Brothers in Arms

Immuncheckpoint Inhibitoren bei Nebennierenmetastasen

Philipp J. Jost – Medical University of Graz

Stereotaxie Symposium Graz 06.02.2026

DISCLOSURE

○ Ich habe keinen potenziellen Interessenskonflikt zu berichten.

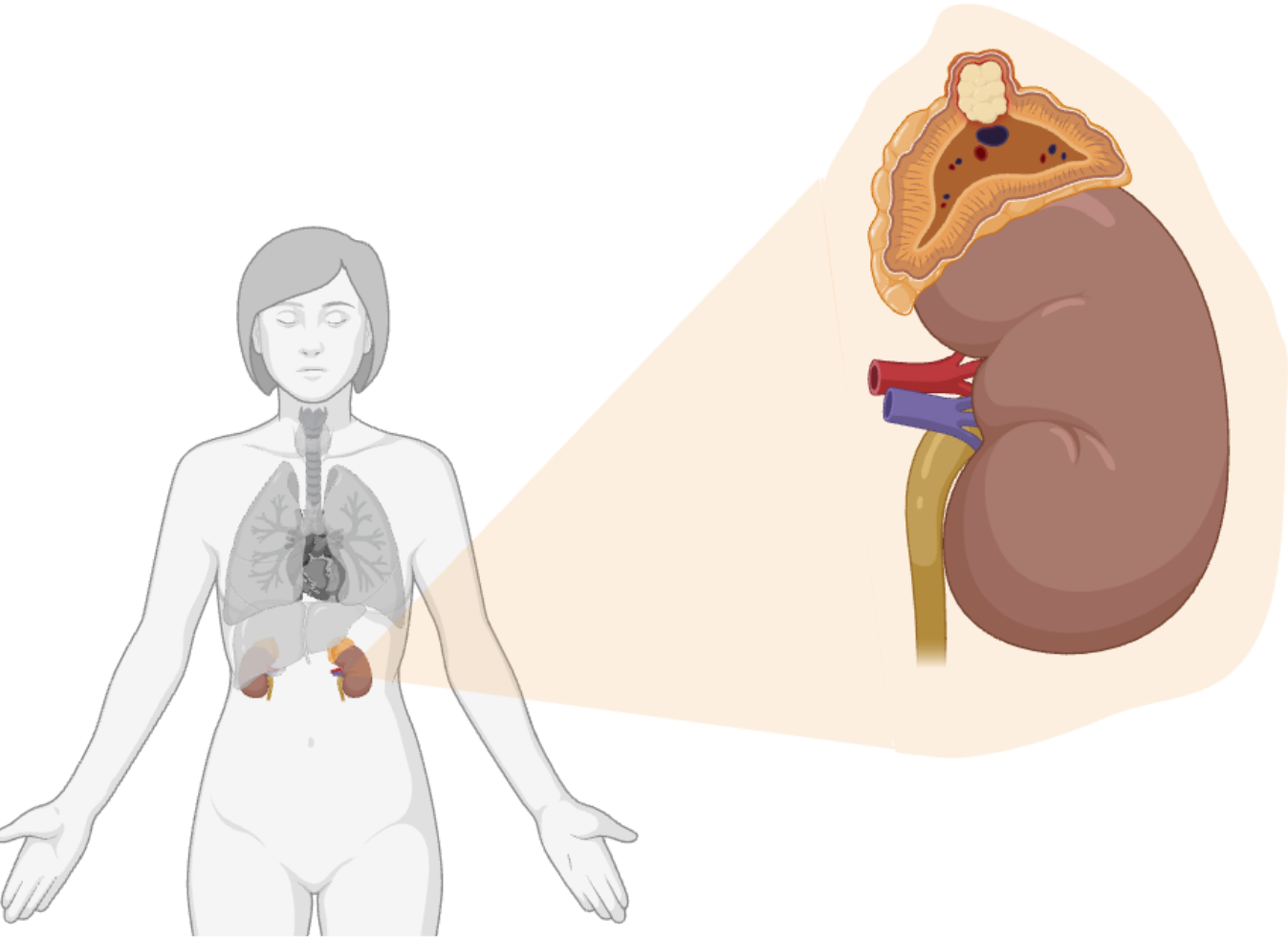
⊗ Ich habe folgende(n) potenzielle(n) Interessenskonflikt(e) zu berichten:

Stereotaxiesymposium

6.2. – 7.2.2026

P.J.J. has had a consulting or advisory role, received honoraria, research funding, and/or travel/accommodation expenses from: Astra Zeneca, Bayer, Boehringer, Novartis, Pfizer, Servier, Roche, BMS and Celgene, Pierre Fabre, Janssen / Johnson&Johnson, MSD, Merck, Sanofi/Aventis, Ipsen, Amgen, Vessel, Cycuria Therapeutics

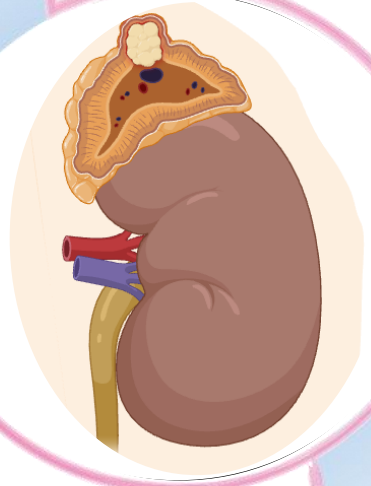
Agenda



1. Inzidenz
2. Biomarker
3. IO Kombination ohne RTx
4. Merkmale adrenaler Metastasen
5. Kombination von IO plus SBRT
6. Immunexklusivität

Biomarker für SBRT und IO im NSCLC

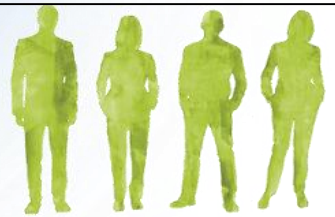
NSCLC mit adrenaler Metastasierung



PD-L1

Genetik

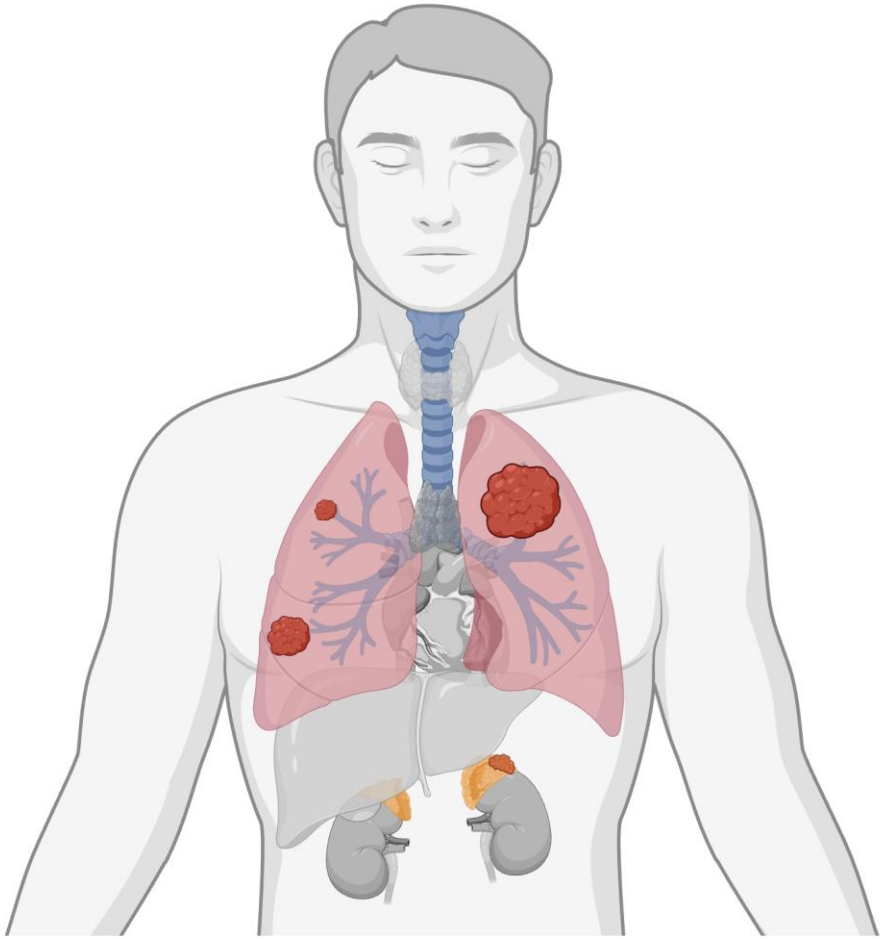
Oligometastasen



ECOG

Histologie, Dynamik, IO Toxizität, etc.

Prävalenz: 18 % - 42 % (NSCLC)
Erstdiagnose: < 10 % (NSCLC)
Bilaterale Beteiligung: ca. 10 % (NSCLC)
Häufigste Primärtumore: Häufigste Entität ist NSCLC

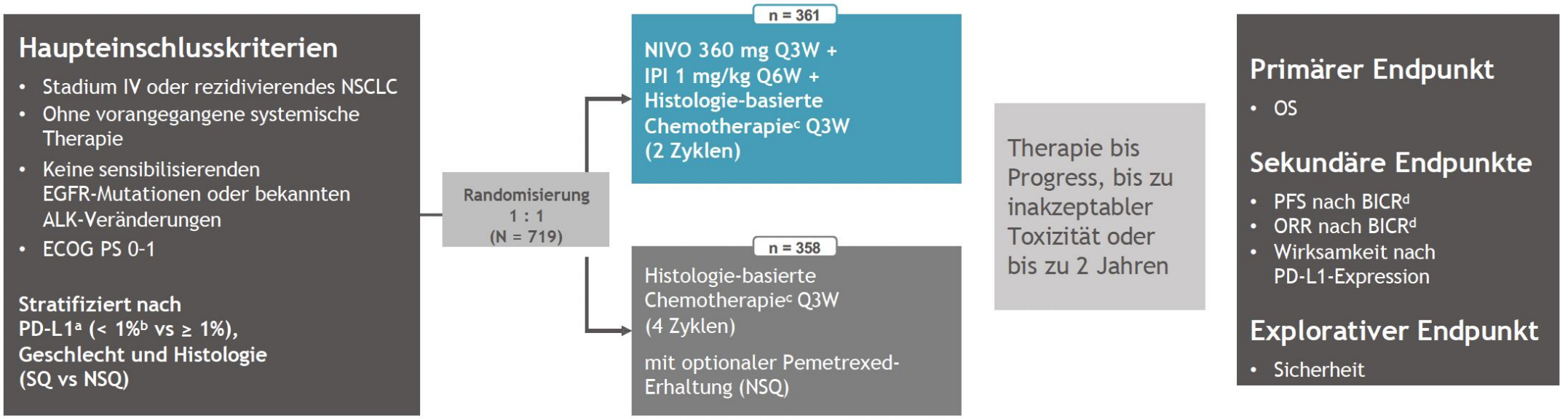


CheckMate 9LA

IO Kombination nur 16% Langzeitüberleben

Check Mate 9LA: final 6 year OS analysis

CheckMate 9LA: Studiendesign[1]



- In die Studie wurden Patient:innen unabhängig von der PD-L1-Expression und Histologie eingeschlossen

Database lock: 13. Februar 2023; Minimum Follow-up für OS: 47,9 Monate.

a Bestimmt durch den PD-L1 IHC 28-8 pharmDx Assay (Dako); b Patient:innen, die für PD-L1 nicht auswertbar waren, wurden nach PD-L1 < 1% stratifiziert und auf 10% aller randomisierten Patient:innen begrenzt; c Im Rahmen der CM 9LA wurden folgende Chemotherapien verwendet: NSQ: Pemetrexed + Cisplatin oder Carboplatin; SQ: Paclitaxel + Carboplatin. Bitte beachten Sie: Bezüglich der Wahl der Histologie-basierten Chemotherapie sind Sie gemäß der Fachinformation nicht an bestimmte Substanzen gebunden; d Hierarchisch statistisch getestet.

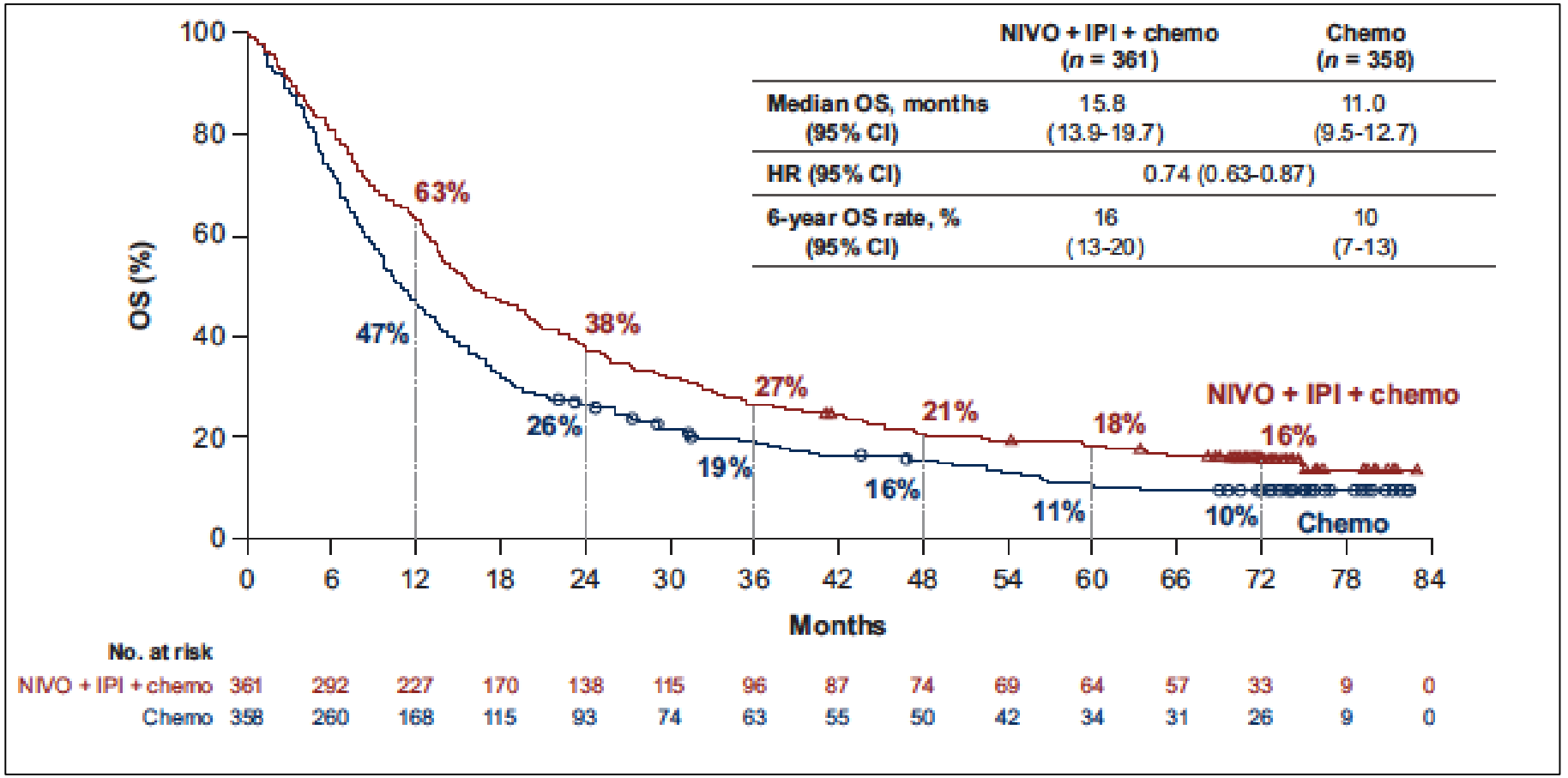
NSCLC = Non-small cell lung cancer; BICR = blinded independent central review; IHC = Immunohistochemie; NSQ = nicht-plattenepithelial (non-squamous); PD-L1 = Programmed Death Ligand-1; PS = Performance Status; Q3W= alle 3 Wochen; Q6W = alle 6 Wochen; R = randomisiert; SQ = plattenepithelial (squamous).

1. Carbone DP et al. *ASCO*, 2023; Abstract #LBA9023.

Carbone et al., ESMO Open, 2025

Check Mate 9LA: final 6 year OS analysis - Allcomer

Allcomer



Fortgeschrittenes NSCLC:
6-Jahres Überleben mit kombinierter Checkpoint Inhibition nur 16%.

Carbone et al., ESMO Open, 2025

Check Mate 9LA: Benefit for PD-L1 negative patients

STATE OF THE ART: CONCISE REVIEW

Adrenal Metastases in Lung Cancer

Clinical Implications of a Mathematical Model

Lyudmila Bazhenova, MD, Paul Newton, PhD,†‡ Jeremy Mason, PhD,†‡*
Kelly Bethel, MD,§ Jorge Nieva, MD,‖ and Peter Kuhn, PhD¶

Abstract: Adrenal gland metastases are common in lung cancer. It is well recognized that aggressive treatment of solitary adrenal metastases leads to improved outcomes but the exact nature of adrenal deposits is not well understood. Controversy exists as to the routing of cancer cells to the adrenal gland with some believing that this transmission is lymphatic, in contrast to the more generally accepted theory of hematogenous spread. Recently published mathematical modeling of cancer progression strongly supports the lymphatic theory. With that in mind, we performed a literature review to look for biological plausibility of simulation results and believe that evidence supports the contention that metastases to the adrenal gland can be routed by means of lymphatic channels. This could explain improved survival for patients in whom solitary adrenal metastases are managed aggressively with surgical or radiation modalities. We are calling for clinical trials prospectively testing this hypothesis.

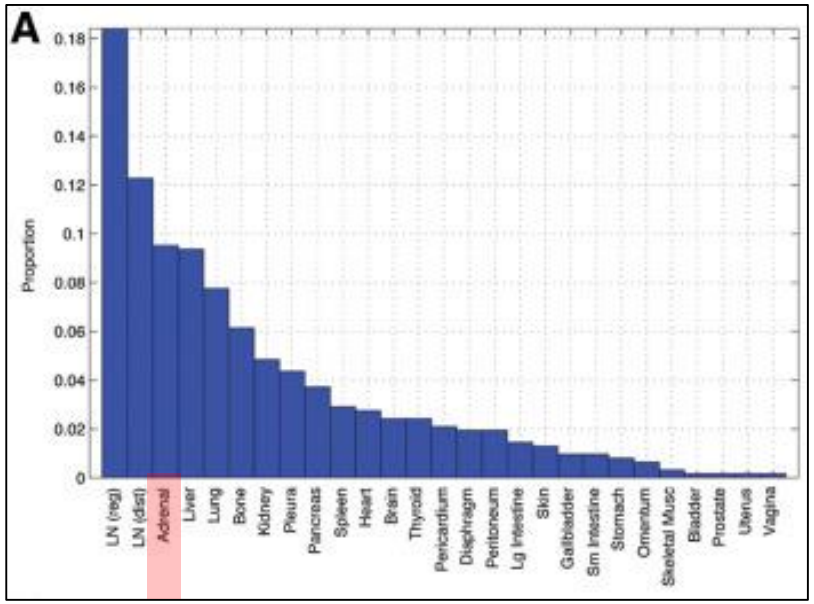
Key Words: Non–small-cell lung cancer, Adrenal metastasis, Lymphatogenous spread.

(*J Thorac Oncol.* 2014;9: 442–446)

For over a century, metastases have been acknowledged to be unpredictable. White[1] observed in his book *Tumors* in 1913 that "We may have a carcinoma with extensive involvement of the lymph glands and no visceral deposits, while we may find another similar carcinoma with extensive visceral tumors and no affection of the glands; or, again, we may find an extensive primary tumor without involvement of either glands or viscera." Despite advancements in medical knowledge, we have failed to quantify our understanding of metastatic progression patterns. One example is the controversy in primary lung cancer and adrenal metastases. In lung cancer, although adrenal metastases are common, there is no clear consensus as to whether they occur by means of a lymphatic or hematogenous route. Perhaps because lung anatomy does not clearly reinforce connections of lymphatics between lungs and adrenals, many would regard these metastases as primarily hematogenous. Although the lymphatic theory of adrenal gland spread is not novel as it was described by Onuigbo[2] in 1957, to date this finding is not usually acknowledged in clinical practice. A recently published Markov chain–based mathematical model of metastatic progression of primary lung cancer supports the lymphatic pathway of spread.[3,4] In this article, we briefly review the literature, discuss the new mathematical model of metastasis, and examine the strength of the evidence pointing to lymphatic connections between primary lung tumor and the adrenal gland. Proven correct, this would result in a down staging of this patient population to stage III and the related modification in treatment plan for curative intent.

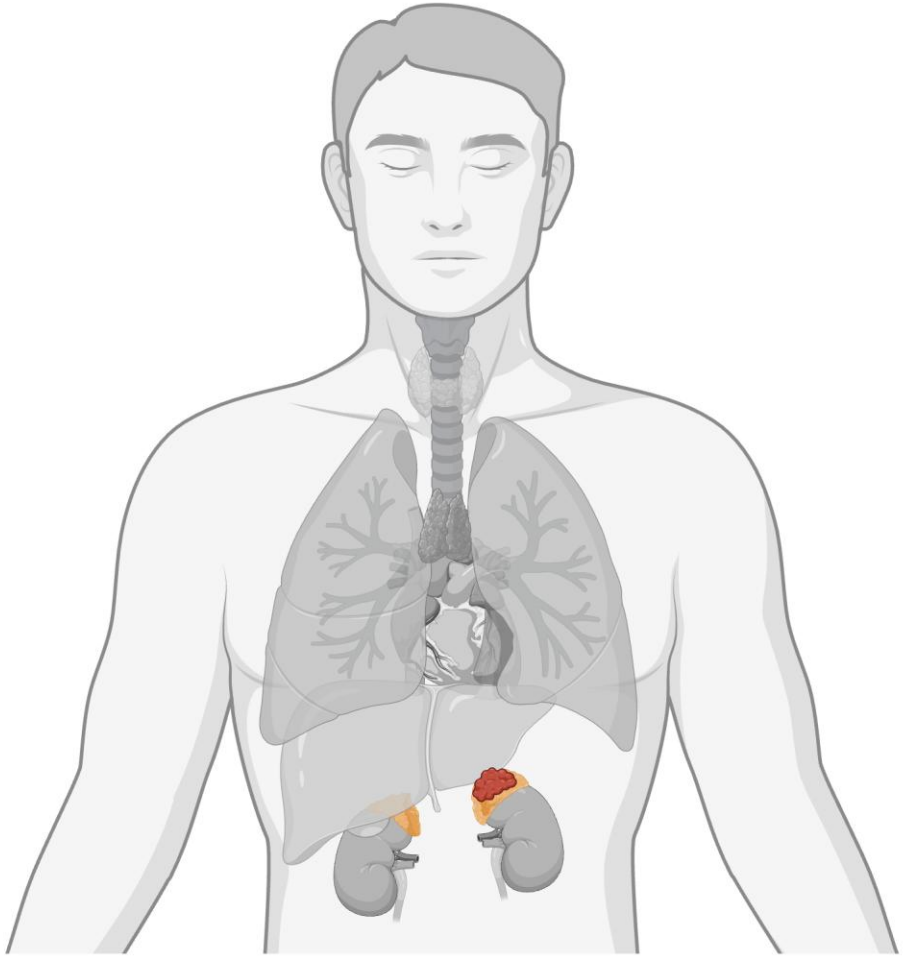
MARKOV CHAIN MODEL'S CONFIRMATION OF LYMPHATIC ADRENAL SPREAD

The mathematical model,[3,4] which we refer to as the "Newton" model, uses probabilistic methods such as Markov chain dynamics, random walkers, and Monte Carlo simulations to simulate how a tumor cell moves from the primary



Adrenale Metastasierung (NSCLC):
Häufigste nicht-nodale Metastasierung
Überwiegend lymphogener Metastasierungsweg

Bazhenova et al., J Thorac Oncol, 2014



Was unterscheidet adrenale Metastasierung von anderen Lokalisationen?

Adrenal metastasis as immune excluded space

The Adrenal Gland as a Sanctuary Site of Metastases After Pembrolizumab Treatment: A Case Series

Michelle C. Nguyen, MD, MPH[a]; Manisha H. Shah, MD[b]; David A. Liebner, MD[b]; Floor J. Backes, MD[b]; John Phay, MD[b]; and Lawrence A. Shirley, MD[b]

Abstract

Therapeutic agents targeting the PD-1/PD-L1 axis have shown durable clinical responses in patients with various cancer types. Although objective responses are common, intrapatient heterogeneous responses have been described, and the mechanism for the different organ responses remains unknown. We present a series of patients in whom a lack of response was noted solely in the adrenal glands. This is the first case series describing 3 patients with heterogeneous patterns of response to pembrolizumab with progression of adrenal metastatic disease despite objective response (complete or partial response) in all other sites of metastatic disease. Two patients, one with melanoma and one with uterine carcinosarcoma, underwent robotic adrenalectomy for enlarging adrenal metastases. An additional patient with melanoma underwent laparotomy with attempted resection, but infiltration of the adrenal tumor into the inferior vena cava prohibited safe excision. This report provides additional insight into the heterogeneous patterns of disease response to anti–PD-1 therapy, highlighting the adrenal gland as a potential sanctuary site for this immunotherapy. These cases display the potential benefit of early surgical resection in this scenario and the pitfalls of delaying referral to a surgeon for assessment of operative intervention.

J Natl Compr Canc Netw 2018;16(11):1279–1283
doi: 10.6004/jnccn.2018.7059

Nebennierenmetastase:
Progression der Nebennierenmetastase unter Immuncheckpoint-Inhibitoren trotz Remission aller anderen Metastasen.

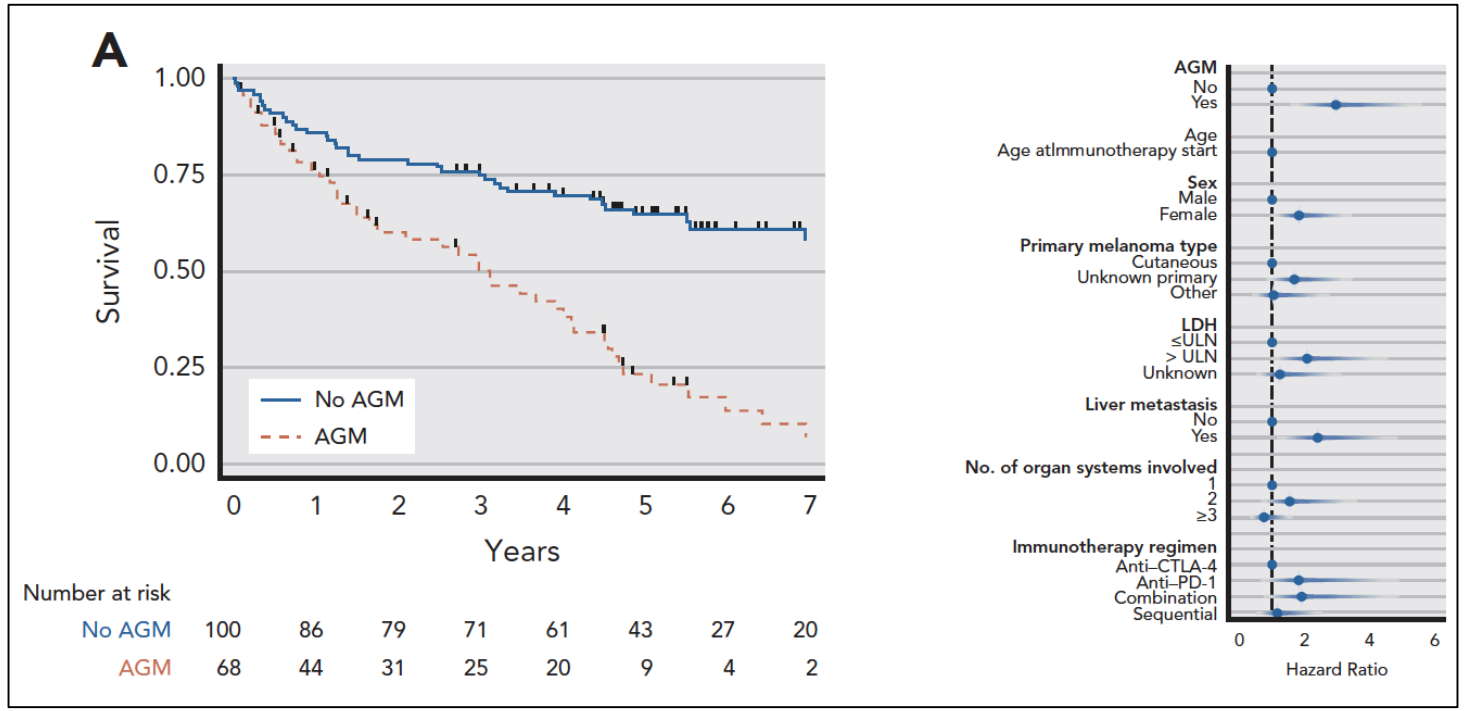
Nguyen et al., J Natl Compr Canc Net, 2018

Adrenal metastasis as immune excluded space

ORIGINAL RESEARCH

Melanoma Metastases to the Adrenal Gland Are Highly Resistant to Immune Checkpoint Inhibitors

Jessica S.W. Borgers, MD[1,2,*]; Richard P. Tobin, PhD[1,3,4,*]; Robert J. Torphy, MD[1]; Victoria M. Vorwald, BS[1,3,4]; Robert J. Van Gulick, BS[3,4,5]; Carol M. Amato, MS[3,4,5]; Dasha T. Cogswell, MS[1,3,4]; Tugs-Saikhan Chimed, MS[5]; Kasey L. Couts, PhD[4,5]; Adrie Van Bokhoven, PhD[6]; Christopher D. Raeburn, MD[7]; Karl D. Lewis, MD[4,5]; Joshua Wisell, MD[4,6]; Martin D. McCarter, MD[1,3,4]; Rao R. Mushtaq, MD[5]; and William A. Robinson, MD, PhD[3,4,5]



Melanom:
Patienten mit Nebennierenmetastasen haben ein signifikant schlechteres Gesamtüberleben.

Borgers et al., J Natl Compr Canc Net, 2021

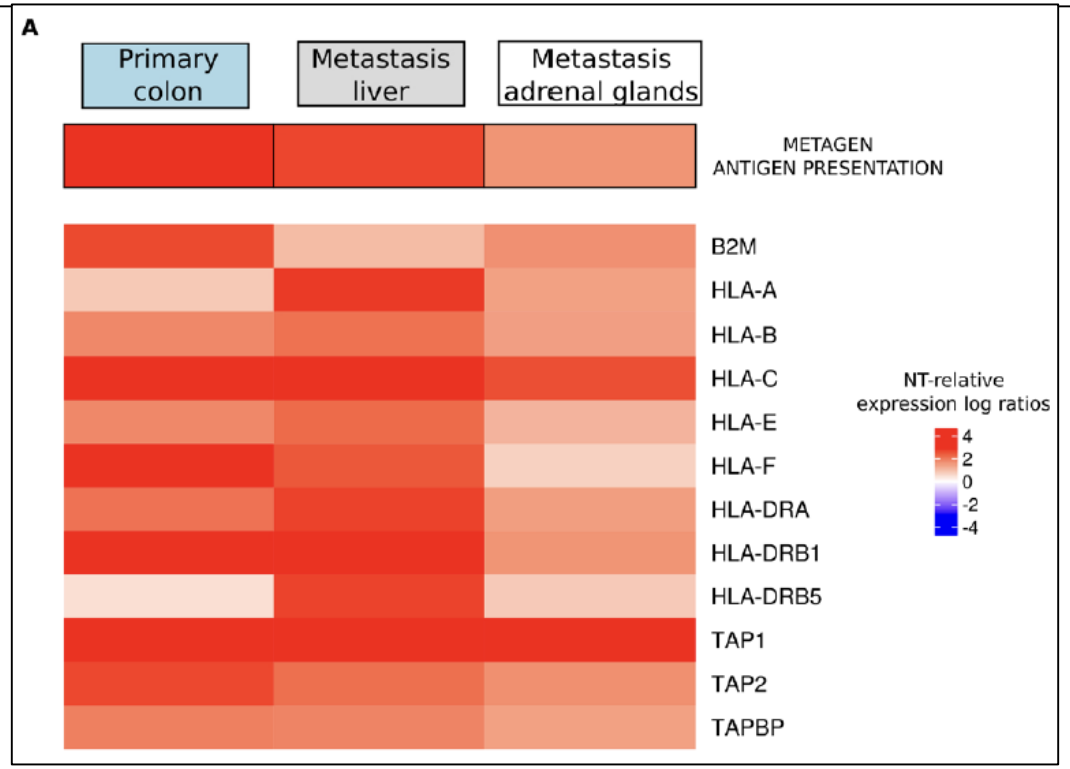
Adrenal metastasis as immune excluded space

Open access Case report

Journal for ImmunoTherapy of Cancer

Adrenal gland as a sanctuary site for immunotherapy in patients with microsatellite instability-high metastatic colorectal cancer

Romain Cohen [1,2] Vincent Jonchère [2] Christelle De La Fouchardière,[3] Toky Ratovomanana,[2] Quentin Letourneur,[2] Mira Ayadi,[4] Lucile Armenoult,[4] Adrien Buisson,[5] Matthieu Sarabi,[3] Anna Pellat,[1] Raphael Colle,[1] Francois Paye,[6] Pierre Meeus,[7] Magali Svrcek,[2,8] Alex Duval,[2] Thierry Andre [1,2]



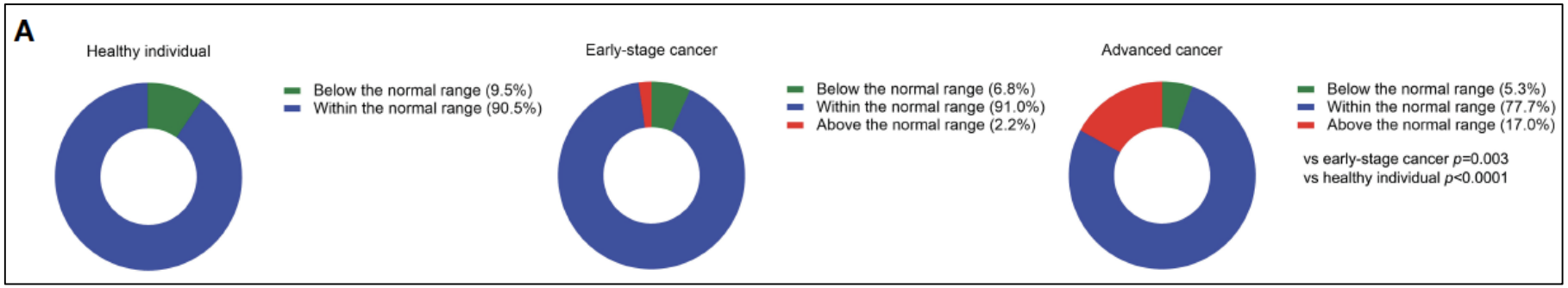
Nebenniere:
Immunologisch kalt aufgrund einer ausgeprägten Beeinträchtigung des Antigenpräsentationswegs.

Cohen et al., J Immunother Cancer, 2021

Adrenal metastasis as immune excluded space

Impact of endogenous glucocorticoid on response to immune checkpoint blockade in patients with advanced cancer

Yu Cui[1,2,3†], Xinyue Han[1,2,3†], Hongtao Liu[4†], Qi Xie[1,2,3], Yaping Guan[1,2,3], Beibei Yin[1,2,3], Junjuan Xiao[1,2,3], Dongfeng Feng[1,2,3], Xuan Wang[1,2,3], Junwei Li[1,2,3], Jinghua Chen[1,2,3], Xiaolin Liu[1,2,3], Xingyu Li[1,2,3], Weiwei Nie[1,2,3], Lin Ma[1,2,3], Hairong Liu[1,2,3], Jing Liang[1,2,3], Yan Li[1,2,3], Baocheng Wang[5] and Jun Wang[1,2,3*]



Cui et al., Front Immunol, 2023

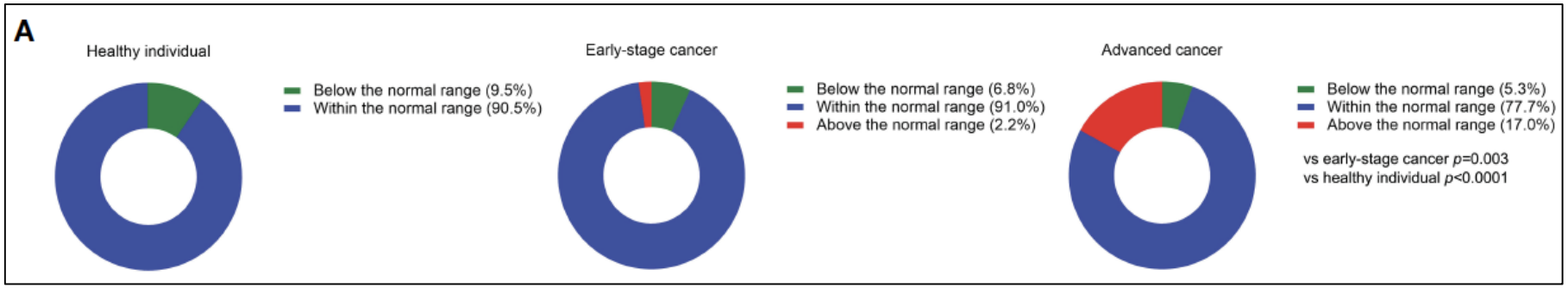
Adrenal metastasis as immune excluded space

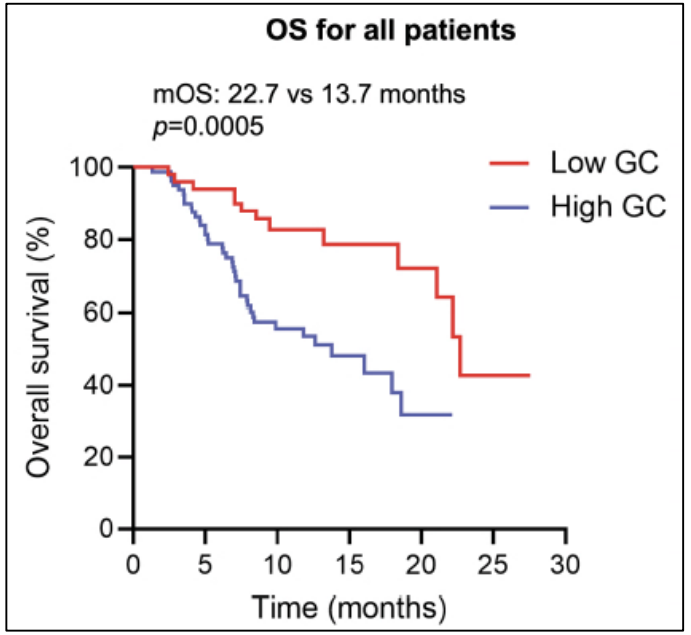
Med Uni Graz

Impact of endogenous glucocorticoid on response to immune checkpoint blockade in patients with advanced cancer

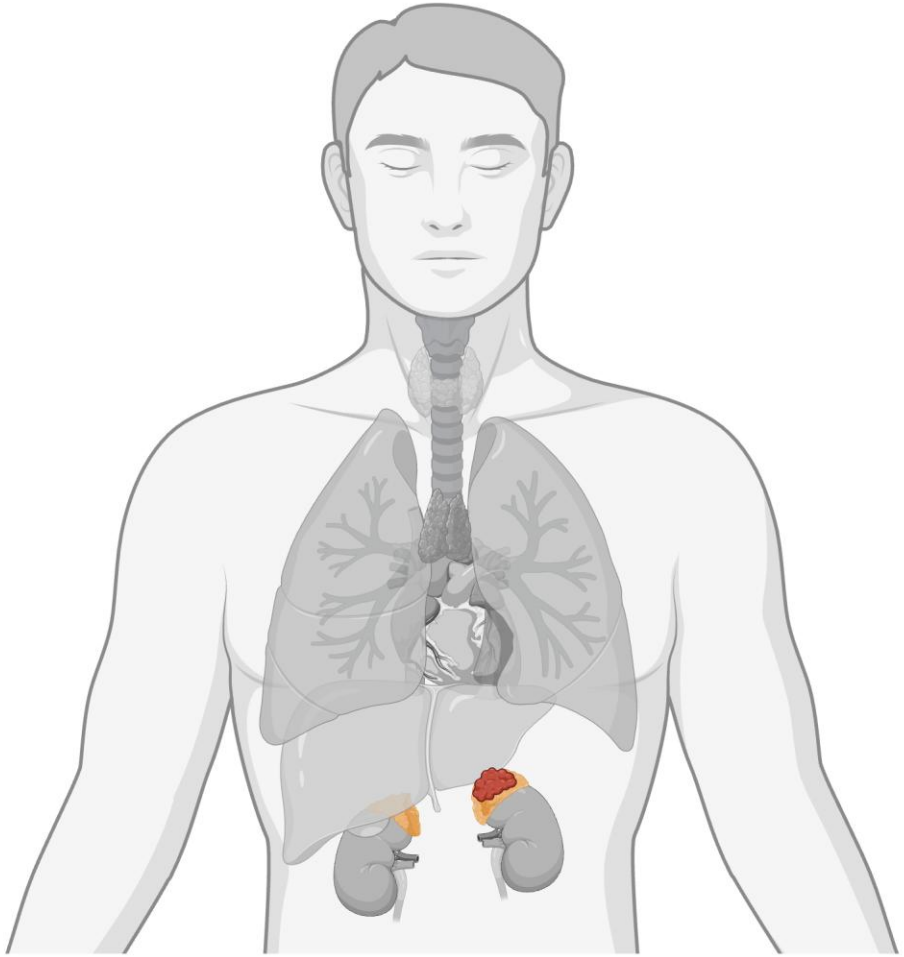
Yu Cui[1,2,3†], Xinyue Han[1,2,3†], Hongtao Liu[4†], Qi Xie[1,2,3], Yaping Guan[1,2,3], Beibei Yin[1,2,3], Junjuan Xiao[1,2,3], Dongfeng Feng[1,2,3], Xuan Wang[1,2,3], Junwei Li[1,2,3], Jinghua Chen[1,2,3], Xiaolin Liu[1,2,3], Xingyu Li[1,2,3], Weiwei Nie[1,2,3], Lin Ma[1,2,3], Hairong Liu[1,2,3], Jing Liang[1,2,3], Yan Li[1,2,3], Baocheng Wang[5] and Jun Wang[1,2,3*]

Steroidsynthese:
Erhöhte Steroidsynthese in fortgeschrittenen Tumoren als Ursache fehlender T Lymphozyten-aktiverbarkeit in adrenalen Metastasen





Cui et al., Front Immunol, 2023



RT plus Immuncheckpoint Inhibition

SBRT plus Immuncheckpoint Inhibition

RTx verbessert den systemischen Effekt von Pembrolizumab im NSCLC

Med Uni Graz

Previous radiotherapy and the clinical activity and toxicity of pembrolizumab in the treatment of non-small-cell lung cancer: a secondary analysis of the KEYNOTE-001 phase 1 trial

Narek Shaverdian, Aaron E Lisberg*, Krikor Bornazyan, Darlene Veruttipong, Jonathan W Goldman, Silvia C Formenti, Edward B Garon†, Percy Lee†*

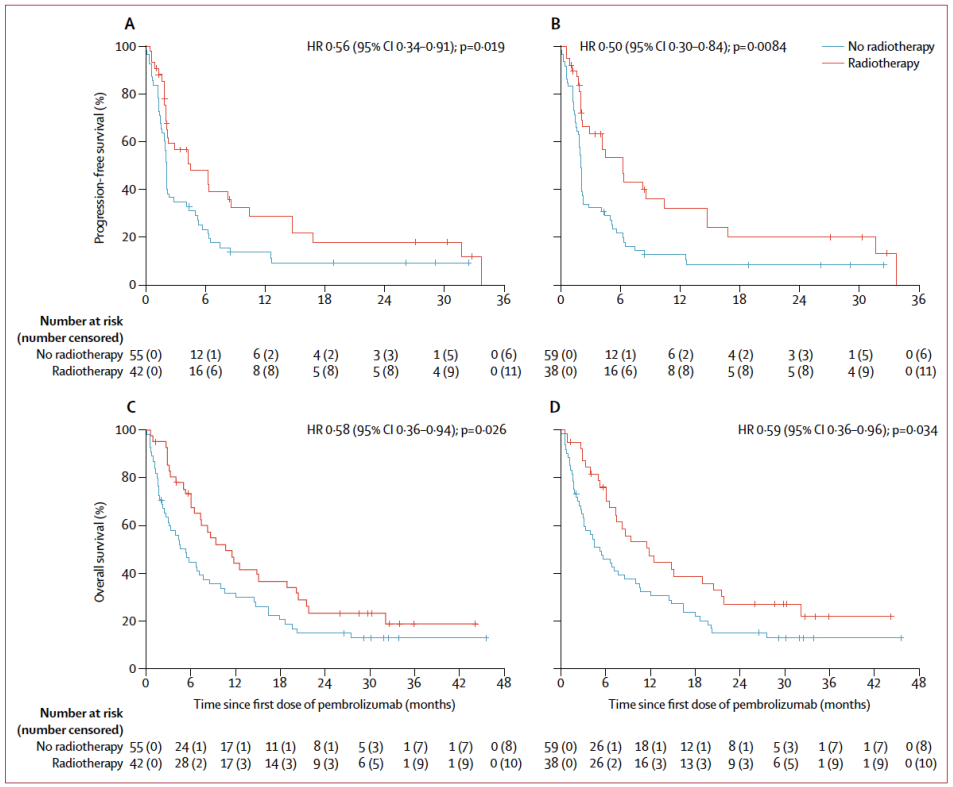
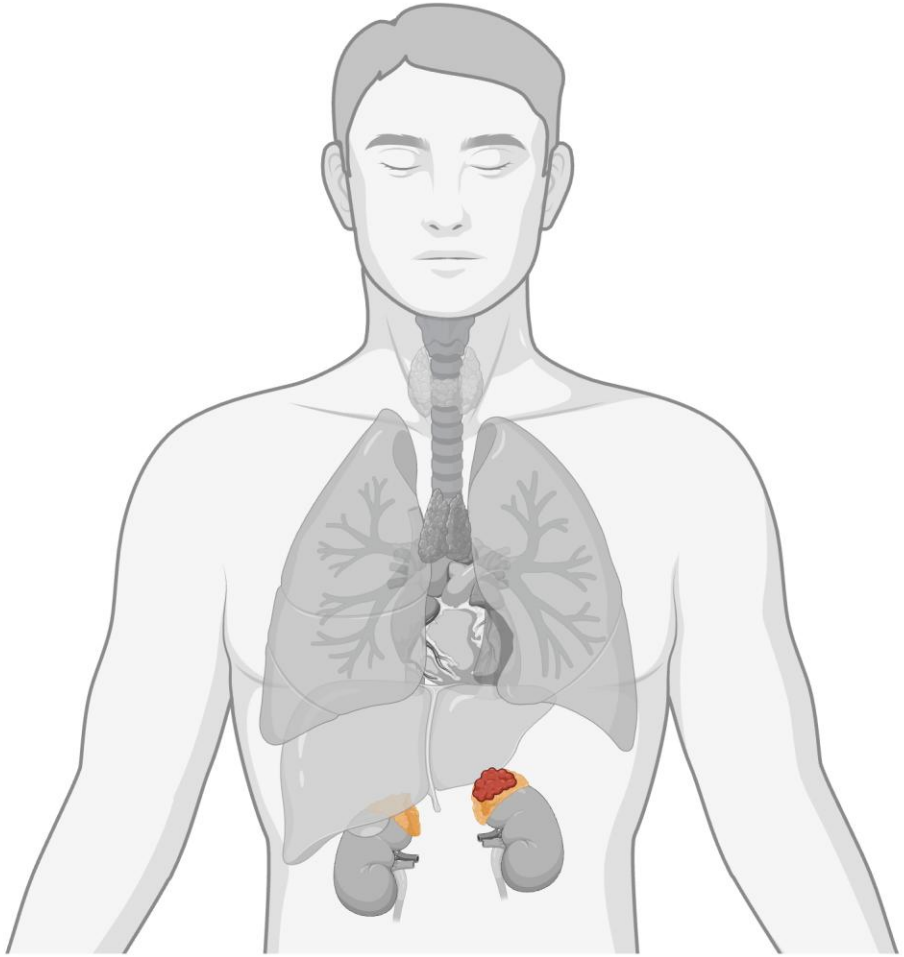


Figure: **Effect of previous radiotherapy on progression-free survival and overall survival**
Progression-free survival in patients according to their history of (A) any radiotherapy and (B) extracranial radiotherapy. Overall survival in patients according to their history of (C) any radiotherapy and (D) extracranial radiotherapy. Hazards Ratios [HR] are shown.

Shaverdian et al., Lancet Oncol, 2017



SBRT plus Immuncheckpoint Inhibition

SBRT plus Immuncheckpoint Inhibition

Pembrolizumab mit SBRT in

Research

JAMA Oncology | Original Investigation

Effect of Pembrolizumab After Stereotactic Body Radiotherapy vs Pembrolizumab Alone on Tumor Response in Patients With Advanced Non–Small Cell Lung Cancer

Results of the PEMBRO-RT Phase 2 Randomized Clinical Trial

Willemijn S. M. E. Theelen, MD; Heike M. U. Peulen, MD, PhD; Ferry Lalezari, MD; Vincent van der Noort, PhD; Jeltje F. de Vries, PhD; Joachim G. J. V. Aerts, MD, PhD; Daphne W. Dumoulin, MD; Idris Bahce, MD, PhD; Anna-Larissa N. Niemeijer, MD; Adrianus J. de Langen, MD, PhD; Kim Monkhorst, MD, PhD; Paul Baas, MD, PhD

Pembro-RT

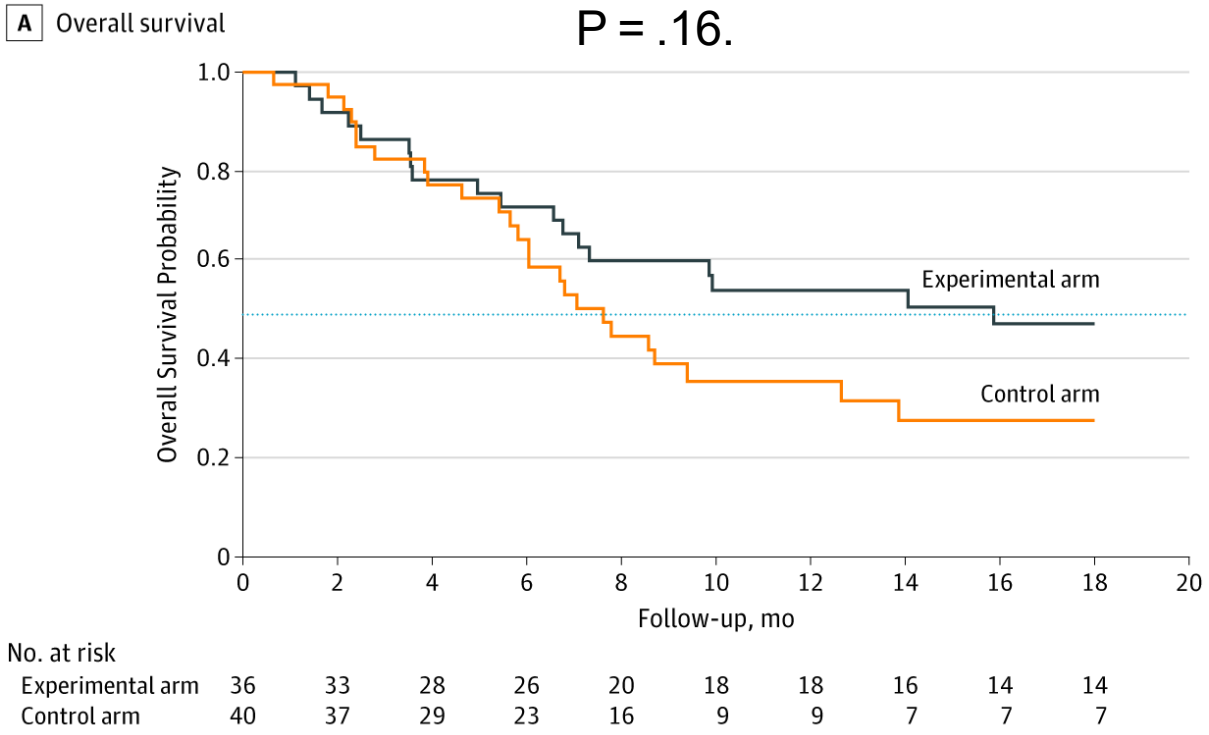
- Metastatic NSCLC
- Phase-2 (n=76)
- Pembrolizumab mono or Pembrolizumab after SBRT

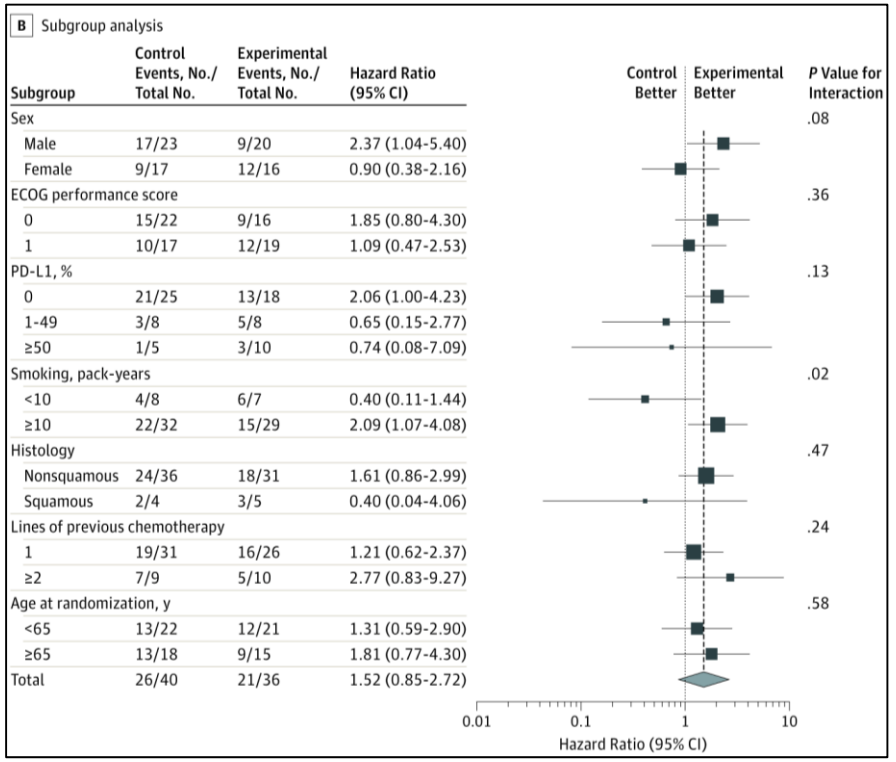
Theelen et al., JAMA Oncol, 2019

SBRT plus Immuncheckpoint Inhibition

SBRT beeinflusst positiv die Mikroumgebung im Tumor

HR: 0.66 (95% CI, 0.37-1.18)
P = .16.





Theelen et al., JAMA Oncol, 2019

SBRT plus Immuncheckpoint Inhibition

SBRT beeinflusst positiv die Mikroumgebung im Tumor

Pembro-RT IO Responses

nature cancer

Article

https://doi.org/10.1038/s43018-025-01018-w

Combination of pembrolizumab and radiotherapy induces systemic antitumor immune responses in immunologically cold non-small cell lung cancer

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Check for updates

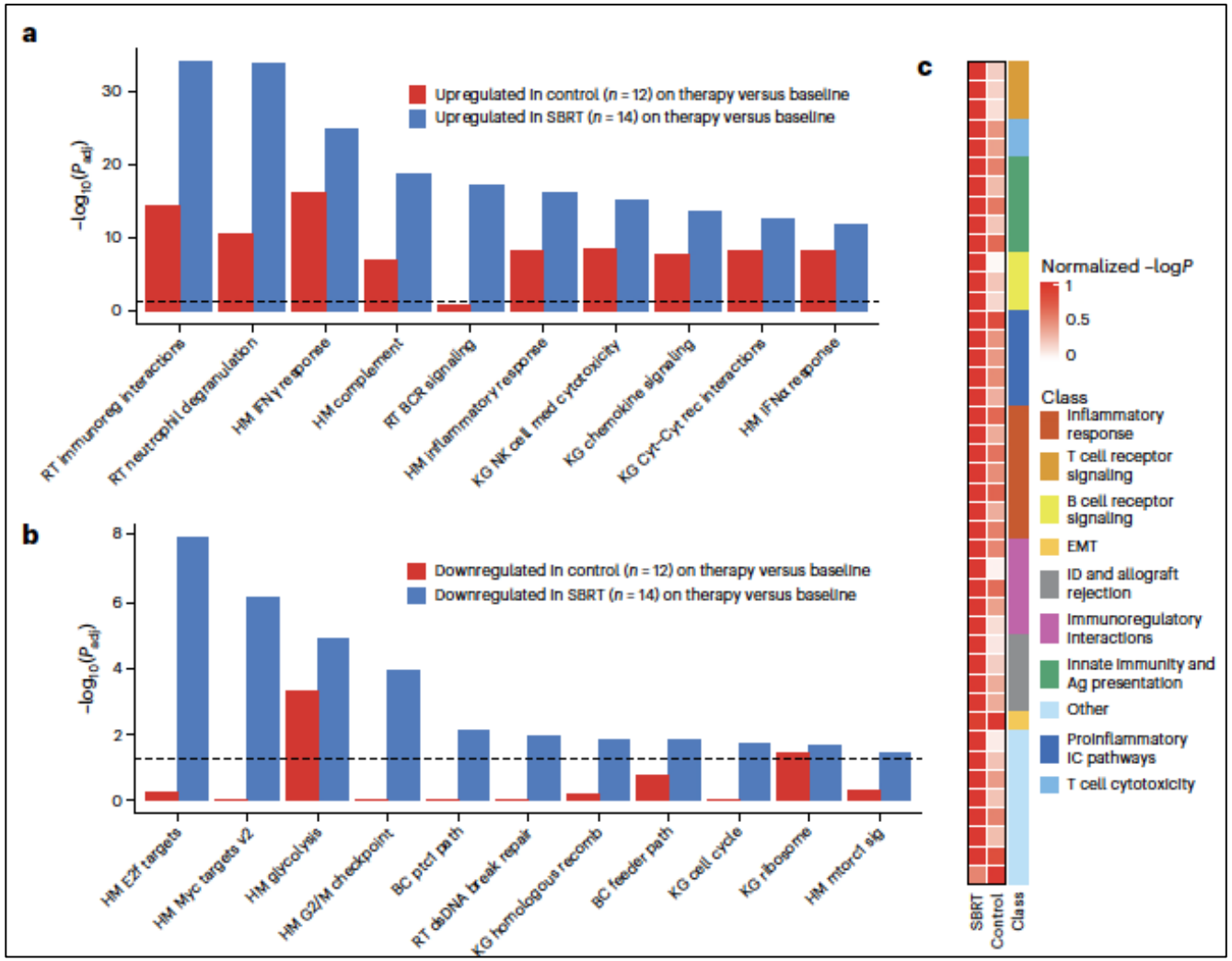
Justin Huang[1,6], Willemijn S. M. E. Theelen[2,6], Zineb Belcaid[1,6], Mimi Najjar[1], Daphne van der Geest[2], Dipika Singh[1,3], Christopher Cherry[1], Archana Balan[1], James R. White[1], Jaime Wehr[1], Rachel Karchin[1,4], Noushin Niknafs[1], Michel M. van den Heuvel[5], Victor E. Velculescu[1], Kellie N. Smith[1,3], Paul Baas[2] & Valsamo Anagnostou[1,3]

SBRT plus Immuncheckpoint Inhibition

SBRT beeinflusst positiv die Mikroumgebung im Tumor

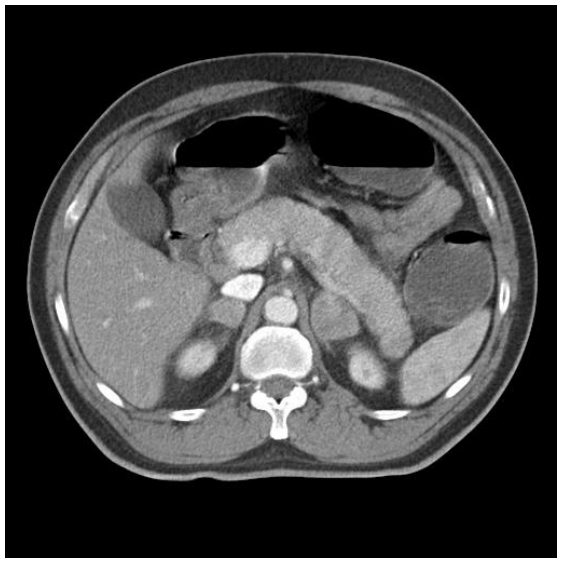
Up-regulated genes:
SBRT (n=14) vs control (n=11)

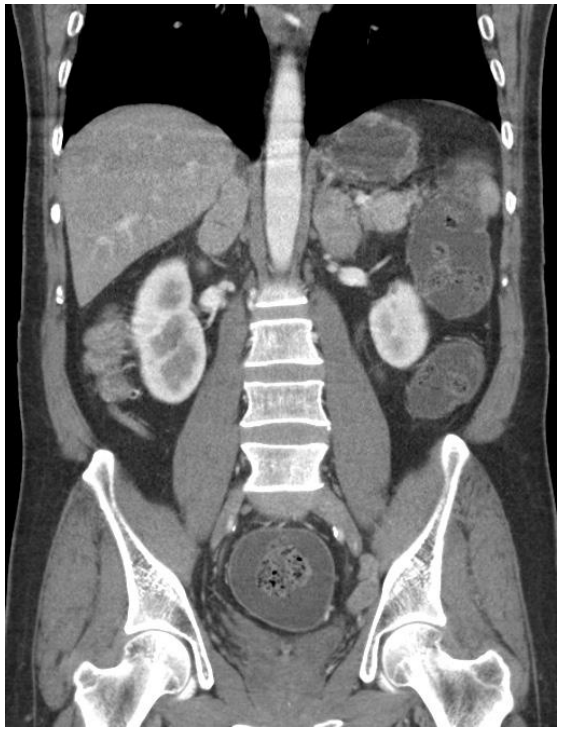
Down-regulated genes:
SBRT (n=14) vs control (n=11)



Huang et al., Nat Cancer, 2024

Zusammenfassung





1. Inzidenz Nebennierenmetastasierung
Häufig im NSCLC und anderen Entitäten

2. Biomarker für Therapie
PD-L1 ungenügender Biomarker für IO Therapie

3. CheckMate 9LA
Nur wenig Langzeitremission im NSCLC trotz IO Kombination

4. Unterscheidungsmerkmale adrenaler Metastasen
Diskordantes Ansprechen auf IO Therapie

5. Kombination von IO und SBRT
Oligometastasierung im NSCLC etc.

6. Immun-exkludierte Metastasen
Reduzierte Antigenpräsentation in der Nebenniere


FWF Austrian Science Fund
European Commission
Horizon Europe 2021-2027
ACCN AUSTRIAN COMPREHENSIVE CANCER NETWORK
LUDWIG BOLTZMANN GESELLSCHAFT
Kooperation
BZKF Bayerisches Zentrum für Krebsforschung
MEFO
FFG Forschung wirkt.
TRANSCAN
UNIV. COMPREHENSIVE CANCER CENTER GRAZ
Krebszentrum
Medizinische Universität & LKH-Univ. Klinikum
DFG
Deutsche Krebshilfe
HELFEN. FORSCHEN. INFORMIEREN.
Dr. Mildred Scheel Stiftung für Krebsforschung