion beim mRCC?





Danke für die Aufmerksamkeit!

