Universitätsmedizin Essen
Universitätsklinikum

Vortrag adjuvante Therapie und Folgescenarien: wie definiert man Therapieversagen und wie behandelt man es?

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Conflicts of interest

Financial Interests
Invited Speaker, Personal: AstraZeneca, Astellas, BMS, EISAI, Ipsen, Janssen-Cilag, Merck, MSD, Pfizer, ONO Pharmaceutical, Novartis/AAA
Advisory Board, Personal: Apogepha, BMS; EISAI, EUSA Pharm, Cureteq, Debiopharm, Gilead, Janssen-Cilag, Merck, MSD, Pfizer, Novartis, Oncorena, PCI Biotech
Stocks/Shares, Personal: AstraZeneca, BMS, MSD, SeaGen
Steering Committee Member: BMS, EISAI, Ipsen, Novartis, PharmaMar
Research Grant, Financial interest, Institutional: AstraZeneca, BMS, MSD, Ipsen, Pfizer
Travel support: AstraZeneca, Ipsen, Merck, Janssen, Pfizer

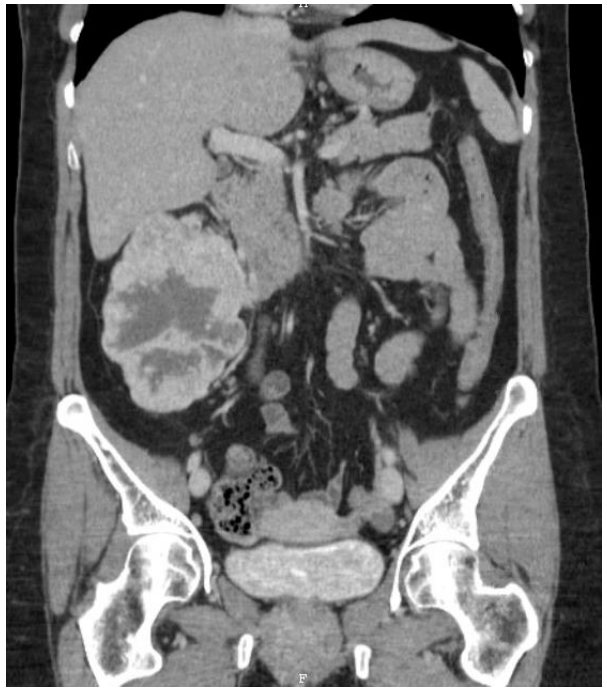
Non-Financial Interests
Membership: ASCO, ESMO, German medical Oncology and Hematology Society
Advisory role: German Cancer Society
Leadership role: Working Group medical oncology (AIO)

Klinischer Fall

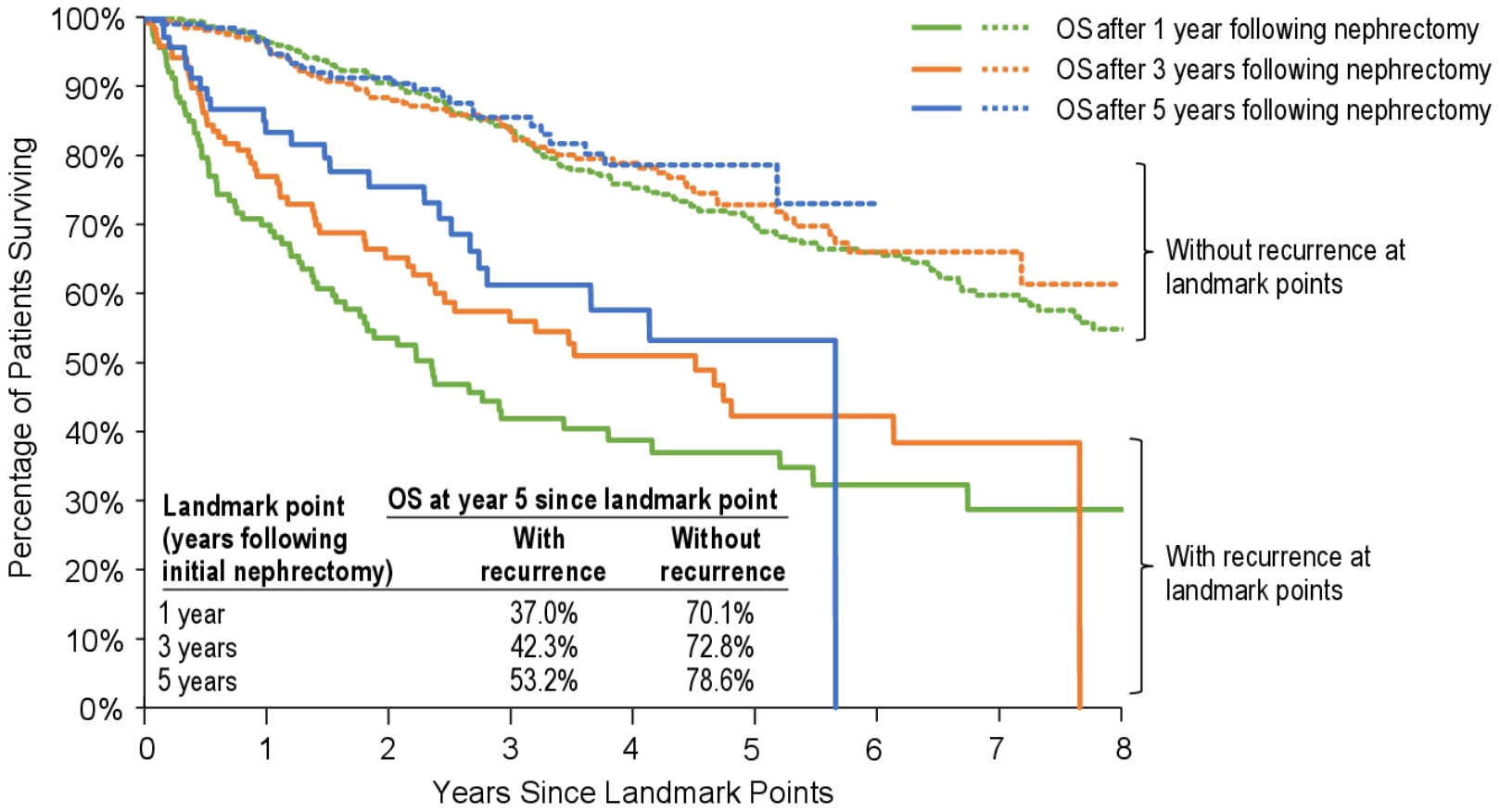
- 55 jähriger Mann ohne Vorerkrankungen
- Rückenschmerzen und asymptomatische Hämaturie
- keine Dysurie
- CT zeigt Nierenläsion rechts

- <u>Therapie:</u>
- radikale Nephrektomie der rechten Niere
- TNM: pT3a, pN0 (0/1), L0 V2 Pn0 R0

🤔 Nachsorge oder adjuvante Therapie?



Rezidive beim NCC sind mit schlechter Prognose assoziiert



	Item	P
Correlation[1] DFS & OS	0.7 (95%CI: 0.65-0.74)	<0.001
Costs[2] w/wo recurrence	$ 4,924 vs. 1,387	<0.001

[1]Kendall T
[2]mean monthly all-cause health care costs

Haas et al, ASCO 2021: 4581. NCC: Nierenzellkarzinom

Internationale Leitlinien empfehlen die adjuvante Therapie

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

1 year of adjuvant therapy with pembrolizumab within 12 wks. after Nx (I, A) or metastasectomy (II, B)*

Powles et al. Ann Oncol 2024. Renal Cell Carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, https://doi.org/10.1016/j.annonc.2024.05.537

*after careful patient counselling regarding potential long-term AEs

eau

Adjuvant pembrolizumab in ccRCC patients, preferably within 12-16 weeks post-nephrectomy, (weak)*

https://uroweb.org/guidelines/renal-cell-carcinoma/chapter/introduction

*Discuss the contradictory results of the available adjuvant ICI trials with patients to facilitate shared decision making.. Inform patients about the potential risk of overtreatment and immune related side effects if adjuvant therapy is considered

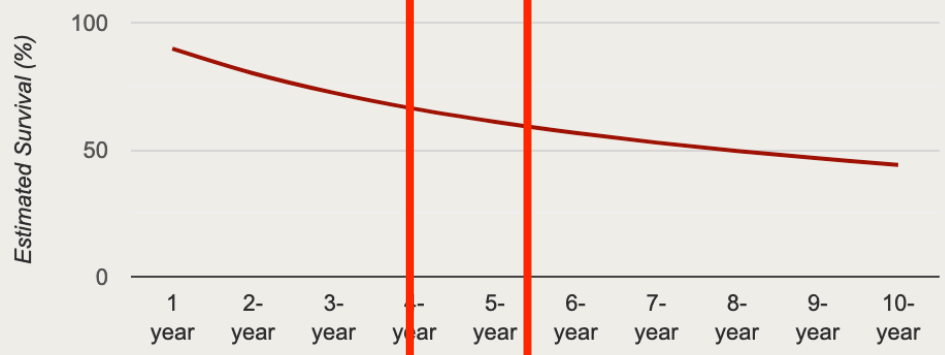
Post-operative TUKO unseres Falls

- Rezidivrisiko:
  - intermediär-hoch
- Angebot:
  adjuvante Therapie mit Pembrolizumab für 1 Jahr

Cancer Prediction Tools

Disease Free Survival (DFS) Probability

1 year	2-year	3-year	4-year	5-year	6-year	7-year	8-year	9-year	10-year
89.8%	80.1%	72.4%	66.1%	61.0%	56.6%	52.8%	49.5%	46.6%	44.0%



https://www.cancernomograms.com/nomograms/492. Correa et al. https://doi.org/10.1016/j.eururo.2021.02.025

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Adjuvant Pembrolizumab after Nephrectomy in Renal-Cell Carcinoma

T.K. Choueiri, P. Tomczak, S.H. Park, B. Venugopal, T. Ferguson, Y.-H. Chang, J. Hajek, S.N. Symeonides, J.L. Lee, N. Sarwar, A. Thiery-Vuillemin, M. Gross-Goupil, M. Mahave, N.B. Haas, P. Sawrycki, H. Gurney, C. Chevreau, B. Melichar, E. Kopyltsov, A. Alva, J.M. Burke, G. Doshi, D. Topart, S. Oudard, H. Hammers, H. Kitamura, J. Bedke, R.F. Perini, P. Zhang, K. Imai, J. Willemann-Rogerio, D.I. Quinn, and T. Powles, for the KEYNOTE-564 Investigators*

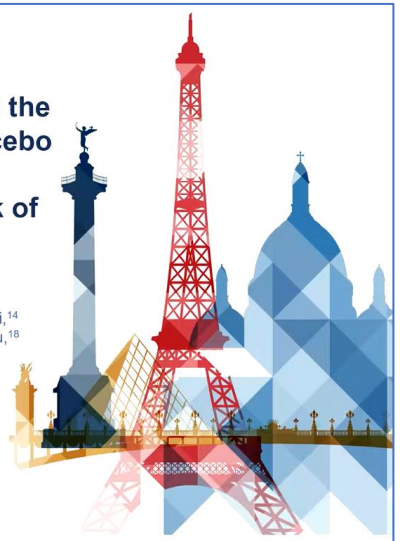
PARIS 2022 ESMO congress

IMmotion010: Efficacy and Safety From the Phase III Study of Atezolizumab vs Placebo as Adjuvant Therapy in Patients With Renal Cell Carcinoma at Increased Risk of Recurrence Following Resection

Axel Bex,[1,2,a] Robert Uzzo,[3,a] Jose Antonio Karam,[4] Viraj A. Master,[5] Frede Donskov,[6,7] Cristina Suarez,[8] Laurence Albiges,[9] Brian Rini,[10] Yoshihiko Tomita,[11] Ariel Kann,[12] Giuseppe Procopio,[13] Francesco Massari,[14] Matthew Zibelman,[15] Igor Antonyan,[16] Mahrukh Huseni,[17] Debasmita Basu,[18] Bo Ci,[17] William Leung,[17] Omara Khan,[18] Sumanta Pal[19]

1. Department of Urology, The Royal Free London NHS Foundation Trust, University College London Division of Surgery and Interventional Science, London, UK; 2. The Netherlands Cancer Institute, Amsterdam, the Netherlands; 3. Department of Urology, Fox Chase Cancer Center, Philadelphia, PA, USA; 4. Department of Urology, University of Texas MD Anderson Cancer Center, Houston, TX, USA; 5. Department of Urology, Winship Cancer Institute, Emory University School of Medicine, Atlanta, GA, USA; 6. Department of Oncology, Aarhus University Hospital, Aarhus, Denmark; 7. Department of Oncology, University Hospital of Southern Denmark, Esbjerg, Denmark; 8. Medical Oncology, Vall d'Hebron Institute of Oncology (VHIO), Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain; 9. Department of Cancer Medicine, Gustave Roussy, Université Paris-Saclay, Villejuif, France; 10. Division of Hematology Oncology, Vanderbilt University Medical Center, Nashville, TN, USA; 11. Division of Urology, Department of Regenerative and Transplant Medicine, Graduate School of Medical and Dental Sciences, Niigata University, Niigata, Japan; 12. Hospital Alemão Oswaldo Cruz, São Paulo, Brazil; 13. Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy; 14. Medical Oncology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy; 15. Department of Hematology and Oncology, Fox Chase Cancer Center, Philadelphia, PA, USA; 16. Regional Medical Clinical Center of Urology and Nephrology n.a. V.I.Shaposval, Kharkiv, Ukraine; 17. Genentech Inc, South San Francisco, CA, USA; 18. Roche Product Ltd, Welwyn Garden City, UK; 19. Department of Medical Oncology, City of Hope Comprehensive Cancer Center, Duarte, CA, USA.

* A.B. and R.U. contributed equally to this work.



THE LANCET

Adjuvant nivolumab plus ipilimumab versus placebo for localised renal cell carcinoma after nephrectomy (CheckMate 914): a double-blind, randomised, phase 3 trial

Published online February 9, 2023 https://doi.org/10.1016/S0140-6736(22)02574-0

Robert J Motzer, Paul Russo, Viktor Grünwald, Yoshihiko Tomita, Bogdan Zurawski, Omi Parikh, Sebastiano Buti, Philippe Barthélémy, Jeffrey C Goh, Dingwei Ye, Alejo Lingua, Jean-Baptiste Lattouf, Laurence Albigès, Saby George, Brian Shuch, Jeffrey Sosman, Michael Staehler, Sergio Vázquez Estévez, Burcin Simsek, Julia Spiridigliozzi, Aleksander Chudnovsky, Axel Bex

PARIS 2022 ESMO congress

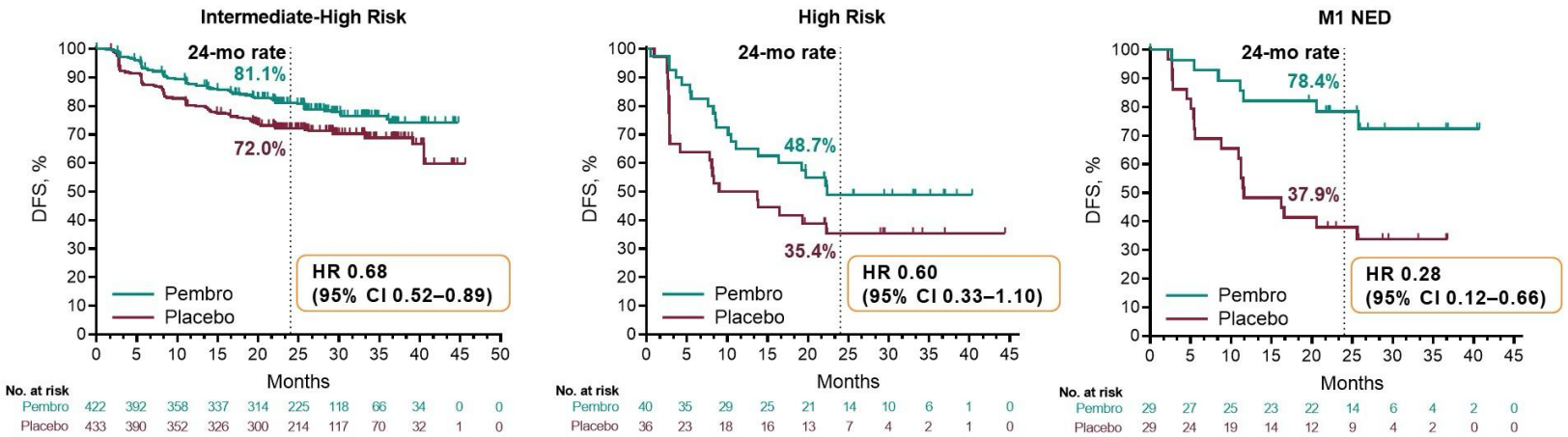
Phase III RandOmized Study Comparing PErioperative Nivolumab (Nivo) versus Observation in Patients with Renal Cell Carcinoma Undergoing Nephrectomy (PROSPER, ECOG-ACRIN EA8143), a National Clinical Trials Network trial

Mohamad E Allaf, MD

Director and Urologist-in-Chief
Johns Hopkins University, Baltimore, Maryland, USA
September 10, 2022

Adjuvante Therapie mit Pembrolizumab: verbessert das DFS in der KN-564 Studie

DFS by Recurrence Risk Subgroups



	Pts w/ Event	Median, mo (95% CI)
Pembro	87	NR (NR–NR)
Placebo	127	NR (40.5–NR)

	Pts w/ Event	Median, mo (95% CI)
Pembro	20	22.4 (11.1–NR)
Placebo	23	11.4 (2.9–NR)

	Pts w/ Event	Median, mo (95% CI)
Pembro	7	NR (25.7–NR)
Placebo	19	11.6 (5.6–NR)

Intermediate-high risk: pT2, grade 4 or sarcomatoid, N0, M0; or pT3, any grade, N0, M0;
High risk: pT4, any grade, N0, M0; or pT any stage, any grade, N+, M0;
M1 NED: No evidence of disease after primary tumor + soft tissue metastases completely resected ≤1 year from nephrectomy.
DFS, disease-free survival; NR, not reached. Data cutoff date: June 14, 2021.

onkopedia

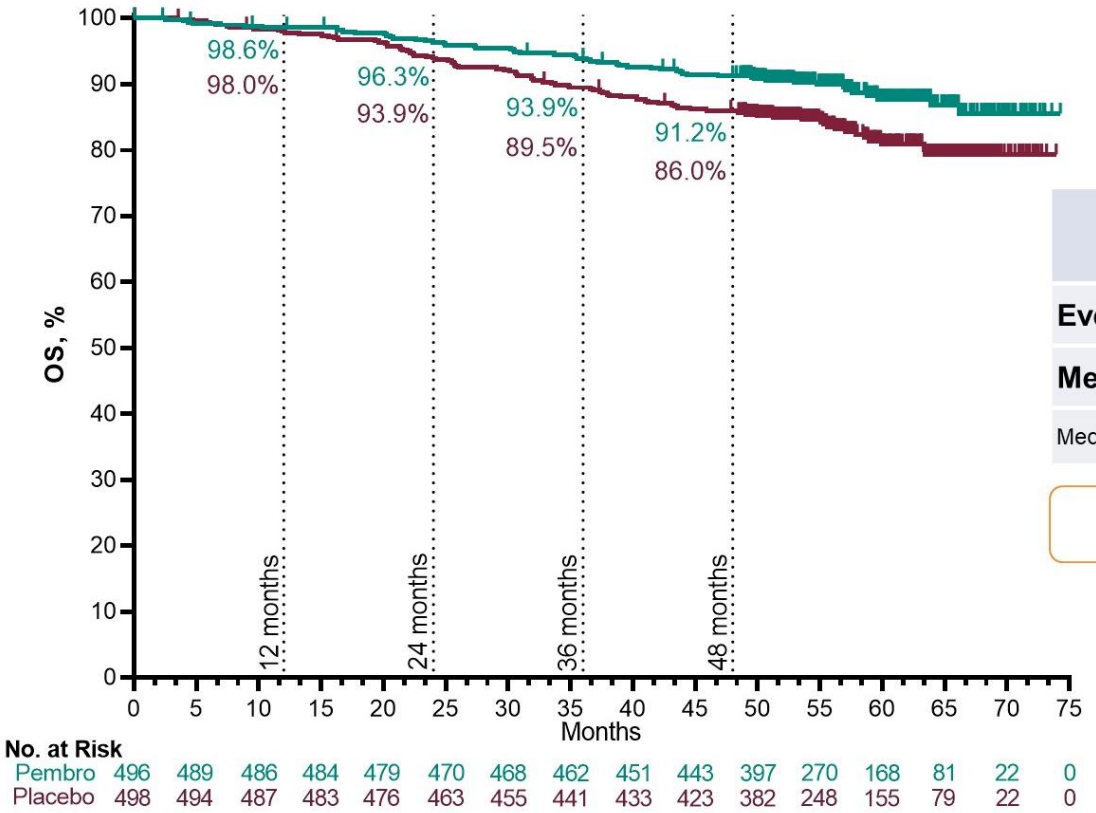
Empfohlen bei hohem Rezidivrisiko:
Tumorstadium 2 mit Fuhrman Grad 4 oder sarkomatoider Differenzierung;
Tumorstadium 3 oder höher, regionale Lymphknotenmetastasen oder Stadium M1 mit NED nach Metastasenresektion

www.onkopedia.com/de

Choueiri et al. ASCO GU22: 290

Die adjuvante Therapie mit Pembrolizumab verbessert das Gesamtüberleben

Overall Survival, Intention-to-Treat Population



	Pembro (N = 496)	Placebo (N = 498)
Events, n	55	86
Median, mo (95% CI)	NR (NR–NR)	NR (NR–NR)
Median follow-up was 57.2 months (range, 47.9–74.5)		

HR 0.62 (95% CI 0.44–0.87); *P* =.002*

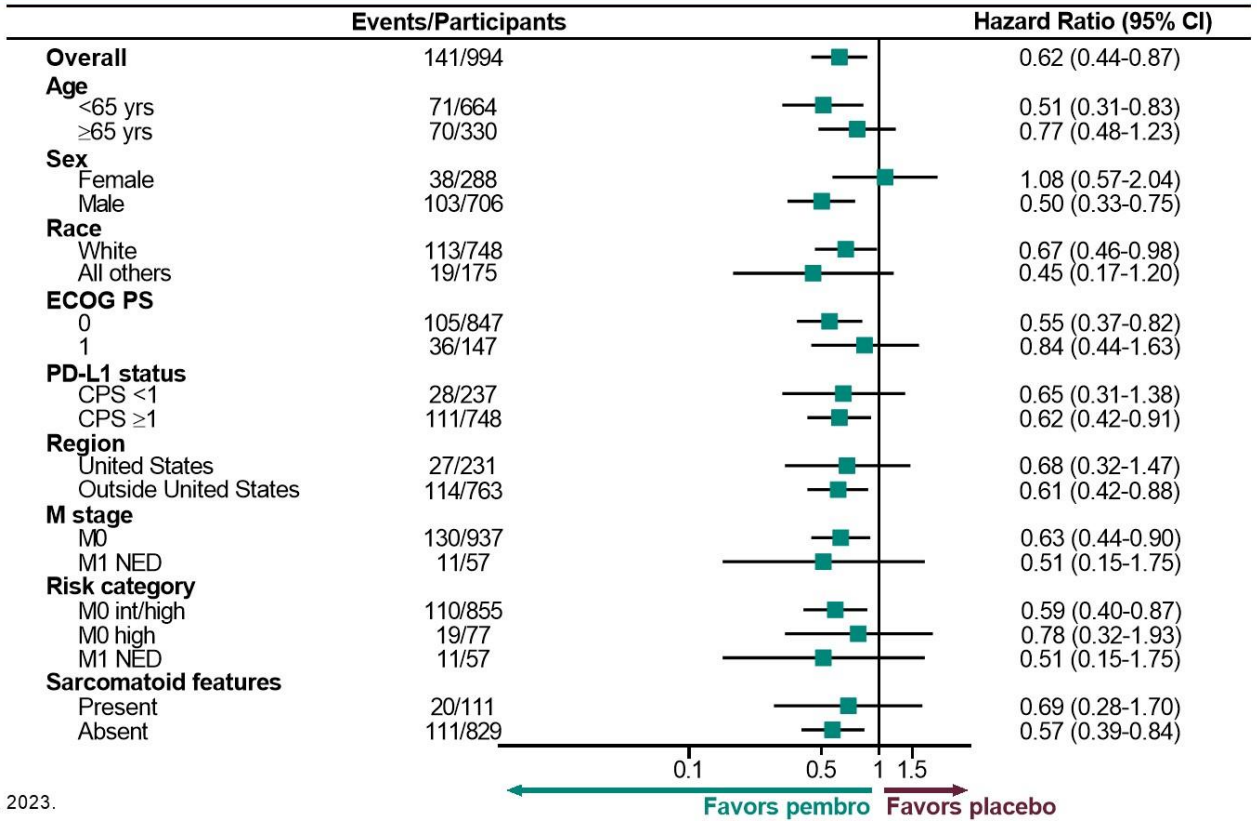
* **denotes statistical significance**. P-value boundary for OS at IA3 was 0.0072 (1-sided) per Lan-DeMets O'Brien-Fleming spending approximation α-spending function. As this key secondary endpoint was formally met, any future OS analyses will be descriptive only.

Data cutoff date: September 15, 2023.

Choueiri et al. ASCO GU 2024: 359

Effekt ist in allen Subgruppen gegeben

Overall Survival by Subgroups



Data cutoff date: September 15, 2023.

Choueiri et al. ASCO GU 2024: 359

Chronische Toxizitäten unterscheiden sich vom Spektrum der akuten irAEs - Beispiel des Melanoms

Table 1. Acute Immune-Related Adverse Events (irAEs) Arising During Anti–Programmed Cell Death 1 Therapy

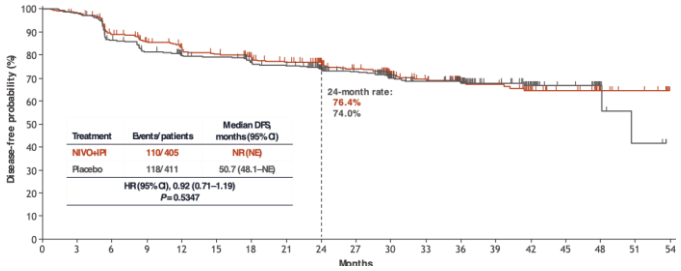
Acute irAEs	No. (%)		
	Patients with acute irAEs	Delayed event after ICI therapy	irAEs Persisted to chronic status
Total acute irAEs	267 (100)	NA	NA
Grade ≥2	171 (64.0)	NA	NA
Grades 3-5	52 (19.5)	NA	NA
irAEs Requiring steroids	109 (40.8)	NA	NA
Grade 2	60 (55.0)	NA	NA
Grades 3-5	49 (45.0)	NA	NA
irAE Type[a]			
Arthritis/arthralgias	41 (10.6)	4 (1.0)	22 (48.9)
Colitis/diarrhea	38 (9.8)	6 (1.6)	6 (13.6)
Dermatitis/pruritus	100 (25.8)	6 (1.3)	19 (17.9)
Hepatitis	24 (6.2)	1 (0.3)	4 (16.0)
Thyroiditis/hypothyroid	63 (16.3)	4 (1.0)	54 (80.6)

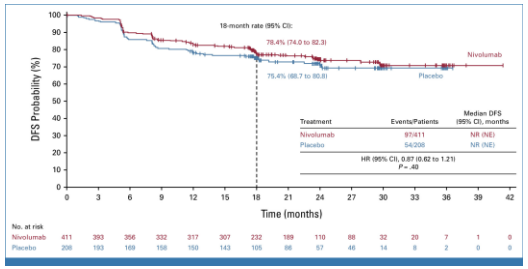
🤔 Risiko der Langzeittoxizität

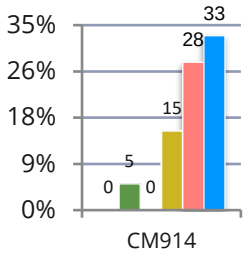
Patrinely et al. JAMA Oncol. doi:10.1001/jamaoncol.2021.0051

Motzer et al. ESMO22: LBA4
Motzer et al. J Clin Oncol 00:1-12

Nivolumab + Ipilimumab
oder Nivolumab
vs.
Placebo

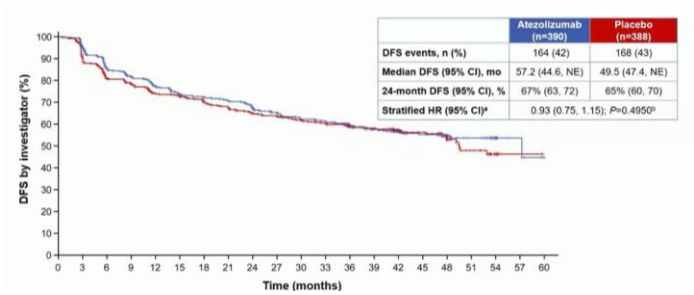


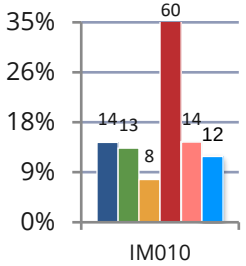




Bex et al. ESMO22: LBA66

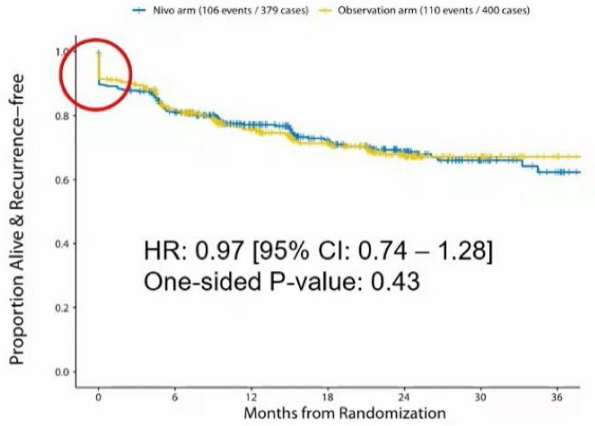
Atezolizumab
vs.
Placebo

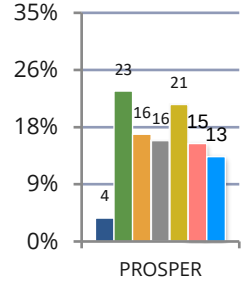




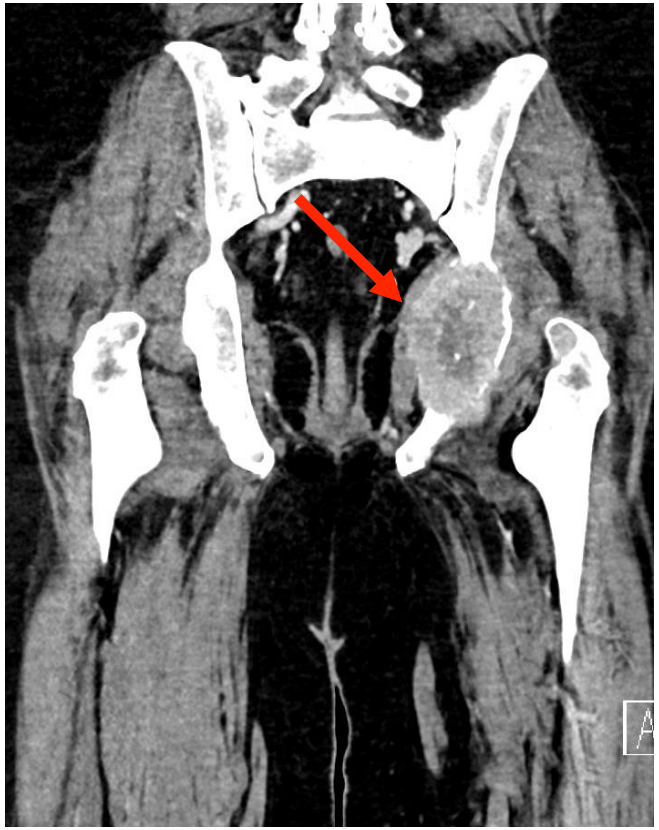
Allaf et al. ESMO22: LBA67

Nivolumab
vs.
Observation





Was tun, wenn die Erkrankung wiederkommt?

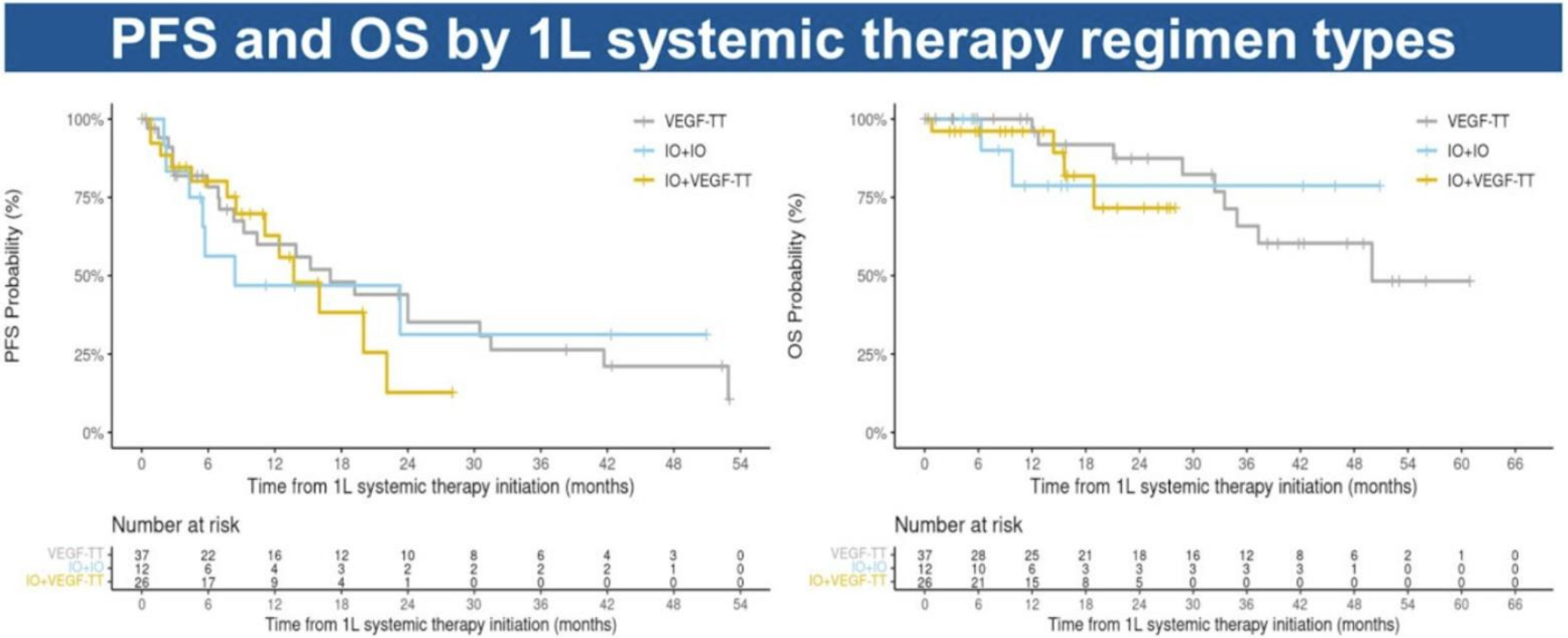


Ist das schon Zweitlinientherapie?



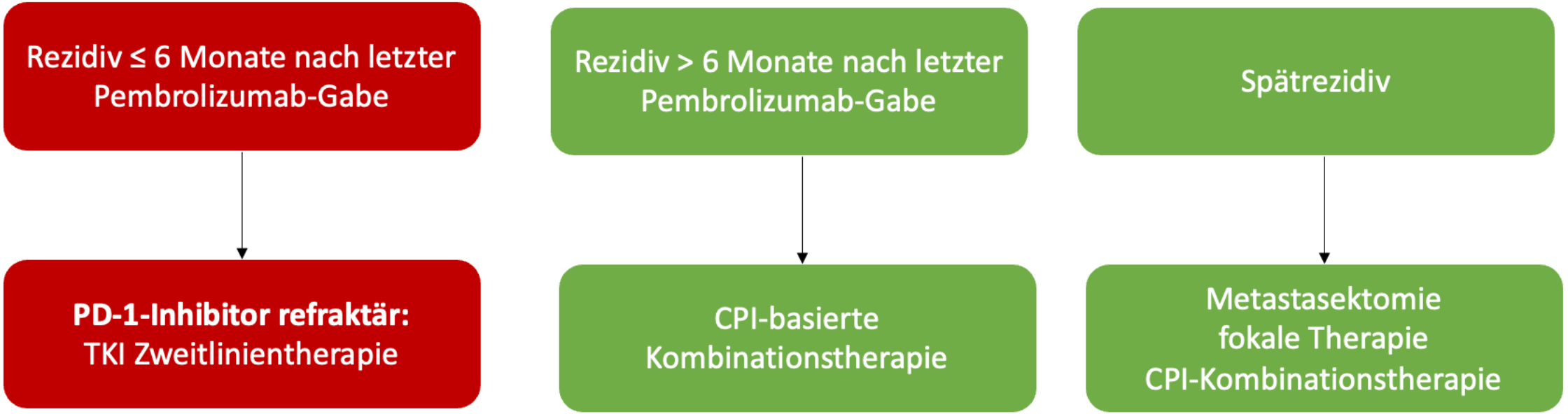

https://www.svgrepo.com/

Bisher nur wenige Daten zur Behandlung nach Versagen einer adjuvanten Therapie



El Zarif T et al., ASCO 2024: 4529

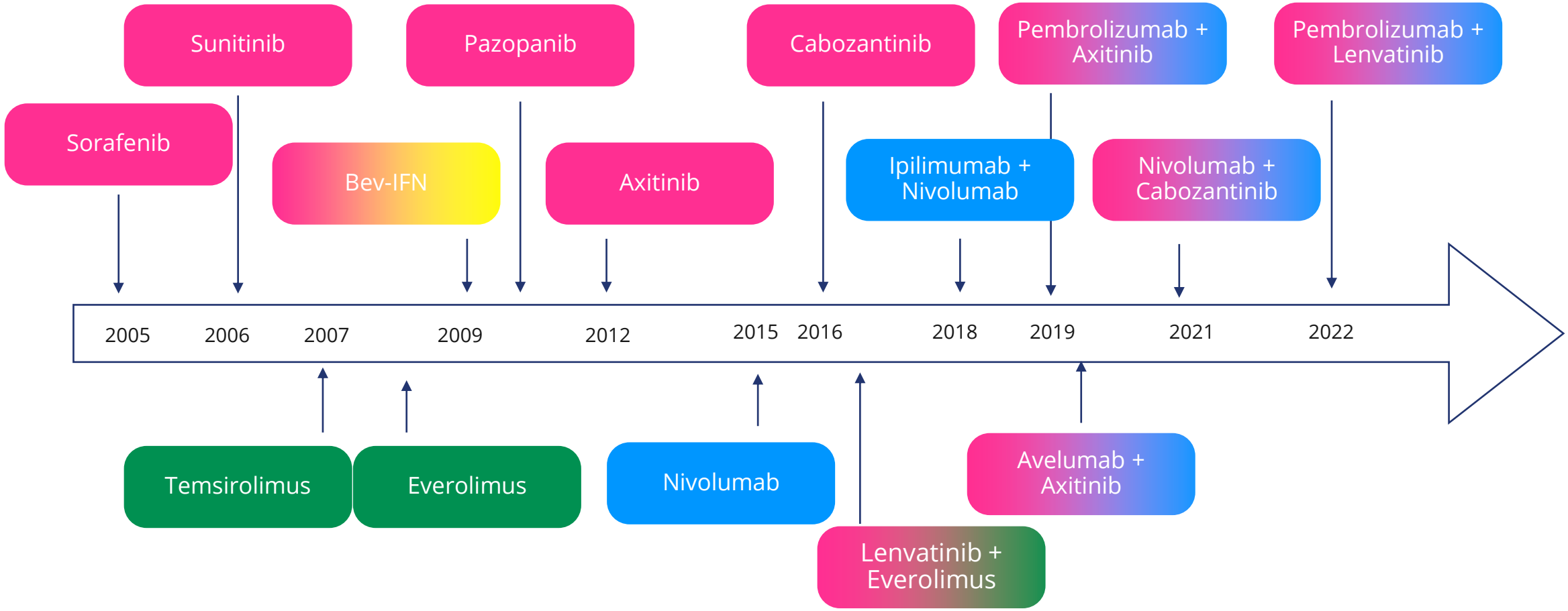
Folgetherapie nach der Adjuvanz - ein pragmatischer Vorschlag zur Therapieentscheidung



Folgetherapie aus KN564*:
Anti-PD-(L)1 inhibitor: 42/102 (41.2%)
VEGF/VEGFR inhibitor: 94/102 (92.2%)
Andere: 32/102 (31.4%)
Strahlentherapie: 31/128 (24.2%)
Operation: 35/128 (27.3%)
Keine Therapie: 28/161 (17.4%)

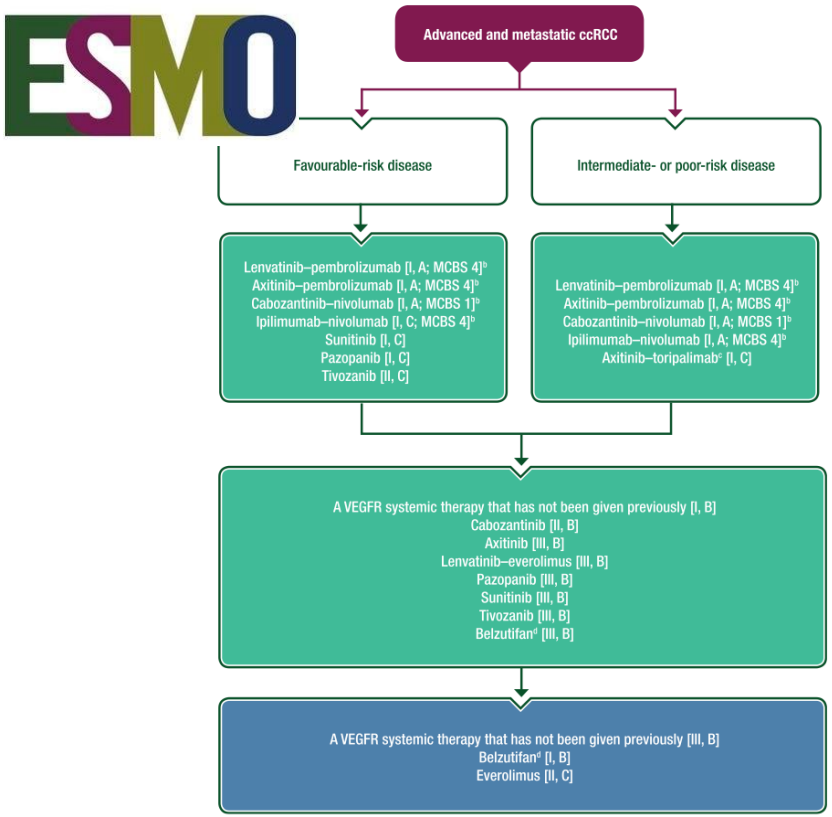
*Choueiri et al. ASCO GU 2024: 359

Therapeutische Landschaft des metastasierten Nierenzellkarzinoms



1. Motzer et al., ASCO, 2002. PMID: 11773181. 2. Motzer at al., J Clin Oncol, 2008. 3. Motzer et al., Cancer, 2022. PMID: 35383908. McKay et al., J Clin Oncol, 2018. PMID: 30372392. U.S. Food and Drug Administration

IO-Kombinationen sind Erstlinienstandards



Powles et al. Annals of Oncology (2024), doi: https://doi.org/10.1016/j.annonc.2024.05.537

Figure 7.1: Updated EAU Guidelines recommendations for the first-line treatment of cc-mRCC

	Standard of Care	Alternative in patients who can not receive or tolerate immune checkpoint inhibitors
IMDC favourable risk	Nivolumab/Cabozantinib [1b] Pembrolizumab/Axitinib [1b] Pembrolizumab/Lenvatinib [1b] Sunitinib [2b] Pazopanib [1b]	
IMDC intermediate and poor risk	Nivolumab/Cabozantinib [1b] Pembrolizumab/Axitinib [1b] Pembrolizumab/Lenvatinib [1b] nivolumab/Ipilimumab [1b]	Cabozantinib [2a] Sunitinib[1b] Pazopanib [1b]

Diagnosis Treatment Follow-up

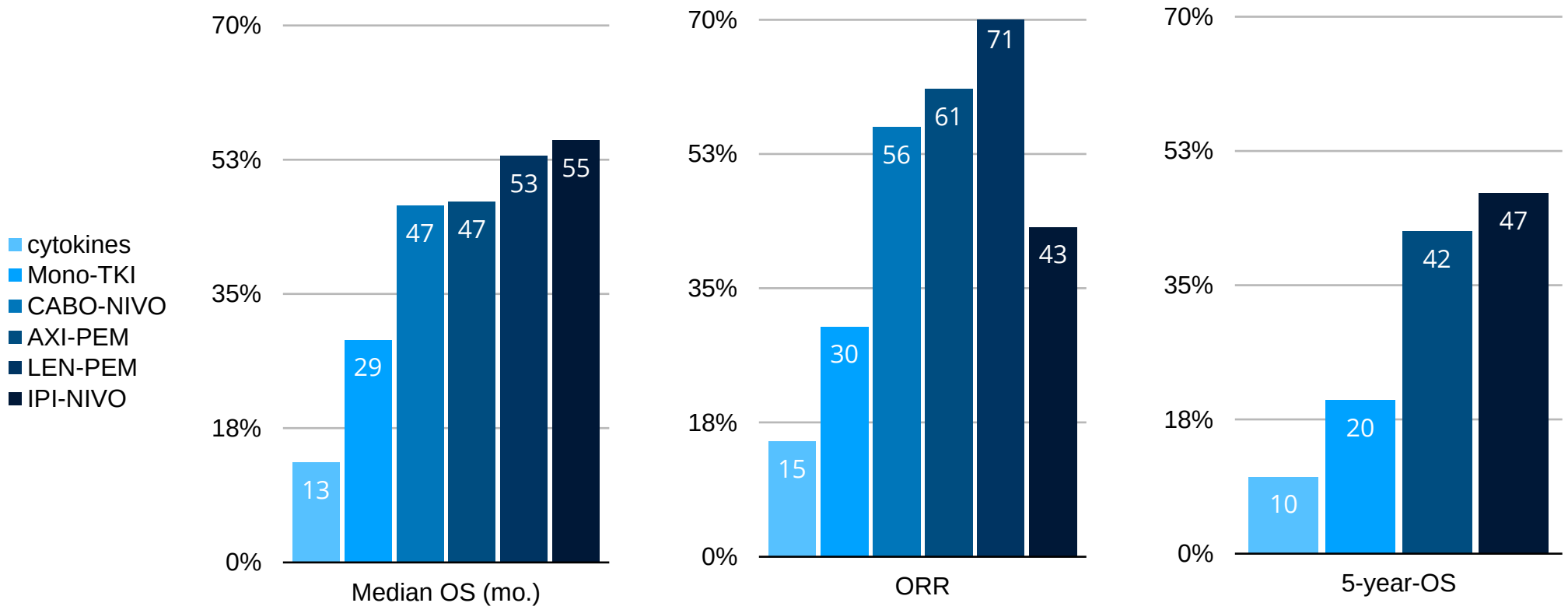
EAU Leitlinien Stand 2024

Das Ansprechen in der Erstlinie unterscheidet sich zwischen den Regimen

Follow-up
8y
34 mo
5y
20 mo
4.6y
4.2y

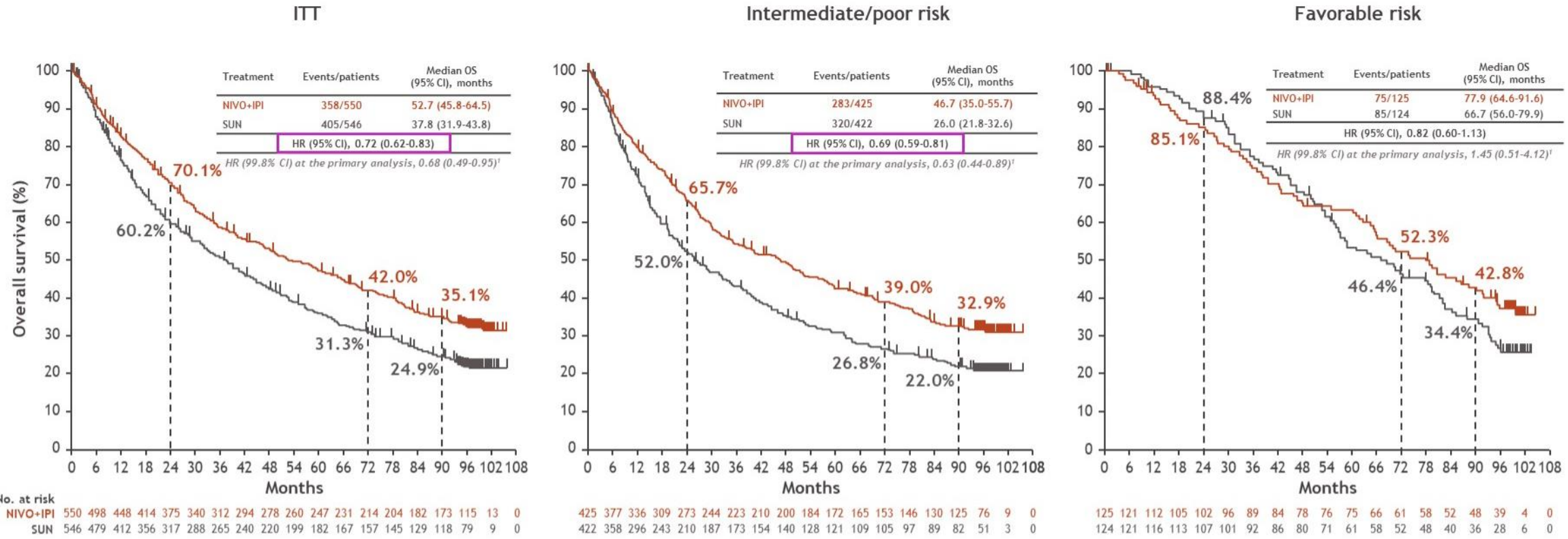
1. CLEAR: Hutson et al. ASCO 2023: 4502. 2. CM9ER: Bourlon et al. ASCO GU 2024: 362. 3. KN426: Rini et al. ASCO 2023: LBA4501. 4. CM214: Tannir et al. ASCO GU 2024: 363. 5. CPSMIC: Choueiri et al. DOI: 10.1056/NEJMoa2026982. 6. JR101: Tomita et al, ESMO Open 2023 DOI:https://doi.org/10.1016/j.esmoop.2023.102034

IO-Kombinationen sind der TKI Monotherapie überlegen



Coppin, C. *et al. Cochrane database of systematic reviews (Online)* (2005) doi:10.1002/14651858.cd001425.pub2. Motzer et al. *Journal of clinical oncology* 20, 289–296 (2002). Motzer RJ et al. *N Engl J Med* 2014;370:1769–1770. Motzer, R.J. et al. ESMO 2021: 661P. Hutson et al. ASCO Abstract 4502. Rini et al. ASCO 2023: LBA4501. Bourlon et al. ASCO GU 2024: 362

Ipilimumab + Nivolumab mit Langzeit-Ansprechen (8 Jahre Nachbeobachtung)



Tannir et al. ASCO GU 2024: 363

Meta-Netzwerk-Analyse für Erstlinienoptionen

Figure 4. PFS (FDA Censoring) Results – LEN + PEM vs. Other Treatments (ITT population, RE)

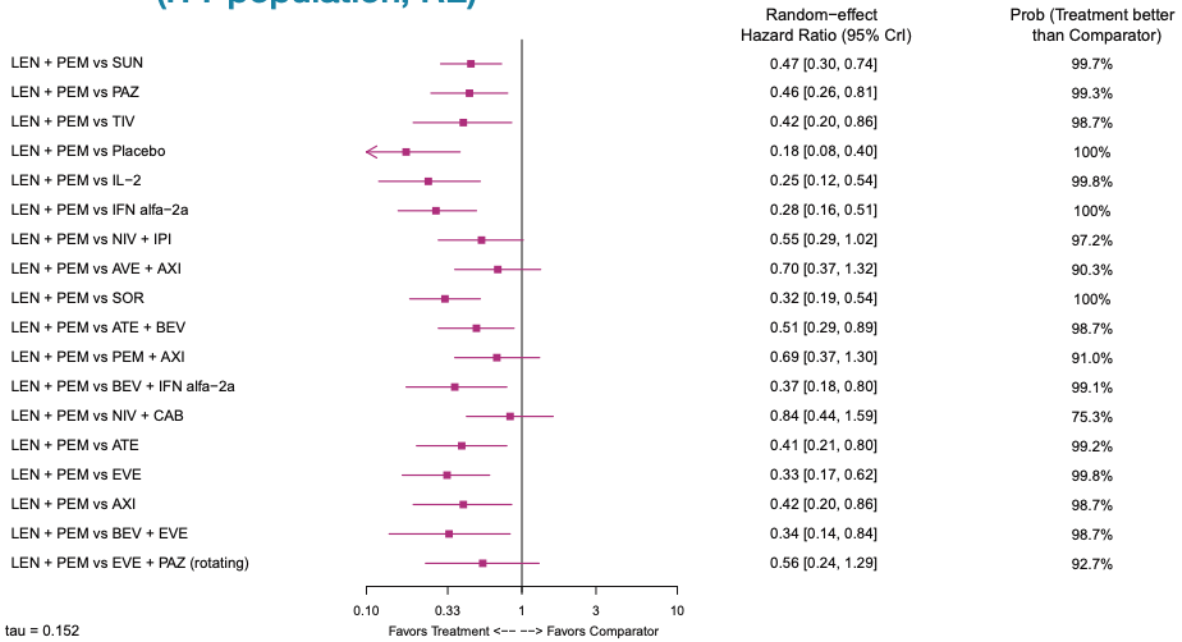
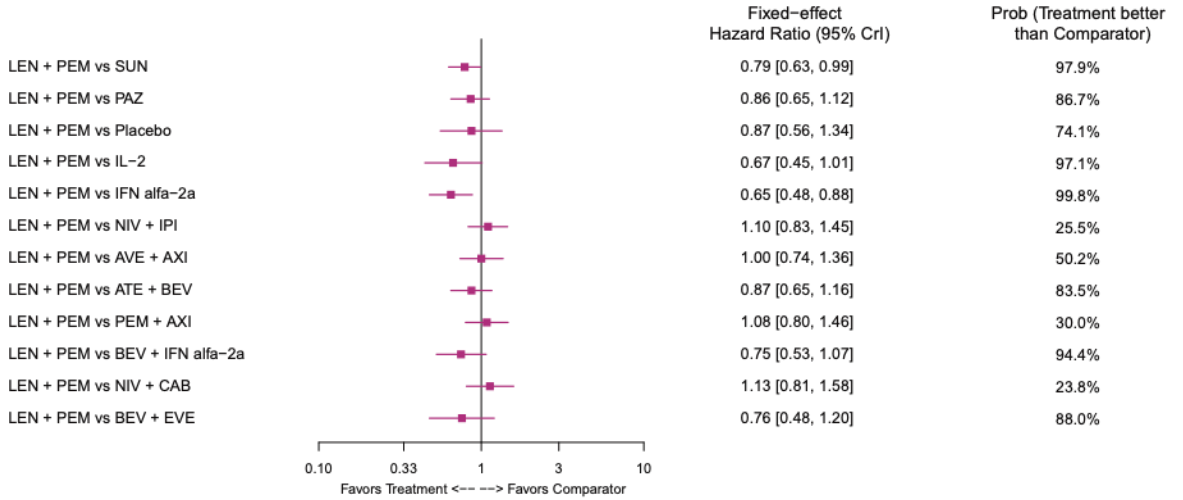


Figure 2. OS Results – LEN + PEM vs. Other Treatments (ITT population, FE)

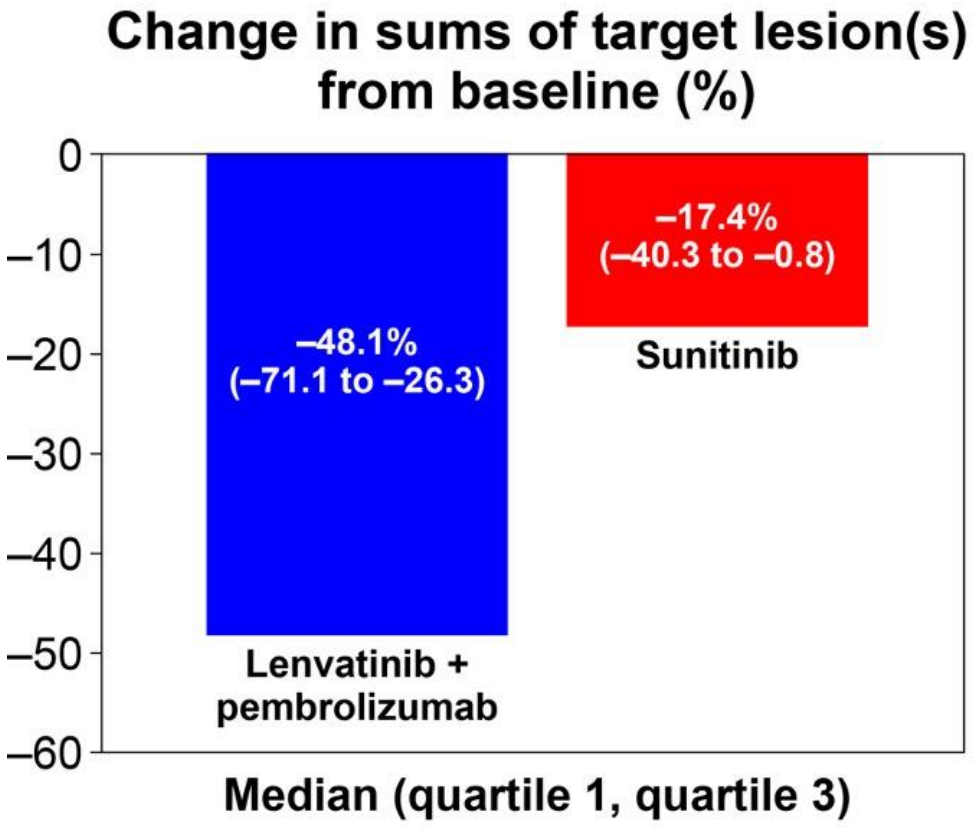


👉 Bestätigt Studiendaten. Ähnliches OS, aber Unterschiede in der Wirksamkeit

Inverse Probability of Treatment Weighting (IPTW)

Grünwald et al. ASCO GU 2024: 482

Patienten mit Progression nach LEN-PEM haben eine geringere Tumorlast



Reine 2. Linie	Lenvatinib + Pembrolizumab (n = 355)	**Sunitinib (n = 357)**
alle, Mo.	10.6 (3.7, NE)	10.9 (3.7, 35.8)
Cabozantinib, Mo.	13.2 (6.9, NE)	7.1 (4.1, 25.8)
Axitinib, Mo.	23.7 (5.3, NE)	12.6 (7.7, NE)

Grünwald et al. ASCO 24: 4524

Wirkt IO noch in der Folgetherapie?

nach adjuvanter IO Therapie

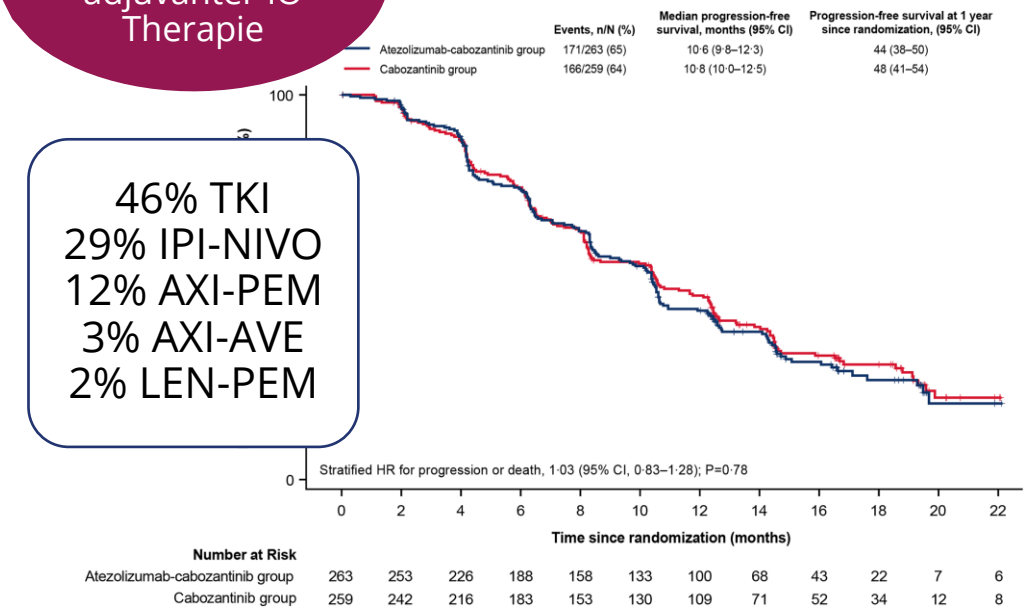
nach IO-IO in der 1. Linie

nach TKI-IO in der 1. Linie

TKI Monotherapie bleibt der Standard in der Folgetherapie

4 Patienten (<1%) nach adjuvanter IO Therapie

Cabozantinib +/- Atezolizumab

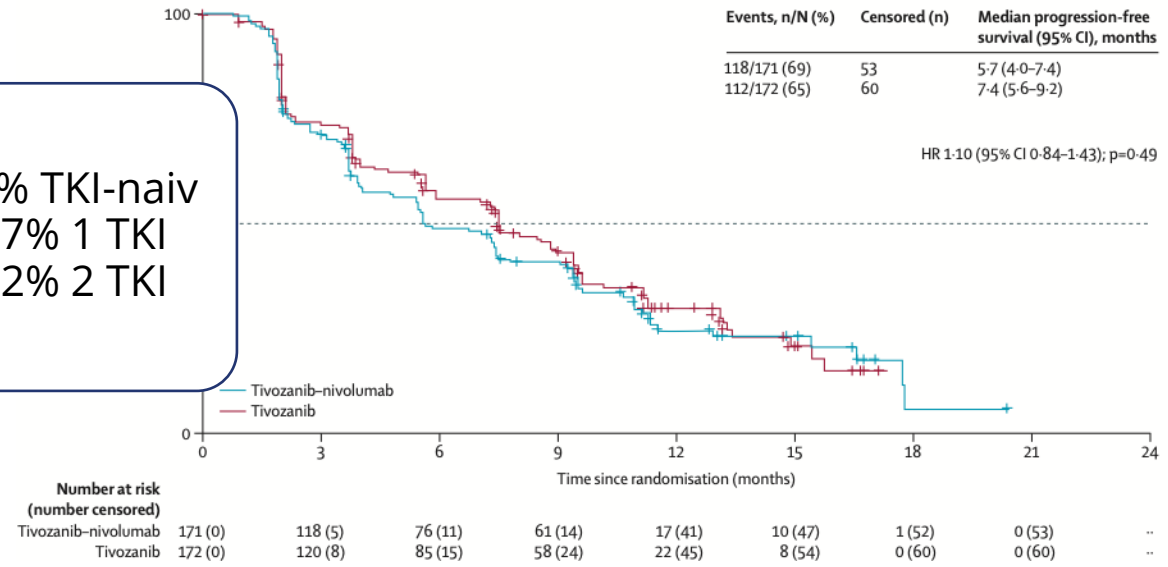


46% TKI
29% IPI-NIVO
12% AXI-PEM
3% AXI-AVE
2% LEN-PEM

Pal et al. Lancet. 2023 Jul 15; 402(10397): 185–195.

24 Patienten (14%) nach adjuvanter IO Therapie

Tivozanib +/- Nivolumab

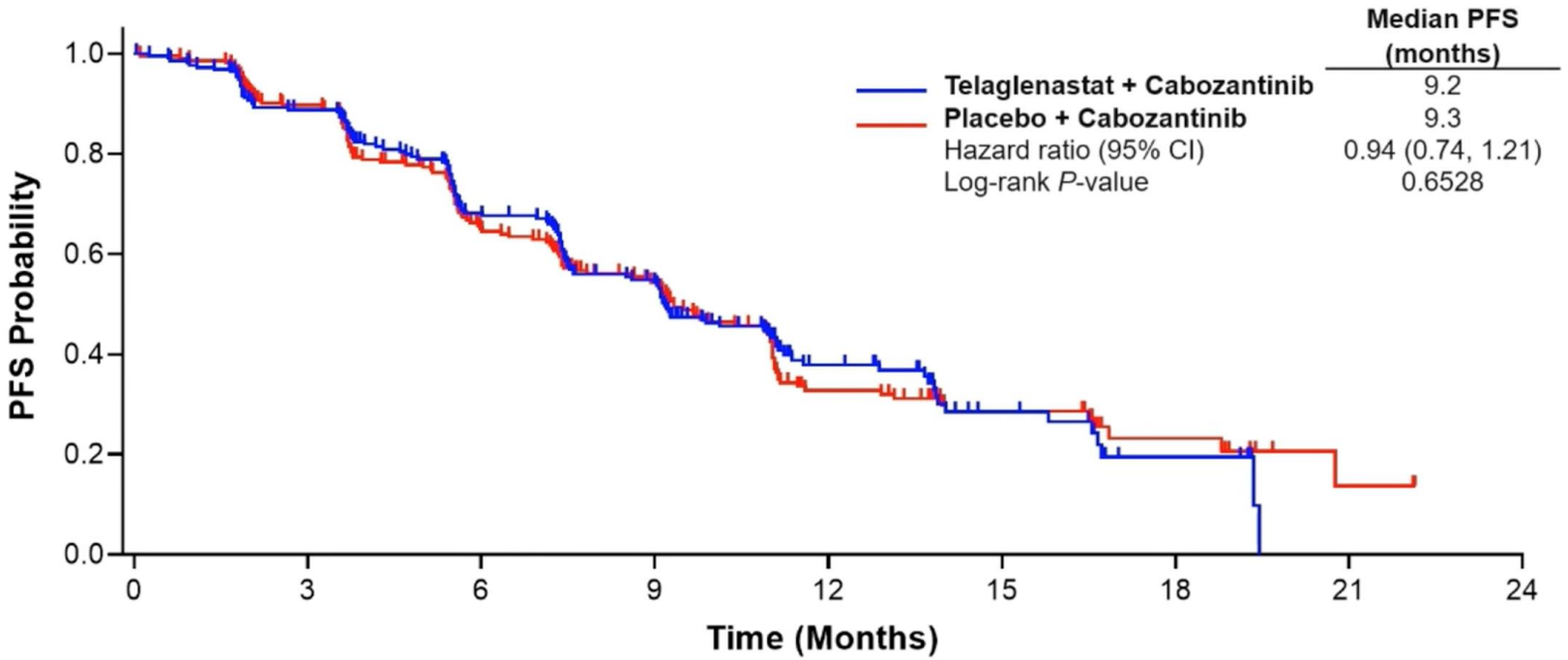


31% TKI-naiv
57% 1 TKI
12% 2 TKI

Choueiri et al. Lancet 2024 https://doi.org/10.1016/S0140-6736(24)01758-6

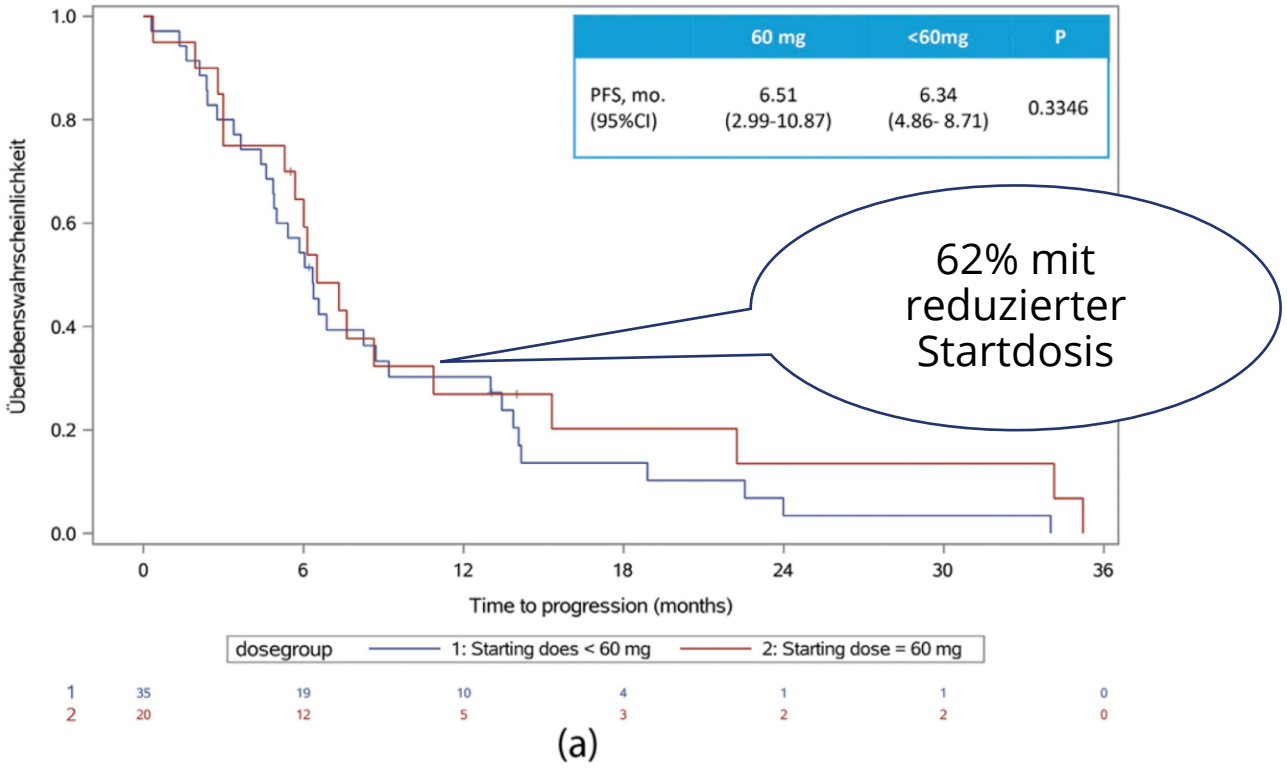
Metabolische Optimierung von Cabozantinib ohne Mehrwert in der Folgetherapie

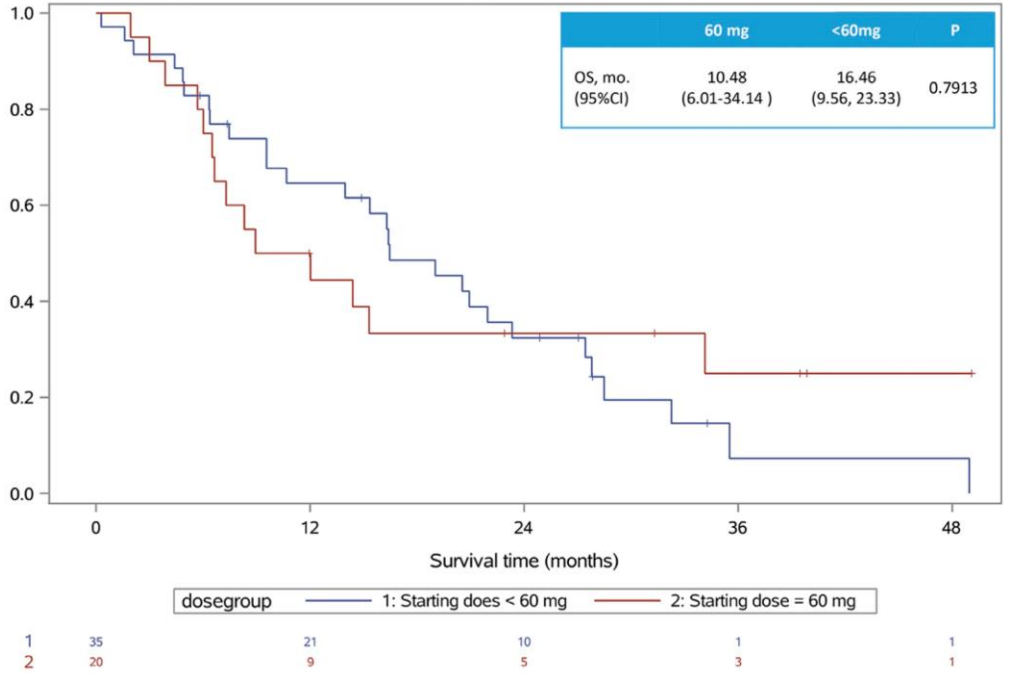
ccRCC
1-2 Vortherapien
62% post-IO



Tannir *et al.,* 4501 ASCO 21: CANTATA: Primary analysis of a global, randomized, placebo (Pbo)-controlled, double-blind trial of telaglenastat (CB-839) + cabozantinib versus Pbo + cabozantinib in advanced/metastatic renal cell carcinoma (mRCC) patients (pts) who progressed on immune checkpoint inhibitor (ICI) or anti-angiogenic therapies.

Dosierung von Cabozantinib im Alltag weicht von den Zulassungsstudien ab

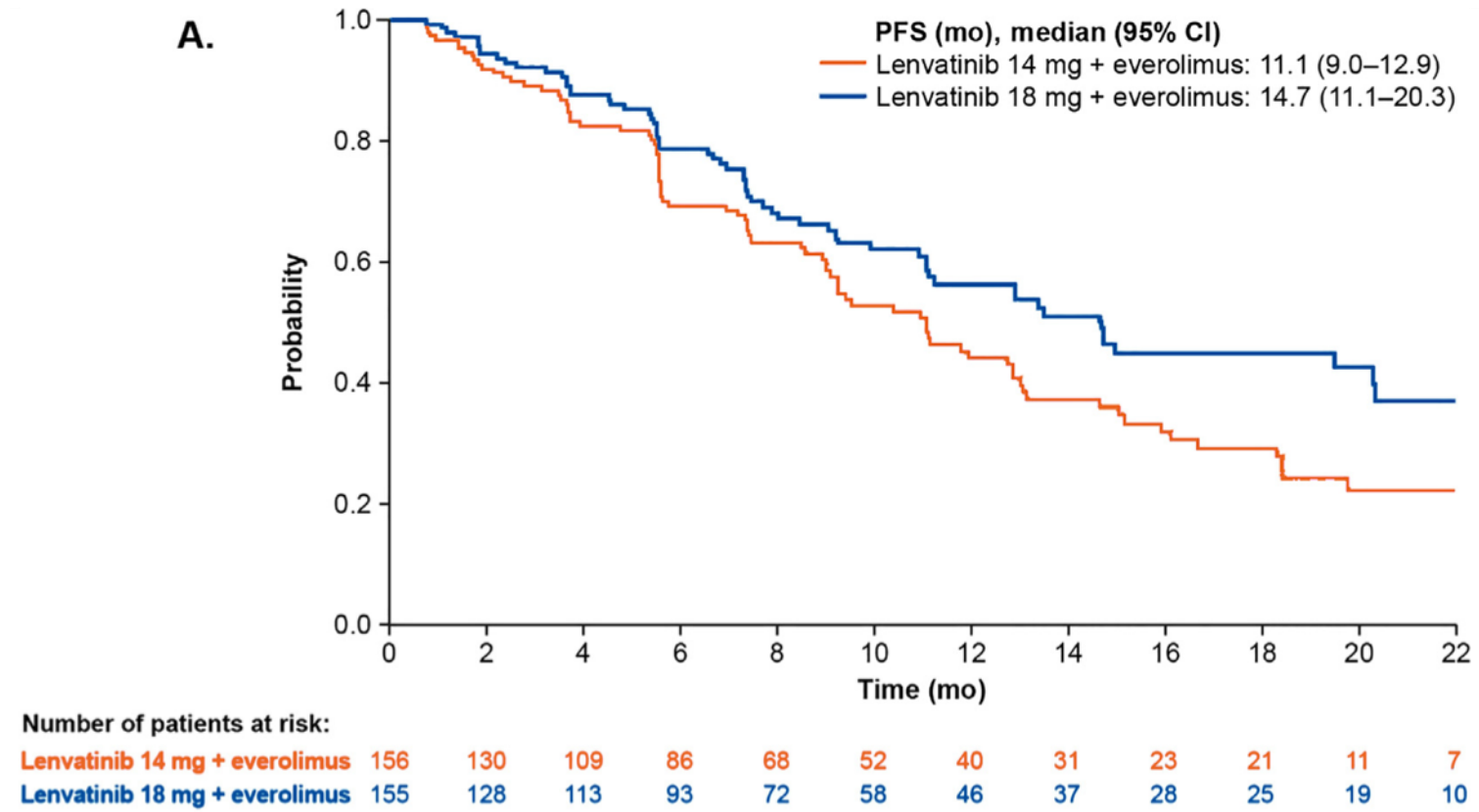




Grünwald et al. CCGU 2024 https://doi.org/10.1016/j.clgc.2024.102159

Lenvatinib + Everolimus - eine weitere Option nach Vorbehandlung

ccRCC
78% 1 prior therapy
26% post-IO



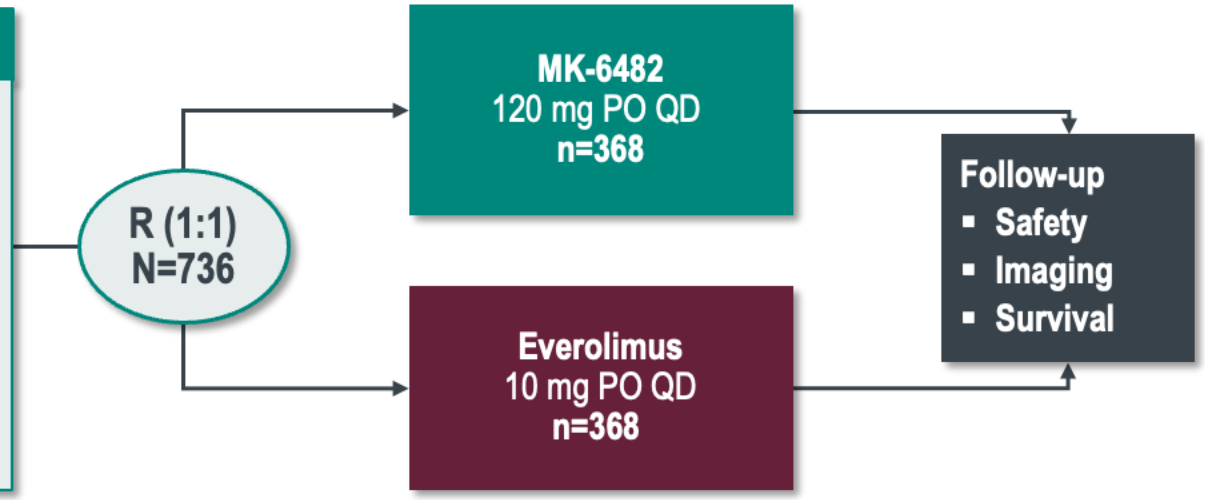
Pal et al. EUR UROL 2022: 283-292

NCT04195750 (LITESPARK-005): Study Design and Objectives[1,2]

Objectives: Phase 3 open-label randomized trial of 2L+ **belzutifan (MK-6482/PT2977)** vs everolimus in advanced ccRCC patients

Key Inclusion Criteria

- Age ≥18 years
- Unresectable, locally advanced or metastatic ccRCC
- Prior PD-1/PD-L1 checkpoint inhibitor and VEGF-targeted therapy, as monotherapy or in combination
- ≤3 prior systemic therapies
- Measurable disease per RECIST v1.1



Stratification Factors

- IMDC prognostic scores (0 vs 1 or 2 vs 3–6)
- Number of prior anti-VEGF–targeted therapies (1 vs 2 or 3)

Dual Primary End Points

- PFS (RECIST v1.1, BICR) in ITT
- OS

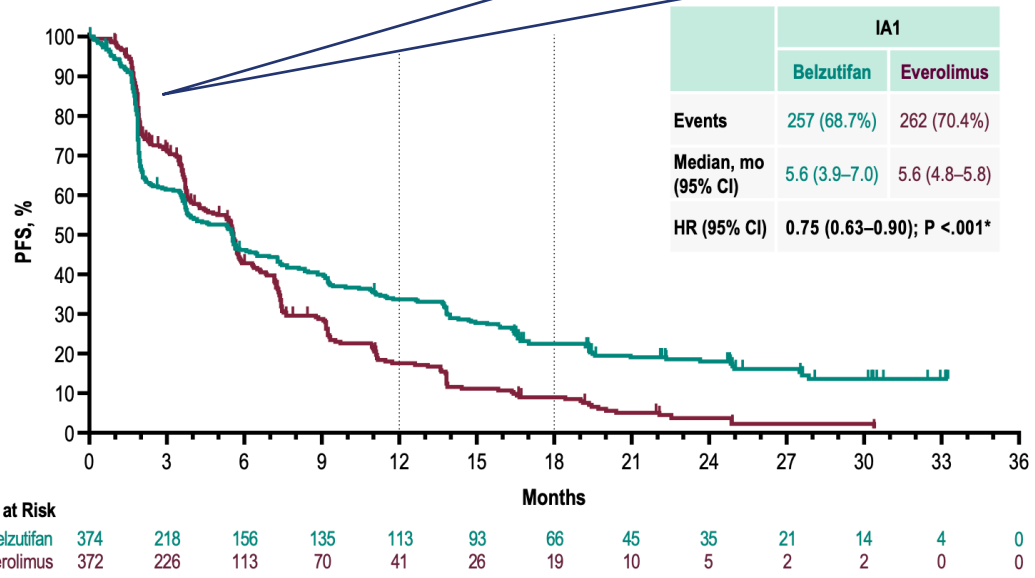
Secondary End Points

- ORR (RECIST v1.1, BICR) in ITT
- DOR (RECIST v1.1, BICR) in ITT
- PROs
- Safety and tolerability

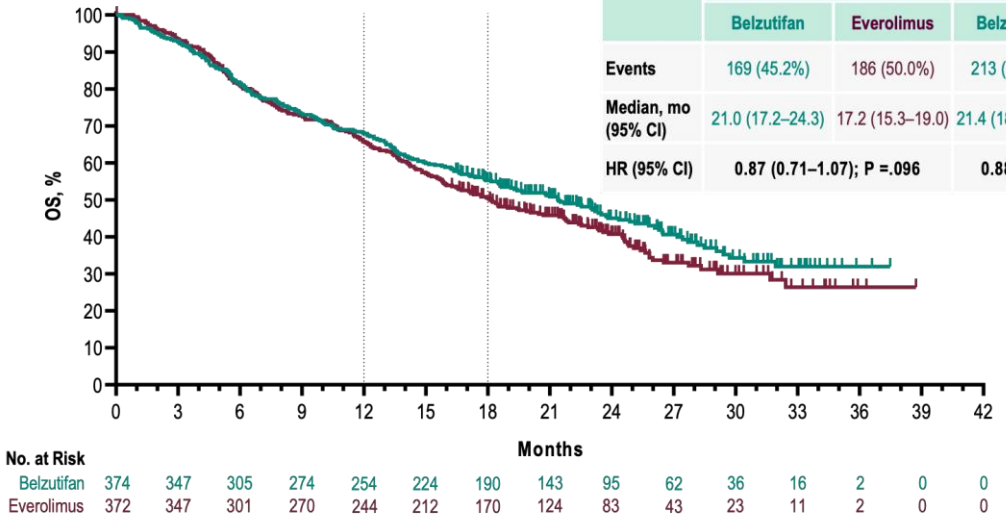
1. Choueiri TK et al. Presented at ASCO 2020. 2. https://clinicaltrials.gov/ct2/show/NCT04195750 Accessed 21 December 2021.

Der HIF-Inhibitor Belzutifan mit PFS Vorteil gegenüber Everolimus in späten Therapielinien

>80% in 3./4. line



	IA1	
	Belzutifan	Everolimus
Events	257 (68.7%)	262 (70.4%)
Median, mo (95% CI)	5.6 (3.9–7.0)	5.6 (4.8–5.8)
HR (95% CI)	0.75 (0.63–0.90); P <.001*	



	IA1		IA2	
	Belzutifan	Everolimus	Belzutifan	Everolimus
Events	169 (45.2%)	186 (50.0%)	213 (57.0%)	228 (61.3%)
Median, mo (95% CI)	21.0 (17.2–24.3)	17.2 (15.3–19.0)	21.4 (18.2–24.3)	18.1 (15.8–21.8)
HR (95% CI)	0.87 (0.71–1.07); P =.096		0.88 (0.73–1.07); *P* =.099	

Albiges et al. ESMO 2023: LBA87

Aktuelle Phase 3 Studien in reiner 2. Linie nach IO-Kombination

NCT04586231 (LITESPARK-011): Study Design and Objectives[1]

Objectives: Phase 3 randomized trial to compare the efficacy and safety of **belzutifan (MK-6482)** with lenvatinib vs cabozantinib for 2L or 3L treatment in advanced ccRCC

Key Inclusion Criteria (N=708)

- Unresectable, locally advanced or metastatic clear cell RCC
- Disease progression on or after having received systemic treatment for locally advanced or metastatic RCC with PD-1/L1
- Measurable disease per RECIST 1.1 criteria as assessed by local study investigator
- Karnofsky performance status (KPS) score of at least 70% assessed within 10 days prior to the first dose of study intervention
- Received no more than 2 prior systemic regimens for locally advanced or metastatic RCC
- Received only 1 prior anti-PD-1/L1 therapy for locally advanced or metastatic RCC

R

- **Belzutifan (MK-6482) 120 mg + Lenvatinib 20 mg orally QD**
- **Cabozantinib 60 mg orally QD**

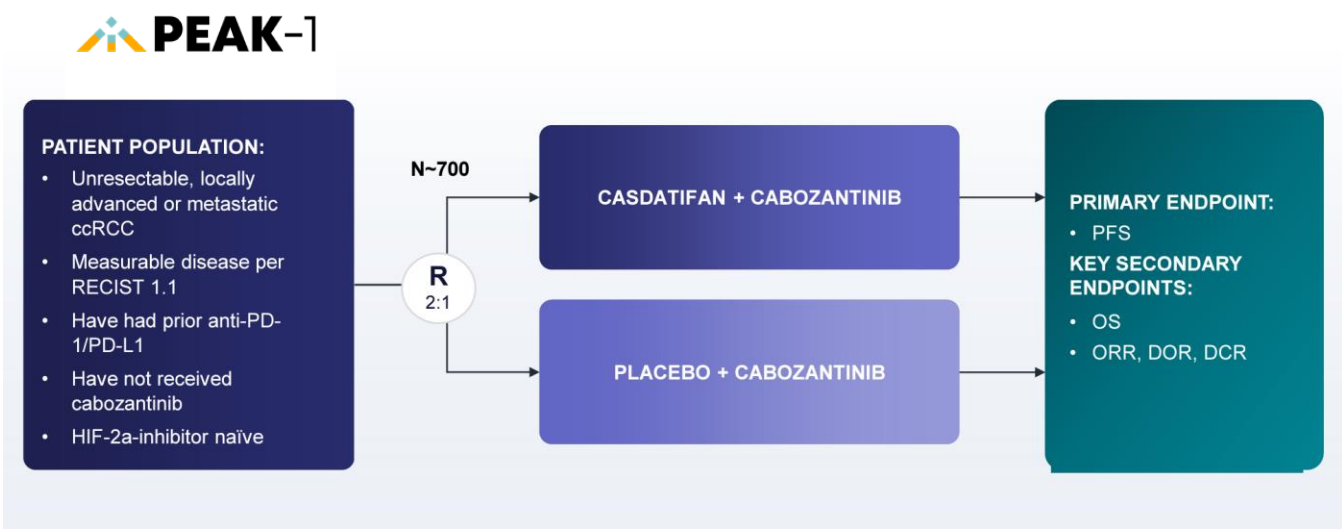
Primary End Points

- PFS (RECIST v1.1, BICR)
- OS

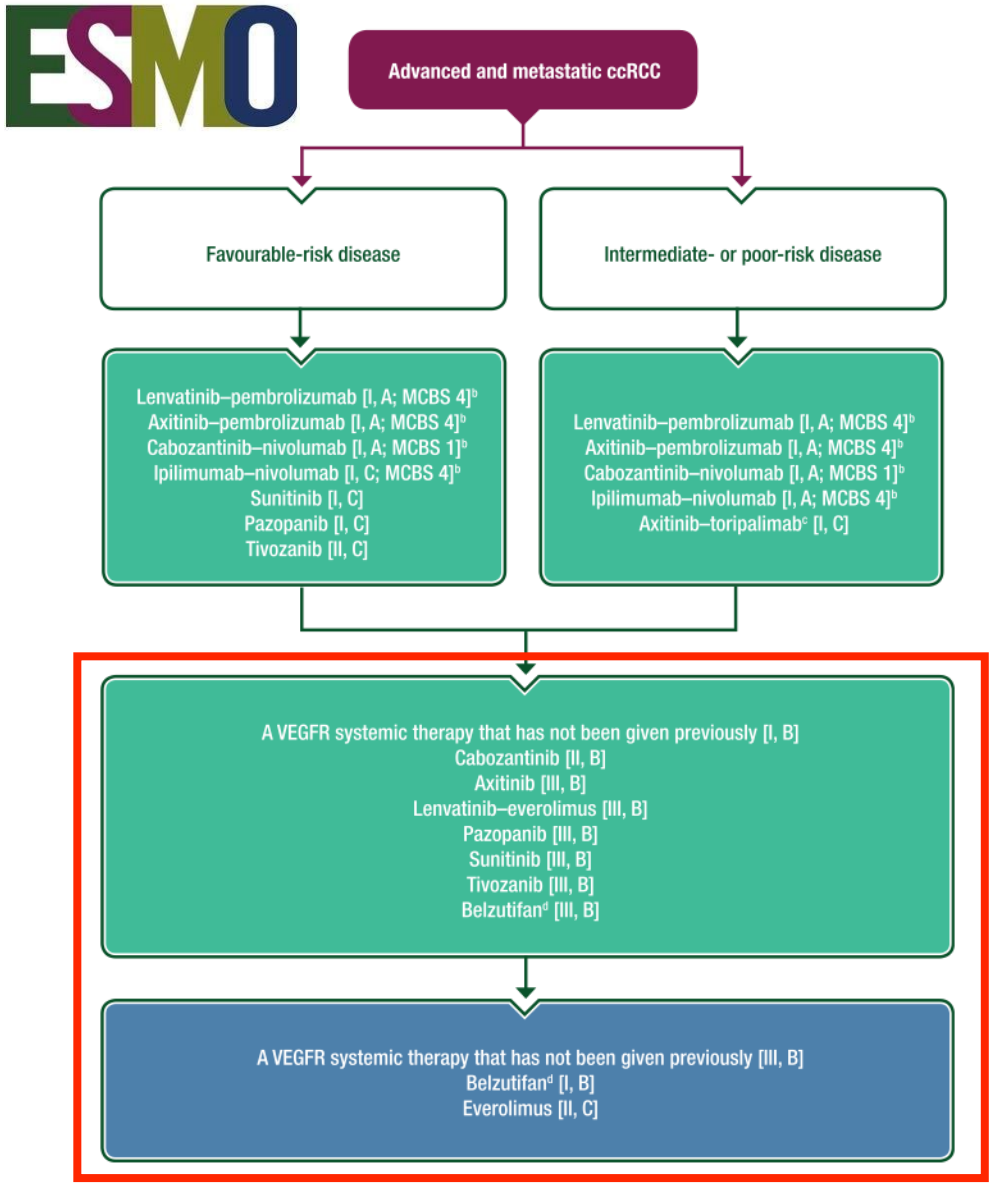
Secondary End Points

- ORR (RECIST v1.1, BICR)
- DOR (RECIST v1.1, BICR)
- Safety and tolerability

1. https://clinicaltrials.gov/ct2/show/NCT04586231. Accessed 21 December 2021.



Arcus corporate presentation 8th August 2024



Aktuelle Empfehlungen

2. Linie:
TKI-basierte Therapie

3. Linie:
mTORi oder HIF2i

Powles et al. Annals of Oncology (2024), doi: https:// doi.org/10.1016/j.annonc.2024.05.537

Fazit

Adjuvante Therapie mit Pembrolizumab ist der Standard

Folgetherapie nach Versagen der Adjuvanz noch undefiniert

2. Linientherapien bleibt TKI-basiert

Vielen Dank!

Prof. Dr. med. Viktor Grünwald

Interdisciplinary GU Oncology

University Hospital Essen

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