



Universitätsmedizin Essen
Universitätsklinikum

Behandlung des metastasierten Nierenzellkarzinoms: Leitlinien und Entscheidungskriterien

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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

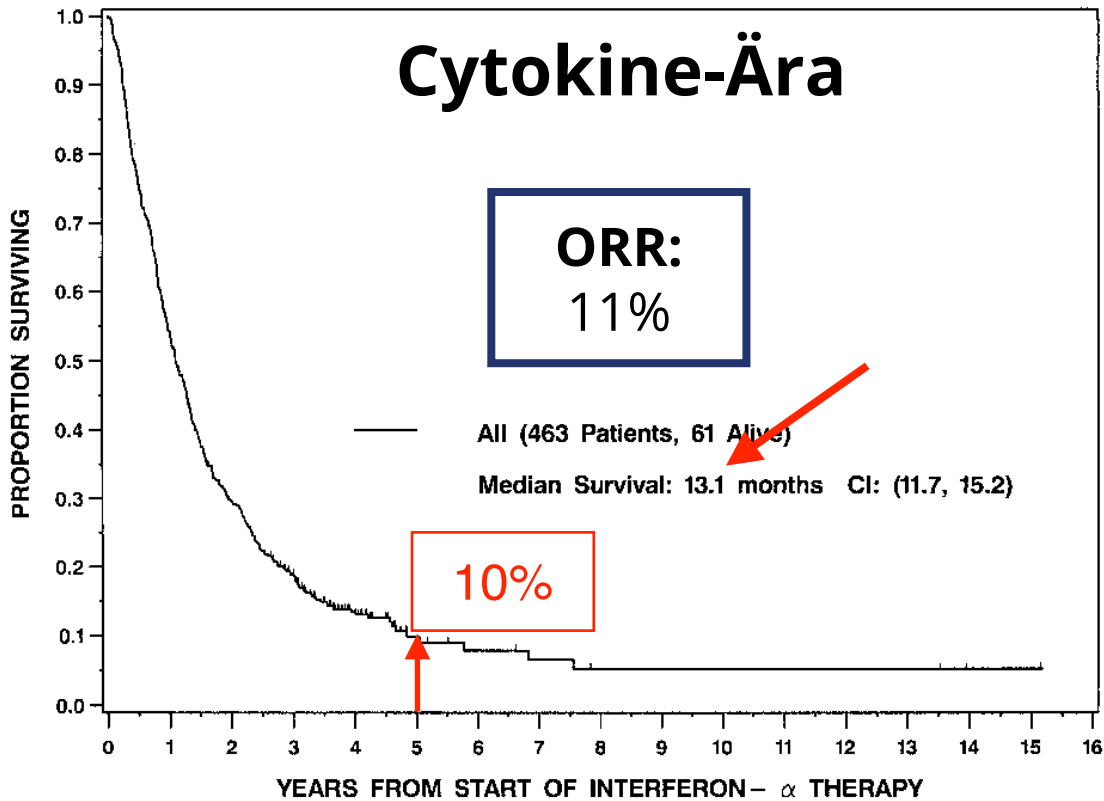
Non-Financial Interests

Membership: ASCO, ESMO, German medical Oncology and Hematology Society

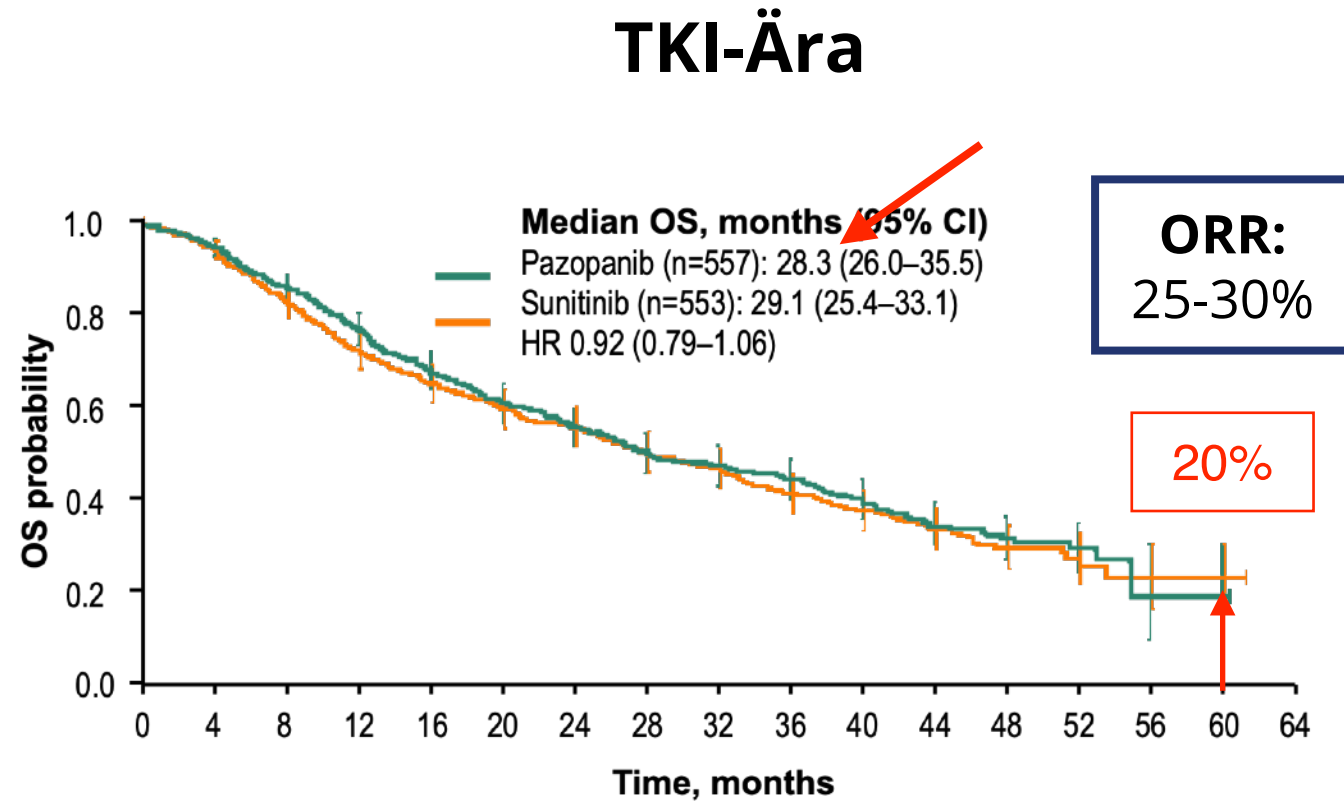
Advisory role: German Cancer Society

Leadership role: Working Group medical oncology (AIO)

TKI Therapien verbesserten das OS in den frühen 2000er

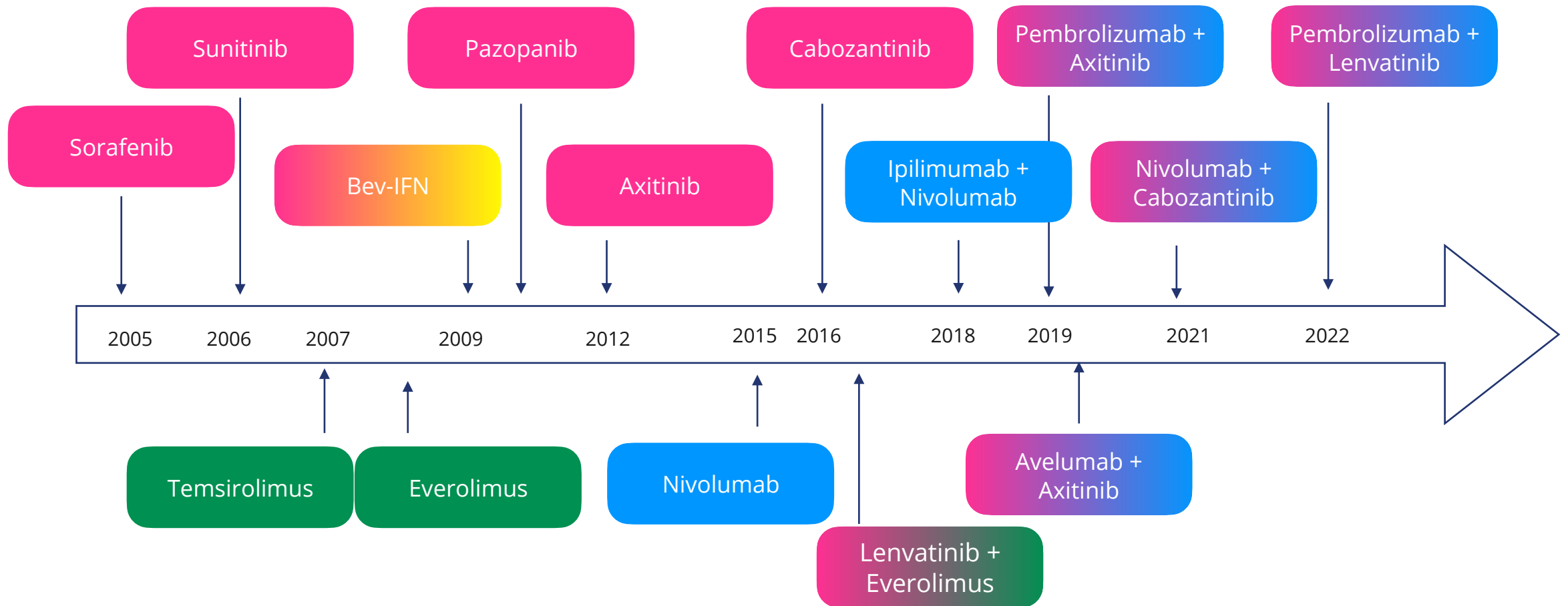


Motzer et al. *Journal of clinical oncology* **20**, 289–296 (2002).



Motzer RJ et al. *N Engl J Med* 2014;370:1769–1770.

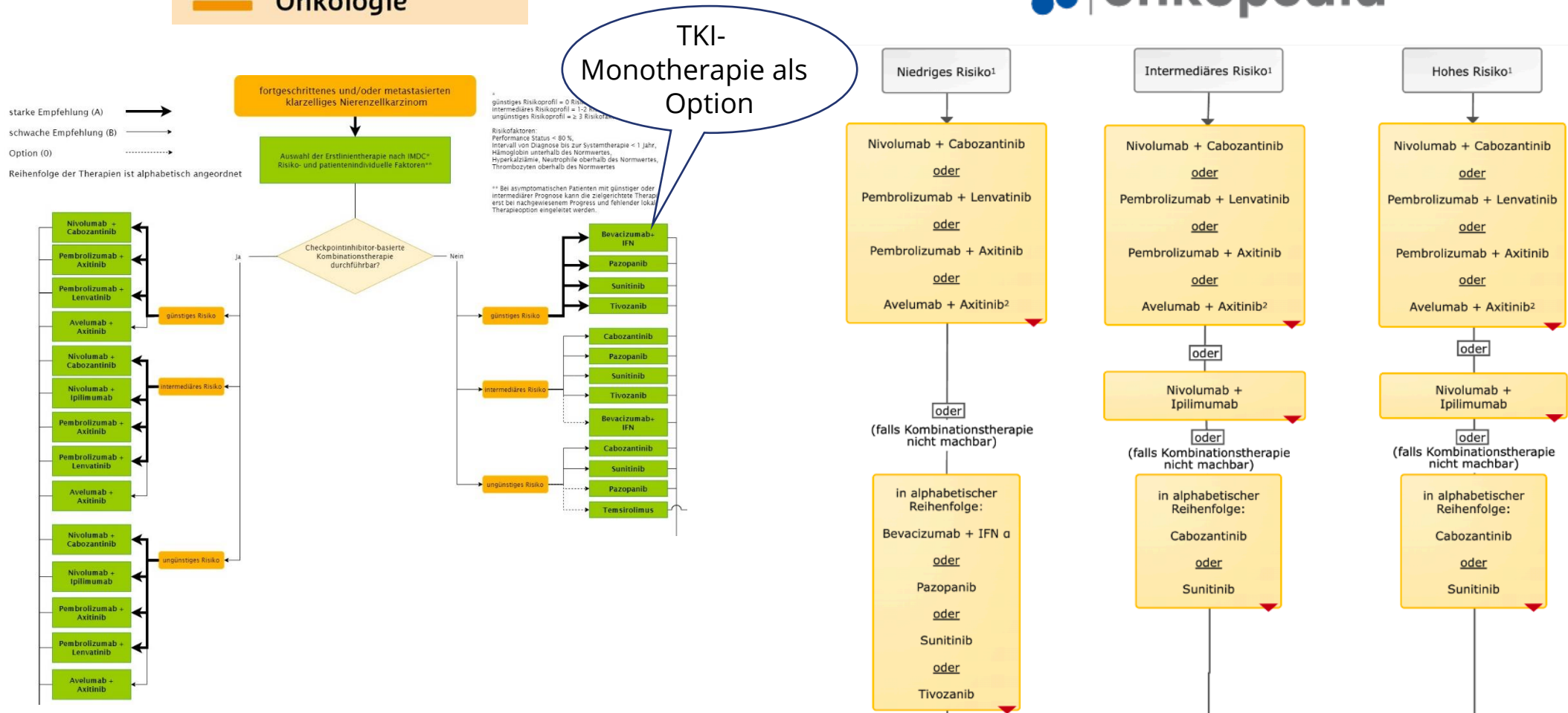
Die heutige Therapielandschaft ist wesentlich bunter



■ VEGFi ■ ICI
■ Cytocines ■ mTORi

Leitlinien empfehlen IO-Kombinationstherapie

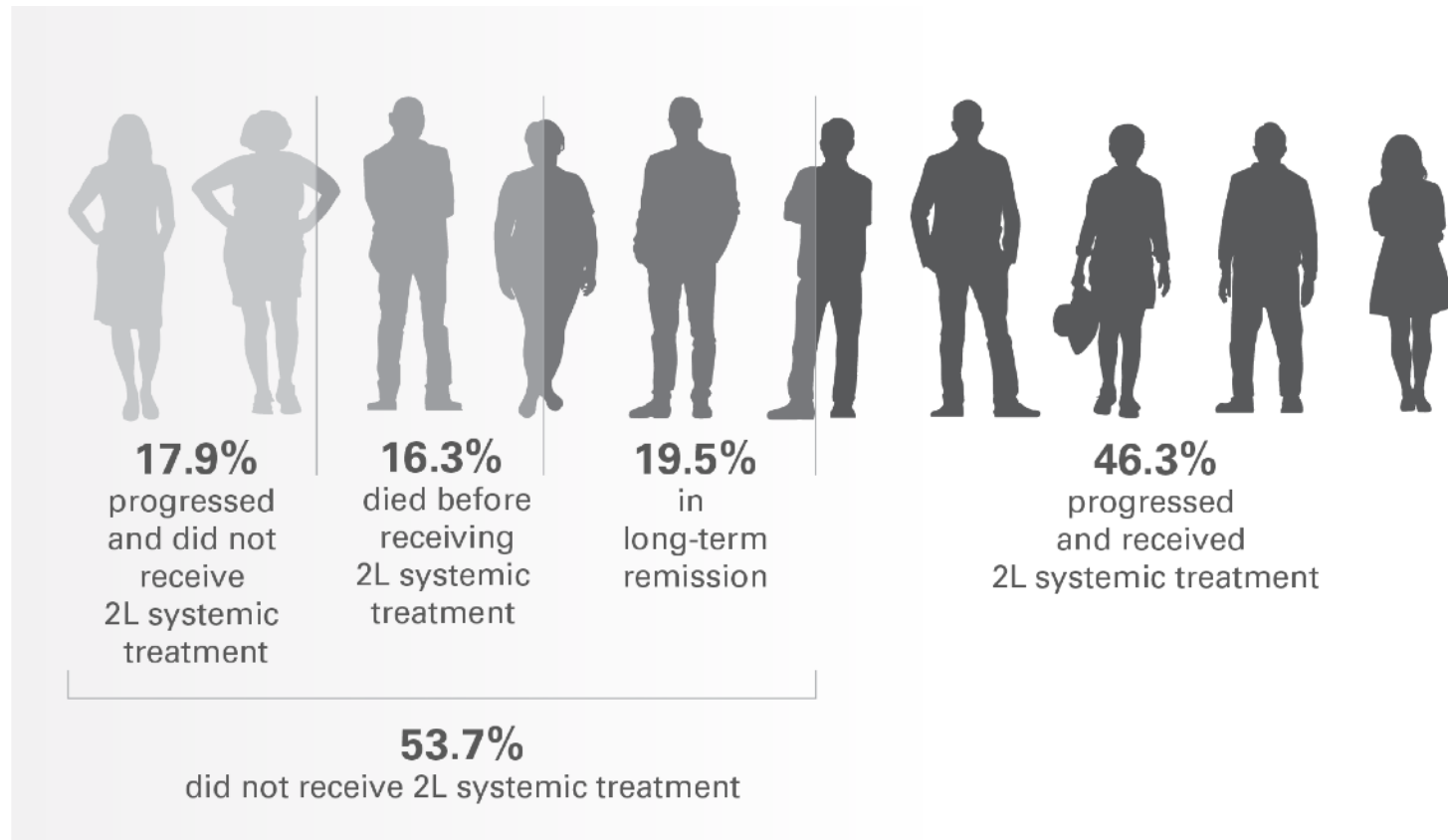
Leitlinienprogramm
Onkologie



Warum sind Kombinationen so erfolgreich?

>50% der Patient:innen erhalten im Alltag keine Folgetherapie

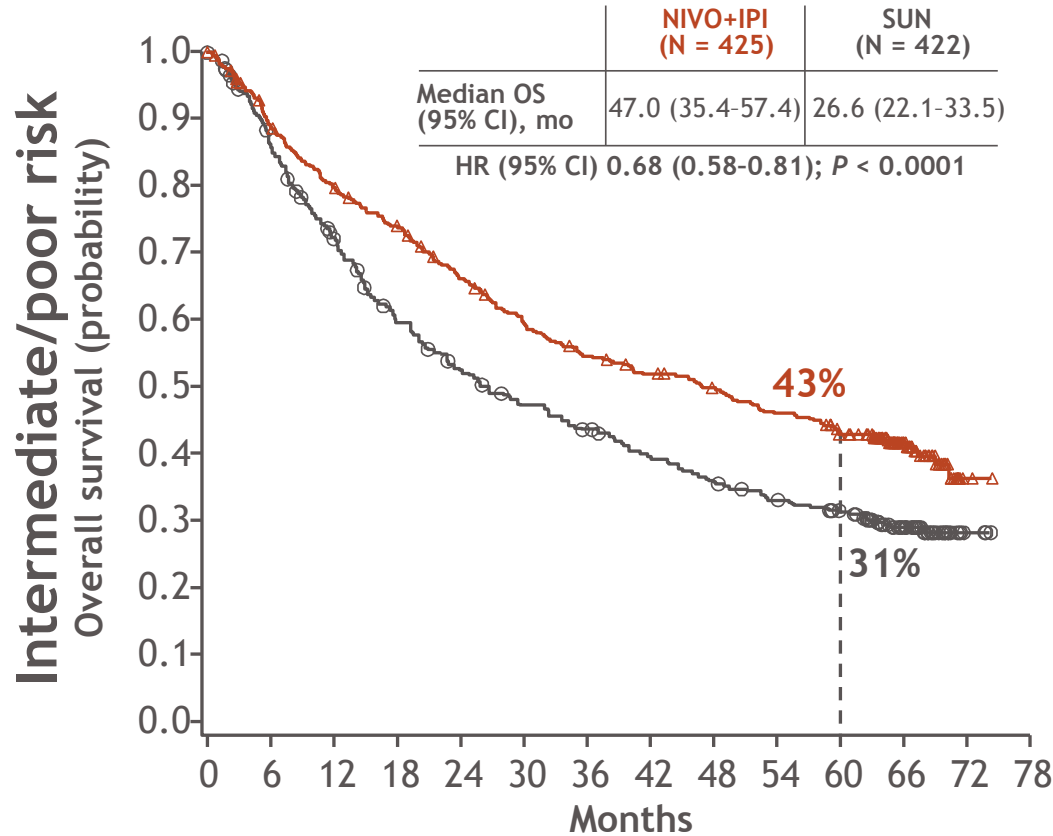
Survey among 103 physicians who treated overall 4.509 patients in 5 European countries^a in 2020¹.



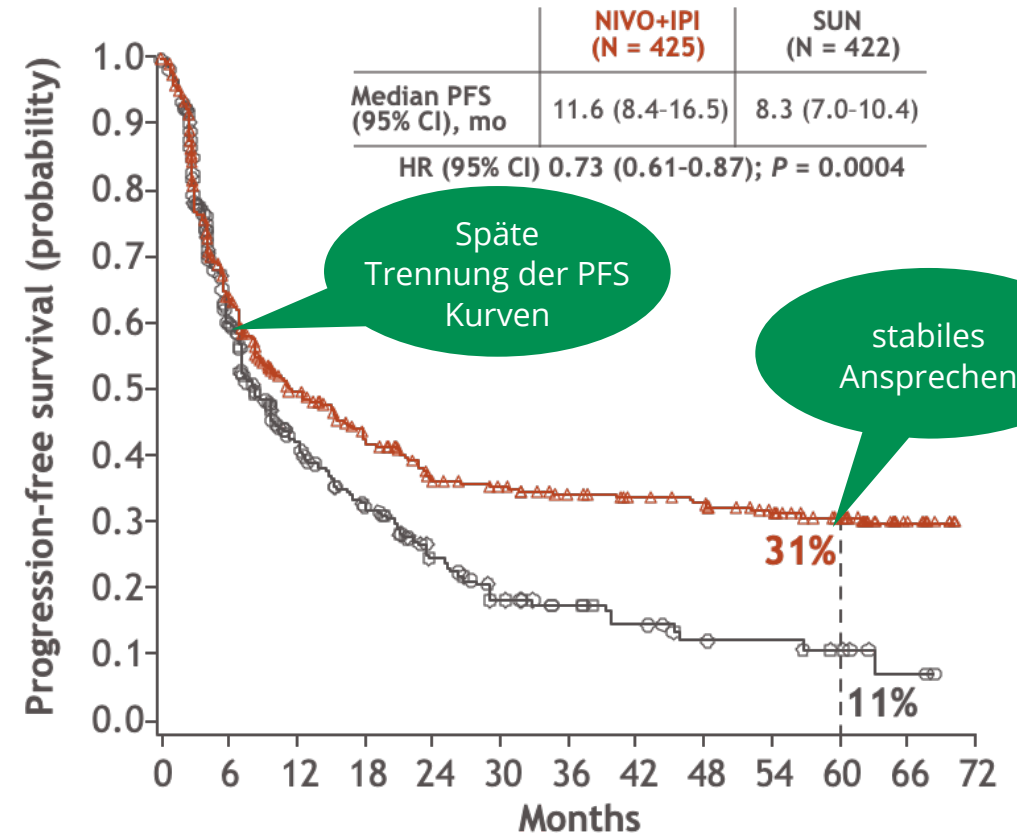
^aFrance, Germany, Italy, Spain, United Kingdom.
2L, second-line; RCC, renal cell carcinoma.

1. Kantar Health, Treatment Architecture: Renal Cell Carcinoma. Cancer Mpac[®]. EU5. 2020;1[7]89.

Ipilimumab + Nivolumab ist die erste Studie mit reifem 5-Jahres OS (nur Pts. ≥ 1 Riskofaktor gezeigt)

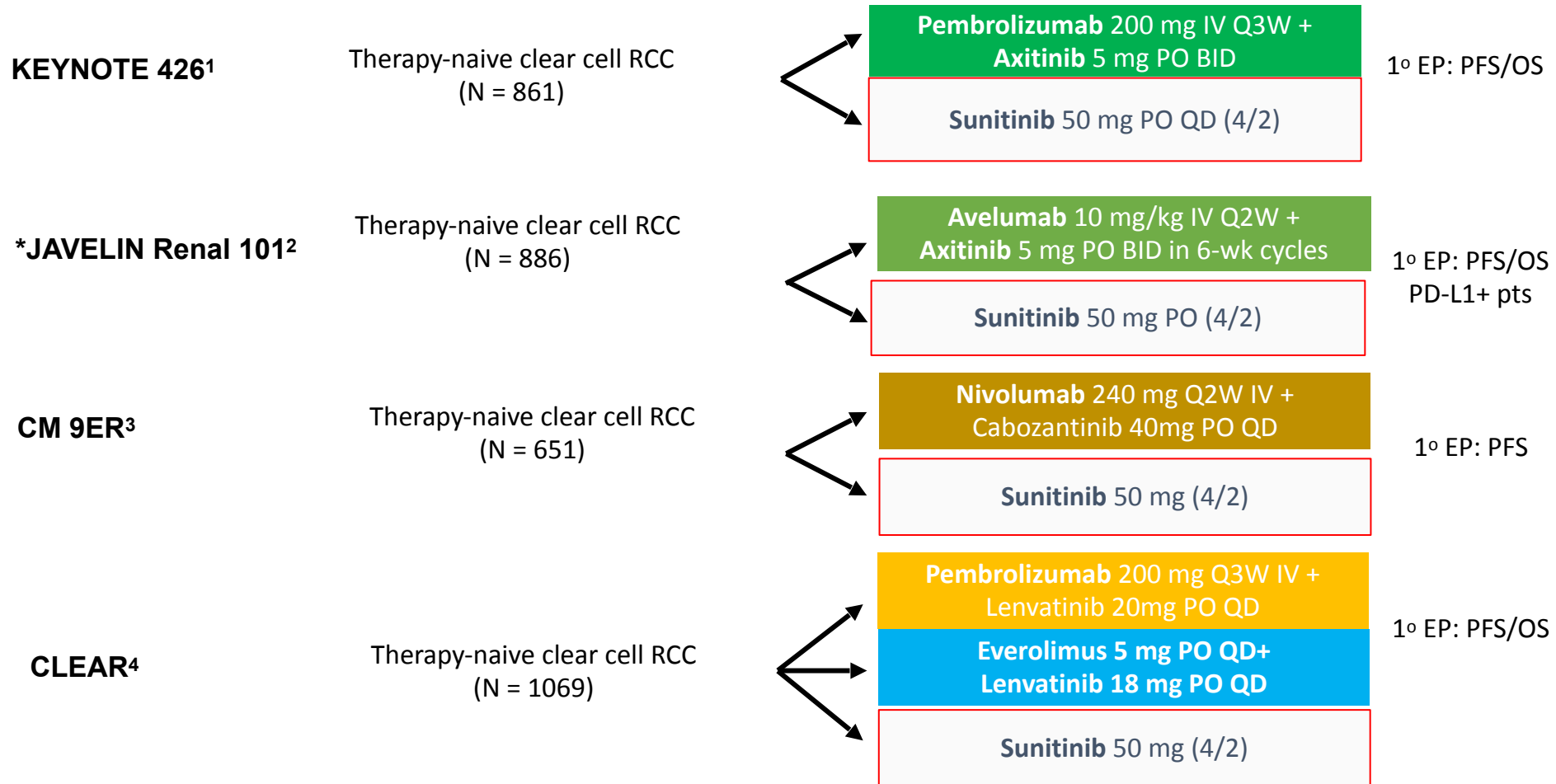


No. at risk		425	372	332	306	270	241	220	207	196	181	163	79	2	0
NIVO+IPI		425	372	332	306	270	241	220	207	196	181	163	79	2	0
SUN		422	353	291	237	206	184	169	151	137	125	112	58	3	0



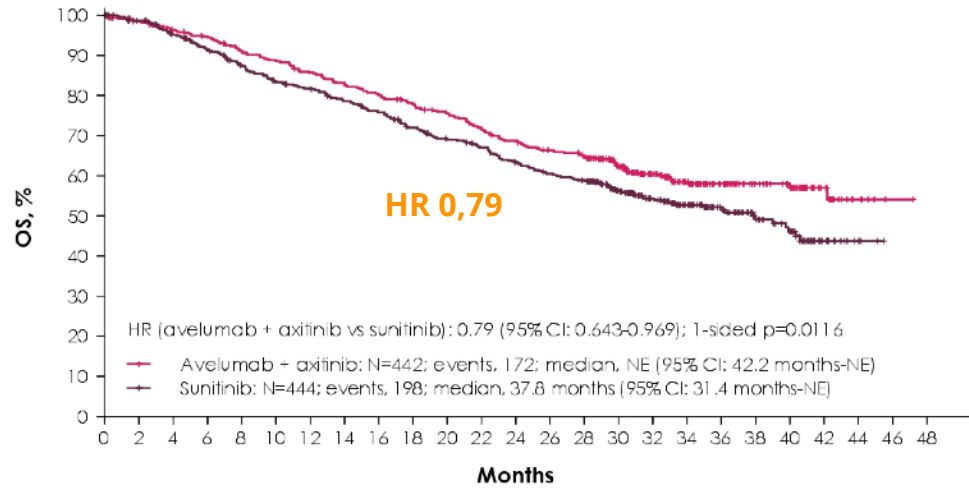
No. at risk		425	233	164	130	101	94	81	74	70	60	48	10	0
NIVO+IPI		425	233	164	130	101	94	81	74	70	60	48	10	0
SUN		422	188	106	74	46	29	21	15	10	9	6	2	0

Design der zugelassenen TKI-IO Kombinationstherapien



*without significant OS benefit

Axitinib + Avelumab

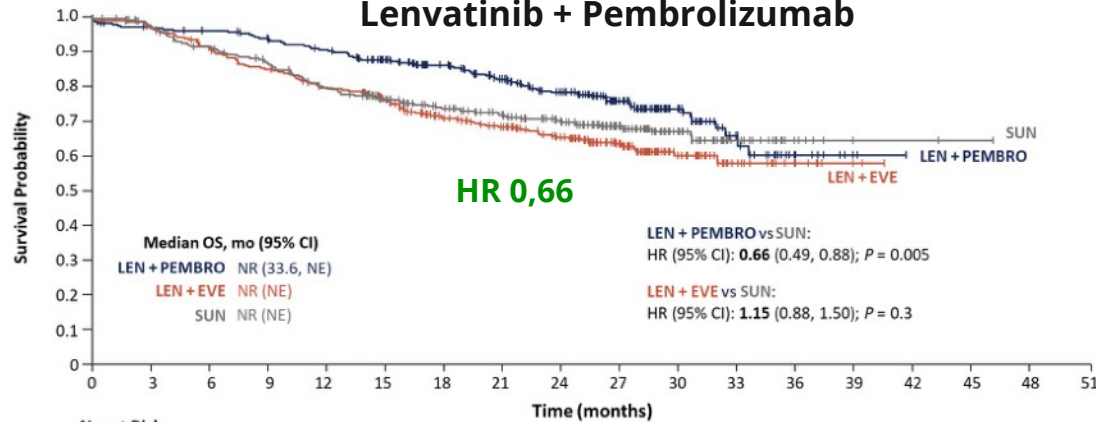


No. at risk

Avelumab + axitinib	442	425	411	402	386	375	362	349	339	327	315	300	286	273	263	223	168	133	92	66	54	22	7	1	0
Sunitinib	444	428	407	387	366	346	338	322	309	290	275	265	250	237	230	184	143	113	79	57	45	15	4	0	0

Haanen J, et al. 2021 ASCO.:4574.

Lenvatinib + Pembrolizumab



No. at Risk

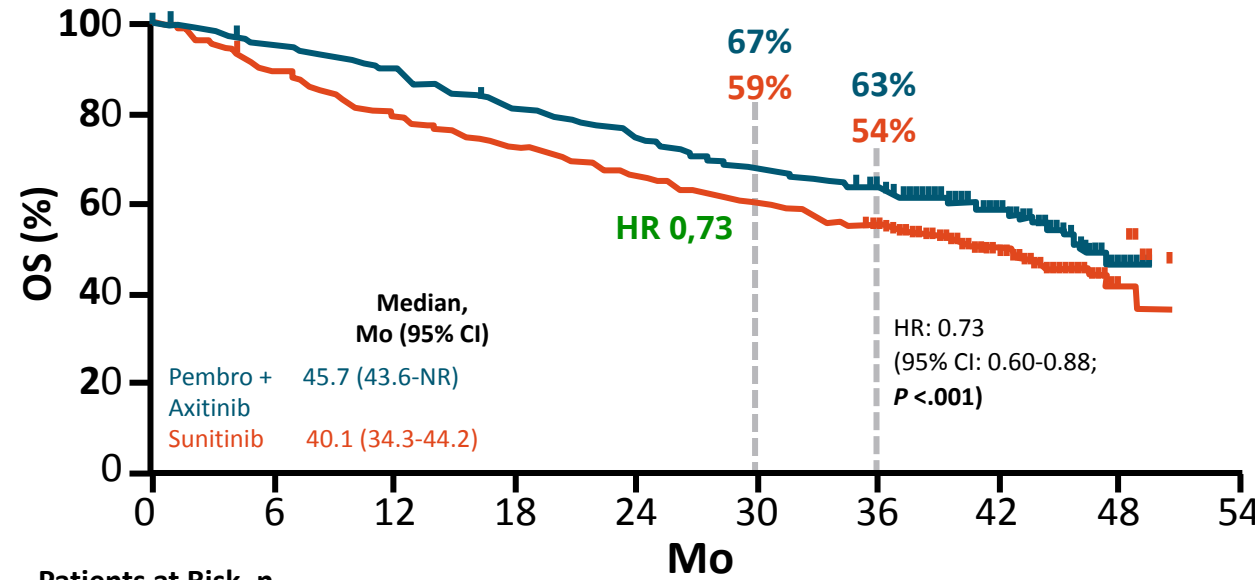
LEN + PEMBRO	355	342	338	327	313	280	253	222	188	129	66	26	10	2	0		
LEN + EVE	357	346	321	299	277	246	205	183	154	109	46	22	8	2	0		
SUN	357	332	307	289	264	236	207	186	160	112	60	25	7	2	2	1	0

IE, not estimable; NR, not reached.

269 Motzer et al. ASCO GU 2021

in the absence of head-to-head studies, cross trial comparisons cannot be made as the trials differ in design, size, time period of recruitment, location of study sites etc.

Axitinib + Pembrolizumab

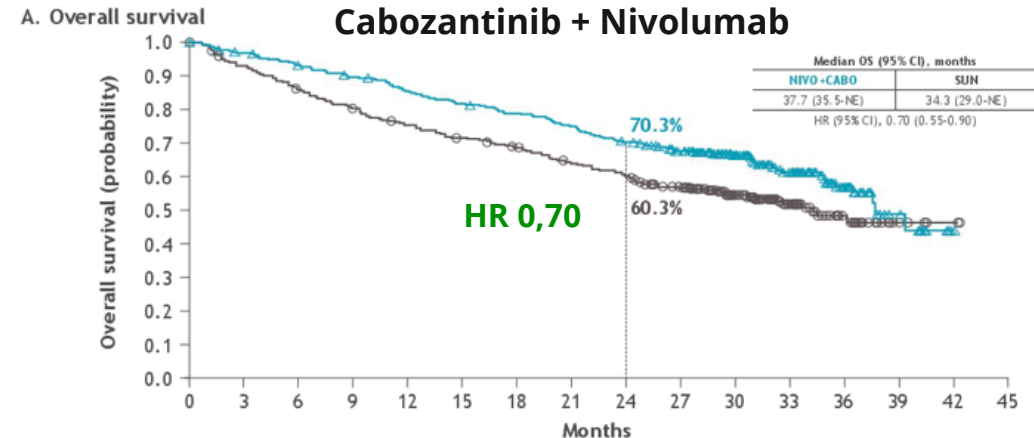


Patients at Risk, n

Mo	0	6	12	18	24	30	36	42	48	54
Pembro + Axitinib	432	407	384	345	318	286	259	141	16	0
Sunitinib	429	379	336	306	279	252	252	110	12	0

Rini. ASCO 2021. Abstr 4500.

Cabozantinib + Nivolumab

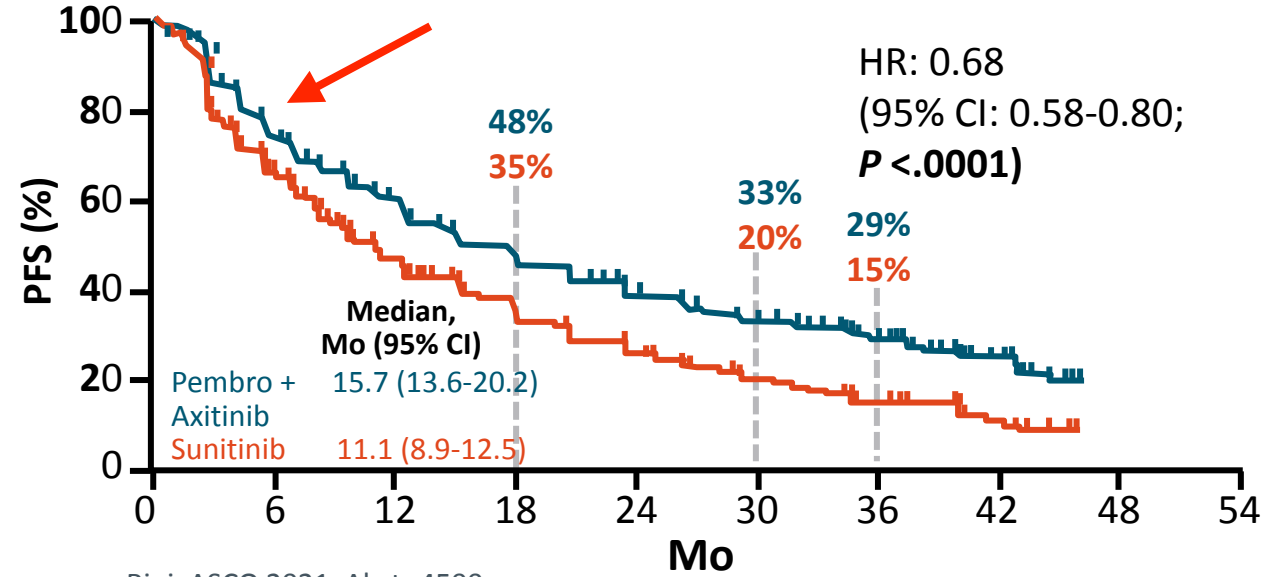
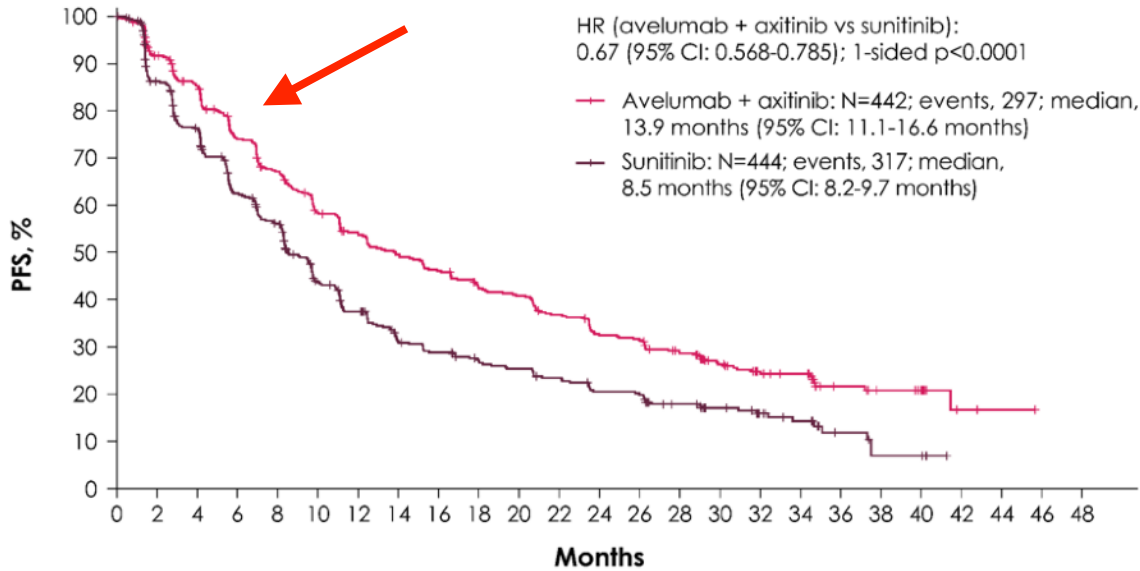


No. at risk

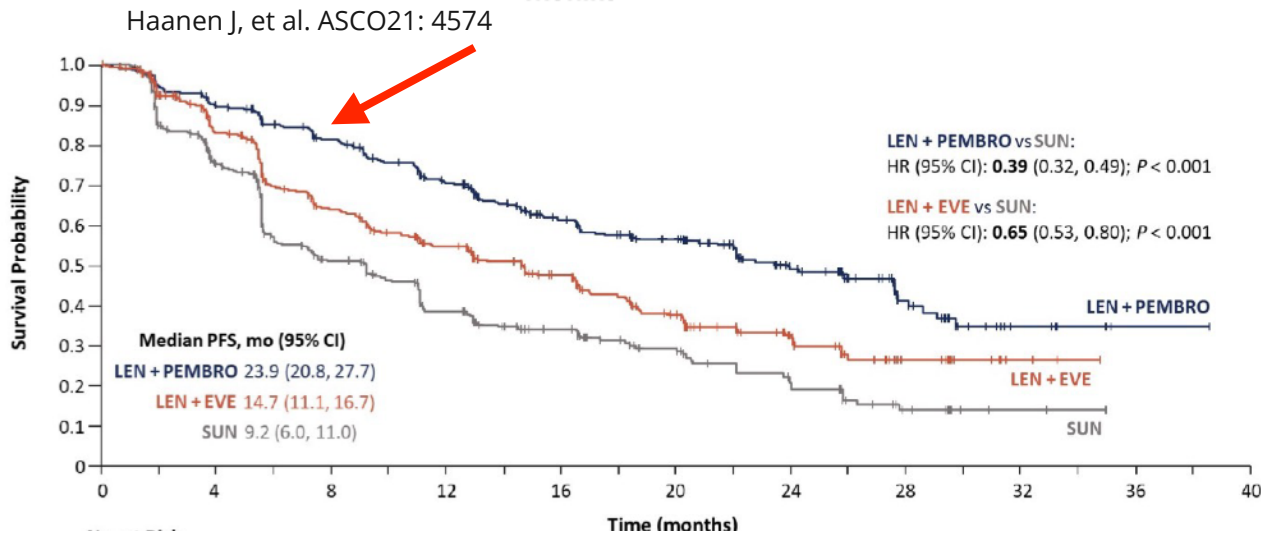
Mo	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45
NIVO+CABO	323	310	297	284	270	258	247	235	219	199	138	80	42	11	1	0
SUN	328	299	275	257	239	226	215	198	187	166	109	59	23	6	2	0

Powles et al. ASCO GU 2022: 350

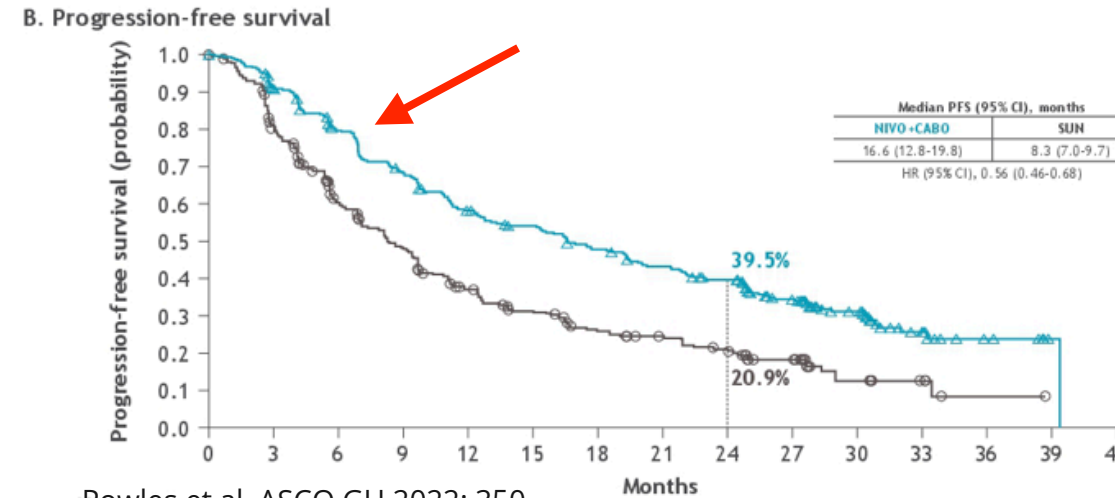
TKI-IO Kombinationen verbessern das ORR & PFS



Rini. ASCO 2021. Abstr 4500.

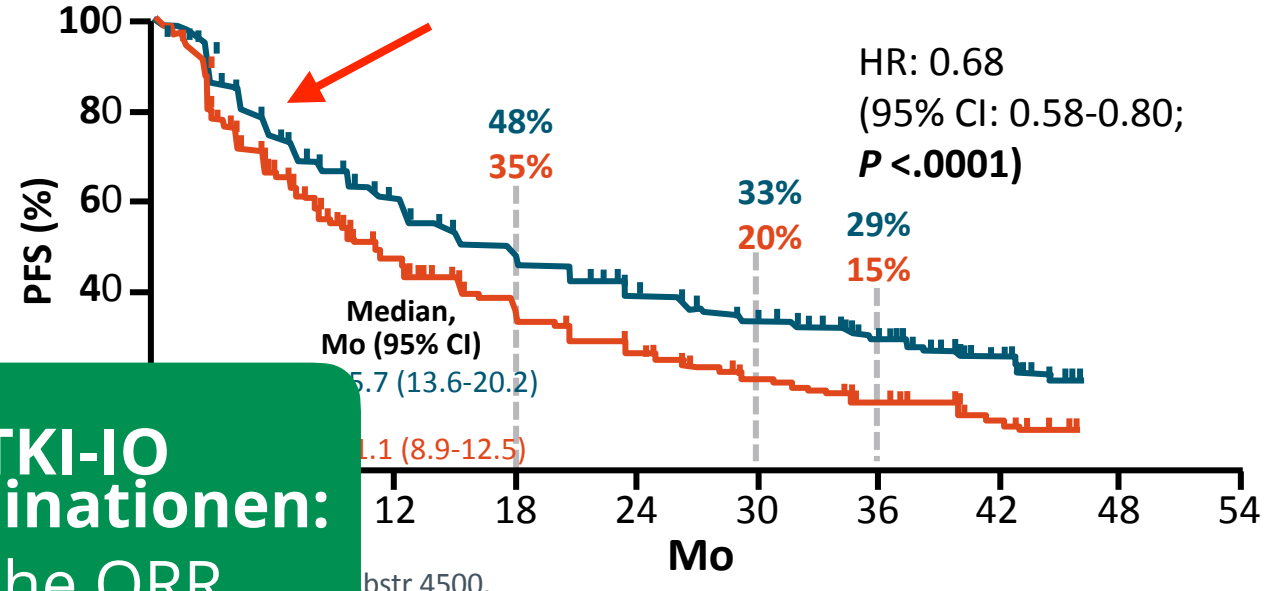
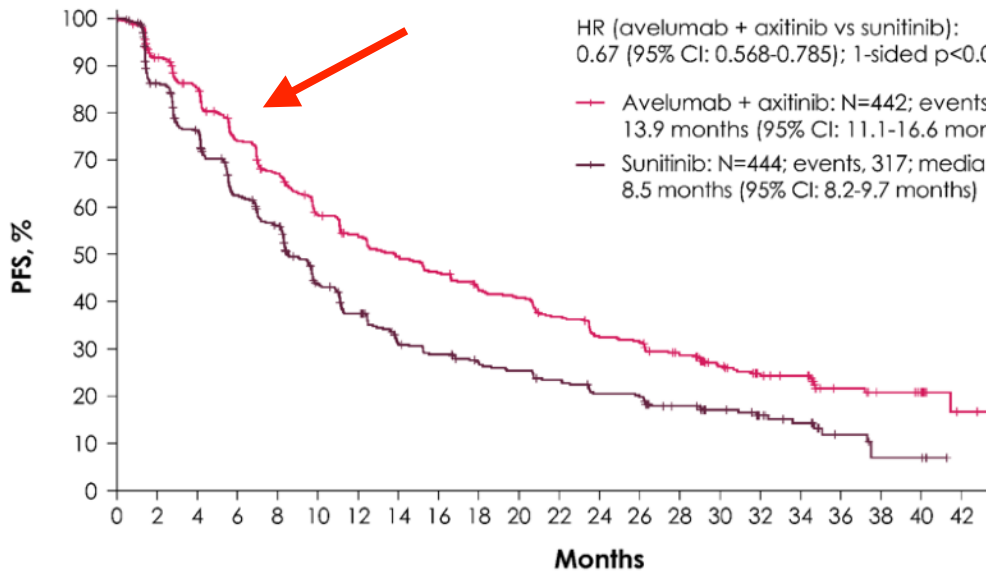


269 Motzer et al. ASCO GU 2021

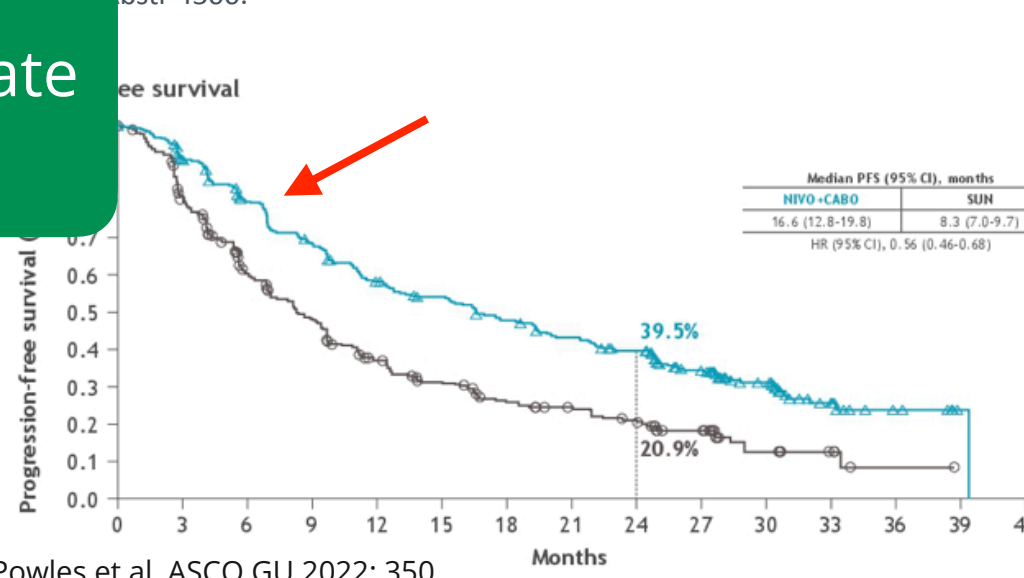
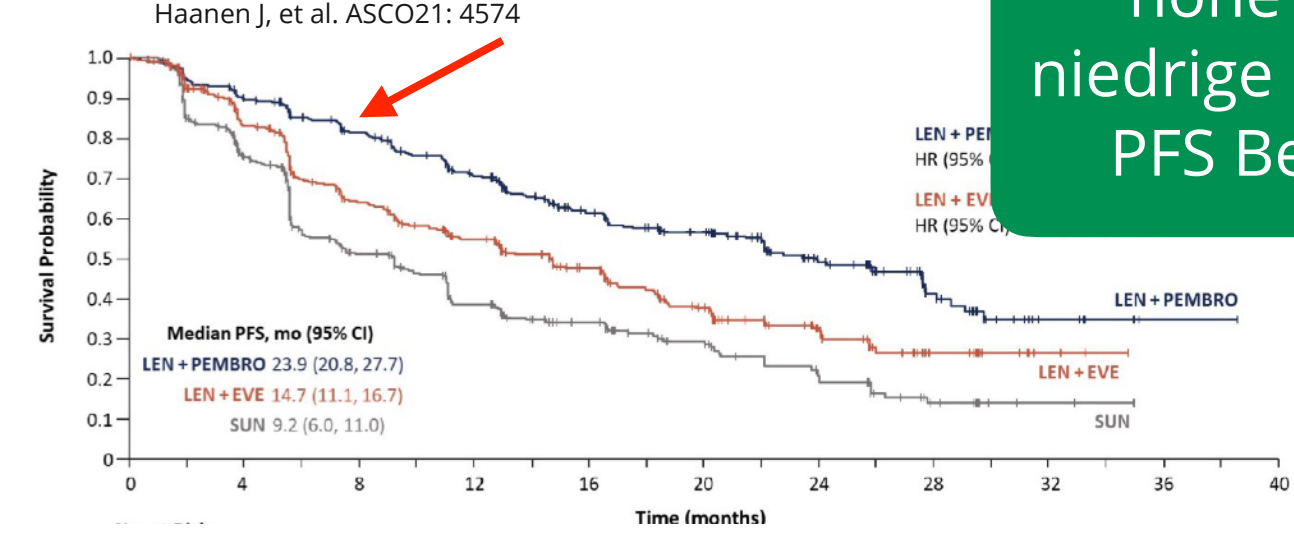


Powles et al. ASCO GU 2022: 350

TKI-IO Kombinationen verbessern das ORR & PFS



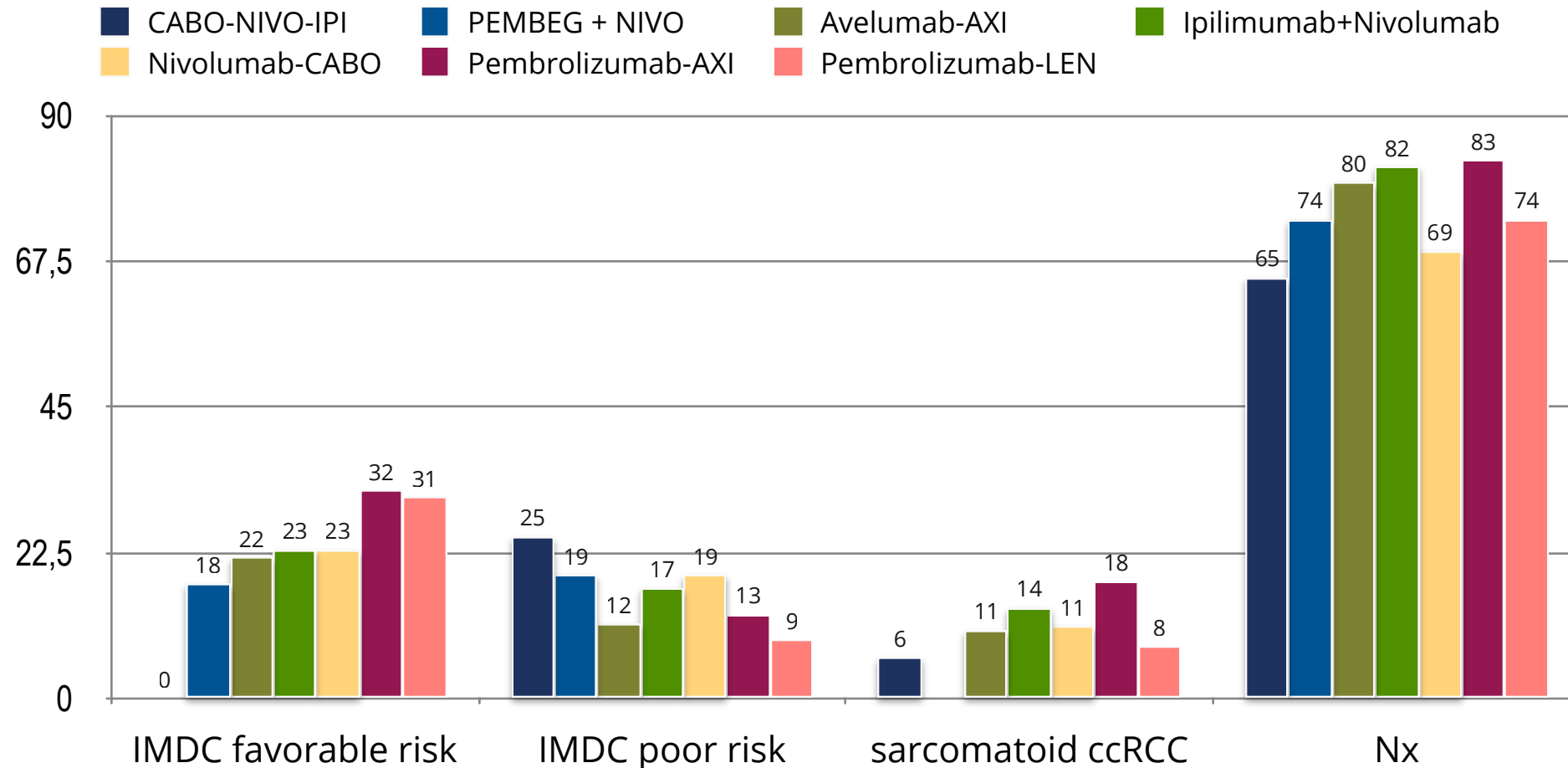
**TKI-IO
Kombinationen:
hohe ORR
niedrige PD Rate
PFS Benefit**



269 Motzer et al. ASCO GU 2021

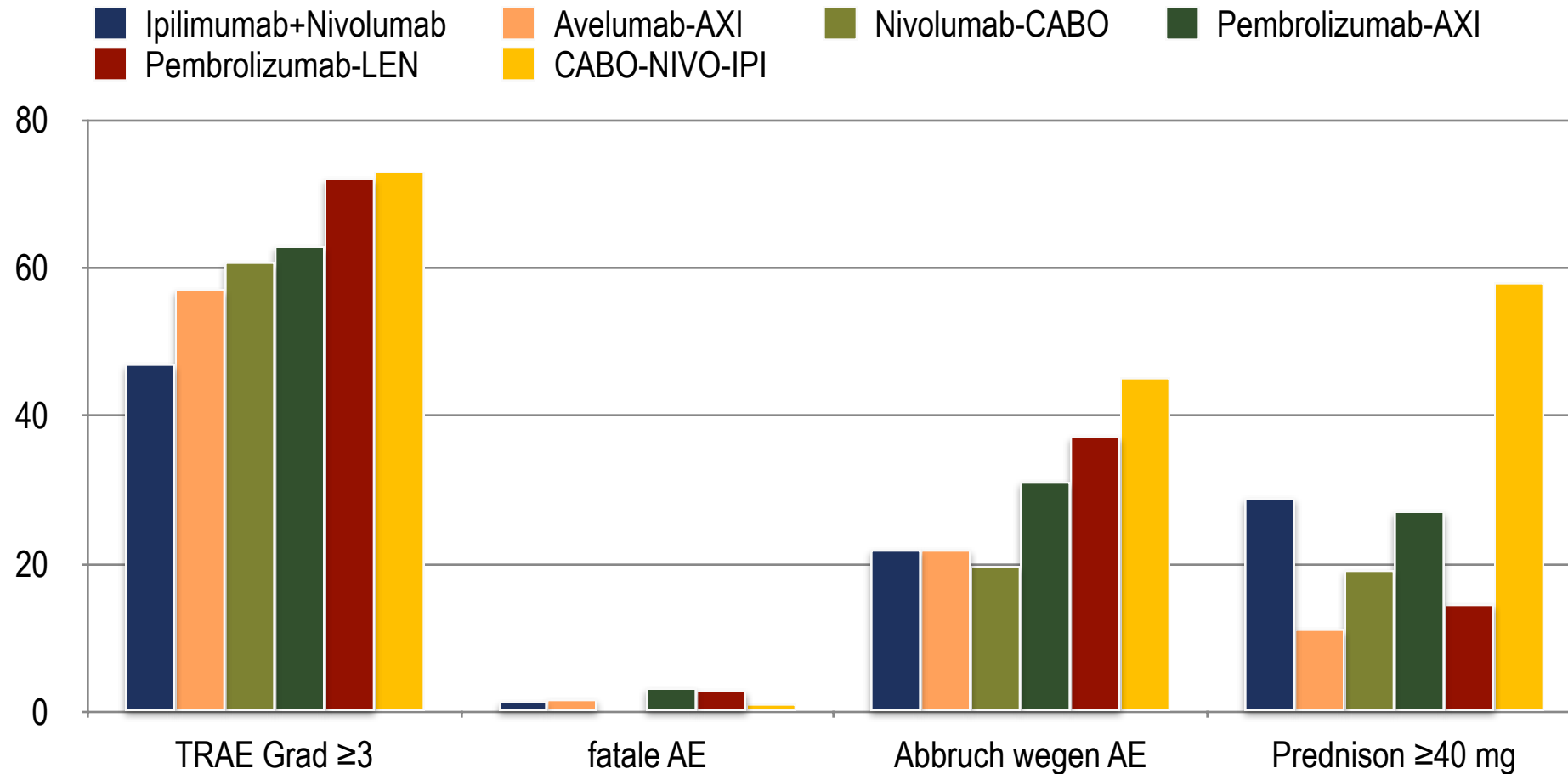
Powles et al. ASCO GU 2022: 350

Patientencharakteristika unterscheiden sich zwischen den Studien



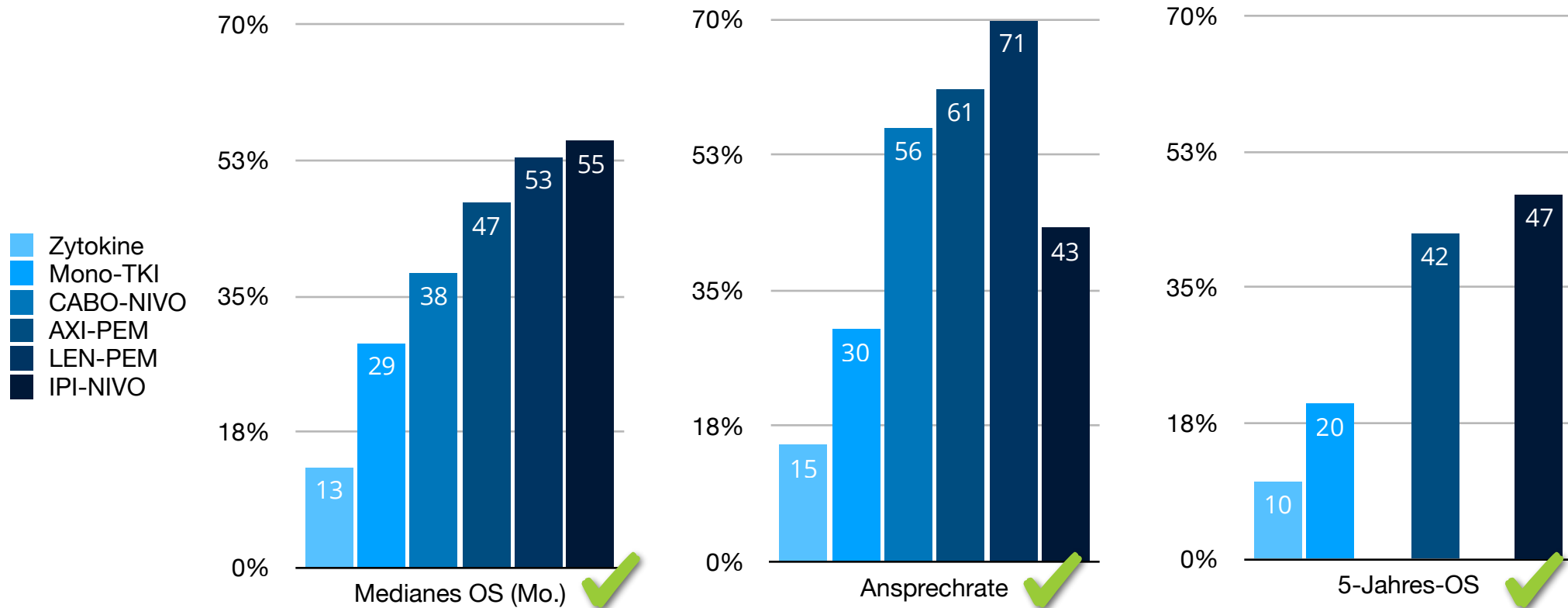
Motzer et al. *Lancet Oncol* 2019 [http://dx.doi.org/10.1016/S1470-2045\(19\)30413-9](http://dx.doi.org/10.1016/S1470-2045(19)30413-9). Motzer et al. *N Engl J Med* NEJMoa1816047 (2019). doi:10.1056/NEJMoa1816047. Rini, B. I. et al. *N Engl J Med* NEJMoa1816714-12 (2019). Motzer, R. et al. *New Engl J Med* (2021) doi:10.1056/nejmoa2035716. Choueiri et al. ESMO22: LBA8. Choueiri, et al. ESMO Open 2021;6.DOI 10.1016/j.esmoop.2021.100101. Tannir et al. ESMO22: LBA68

Sicherheitsparameter variieren zwischen den verschiedenen Studien



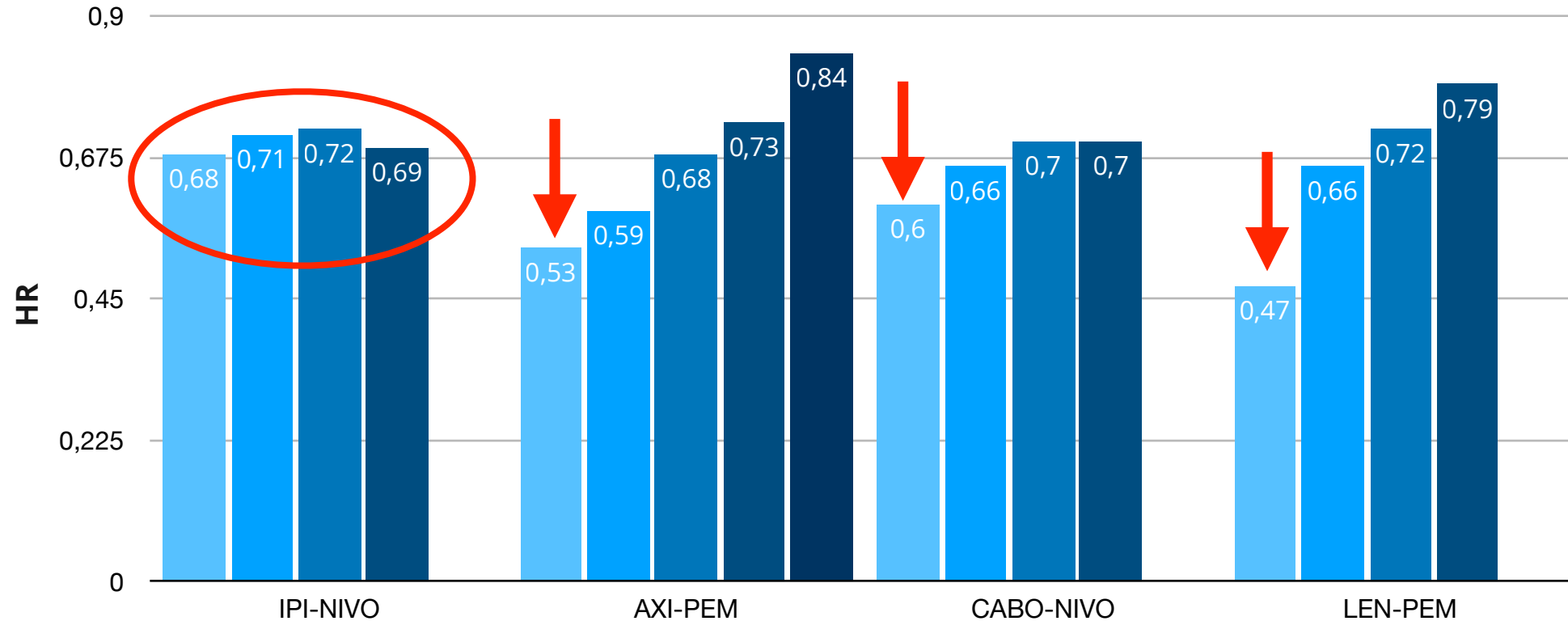
Motzer et al. Lancer Oncol 2019 [http://dx.doi.org/10.1016/S1470-2045\(19\)30413-9](http://dx.doi.org/10.1016/S1470-2045(19)30413-9). Motzer et al. N Engl J Med NEJMoa1816047 (2019). doi:10.1056/NEJMoa1816047. Rini, B. I. et al. N Engl J Med NEJMoa1816714–12 (2019). Motzer, R. et al. New Engl J Med (2021) doi:10.1056/nejmoa2035716. Choueiri et al. ESMO22: LBA8.

IO-Kombinationstherapien verbessern das Überleben unserer Patient:innen



IO-TKI Kombinationen beeinflussen vor allem die Frühsterblichkeit

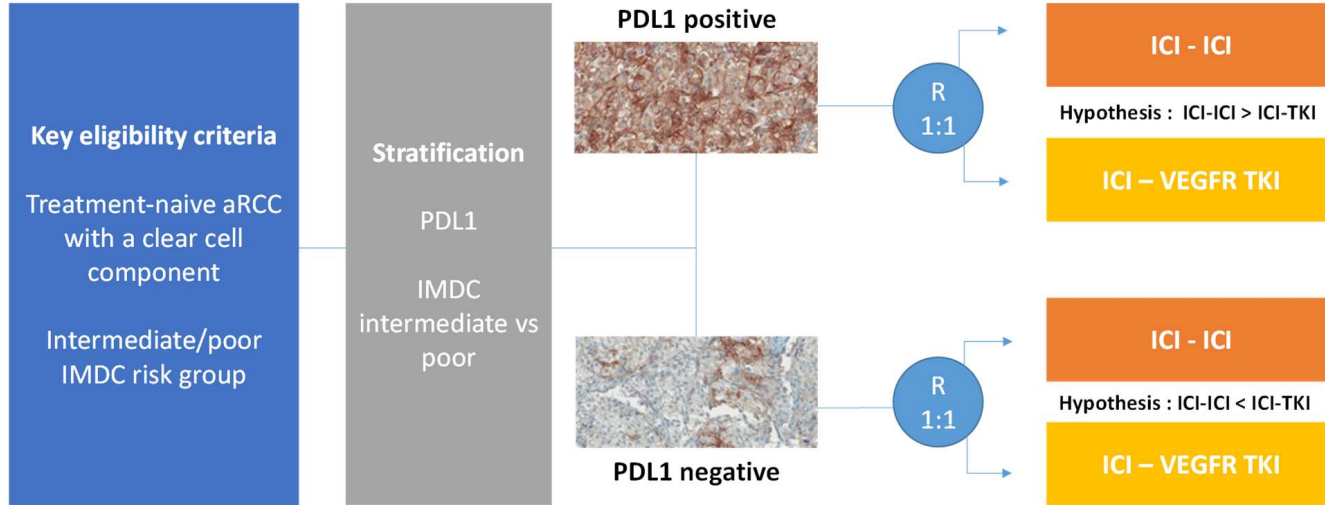
(HR wurden zu verschiedenen Zeitpunkten gemessen und sind nicht vergleichbar)



1. Motzer et al. NEJM 2108: [doi: 10.1056/nejmoa1712126](https://doi.org/10.1056/nejmoa1712126) 2. Motzer et al. Lancet Oncol 2019, 20: 1370-1385. 3. Motzer, R. J. et al. *J Immunother Cancer* **8**, e000891 (2020). 4. Albiges, L. et al. *Esmo Open* **5**, e001079 (2020). 5. Rini et al. NEJM 2019, DOI: 10.1056/NEJMoa1816714. 6. EPAR Pembrolizumab www.ema.europa.eu 7. Plimack ASCO 2020: abstr. 5001. 8. Powles et al. Lancet Oncol 2020: doi.org/10.1016/S1470-2045(20)30436-8. 9. Rini et al. ASCO 2021: abstr. 4500. 10. Choueiri et al. NEJM 2021;384:829-41. DOI: 10.1056/NEJMoa2026982. 11. Motzer et al. ASCO GU 2021: abstr. 308. 12. Motzer et al. DOI: 10.1056/NEJMoa2035716. 13. Porta et al. ESMO 2022: 1449MO. Burotto et al. ASCO GU23: 603 Motzer et al. ASCO 23: 4502. Rini et al. ASCO23: 4501



Europas Initiative zur Beantwortung dieser Fragestellung

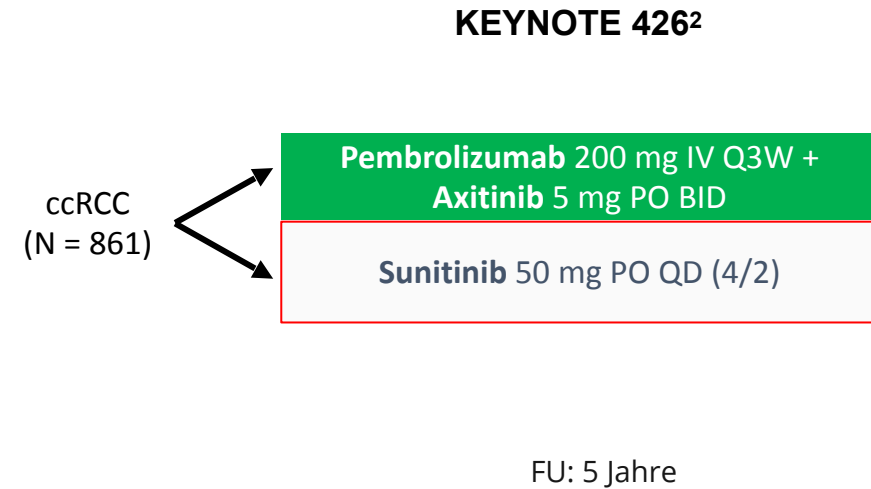
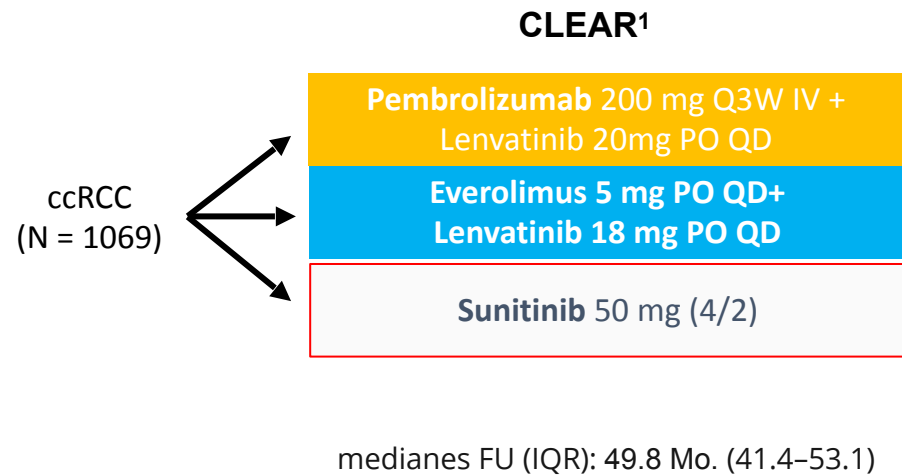


Ambitions	CARE 1 Main assets	Outputs
1 Improve mRCC first line treatment outcome by implementing a routine biomarker	<p>Head to Head comparison of 2 Standard Regimens Increasing the benefit for patient (OS), decreasing the cost of treatment</p> <p>Real life assessment of the CARE 1 classifier across countries</p> <p>Multicentric clinical trial based on patient stratification</p> <p>Efficacy assessment on functional markers</p>	<p>Functional markers Biomarker based treatment decision</p> <p>New EU guidelines Increase patient outcome Change of practice</p>
2 Leverage a unique academic network in mRCC	<p>Up and running CARE 1 PCT in France and Spain</p> <p>State of the art Clinical Infrastructures & Teams, biobanking facilities</p> <p>Experts in health economy, data extraction</p>	<p>Performance of the CARE 1 PCT Phase III trial as a « platform »</p>
3 Provide robust diagnostic and prognostic pathomic tools	<p>Validation of PD-L1 based stratification tool : SOP, reproducibility, concordance</p> <p>Identification of new Pathomic prognostic tools : Training models</p>	<p>Friendly user AI tools</p>
4 Embark innovative biotech SMEs to increase diffusion of innovation	<p>AI-based software for automated and accurate histological diagnoses</p> <p>Digital app. for automatized PRO and patient education</p>	<p>All-in-one sharing platform of personalised telemonitoring</p>
5 Knowledge learning from CARE 1 PCT	<p>Cost-effectiveness study for low cost / sustainable trials</p> <p>Data Reporting tools for Pragmatic implementation</p> <p>Translational (radiomics / circulating markers)</p>	<p>New guidelines New reporting tools New hypotheses / POC</p>
6 Fully engage with patients, and society	<p>2 EU patient associations incl. patient advocates</p> <p>Importance of PRO in the clinical design</p> <p>RGPD and Personal Data Protection</p>	<p>New clinical trial design taking into account patient-preferences</p>



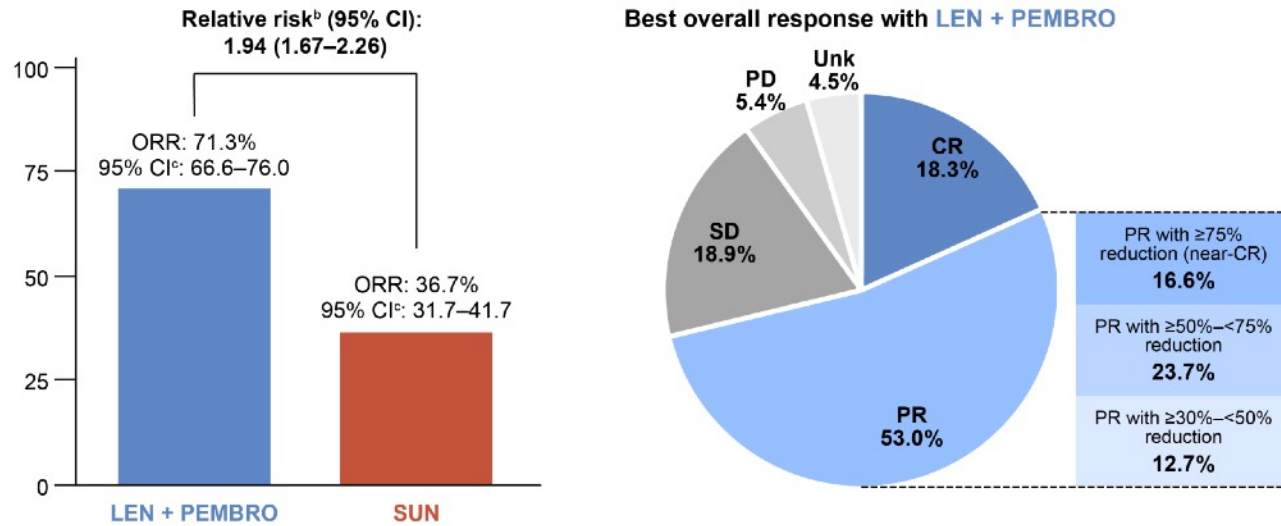
Wie sehen die Langzeitergebnisse der TKI-IO Kombinationen aus?

TKI-IO Studien mit Langzeitdaten



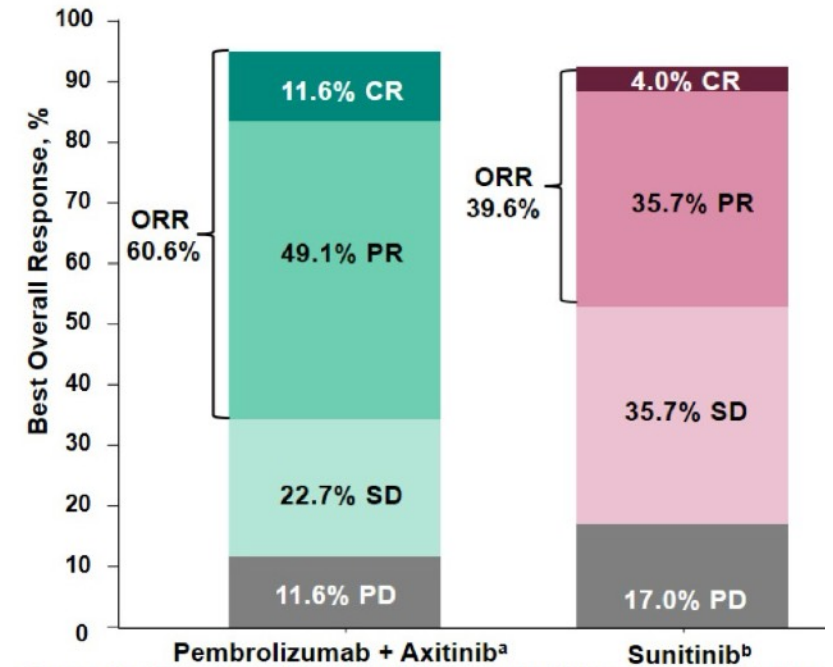
Objektivierbare Remissionsrate

CLEAR: Lenvatinib + Pembrolizumab



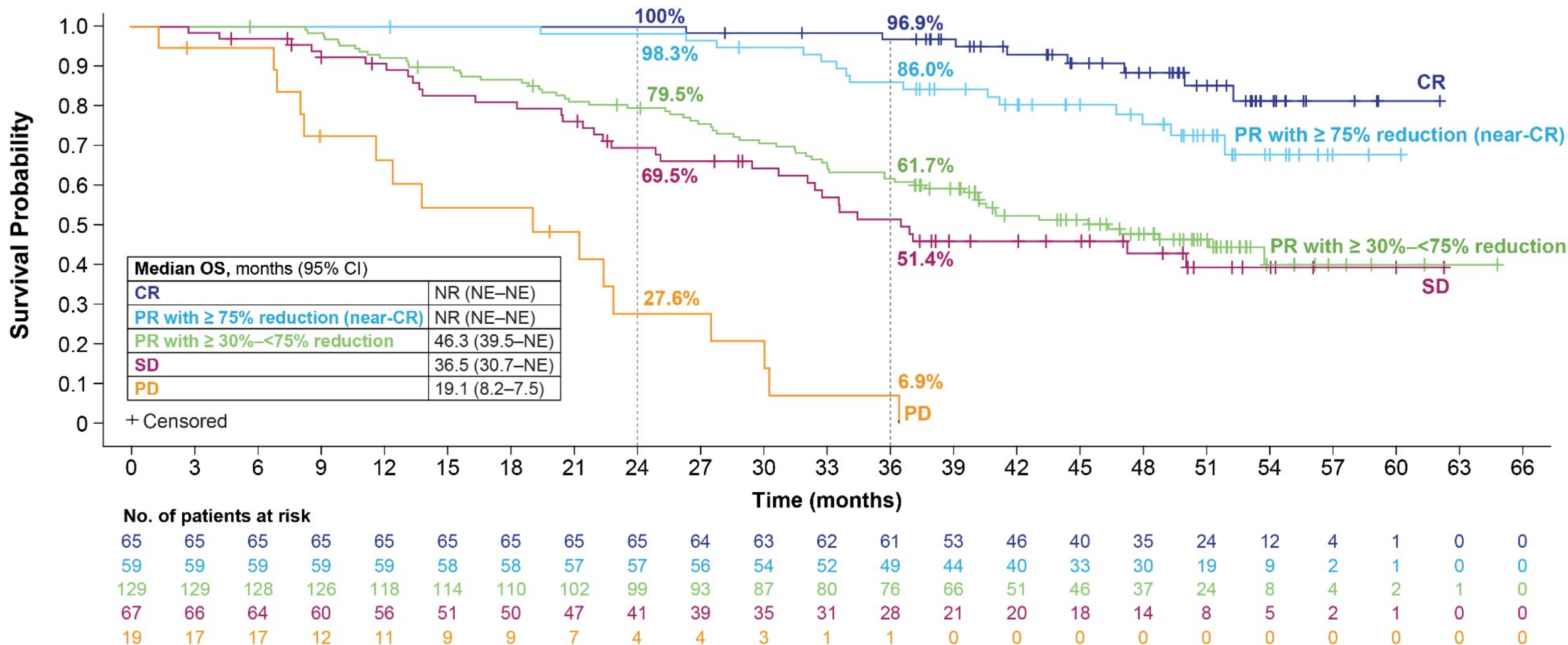
Hutson et al. ASCO 2023: #4502

KN426: Axitinib + Pembrolizumab



Rini et al. ASCO 2023: LBA4501

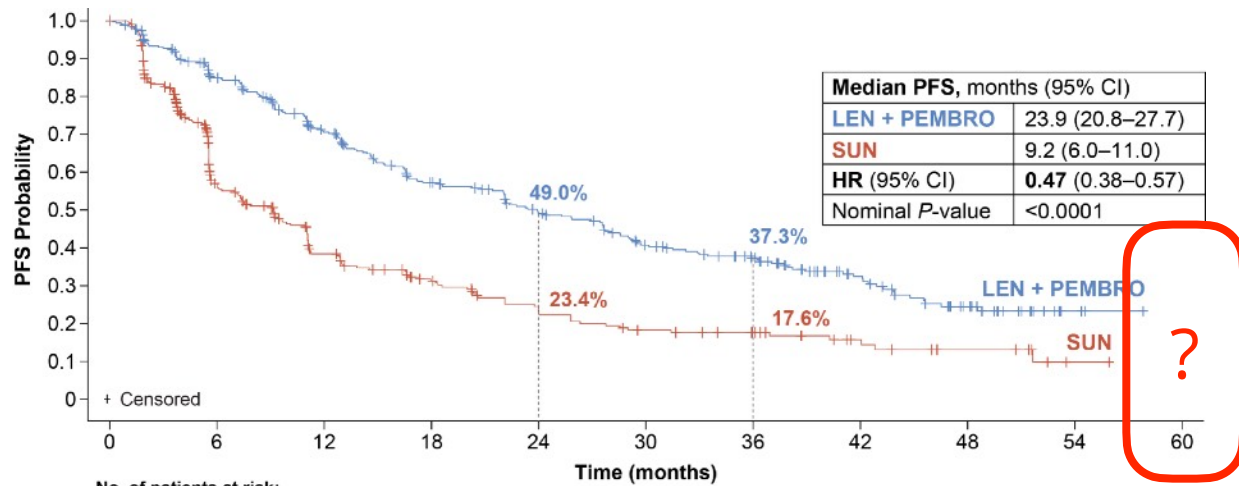
CLEAR: Tiefe der Remission ist prognostisch relevant



Near-CR refers to partial responders who showed a maximum tumor reduction of $\geq 75\%$.

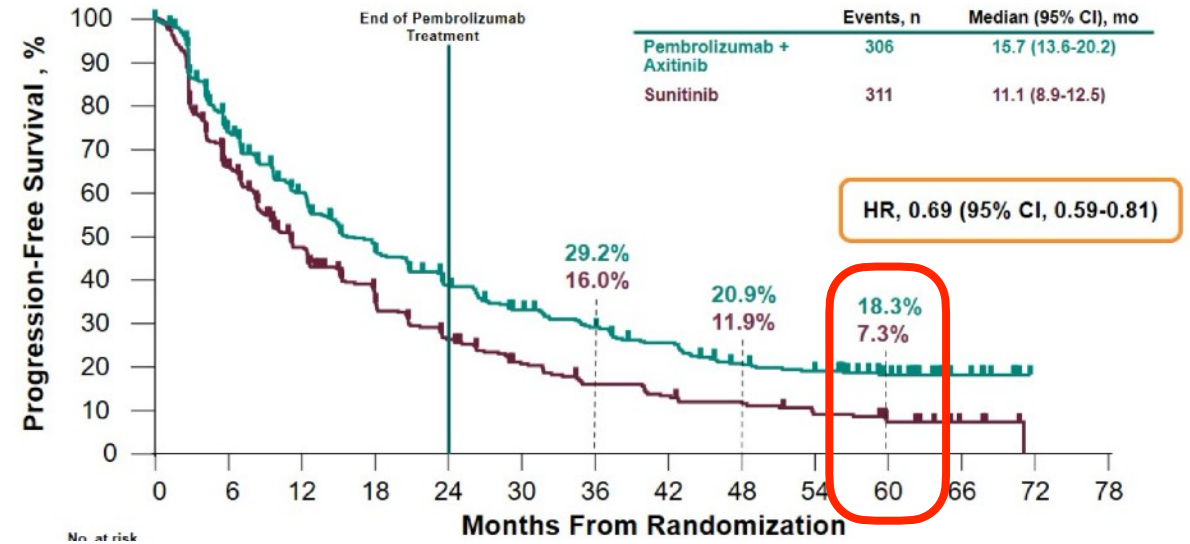
Progressionsfreies Überleben

CLEAR: Lenvatinib + Pembrolizumab



Hutson et al. ASCO 2023: #4502

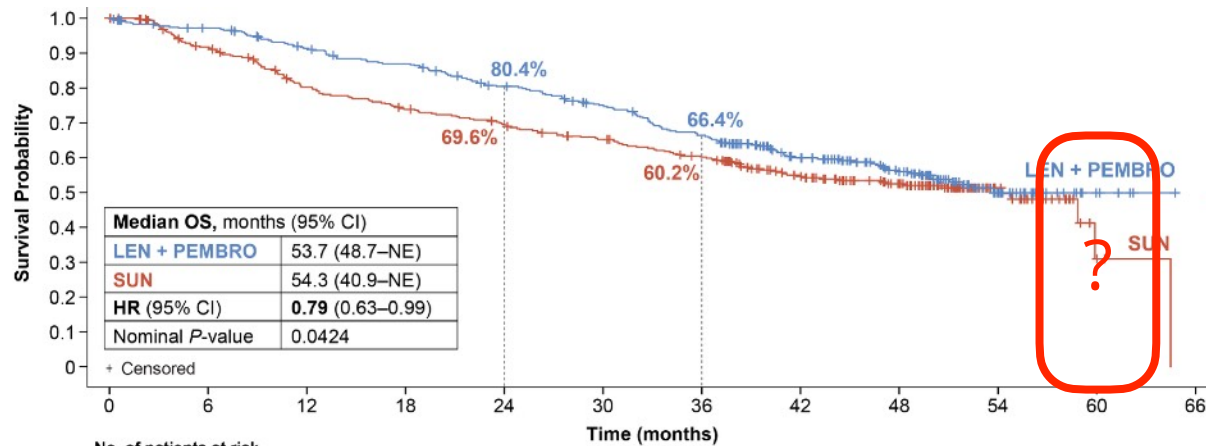
KN426: Axitinib + Pembrolizumab



Rini et al. ASCO 2023: LBA4501

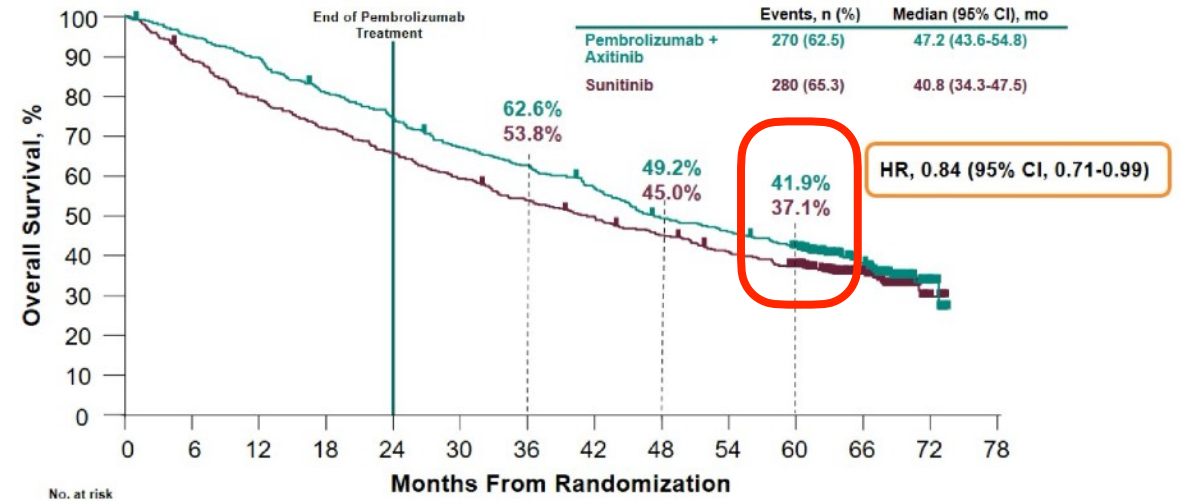
Finale Gesamtüberlebensdaten der Phase 3 Studien

CLEAR: Lenvatinib + Pembrolizumab



Hutson et al. ASCO 2023: #4502

KN426: Axitinib + Pembrolizumab



Rini et al. ASCO 2023: LBA4501

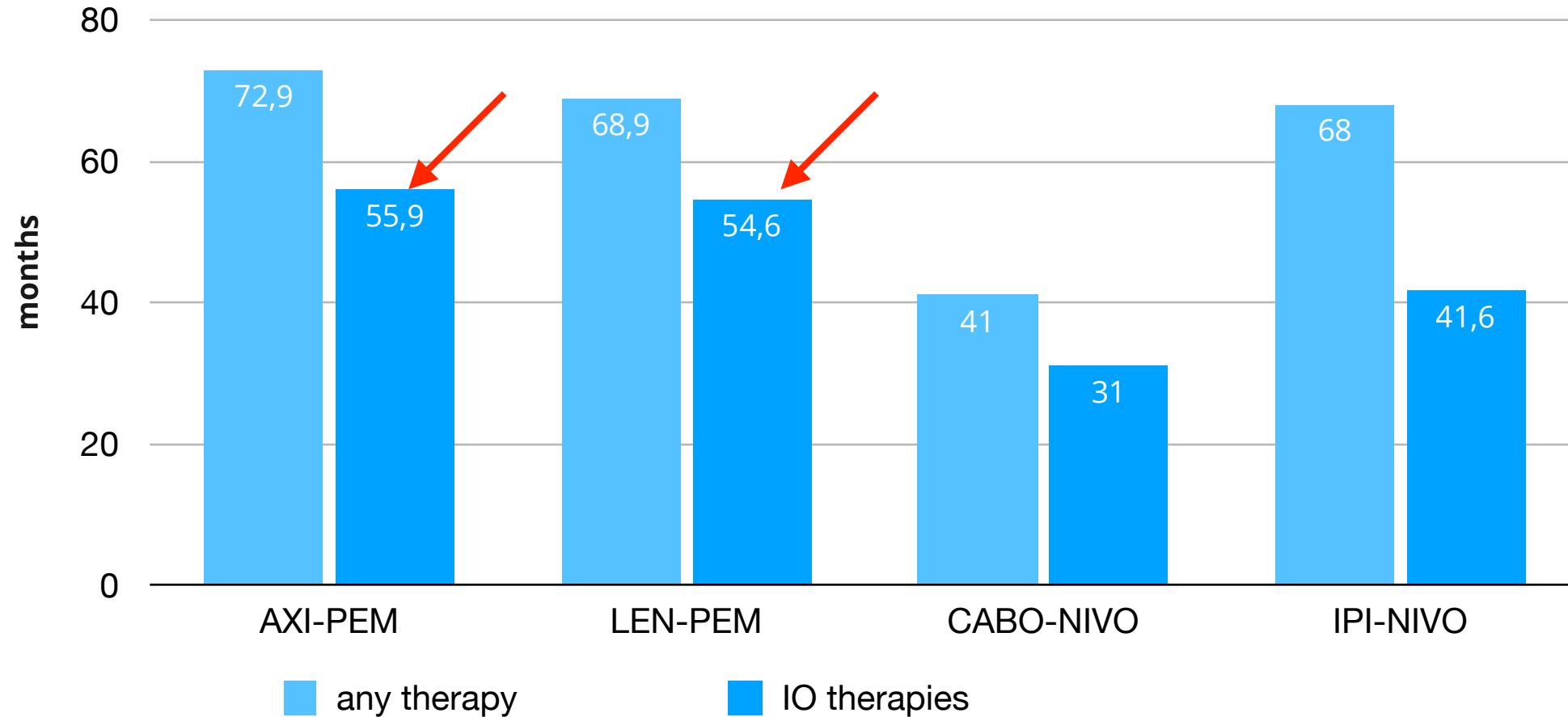
Sind Studienunterschiede relevant?

Ergebnisse der Standardtherapie (Sunitinib) der Zulassungsstudien

Studie	med. FU (Mo.)	CR (%)	ORR (%)	PFS (Mo.)	DOR (Mo.)	OS (Mo.)
CM214 ¹	67,7	3,1	32,3	12,3	24,8	38,4
KN426 ²	42,8	3,5	39,6	11,1	15,3	40,1
JR100 ³	11,6	1,8	25,7	8,4	-	-
CM9ER ⁴	44,0	5,2	28,4	8,4	15,2	35,5
CLEAR ⁵	27,0	4,2	36,1	14,6	14,6	54,3

1. Motzer et al. Cancer 2022. 2. Rini et al. ASCO 2021: 4500. 3. Choueiri TK *et al.* (2020) doi:10.1016/j.annonc.2020.04.010. 4. Haanen J, et al. Abstract No. 4574. Presented at 2021 ASCO Annual Meeting, June 4-8, 2021 5. Burotto et al. ASCO GU 2023: 603. 6. Motzer. *et al.* (2021) doi:10.1056/nejmoa2035716. Hutson et al. ASCO 2023: #4502

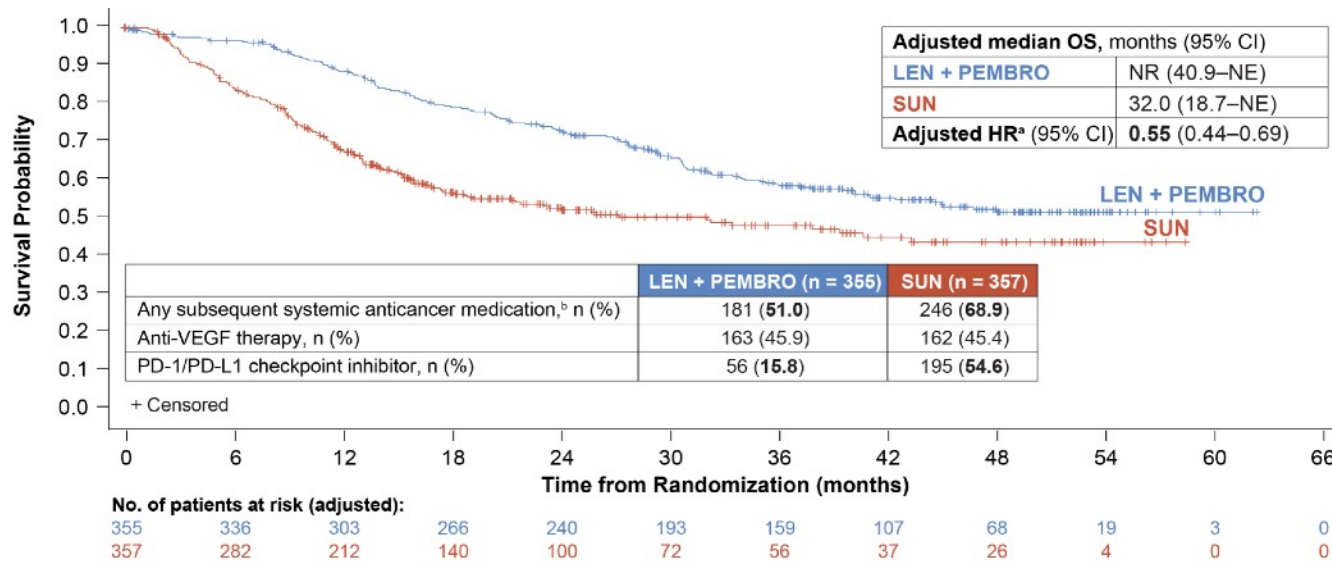
Folgetherapien unterscheiden sich in den Kontrollarmen (Sunitinib)



Motzer et al. Cancer 2022. Rini et al. ASCO23: 4501. Burotto et al. ASCO GU23: 603. Motzer et al. ASCO 23: 4502.

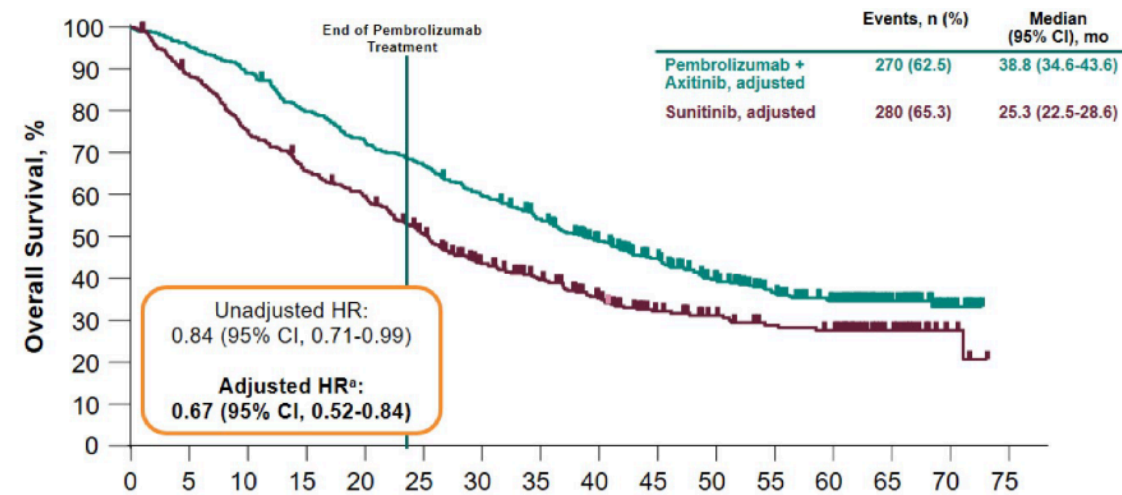
Folgetherapien beeinträchtigen das Gesamtüberleben

Lenvatinib + pembrolizumab



Hutson et al. ASCO 2023: 4502

Axitinib + pembrolizumab

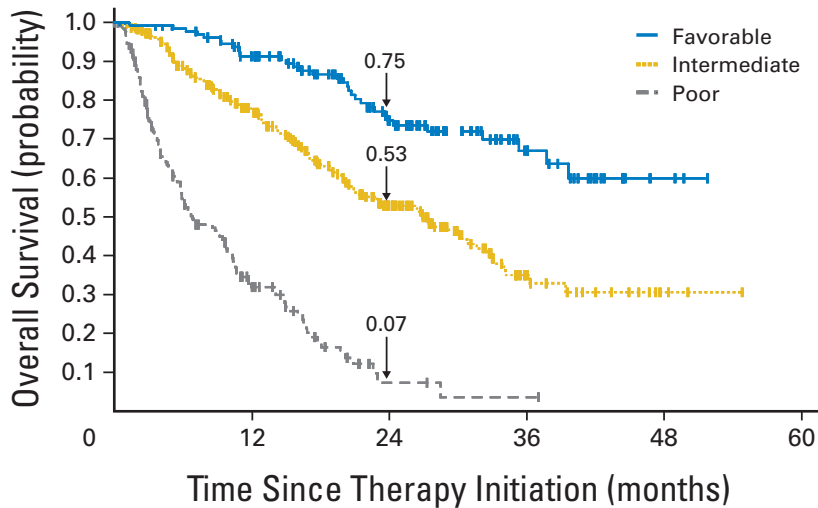


Rini et al. ASCO 2023: LBA4501

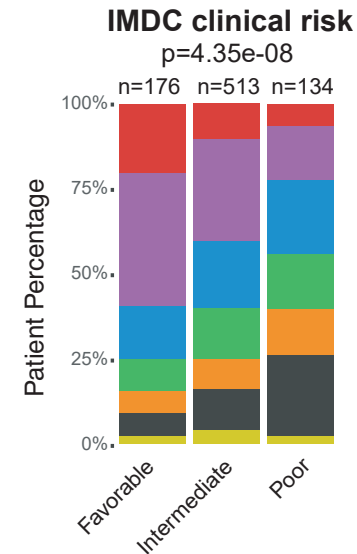
Data shown indicate effects of subsequent therapies in different trials. Data should not be compared between studies

Welche Patient:innen-Gruppen profitieren von der TKI-IO Combo?

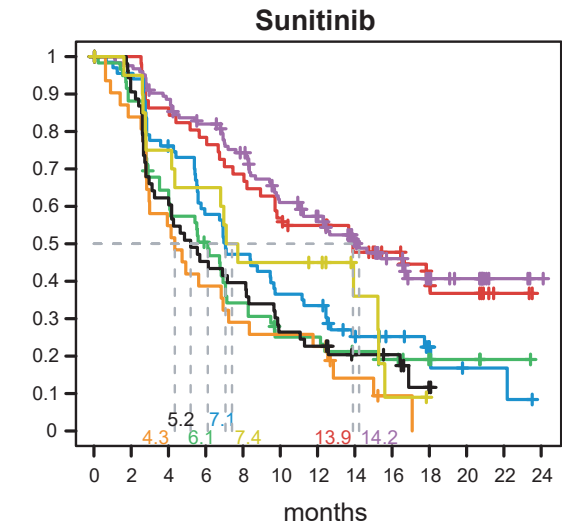
IMDC Risiko - reicht für TKI-Sensitivität an



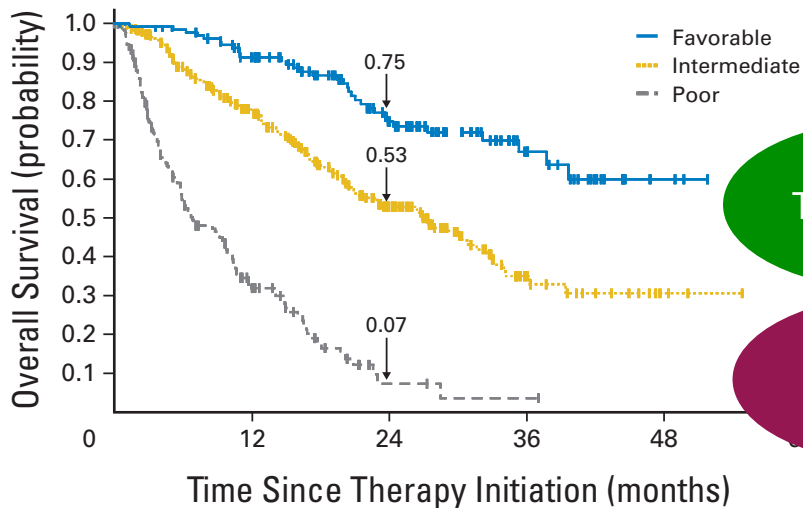
No. of events/No. at risk	0-6	6-12	12-18	18-24	24-30
Favorable	11/133	16/110	4/62	2/22	0/3
Intermediate	61/301	50/182	17/82	2/18	0/3
Poor	94/152	19/36	1/3	0/1	0/0



- 1 - Angio/Stromal
- 2 - Angiogenic
- 3 - Complement/Ω-ox.
- 4 - T-eff/Proliferative
- 5 - Proliferative
- 6 - Stromal/Proliferative
- 7 - snoRNA



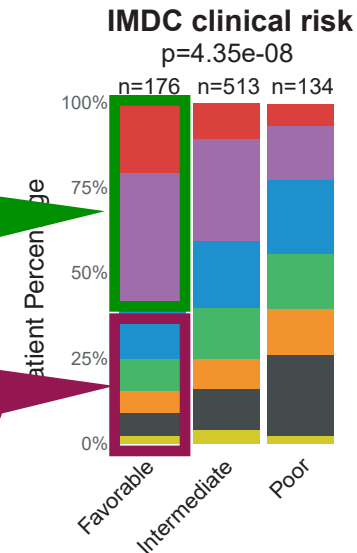
IMDC Risiko - reichert für TKI-Sensitivität an



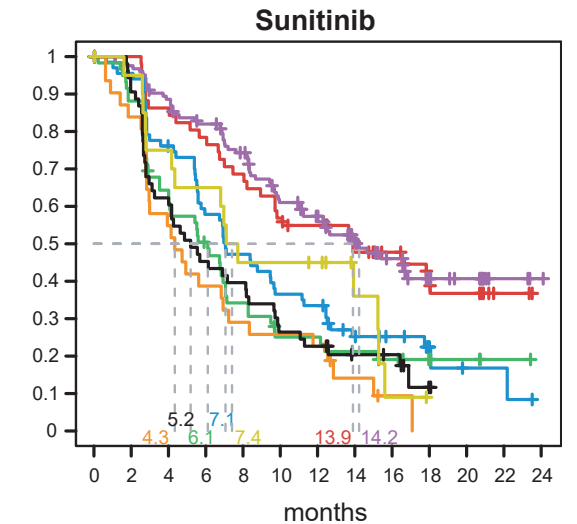
No. of events/No. at risk	0-6	6-12	12-18	18-24	24-30
Favorable	11/133	16/110	4/62	2/22	0/3
Intermediate	61/301	50/182	17/82	2/18	0/3
Poor	94/152	19/36	1/3	0/1	0/0

TKI-sensibel

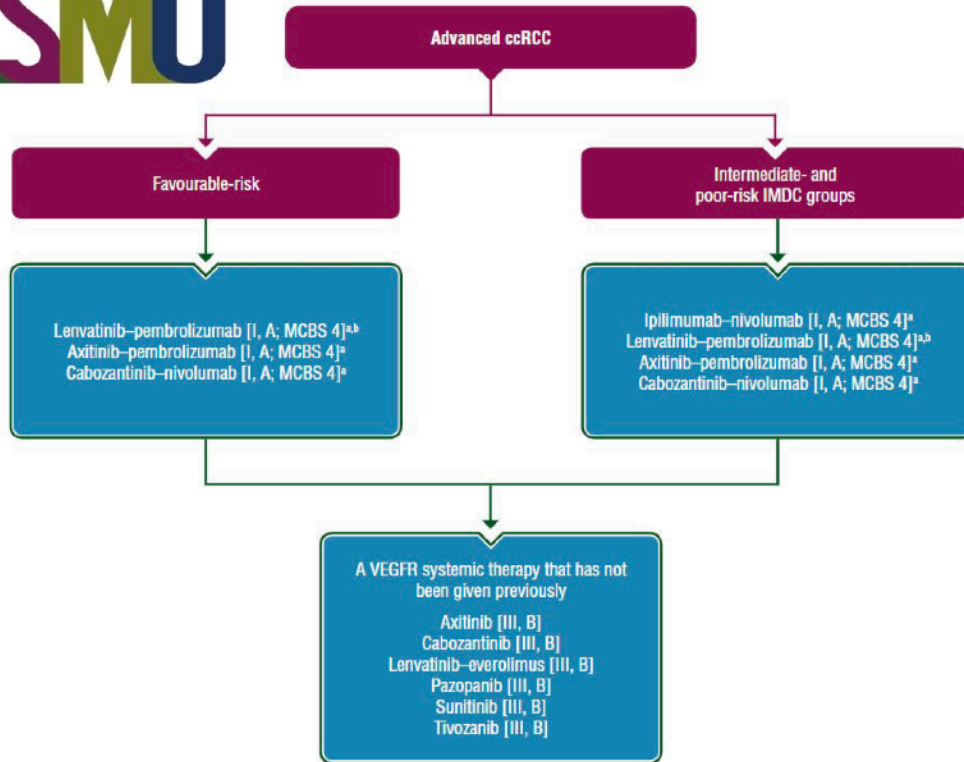
inflammatorisch



- 1 - Anglo/Stromal
- 2 - Angiogenic
- 3 - Complement/Ω-ox.
- 4 - T-eff/Proliferative
- 5 - Proliferative
- 6 - Stromal/Proliferative
- 7 - snoRNA



IMDC Risiko ist die Basis der Empfehlungen in der Erstlinie



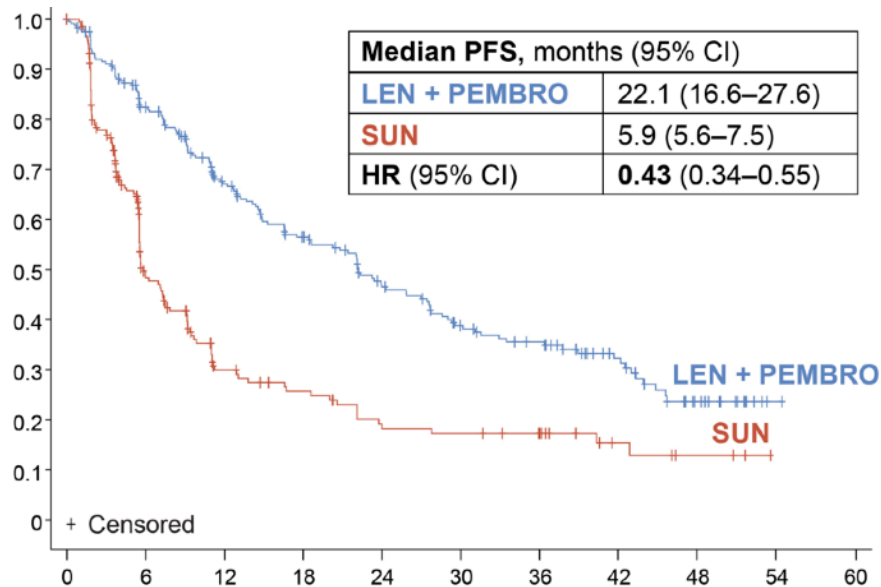
	Standard of Care	Alternative in patients who can not receive or tolerate immune checkpoint inhibitors
IMDC favourable risk	nivolumab/cabozantinib [1b] pembrolizumab/axitinib [1b] pembrolizumab/lenvatinib [1b]	sunitinib* [1b] pazopanib* [1b]
IMDC intermediate and poor risk	nivolumab/cabozantinib [1b] pembrolizumab/axitinib [1b] pembrolizumab/lenvatinib [1b] nivolumab/ipilimumab [1b]	cabozantinib* [2a] sunitinib* [1b] pazopanib* [1b]

eUpdate SEP 2021 Powles et al. (www.esmo.org) for reference: Escudier B, Porta C, Schmidinger M et al. Ann Oncol 2019; 30(5): 706–720.

<https://uroweb.org/guidelines/renal-cell-carcinoma/chapter/disease-management>
Stand 2023, Zugriff: 28.09.23

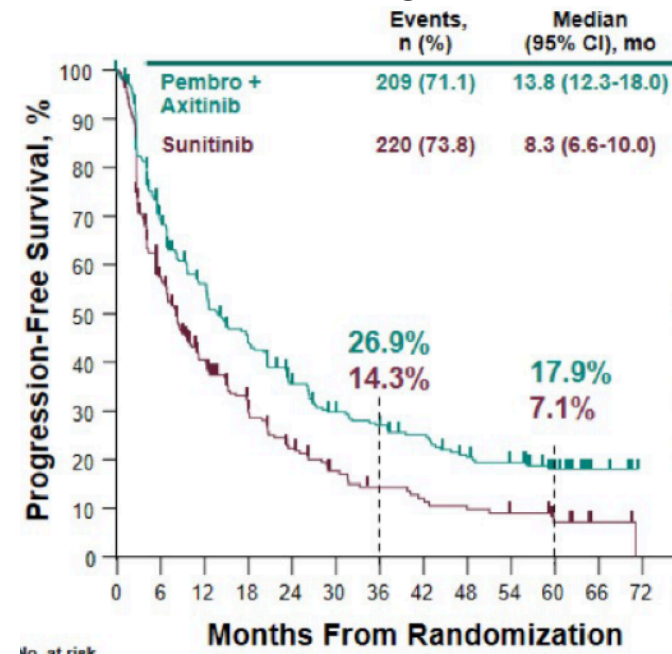
TKI-IO Combos verbessern die Wirksamkeit bei Patient:innen mit ≥ 1 Risikofaktor

CLEAR



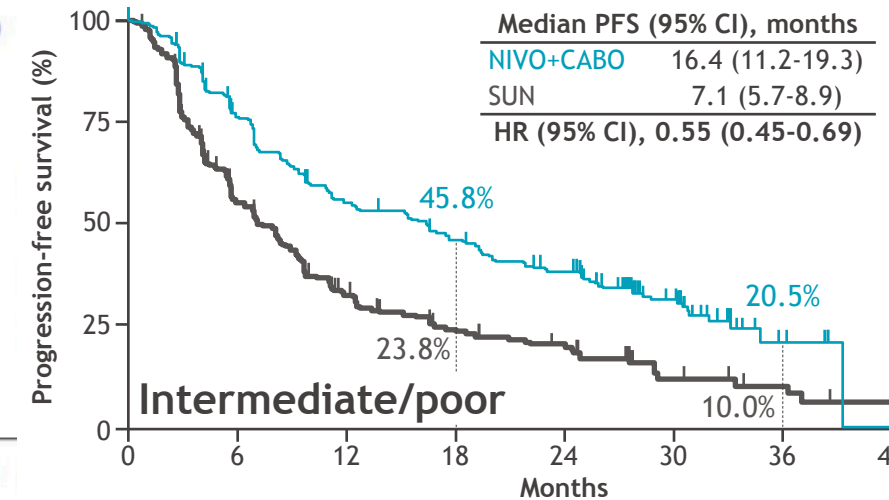
Hutson et al. ASCO 23: 4502

KN426



Rini et al. ASCO 23: LBA4501

CM9ER

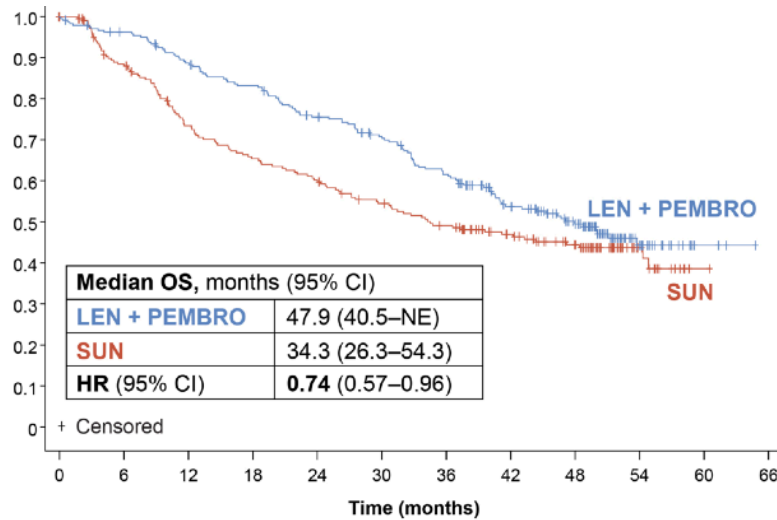


Burotto et al. ASCO GU 23: 603

in the absence of head-to-head studies, cross trial comparisons cannot be made as the trials differ in design, size, time period of recruitment, location of study sites etc.

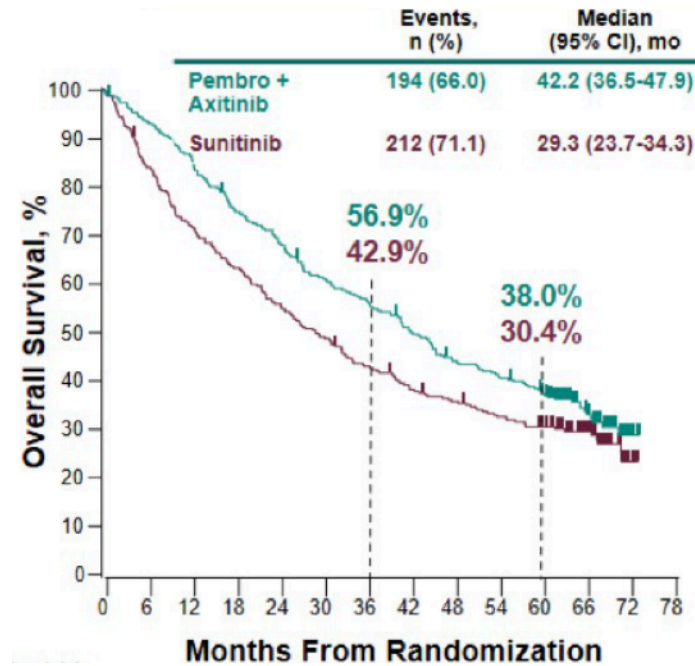
...und das Gesamtüberleben

CLEAR



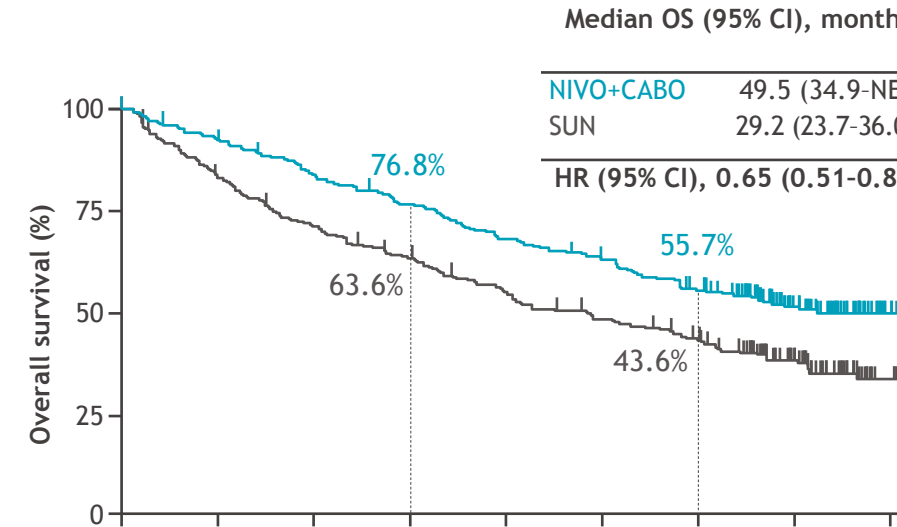
Hutson et al. ASCO 23: 4502

KN426



Rini et al. ASCO 23: LBA4501

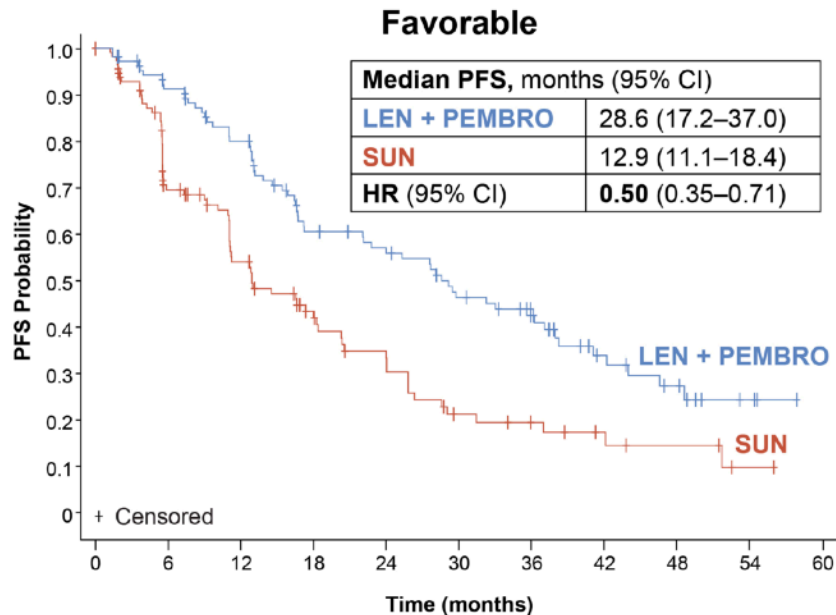
CM9ER



Burotto et al. ASCO GU 23: 603

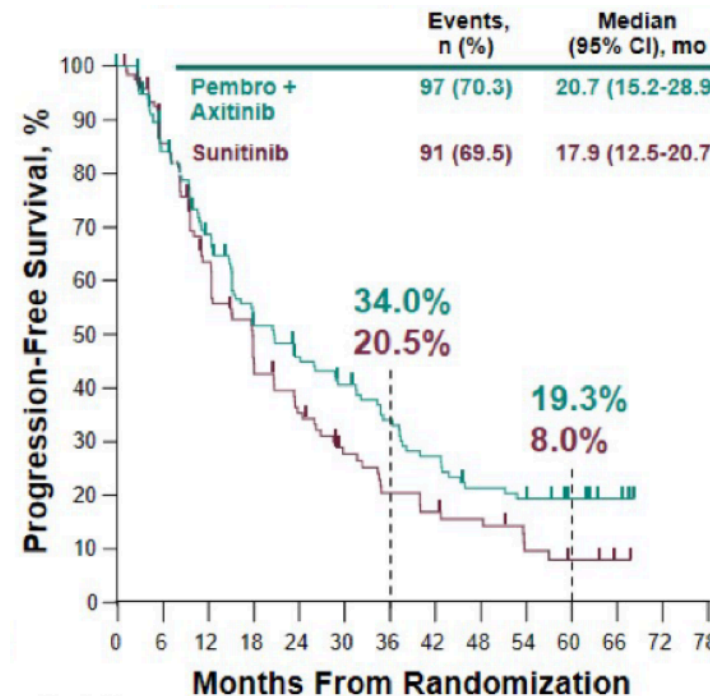
TKI-IO Combos verbessern die Wirksamkeit bei Patient:innen ohne Risikofaktor (günstiges Risiko)

CLEAR



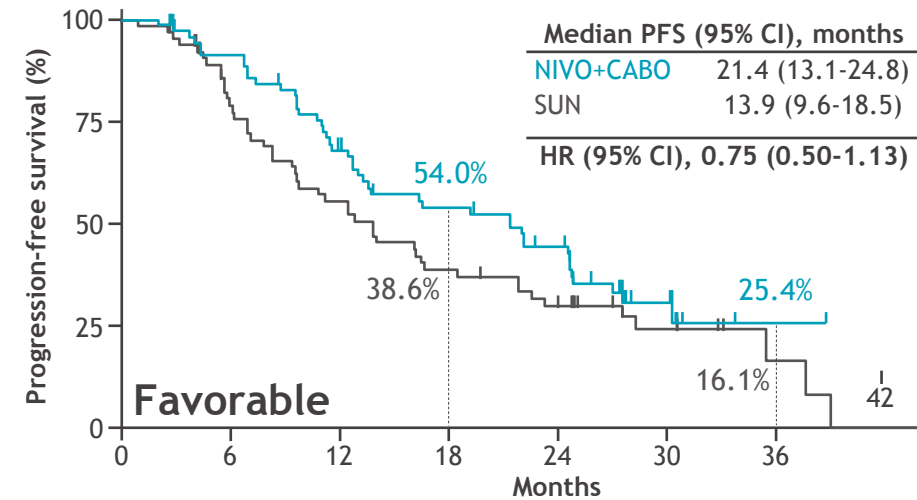
Hutson et al. ASCO 23: 4502

KN426



Rini et al. ASCO 23: LBA4501

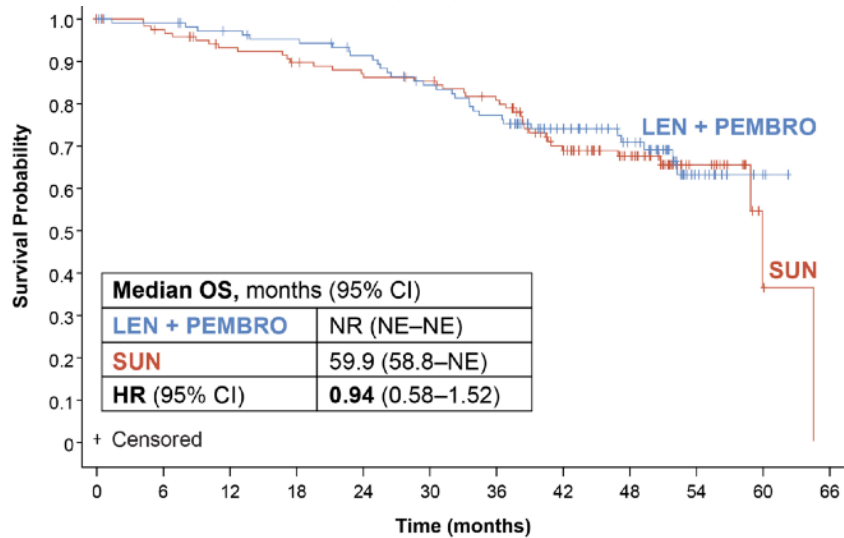
CM9ER



Burotto et al. ASCO GU 23: 603

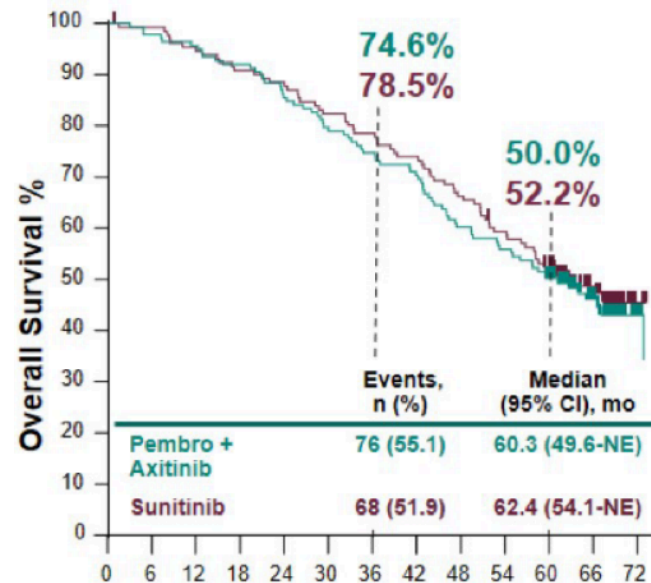
Bei günstigem Risiko gibt es kein Signal für ein besseres Gesamtüberleben

CLEAR



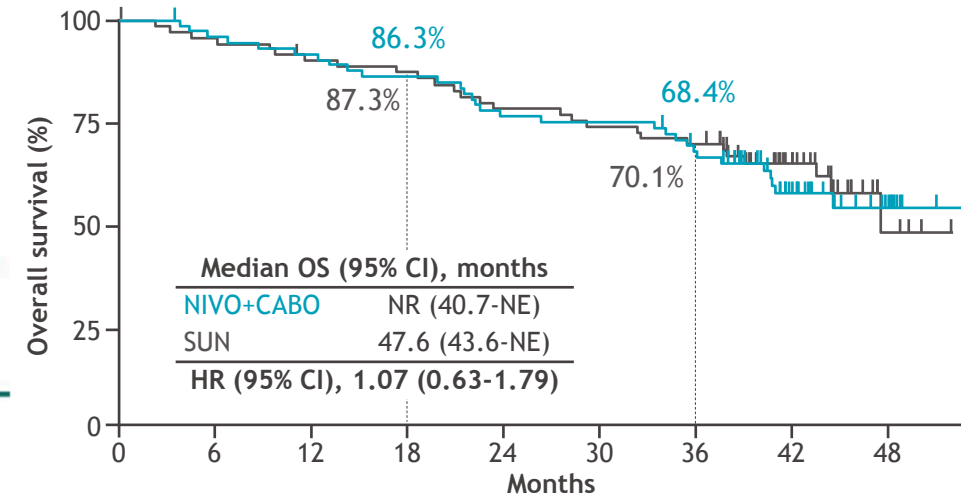
Hutson et al. ASCO 23: 4502

KN426



Rini et al. ASCO 23: LBA4501

CM9ER

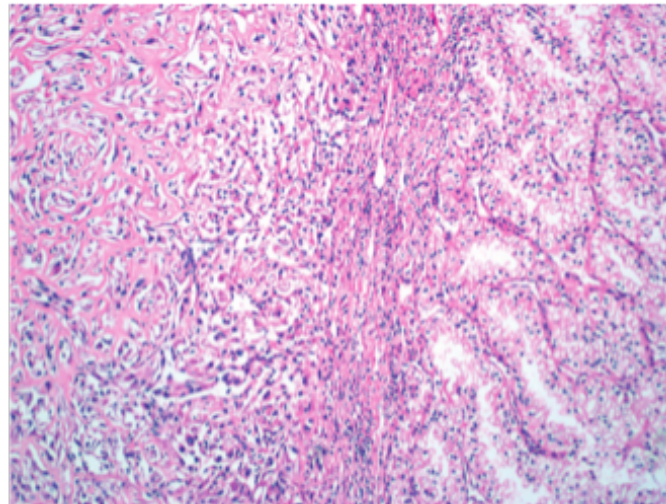


Burotto et al. ASCO GU 23: 603

Sarkomatoide NCC - eine Subgruppe von Tumoren mit besonders aggressivem Verlauf

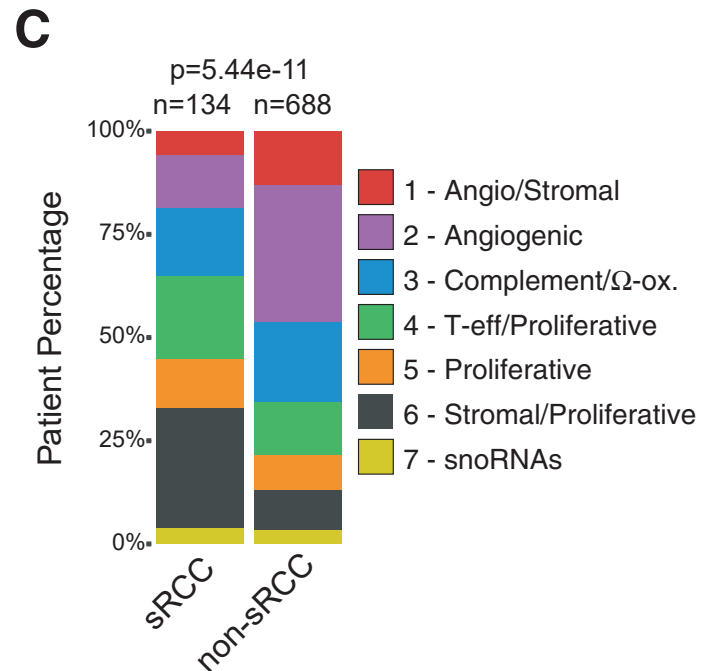


- kommt in allen NCC Subtypen vor
- entspricht ent-differenziertem NCC
- Ist keine eigene Entität
- Ist kein Sarkom



sarcomatoid

clear cell



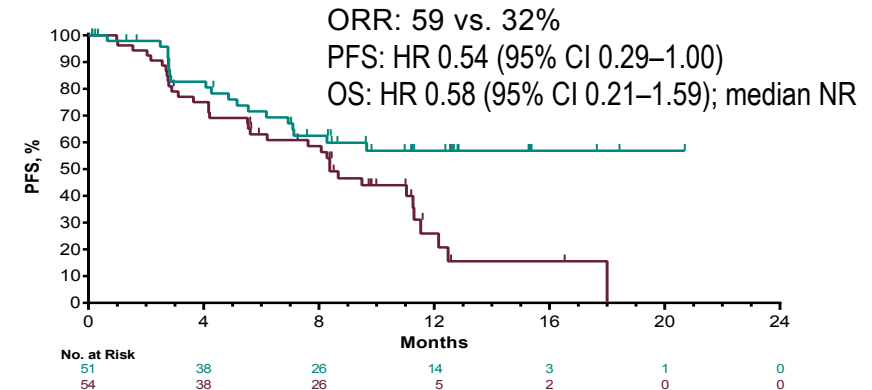
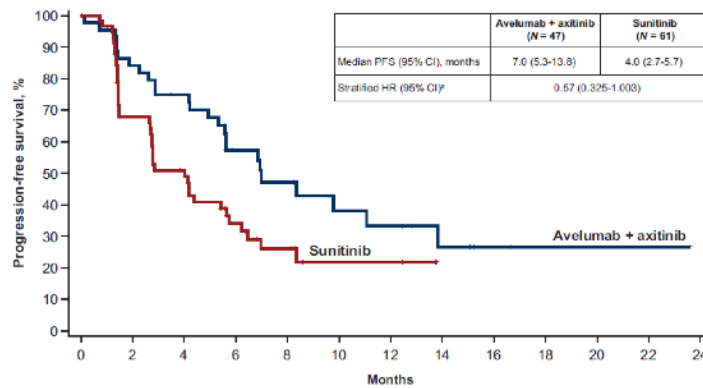
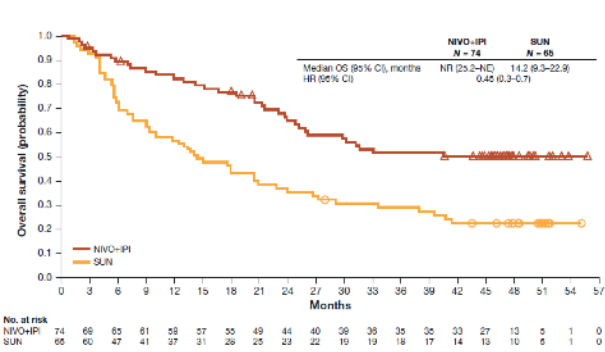
Lopez-Beltran et al. (2009). International Journal of Urology 16(5), 432-443. doi:10.1111/j.1442-2042.2009.02302.x

Golshayan et al. (2008). Journal of Clinical Oncology 27(2), 235-241

Golshayan et al. (2008). Journal of Clinical Oncology 27(2), 235-241

Motzer, R. J. et al. Cancer Cell (2020) doi:10.1016/j.ccell.2020

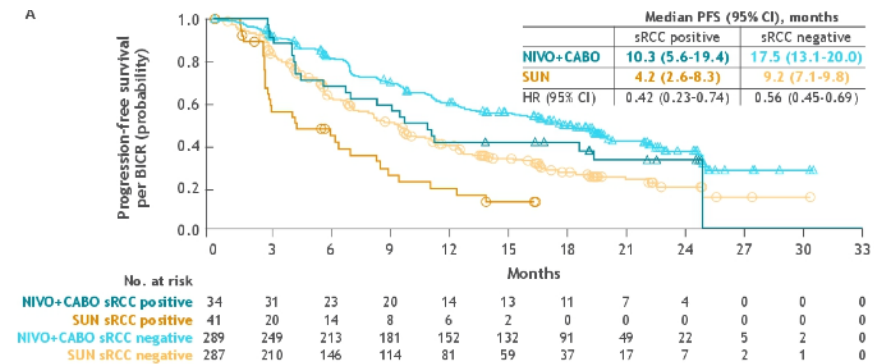
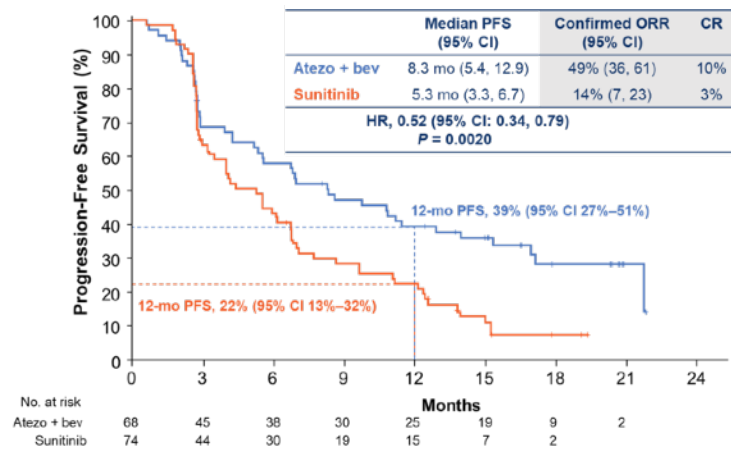
Sarkomatoide NCC sind besonders IO-sensitiv



Tannir N. et al., *Clin Cancer Res.*, 2021. PMID: 32873572.

Choueiri, et al. ESMO Open 2021;6.DOI 10.1016/j.esmoop.2021.100101

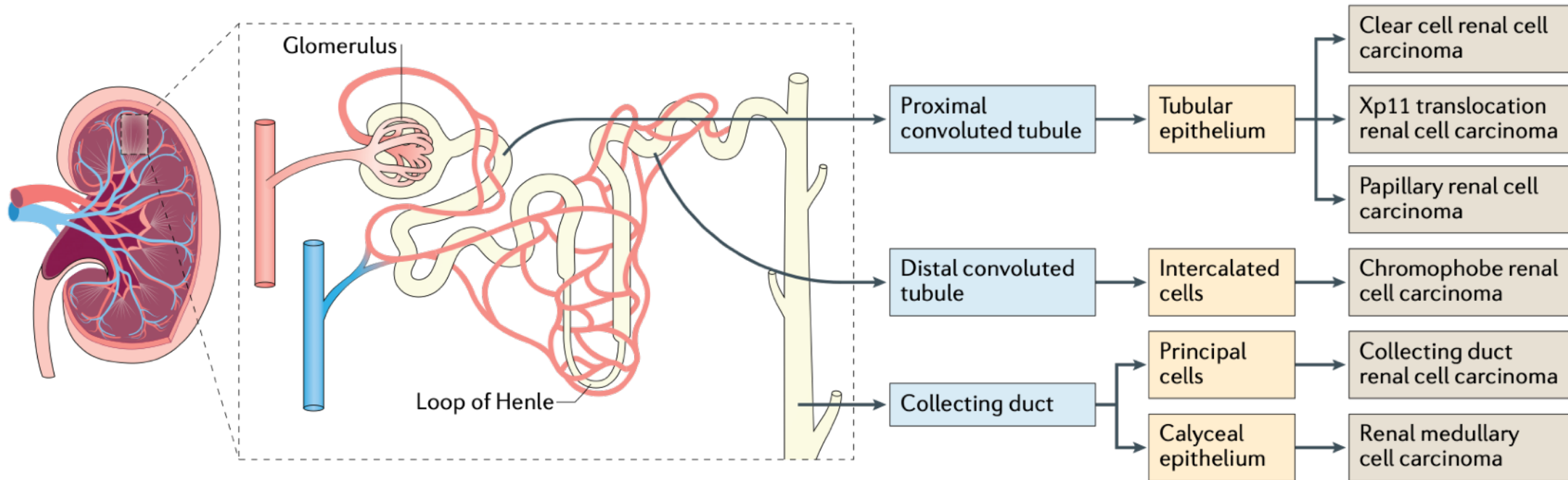
Rini BI, et al. ASCO 2019: 4500 (KN426)



Motzer et al, ASCO GU 21: 308

Rini BI, et al. ASCO 2019: 4512

Das Nierenzellkarzinom (NCC) besteht aus verschiedenen Entitäten



Neue WHO Klassifikation

Einführung von molekularen Entitäten in die Diagnostik



Nur noch 1 pRCC Typ

Molekular definierte Entitäten

ICD-O-3.2	ICD-O label (subtypes are indicated in grey text, with the label indented)
Renal cell tumours	
Clear cell renal tumours	
8110/3	Clear cell renal cell carcinoma
8116/3	Multilocular cystic renal neoplasm of low malignant potential
Papillary renal tumours	
	Papillary adenoma
	Papillary renal cell carcinoma *
Oncocytic and chromophobe renal tumours	
8290/0	Oncocytoma
8317/3	Chromophobe cell renal carcinoma
	Other oncocytic tumours of the kidney
Collecting duct tumours	
8319/3	Collecting duct carcinoma
Other renal tumours	
8321/1	Clear cell papillary renal cell tumour*
8480/3	Mucinous tubular and spindle cell carcinoma
8316/3	Tubulocystic renal cell carcinoma
8316/3	Acquired cystic disease-associated renal cell carcinoma
8311/3	Embryonic, solid and cystic renal cell carcinoma
8312/3	Renal cell carcinoma, NOS
Molecularly defined renal carcinomas	
8313/3	TFE2-rearranged renal cell carcinomas
8313/3	TFEB-altered renal cell carcinomas
8311/3	HLX3 (formerly TCE3)-mutated renal cell carcinoma
8311/3	Fumarate hydratase-deficient renal cell carcinoma
8311/3	Hereditary leiomyomatosis and renal cell carcinoma syndrome-associated renal cell carcinoma
8311/3	Succinate dehydrogenase-deficient renal cell carcinoma
8311/3	ALE-rearranged renal cell carcinomas
8510/3	Medulляр carcinoma, NOS
8510/3	SMARCB1-deficient medullary-like renal cell carcinoma
8510/3	SMARCB1-deficient undifferentiated renal cell carcinoma, NOS
8510/3	SMARCB1-deficient dedifferentiated renal cell carcinoma of other specific subtypes
Metastatic tumours	
8350/0	Metastatic adenoma
901.30	Metastatic adenofibroma
8950/0	Metastatic stromal tumour
Mixed epithelial and stromal renal tumours	
8959/0	Mixed epithelial and stromal tumour
8959/0	Adult cystic nephroma
8959/0	Pandiatric cystic nephroma
Renal mesenchymal tumours	
Adult renal mesenchymal tumours	
8850/0	Angiomyolipoma
8850/0	Dysplastic angiomyolipoma
8850/0	Angiomyolipoma with epithelial cysts
8850/1	Angiomyolipoma, epithelioid
9111/1	Hemangioblastoma
8381/0	Juxtaglomerular tumour
8381/0	Functioning juxtaglomerular cell tumour
8381/0	Nonfunctioning juxtaglomerular cell tumour
8966/0	Renomedullary interstitial cell tumour
Pediatric renal mesenchymal tumours	
8967/0	Ossifying renal tumour of infancy
8960/1	Mesoblastic nephroma
8960/1	Classic congenital mesoblastic nephroma
8960/1	Cellular congenital mesoblastic nephroma
8960/1	Mixed congenital mesoblastic nephroma
8963/3	Malignant fibroblast tumour of the kidney
8964/3	Clear cell sarcoma of kidney
Embryonal neoplasms of the kidney	
Nephroblastic tumours	
	Nephrogenic rests
	Perilobar nephrogenic rests
	Intralobar nephrogenic rests
	Nephroblastomatosis
8969/1	Cystic partially differentiated nephroblastoma
8969/3	Nephroblastoma

👉 nicht-klarzelliges Nierenzellkarzinom ist keine Diagnose

👉 Benenne jede Entität mit Ihrem Namen

Empfehlungen der Leitlinien zur Systemtherapie


**Leitlinienprogramm
Onkologie**

10.5	Für die nicht-klarzelligen Nierenzellkarzinome gibt es keine entitätsbezogenen Standards.	EK		
10.7	Die nicht-klarzelligen Nierenzellkarzinome sollen außerhalb von Studien mit einer IO/IO oder IO/TKI Kombination analog zu den klarzelligen Nierenzellkarzinomen behandelt werden.	A	1+	[217] ; [218] ; [143] ; [219] ; [220] ; [221] ; [222] ; [223] ; [224] ; [146]
10.8	Im Falle einer Monotherapie sollten bei metastasiertem nicht-klarzelligen Nierenzellkarzinom TKI-Inhibitoren, präferenziell Sunitinib, eingesetzt werden.	B	1+	[225] ; [226] ; [227] ; [158]
10.9	mTOR-Inhibitoren können beim chromophoben Nierenzellkarzinom als Alternative eingesetzt werden.	EK		



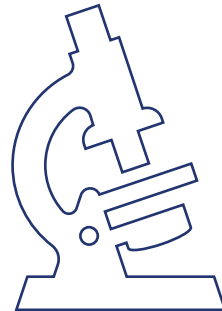
Es wird empfohlen,
 Patienten mit nicht -
 klarzelligem
 Nierenzellkarzinom
 analog dem
 Algorithmus der
 klarzelligen
 Karzinome zu
 behandeln

Faktoren in der Behandlungsentscheidung

Zulassung



**Tumor-assoziierte
Parameter**



**Patient-
assoziierte
Parameter**



Zusammenfassung

**IO-Combos sind
der Standard in
der Therapie des
mets. NCC**

Zusammenfassung

**IO-Combos sind
der Standard in
der Therapie des
mets. NCC**

**Langzeitdaten der
Therapien sind
robust**

Zusammenfassung

**IO-Combos sind
der Standard in
der Therapie des
mets. NCC**

**Langzeitdaten der
Therapien sind
robust**

**Klinische
Parameter
beeinflussen die
Auswahl der
(Mono-)Therapie**

Vielen Dank für Ihre Aufmerksamkeit



Prof. Dr. med. Viktor Grünwald

Interdisciplinary GU Oncology

University Hospital Essen

 @ViktorGruenwald

