Kombination von Stereotaxie mit Targeted agents und Immuntherapie: Synergien und Toxizitäten

PD Dr. Marlen Haderlein

Strahlenklinik Erlangen
Direktor: Prof. Dr. R. Fietkau
30.09.2022

Universitätsklinikum Erlangen

Interaktionen- stereotakt.RT und targeted Agents/Immuntherapie wann und warum relevant?

Aktuell in der metastasierten Situation relevant bei:
- Oligometastasierung
- Oligoprogress
- Symptomatische Metastasen

Immer mehr ZNS-gängige Medis, z.B.Alectinib, Osimertinib
→ Auch für kranielle Stereotaxie relevant

Studien zur Kombinationstherapie in der primären Situation laufen (z.B. KeyNote867 (NSCLC St1 und IIA, STX plus Pembro, STX plus Osimertinib PACIFIC-4)

Erhöhte Toxizität????
Oder möglicherweise auch synergistische Effekte????

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Interaktionen- stereotakt.RT und targeted Agents/Immuntherapie häufige Medikation bei Patienten in der Strahlentherapie

„Klassische"Antikörper (–ab): Cetuximab, Bevacizumab, Trastuzumab

Small molecules (-ib): Vemurafenib/Dabrafenib, Osimertinib, Crizotinib, Alectinib, CDK4/6-Inhibitoren

Checkpointinhibitoren (CTLA4-, PD1-, PD-L1-Inhibitoren)

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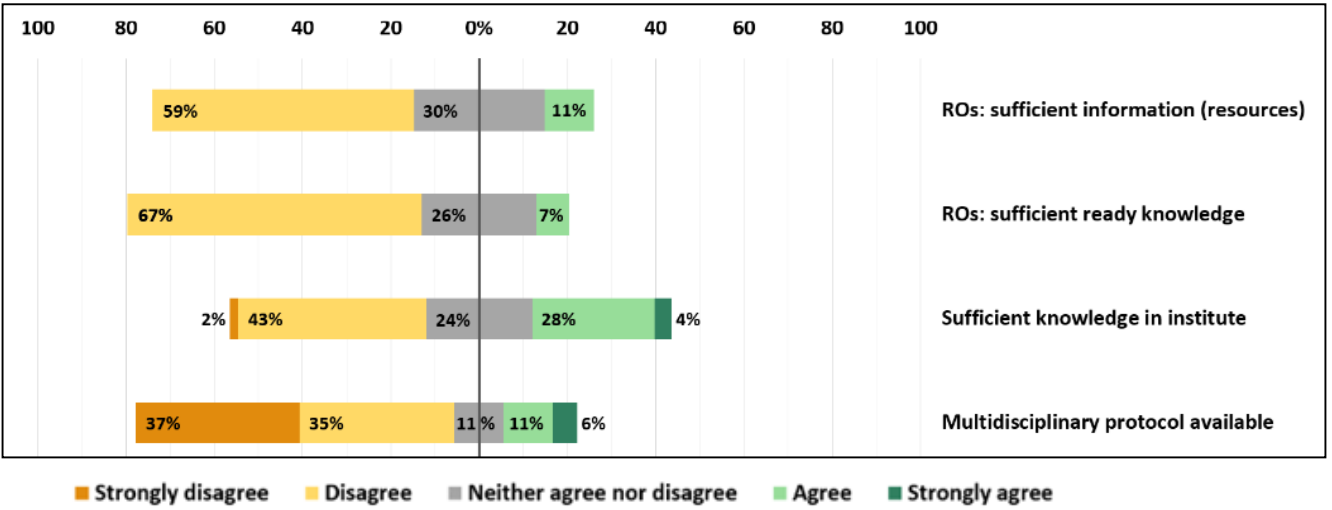
Original Research Article

Hypofractionated radiotherapy combined with targeted therapy or immunotherapy: Dutch survey on current practice, knowledge and challenges

Evert S.M. van Aken [a], Yvette M. van der Linden [b], Johannes V. van Thienen [c],

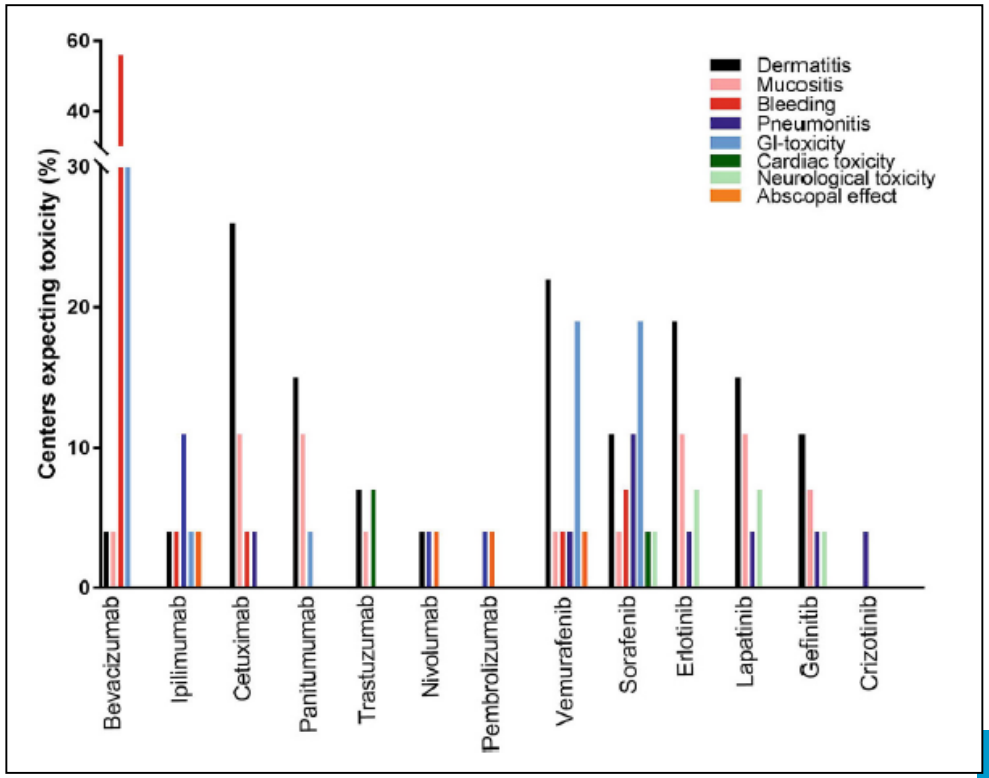


Strahlenther Onkol (2019) 195:199–206
https://doi.org/10.1007/s00066-018-01422-5

ORIGINAL ARTICLE

Combination of stereotactic radiotherapy and targeted therapy: patterns-of-care survey in German-speaking countries

S. G. C. Kroeze[1] · C. Fritz[1] · L. Basler[1] · E. Gkika[2,3,4] · T. B. Brunner[5] · A. L. Grosu[2,3,4] · M. Guckenberger[1]



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OXFORD

JNCI Cancer Spectrum (2021) 5(4): pkab050

doi: 10.1093/jncics/pkab050
First published online 19 May 2021
Meta-Analysis

ROCKIT – „Combination does not increase survival but worsens toxicity“

Radiotherapy and Receptor Tyrosine Kinase Inhibition for Solid Cancers (ROCKIT): A Meta-Analysis of 13 Studies

Leila T. Tchelebi, MD,[1,†] Emma Batchelder, BS,[1,†] Ming Wang, PhD,[2] Eric J. Lehrer, MD, MS,[3] Joseph J. Drabick, MD,[4] Navesh Sharma, DO, PhD,[1] Mitchell Machtay, MD,[1] Daniel M. Trifiletti, MD,[5] Nicholas G. Zaorsky, MD, MS[1,2,*]

v.a. Studien mit Cetuximab, wenige mit Bevacizumab,, Lapatinib oder Erlotinib

Subgroup stratification and randomization	Overall survival					Toxicity				
	Studies, No.	Patients, No.	HR (95% CI)	I^2, %	*P*	Studies, No.	Patients, No.	RR (95% CI)	I^2, %	*P*
RT or CRT										
CRT ± any type of RTKi	10	4835	1.00 (0.91 to 1.12)	41.0	.95	6	2970	1.18 (1.09 to 1.28)	27.0	.003
RT ± any type of RTKi	3	843	1.51 (0.66 to 3.45)	87.0	.33	1	NA	NA	NA	NA
Drug type										
RT or CRT ± small molecule RTKi	3	949	0.97 (0.71 to 1.33)	64	.87	2	NA	NA	NA	NA
RT or CRT ± antibody RTKi	10	4729	1.04 (0.90 to 1.19)	64.0	.62	5	1942	1.18 (1.06 to 1.32)	39.0	.01
Overall	13	5678	1.02 (0.90 to 1.15)	61.0	.76	7	2715	1.18 (1.06 to 1.33)	60.0	.009

[a]CI = confidence interval; CRT = chemoradiotherapy; HR = hazard ratio; NA = not applicable because too few studies; RR = relative risk; RT = radiation therapy; RTKi = receptor tyrosine kinase inhibitor.

„Klassische“ Antikörper

Kombination Cetuximab und Bestrahlung

The NEW ENGLAND JOURNAL of MEDICINE

Severe Cutaneous Reaction during Radiation Therapy with Concurrent Cetuximab

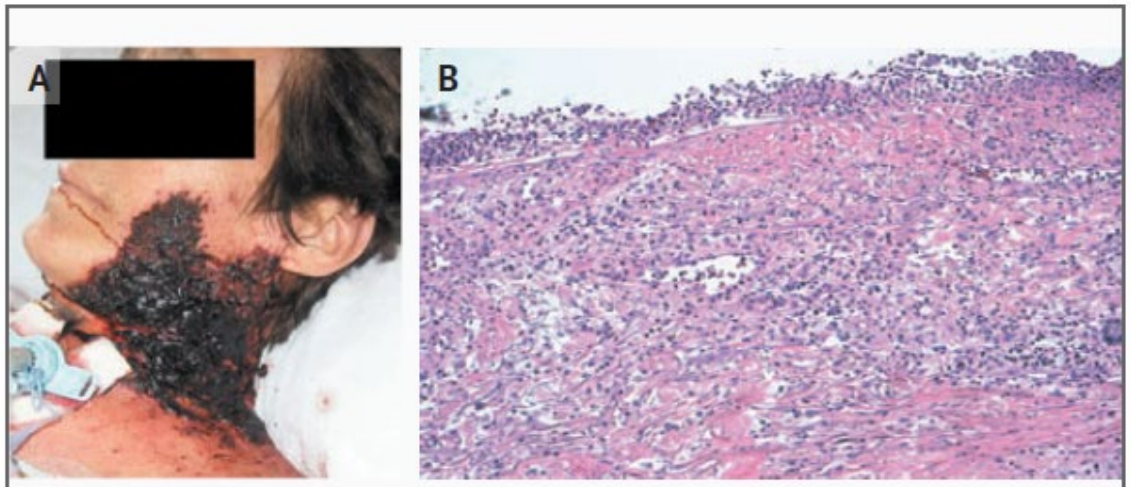


Figure 1. Severe Radiation Dermatitis in a Patient Undergoing Radiotherapy plus Treatment with Cetuximab.

Patient 1, a 57-year-old woman with squamous-cell carcinoma of the head and neck, had dermatitis (common toxicity criteria grade 4) confined to the irradiation field (Panel A). A skin-biopsy specimen from the patient (Panel B, hematoxylin and eosin) shows an acute cytotoxic dermatitis with complete loss of the epidermis owing to subepidermal blister formation, together with a mixed perivascular and interstitial inflammatory infiltrate composed of lymphocytes, histiocytes, neutrophils, and eosinophils.

Phase II-Studien: STX plus Cetuximab

Vargo et al 2014:
STX 40-44Gy in 5Fx plus Cetuximab bei KHT
Tox: akut III° 6%

Lartigau et al 2013:
STX 36 Gy in 6fx bei KHT:
Tox akut u spät III° 30%

→Kombination von stereotakt. RT und Cetuximab ist möglich

Kombination von Bevacizumab und Bestrahlung Lunge

VOLUME 28 · NUMBER 1 · JANUARY 1 2010
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Tracheoesophageal Fistula Formation in Patients With Lung Cancer Treated With Chemoradiation and Bevacizumab

David R. Spigel, John D. Hainsworth, Denise A. Yardley, Eric Raefsky, Jeffrey Patton, Nancy Peacock, Cindy Farley, Howard A. Burris III, and F. Anthony Greco

Trial 1: Induktion mit Irino/Carboplatin/Bev und dann RCT mit Irino/Platin/Bev
SCLC Limited disease: 29 Patienten → 2 Ösophagotracheale Fisteln (1x tödlich), 1 tödliche Blutung obere Atemwege

Trial 2: RCT mit RT bis 61,4 Gy, Chemo mit Bev/Carbo/Pem Woche 1 u 4 und konsolidierend Bev/Carbo/Pem
NSCLC lokal fortgeschritten: 5 Patienten → 2 Ösophagotracheale Fisteln, 1 tödliche Blutung pulmonal

→ Vorzeitiger Abbruch bei erhöhtem Risiko von Fisteln ösophagotracheal und Blutung

Kombination von Bevacizumab und Bestrahlung Abdomen/Becken

Abdomen:

Kabbinvar et al, 2012: prospektive Studie, n= 1953 Pat mit metast. KRK unter Bevacizumab-haltiger Therapie, **bei Patienten mit vorhergehender RT HR von 2.11 für gastroint.Perforation im Vergleich zu Pat ohne RT**

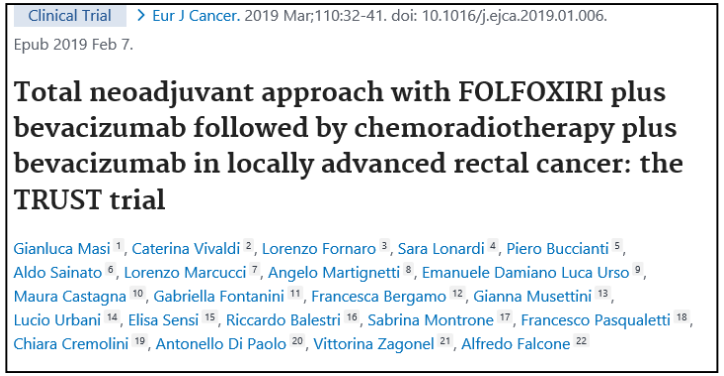
Barney BM et al, 2013: prospektive Studie, n= 67 Pat mit primären oder metast. Tumoren abdominiel, STX mit 10x5Gy, kum. 6Monats-Rate an SBI (serious bowel injury): 38% bei Pat die 3Mo vor oder nach RT Bevacizumab erhalten haben (kein SBI bei Pat ohne Bevacizumab)

Becken:

Phase II randomized trial of capecitabine with bevacizumab and external beam radiation therapy as preoperative treatment for patients with resectable locally advanced rectal adenocarcinoma: long term results

Ramón Salazar[1*], Jaume Capdevila[2], Jose Luis Manzano[3], Carles Pericay[4], Mercedes Martínez-Villacampa[1], Carlos López[5], Ferrán Losa[6], María José Safont[7], Auxiliadora Gómez-España[8], Vicente Alonso-Orduña[9], Pilar Escudero[10], Javier Gallego[11], Beatriz García-Paredes[12], Amalia Palacios[13], Sebastiano Biondo[14], Cristina Grávalos[15], Enrique Aranda[8] and on behalf of the Spanish Cooperative Group for the Treatment of Digestive Tumors (TTD)

Keine erhöhte Toxizität unter Bev, aber auch kein Vorteil bezüglich Remission, Überleben etc



Clinical Trial > Eur J Cancer. 2019 Mar;110:32-41. doi: 10.1016/j.ejca.2019.01.006. Epub 2019 Feb 7.

Total neoadjuvant approach with FOLFOXIRI plus bevacizumab followed by chemoradiotherapy plus bevacizumab in locally advanced rectal cancer: the TRUST trial

Gianluca Masi [1], Caterina Vivaldi [2], Lorenzo Fornaro [3], Sara Lonardi [4], Piero Buccianti [5], Aldo Sainato [6], Lorenzo Marcucci [7], Angelo Martignetti [8], Emanuele Damiano Luca Urso [9], Maura Castagna [10], Gabriella Fontanini [11], Francesca Bergamo [12], Gianna Musettini [13], Lucio Urbani [14], Elisa Sensi [15], Riccardo Balestri [16], Sabrina Montrone [17], Francesco Pasqualetti [18], Chiara Cremolini [19], Antonello Di Paolo [20], Vittorina Zagonel [21], Alfredo Falcone [22]

Keine erhöhte Toxizität, möglicherweise erhöhte Tumorkontrolle

Kombination von Bevacizumab und Bestrahlung - AvAGlio

Neuro-Oncology

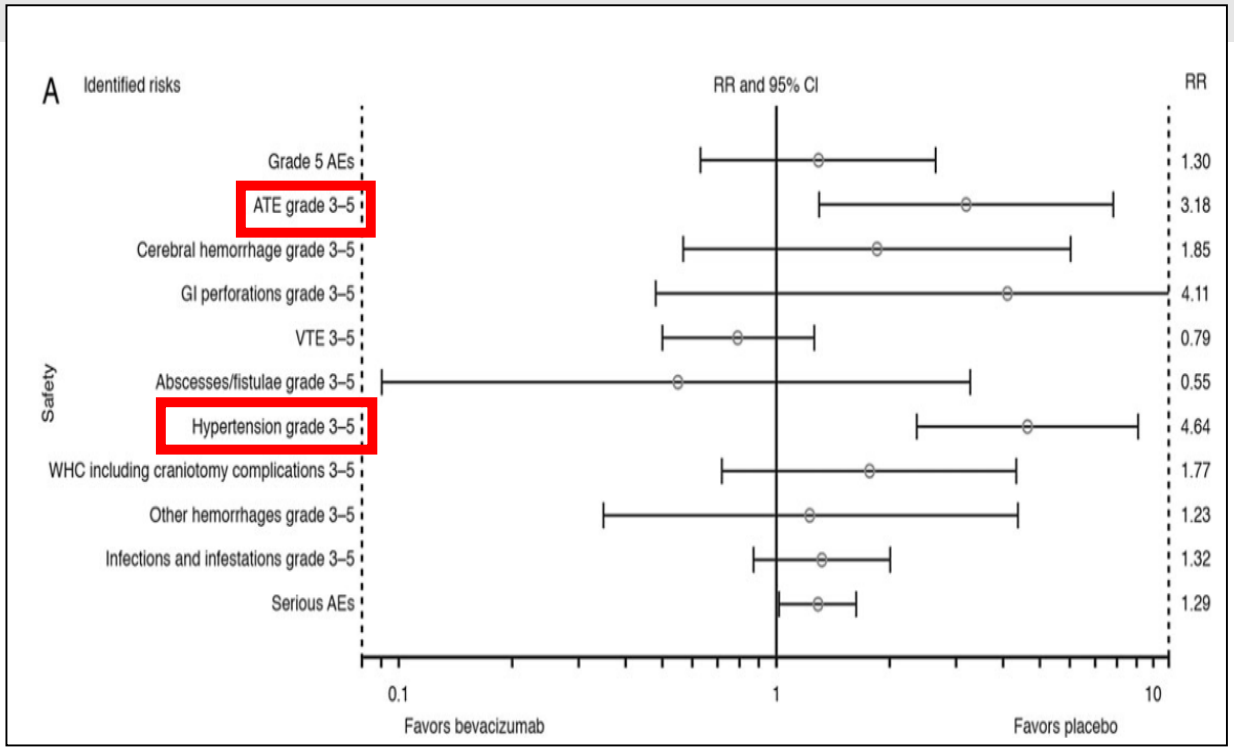
Neuro-Oncology 18(7), 991–1001, 2016
doi:10.1093/neuonc/nov300
Advance Access date 24 January 2016

Bevacizumab, temozolomide, and radiotherapy for newly diagnosed glioblastoma: comprehensive safety results during and after first-line therapy

Frank Saran, Olivier L. Chinot, Roger Henriksson, Warren Mason, Wolfgang Wick, Timothy Cloughesy, Sunita Dhar, Emanuela Pozzi, Josep Garcia, and Ryo Nishikawa

RT & Temozolomid plus Bevacizumab

(n=461Pat)/Placebo (n=450)



Bevacizumab und RT
… ist im Bereich der Lunge kontraindiziert
… im Gehirn und Rektumregion (Becken) möglich
… Pause bei abdominieller Bestrahlung empfohlen (mind. 1 Woche vor u nach RT)

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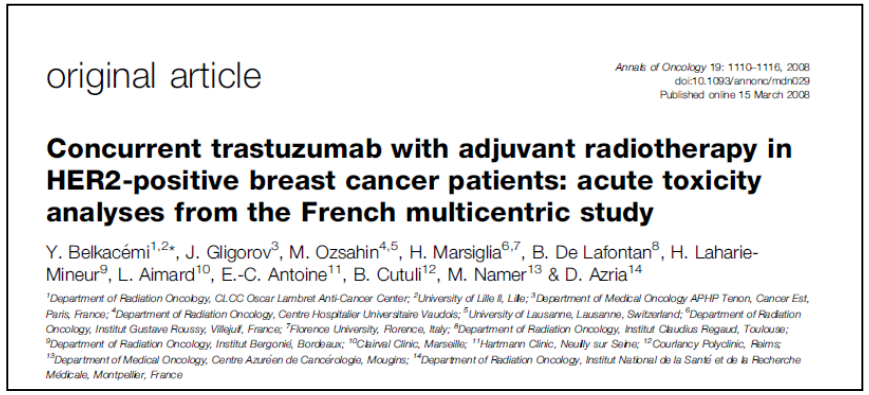
Kombination von Trastuzumab und Bestrahlung


VOLUME 27 · NUMBER 16 · JUNE 1 2009

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Radiotherapy and Adjuvant Trastuzumab in Operable Breast Cancer: Tolerability and Adverse Event Data From the NCCTG Phase III Trial N9831

Michele Y. Halyard, Thomas M. Pisansky, Amylou C. Dueck, Vera Suman, Lori Pierce, Larry Solin, Larry Marks, Nancy Davidson, Silvana Martino, Peter Kaufman, Leila Kutteh, Shaker R. Dakhil, and Edith A. Perez

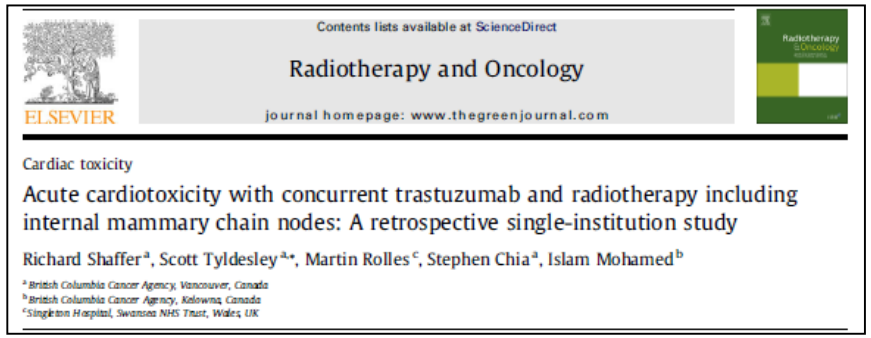

original article

Annals of Oncology 19: 1110–1116, 2008
doi:10.1093/annonc/mdn029
Published online 15 March 2008

Concurrent trastuzumab with adjuvant radiotherapy in HER2-positive breast cancer patients: acute toxicity analyses from the French multicentric study

Y. Belkacémi[1,2*], J. Gligorov[3], M. Ozsahin[4,5], H. Marsiglia[6,7], B. De Lafontan[8], H. Laharie-Mineur[9], L. Aimard[10], E.-C. Antoine[11], B. Cutuli[12], M. Namer[13] & D. Azria[14]

[1]*Department of Radiation Oncology, CLCC Oscar Lambret Anti-Cancer Center;* [2]*University of Lille II, Lille;* [3]*Department of Medical Oncology APHP Tenon, Cancer Est, Paris, France;* [4]*Department of Radiation Oncology, Centre Hospitalier Universitaire Vaudois;* [5]*University of Lausanne, Lausanne, Switzerland;* [6]*Department of Radiation Oncology, Institut Gustave Roussy, Villejuif, France;* [7]*Florence University, Florence, Italy;* [8]*Department of Radiation Oncology, Institut Claudius Regaud, Toulouse;* [9]*Department of Radiation Oncology, Institut Bergonié, Bordeaux;* [10]*Clairval Clinic, Marseille;* [11]*Hartmann Clinic, Neuilly sur Seine;* [12]*Courlancy Polyclinic, Reims;* [13]*Department of Medical Oncology, Centre Azuréen de Cancérologie, Mougins;* [14]*Department of Radiation Oncology, Institut National de la Santé et de la Recherche Médicale, Montpellier, France*


Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

ELSEVIER

Cardiac toxicity

Acute cardiotoxicity with concurrent trastuzumab and radiotherapy including internal mammary chain nodes: A retrospective single-institution study

Richard Shaffer[a], Scott Tyldesley[a,*], Martin Rolles[c], Stephen Chia[a], Islam Mohamed[b]

[a] *British Columbia Cancer Agency, Vancouver, Canada*
[b] *British Columbia Cancer Agency, Kelowna, Canada*
[c] *Singleton Hospital, Swansea NHS Trust, Wales, UK*

Nachbeobachtungs-zeitraum:

1418 Pat,: **keine erhöhte Kardio-oder Pulmotoxizität**, aber nur 44 Pat mit RT Mammaria interna

Med. FU: 3,7JAhre

146 Pat**,: keine erhöhte Kardio-oder Pulmotoxizität**, 103 Pat mit RT Mammaria interna

Med. FU: 16months

59 Pat, 44 Pat mit postop. RT, 13 Pat. Mit Mammaria interna RT: **keine erhöhte Kardiotoxizität** mit RT Mammaria interna

Med. FU: 15months

Auch kleinere retrospektive Studien bei hypofrakt RT. berichten akzeptable Toxizität bei Kombi mit Trastuzumab

Kombination von Trastuzumab und Bestrahlung

original reports

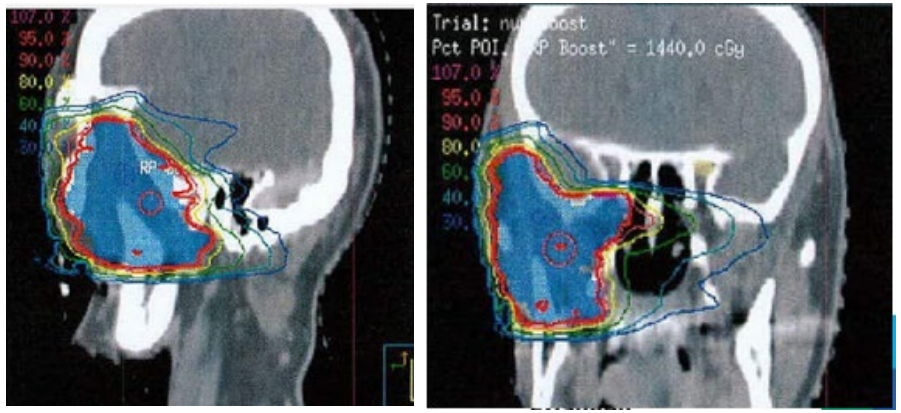
Phase II Feasibility and Biomarker Study of Neoadjuvant Trastuzumab and Pertuzumab With Chemoradiotherapy for Resectable Human Epidermal Growth Factor Receptor 2–Positive Esophageal Adenocarcinoma: TRAP Study

Charlotte I. Stroes[1]; Sandor Schokker, MD[1]; Aafke Creemers, MD[1]; Remco J. Molenaar, MD, PhD[1]; Maarten C.C.M. Hulshof, MD, PhD[1]; Stephanie O. van der Woude, MD[1]; Roel J. Bennink, MD, PhD[1]; Ron A.A. Mathôt, PharmD, PhD[1]; Kausilia K. Krishnadath, MD, PhD[1]; Cornelis J.A. Punt, MD, PhD[1]; Rob H.A. Verhoeven, PhD[2]; Martijn G.H. van Oijen, PhD[1]; Geert-Jan Creemers, MD, PhD[3]; Grard A.P. Nieuwenhuijzen, MD, PhD[3]; Maurice J.C. van der Sangen, MD, PhD[3]; Laurens V. Beerepoot, MD, PhD[4]; Joos Heisterkamp, MD, PhD[4]; Maartje Los, MD, PhD[5]; Marije Slingerland, MD, PhD[6]; Annemieke Cats, MD, PhD[7]; Geke A.P. Hospers, MD, PhD[8]; Maarten F. Bijlsma, PhD[1,9]; Mark I. van Berge Henegouwen, MD, PhD[1]; Sybren L. Meijer, MD, PhD[1]; and Hanneke W.M. van Laarhoven, MD, PhD[1]

→ Keine erhöhte/unerwartete Akuttoxizität

Kombination von Trastuzumab und RT ist möglich (Regelmäßige kardiologische Untersuchung (unabhängig von RT im Thoraxbereich), möglichst alle 3 Monate und bei Beschwerden

2.Rezidiv Speichelgang-Ca d. Parotis, gute Response unter Trastuzumab



3.RT 1,8 bis 59,4Gy (Vorbelastung:138Gy)

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Small Molecules

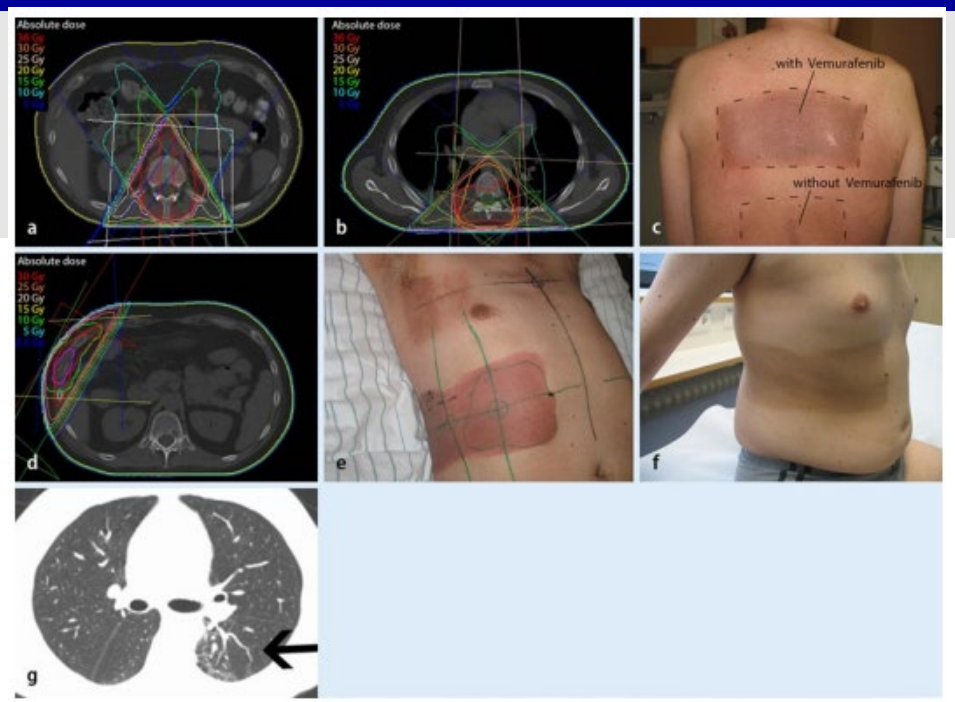
Kombination BRAF Inhibitoren und RT

ORIGINAL ARTICLES MELANOMA | VOLUME 26, ISSUE 6, P1238-1244, JUNE 01, 2015

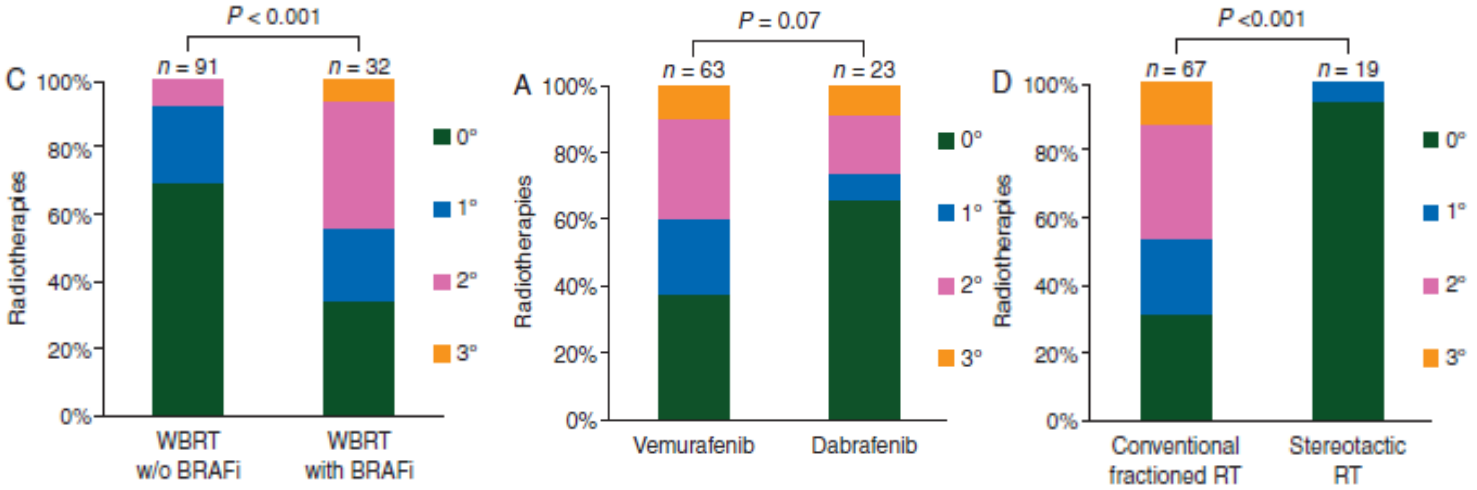
Radiosensitization by BRAF inhibitor therapy—mechanism and frequency of toxicity in melanoma patients

M. Hecht • L. Zimmer • C. Loquai • ... R. Fietkau • L.V. Distel • L. Heinzerling • Show all authors

Open Archive • DOI: https://doi.org/10.1093/annonc/mdv139



- Aktivierende BRAF Mutation in Patienten mit metastasiertem malignem Melanom
- 161 Patienten aus 11 Zentren Deutschlandweit
- Untersuchung der Toxizität bei Patienten mit simultaner Bestrahlung



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Kombination BRAF Inhibitoren und RT

ELSEVIER

International Journal of Radiation Oncology*Biology*Physics

Volume 95, Issue 2, 1 June 2016, Pages 632-646

Clinical Investigation

Avoiding Severe Toxicity From Combined BRAF Inhibitor and Radiation Treatment: Consensus Guidelines from the Eastern Cooperative Oncology Group (ECOG)

Christopher J. Anker MD *, Kenneth F. Grossmann MD, PhD †, Michael B. Atkins MD ‡, Gita Suneja MD §, Ahmad A. Tarhini MD, PhD ||, John M. Kirkwood MD ||

27 Publikationen

"Based on our review, the authors recommend holding RT ≥3 days before and after fractionated RT and ≥1 day before and after SRS. "

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Kombination CDK4/6- Inhibitoren und Radiotherapie

"In all PALOMA studies patients who had bone lesions at the time of their enrolment benefited from palliative RT to improve pain, stopping palbociclib from the day prior to RT to the seventh day following RT."

Role of the Combination of Cyclin-Dependent Kinase Inhibitors (CDKI) and Radiotherapy (RT) in the Treatment of Metastatic Breast Cancer (MBC): Advantages and Risks in Clinical Practice

*Ambrogio Gagliano, Angela Prestifilippo, Ornella Cantale, Gianluca Ferini, Giacomo Fisichella, Paolo Fontana, Dorotea Sciacca and Dario Giuffrida**

Prinzipiell kombinierbar, aber Vorsicht bei RT von viszeralen Organen (gehäuft Kolitis, Ösophagitis!!!) und Lunge (Pneumonitiden, Fibrose), Blutbildveränderungen→ Kontrolle BB

Kombination Crizotinib und Radiotherapie

Int J Radiat Oncol Biol Phys. 2014 March 15; 88(4): 892–898. doi:10.1016/j.ijrobp.2013.11.010.

Stereotactic Radiotherapy Can Safely and Durably Control Sites of Extra-CNS Oligoprogressive Disease in ALK-Positive Lung Cancer Patients on Crizotinib

Gregory N. Gan, M.D., Ph.D.*, Andrew J. Weickhardt, MBBS, D.Med.Sc.‡, Benjamin Scheier,

- 38 Patienten
- SBRT 12-54 Gy in 1-3 Fx/HypoFx RT 30 Gy von

  eZNS Läsionen
- keine III° TOX akut u. chronisch feststellbar
- **Crizotinib pausiert** während der Therapie

Increased Radiation Pneumonitis after Crizotinib and Concurrent Thoracic Radiotherapy in Patients with ALK-positive Non-small-cell Lung Cancer

September 2019 · International Journal of Radiation Oncology, Biology, Physics 105(1):S148-S149

- 15 Patienten mit Crizotinib plus Thorakale RT
- 4 davon Simultan
- Alle entwickelten Grad 2/3 Pneumonitis nachvollziehbar im Bereich der 15-38 Gy
- Empfehlung zur **engmaschigen Überwachung** der Pulm. Tox sowie ggf. **pausieren** der Therapie sofern RT notwendig ist

Kombination Osimertinib und RT

Short Communication

An especially high rate of radiation pneumonitis observed in patients treated with thoracic radiotherapy and simultaneous osimertinib

Wenxiao Jia [a], Hongbo Guo [b], Wang Jing [c], Xuquan Jing [c], Ji Li [c], Min Wang [c], Jinming Yu [c,a,*], Hui Zhu [c,a,*]

- 11 Patienten mit Thorakaler Bestrahlung
- 63% ≥Grad 2 Pneumonitis
- 5 Pat mit Grad 3, 1 Pat verstarb
- **Simultan nicht möglich**

Radiotherapy with Concurrent Versus Sequential Osimertinib for Advanced Non-Small Cell Lung Cancer: a Multi-Center Toxicity Analysis

D. Qian,[1] M. Behera,[2] J. Carlisle,[2] T. Owonikoko,[2] C. Steuer,[2]

- 62 Pat
- Osimertinib Simultan (n=35)vs Osimertinib (n=27) sequentiell
- Kein signifikanter Unterschied der Tox (III+ 7%vs 3% p=0.859)
- **Simultan möglich**
- →*"Treatment with radiotherapy and concurrent osimertinib confers acceptable acute toxicity."*

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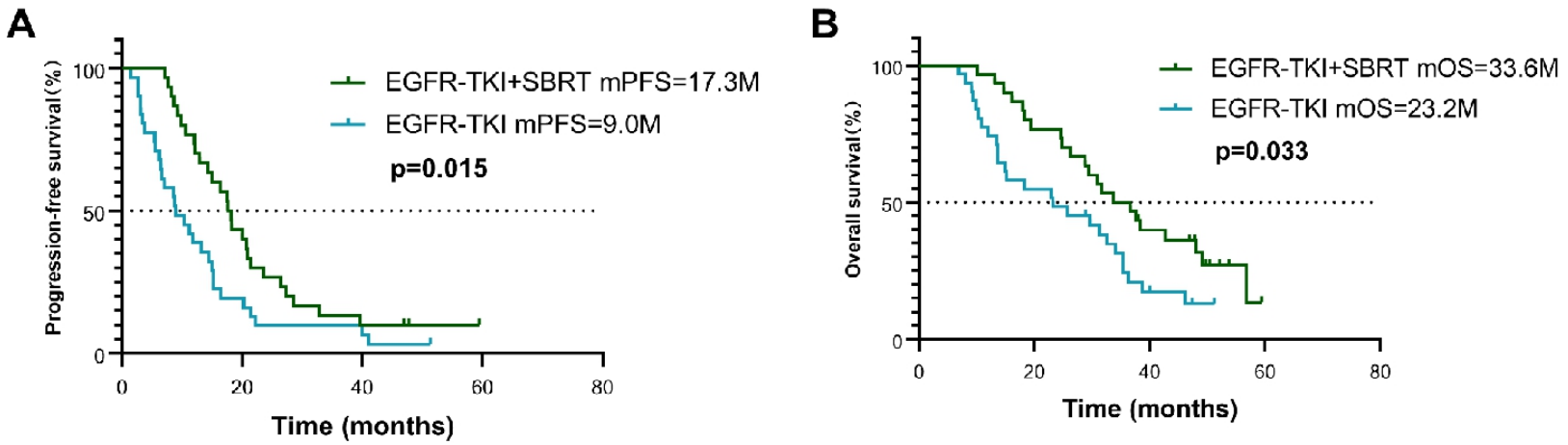
EGFR-TKI und RT

ASCO 2022

Improved survival from early combined radiotherapy: A phase II clinical study and underlying mechanisms of delaying EGFR-TKI acquired resistance in patients with advanced lung cancer.

Li Zhang, Ping Peng, Juejun Gong, Yujie Zhang, Qian Chu, Shu Xia, Rui Meng, Yongshun Chen,

Phase II: Pat. Mit NSCLC St IV mit angehbarer EGFR –Mutation unter 1stLine EGFR-Inhibitor mit response oder stable disease
Randomisation in EGFR-TKI allein vs EGFR-TKI plus SBRT aller Läsionen inkl. Primarius



"Treatment-related adverse events were generally safe and controllable."

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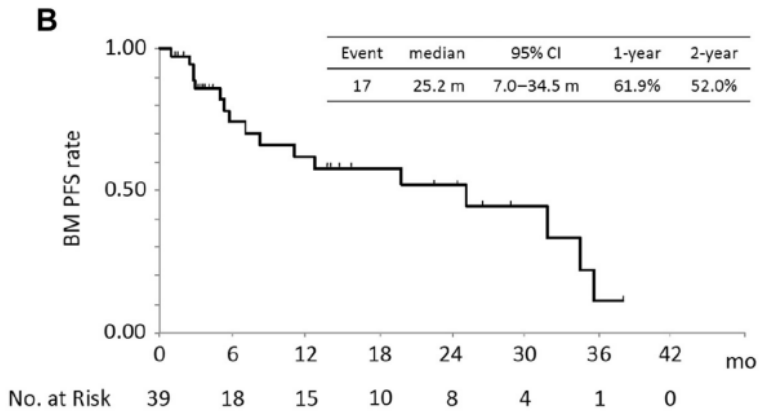
ORIGINAL ARTICLE

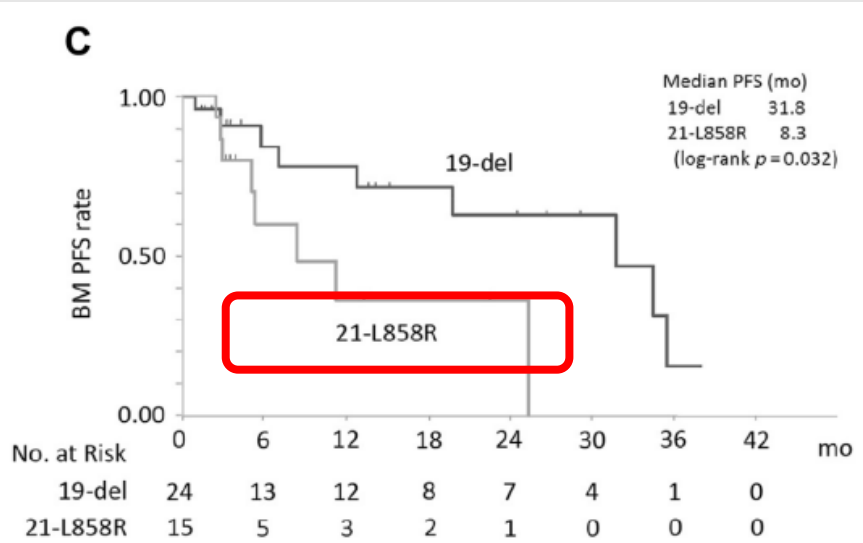
IASLC

A Phase II Study of Osimertinib for Radiotherapy-Naive Central Nervous System Metastasis From NSCLC: Results for the T790M Cohort of the OCEAN Study (LOGIK1603/WJOG9116L)

Check for updates

Hiroyuki Yamaguchi, MD, PhD,[a] Kazushige Wakuda, MD,[b]

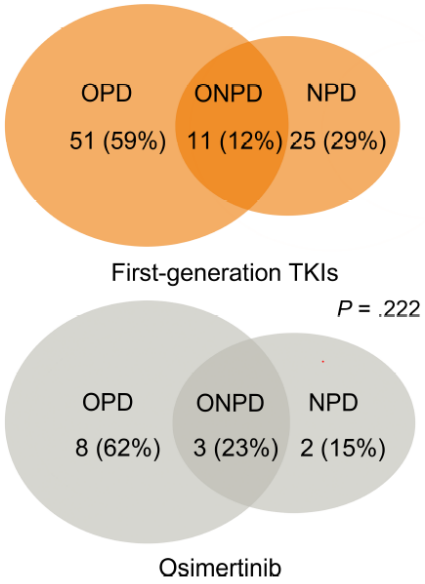




RT Hirnfiliae obsolet????

Zhao Y et al, 2021:First-Line TKIs und Osimertinib, Pat mit Hirnfiliae, n=367Pat, mit und ohne RT

59% PD in vorhandener Metastase



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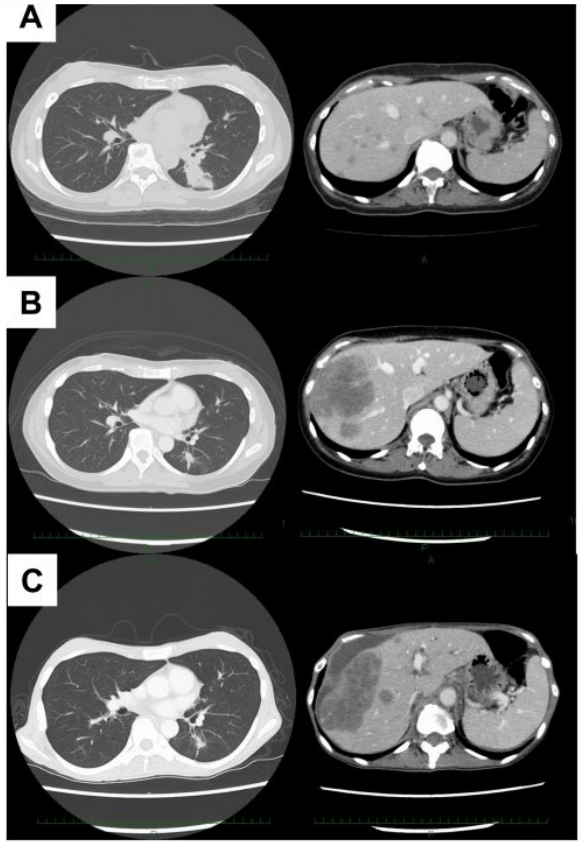
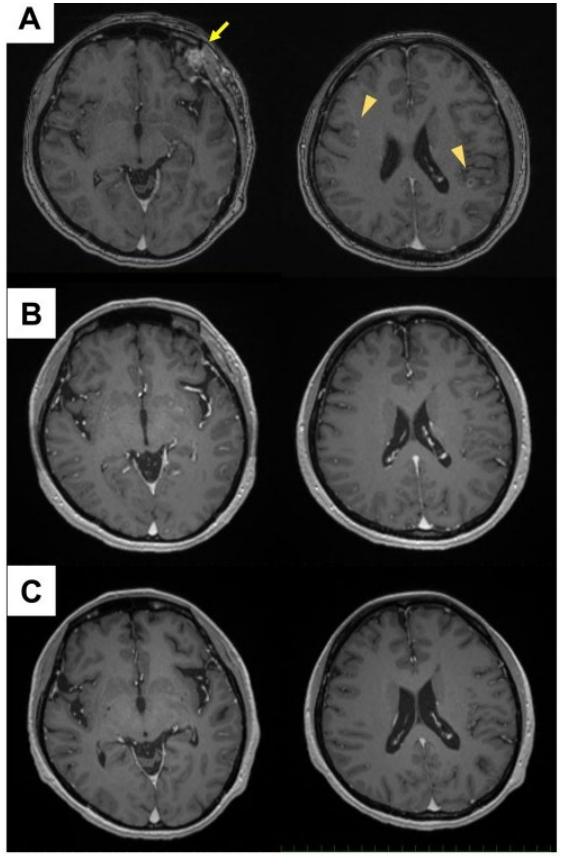
Unterbrechung kann zu „Disease Flare“ führen

- Progress der Erkrankung nach Unterbrechung/Abbrechen der Osimertinib Therapie
- Aus Angst vor möglichen Interaktionen
- CaseReport: Pat mit Leberprogress unter Osimertinib Unterbrechung der Therapie da AE‘s befürchtet wurden in Kombination mit Chx





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Checkpointinhibitoren

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

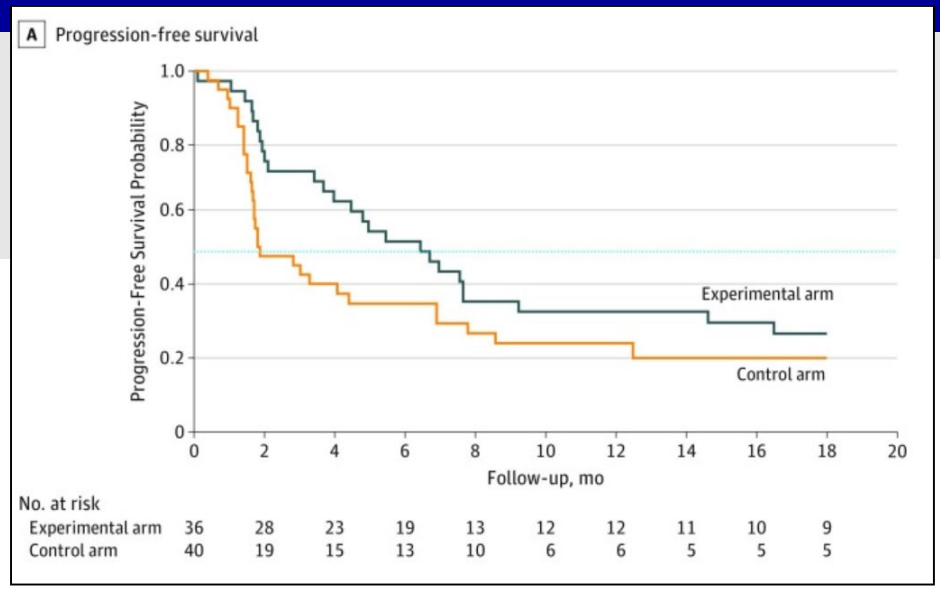
Willemijn S. M. E. Theelen, MD, Heike M. U. Peulen, MD, PhD, [...], and

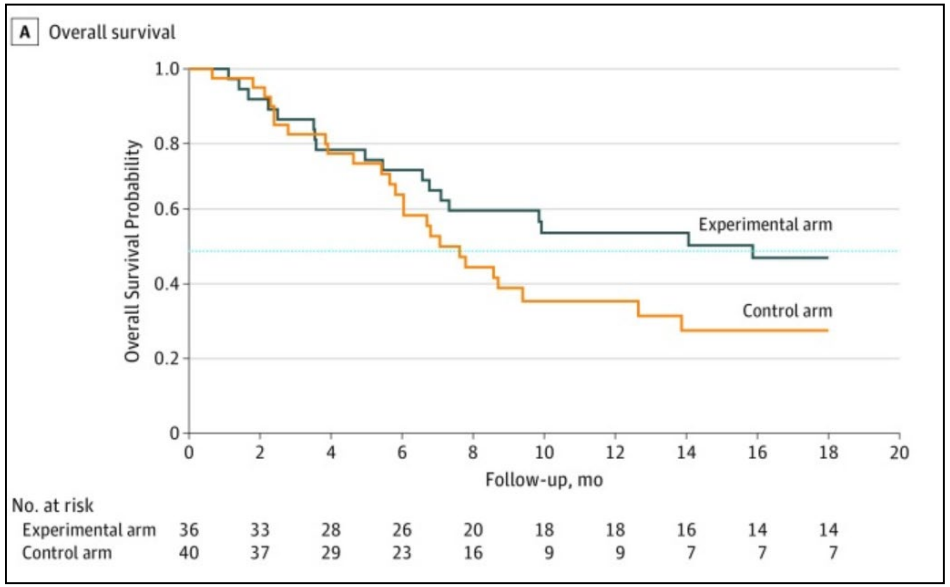
76Pat mit rezidiv. und/oder met NSCLC, mind 2 Läsionen

- Pembro alleine n=40
- Pembro plus STX (3x8Gy) einer Lokalisation n=36

Ziel ORR n 12 Wochen von 20% auf 50%

Ergebnis: 18% vs 36%





"Stereotactic body radiotherapy prior to pembrolizumab was well tolerated. "

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

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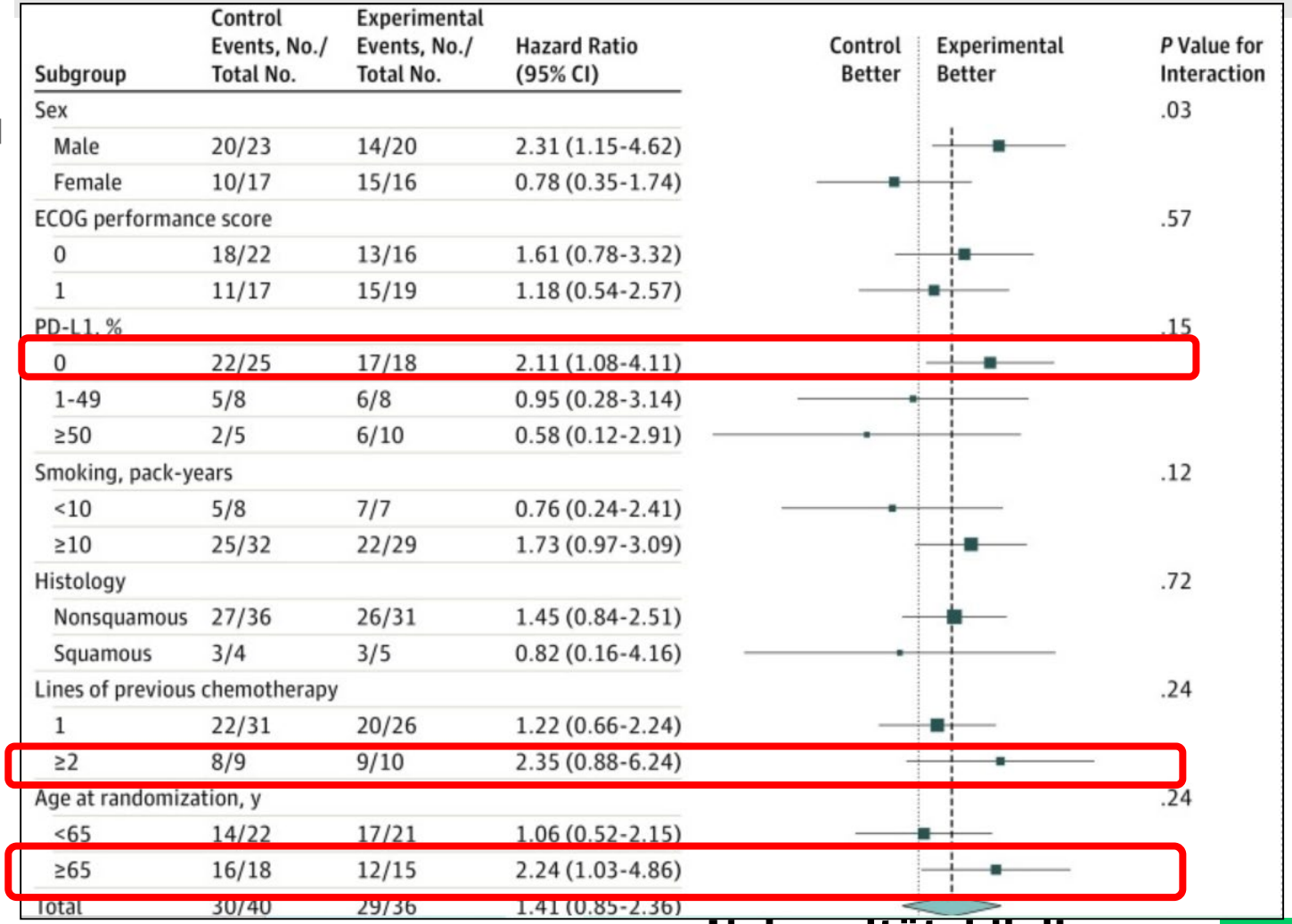

Subgroup	Control Events, No./ Total No.	Experimental Events, No./ Total No.	Hazard Ratio (95% CI)	P Value for Interaction
Sex				.03
Male	20/23	14/20	2.31 (1.15-4.62)	
Female	10/17	15/16	0.78 (0.35-1.74)	
ECOG performance score				.57
0	18/22	13/16	1.61 (0.78-3.32)	
1	11/17	15/19	1.18 (0.54-2.57)	
PD-L1, %				.15
0	22/25	17/18	2.11 (1.08-4.11)	
1-49	5/8	6/8	0.95 (0.28-3.14)	
≥50	2/5	6/10	0.58 (0.12-2.91)	
Smoking, pack-years				.12
<10	5/8	7/7	0.76 (0.24-2.41)	
≥10	25/32	22/29	1.73 (0.97-3.09)	
Histology				.72
Nonsquamous	27/36	26/31	1.45 (0.84-2.51)	
Squamous	3/4	3/5	0.82 (0.16-4.16)	
Lines of previous chemotherapy				.24
1	22/31	20/26	1.22 (0.66-2.24)	
≥2	8/9	9/10	2.35 (0.88-6.24)	
Age at randomization, y				.24
<65	14/22	17/21	1.06 (0.52-2.15)	
≥65	16/18	12/15	2.24 (1.03-4.86)	
Total	30/40	29/36	1.41 (0.85-2.36)	

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Articles

Pembrolizumab with or without radiotherapy for metastatic non-small-cell lung cancer: a pooled analysis of two randomised trials

Willemijn S M E Theelen MD [a*], Dawei Chen MD [c*], Vivek Verma MD [h], Brian P Hobbs PhD [d],

Pembro-RT: Pembro vs STX(3x8Gy) u Pembro sequentiell
MDACC: Pembro plus STX(4x12,5 oder 15x3Gy) u Pembro simultan

In beiden Studien **mindestens 1 unbestrahlte Läsion**

N= 148Pat

	Pembro mono (n=76)	Pembro plus RT (n=72)
Best ARR (abscopal response rate)	19.7 %	41.7 %
ACR (abscopal disease CR)	43%	65%
Med PFS	4.4 mo	9 mo
Med OS	8.7 mo	19.2 mo

No new safety concerns were noted in the pooled analysis.

Clinical Trial > J Thorac Oncol. 2022 Jan;17(1):130-140. doi: 10.1016/j.jtho.2021.08.019.
Epub 2021 Sep 6.

A Phase 1 Trial of Concurrent or Sequential Ipilimumab, Nivolumab, and Stereotactic Body Radiotherapy in Patients With Stage IV NSCLC Study

Christine M Bestvina [1], Kelli B Pointer [2], Theodore Karrison [3], Hania Al-Hallaq [2], Philip C Hoffman [1],

N=37Pat

Concurrent nivolumab, ipilimumab, and SBRT were not more toxic than sequential therapy, and multisite SBRT was well tolerated in widely metastatic patients. Multimodality therapy resulted in durable metastasis control and encouraging early overall survival.

da Silva et al. 2019 Voronova et al. 2020, Gatterbauer et al. 2020 , Minniti et al. 2019 J ,Hadi et al. 2020 , Lehrer et al. 2019.

Checkpointinhibitoren und cerebrale RT

	N	Tumorentität	Radionekrose RT + IT	RT	p
da Silva et al. 2019	135	Malignes Melanom Bei Ipilimumab erhöht	18%		
Voronova et al. 2020	40 Studien 4359	Metaanalyse alle Tumoren	9 %	6 %	
Gatterbauer et al. 2020	182	Malignes Melanom	23 %	23 %	
Minniti et al. 2019	326	Malignes Melanom RT + Nivolumab RT + Ipilimumab	17 % 24 %		
Hadi et al. 2020	28	Malignes Melanom	18 %	18 %	0,935
Lehrer et al. 2019	1570	alle Tumoren	5,3%	-	

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Checkpointinhibitoren

Simultan zur RT keine erhöhte Toxität

Offene Fragen:

- Sequenz der Therapien???
- Anpassung der Zielvolumina
- (kleinere Zielvolumina, LAG kleinvolumiger)????
- Adaptation der Bestrahlungsdosis???

Zusammenfassung

- Kombination von Checkpointinhibitoren und RT ist sicher, aber Sequenz der optimalen Kombi und mögliche praxisrelevante Therapieänderungen (Verkleinerung RT-Volumen, Reduktion RT-Dosis etc) unklar
- Zahlreiche Antikörper und small molecules zugelassen, aber Daten zur Kombinationstherapie oft nicht oder nur spärlich vorhanden
- Bei Vorstellung von Pat mit Antikörper/small molecule: Literaturrecherche
- Systemtherapie möglichst nicht unterbrechen (Flare disease), RT möglichst kleinvolumig/stereotaktisch

Zusammenfassung

DANKE FÜR IHRE AUFMERKSAMKEIT!!!!!

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