Universitätsklinikum
Brandenburg an der Havel

MHB UNIVERSITÄTS KLINIKUM
IM VERBUND

Neue medikamentöse Therapieoptionen in der Uro-Onkologie

Univ.-Prof. Dr. med. Hendrik Borgmann

Universitätsklinikum Brandenburg an der Havel

MHB UNIVERSITÄTS KLINIKUM IM VERBUND

Darlegung potentieller Interessenkonflikte

Der Inhalt des folgenden Vortrages ist Ergebnis des Bemühens um größtmögliche Objektivität und Unabhängigkeit.

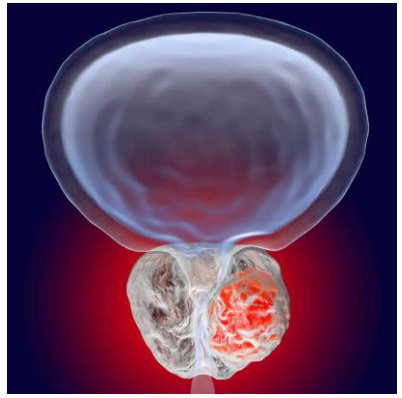
Als Referent versichere ich, dass in Bezug auf den Inhalt des folgenden Vortrags keine Interessenskonflikte bestehen, die sich aus einem Beschäftigungsverhältnis, einer Beratertätigkeit oder Zuwendungen für Forschungsvorhaben, Vorträge oder andere Tätigkeiten ergeben.

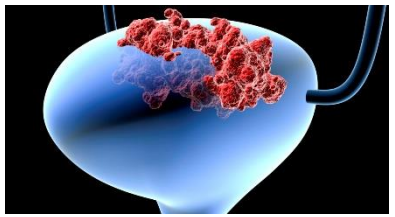
Roadmap

Prostatakarzinom
- mHSPC
- mCRPC

Nierenzellkarzinom
- Erst-Linie
- Adjuvanz

Urothelkarzinom
- Adjuvanz
- Dritt-Linie





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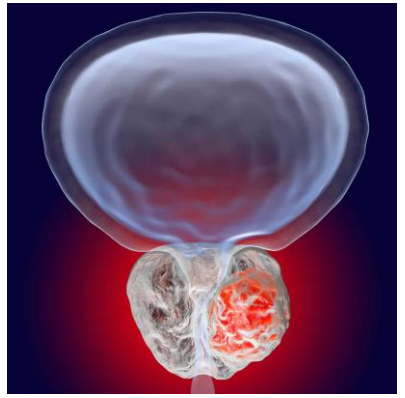
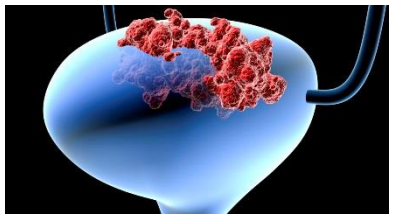




Aktuelle Möglichkeiten der Kombinationstherapie bei mHSPC

mHSPC

ADT mono

ADT + Abi

EMA-Zulassung
Oktober 2017

ADT + Doc + Daro

EMA-Zulassung
März 2023

ADT + Enza

EMA-Zulassung
April 2021

ADT + Doc

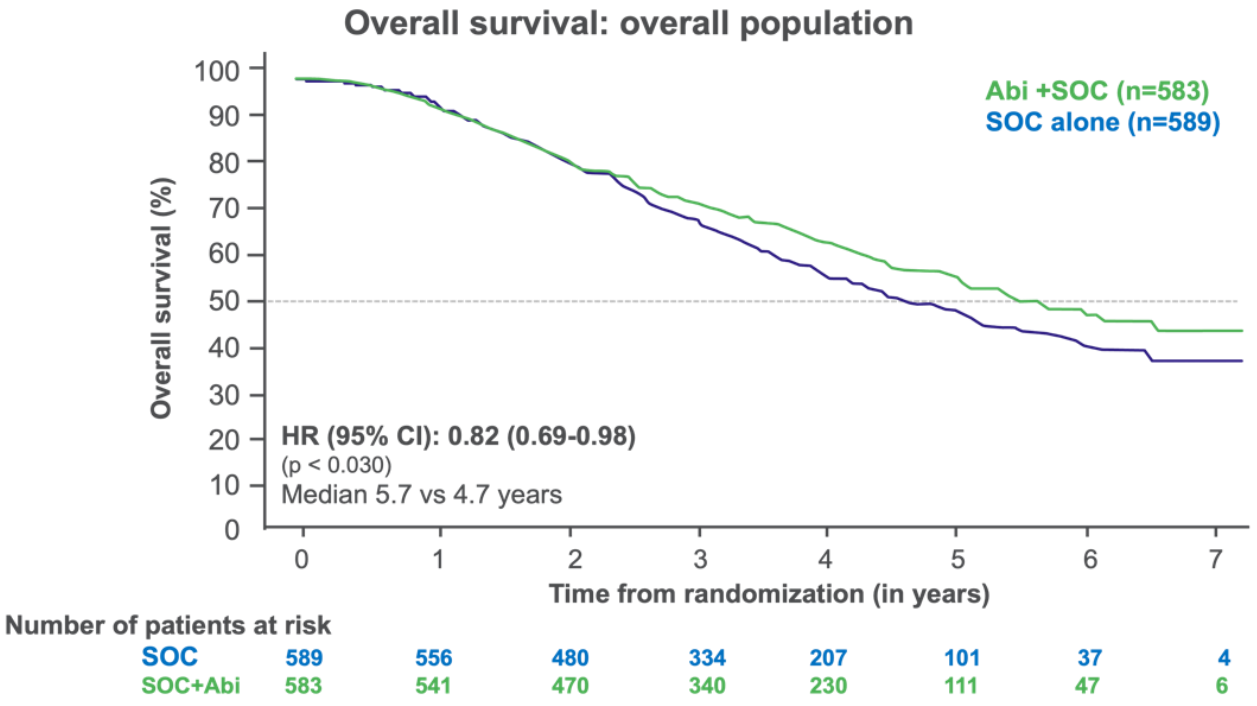
EMA-Zulassung
Dezember 2019

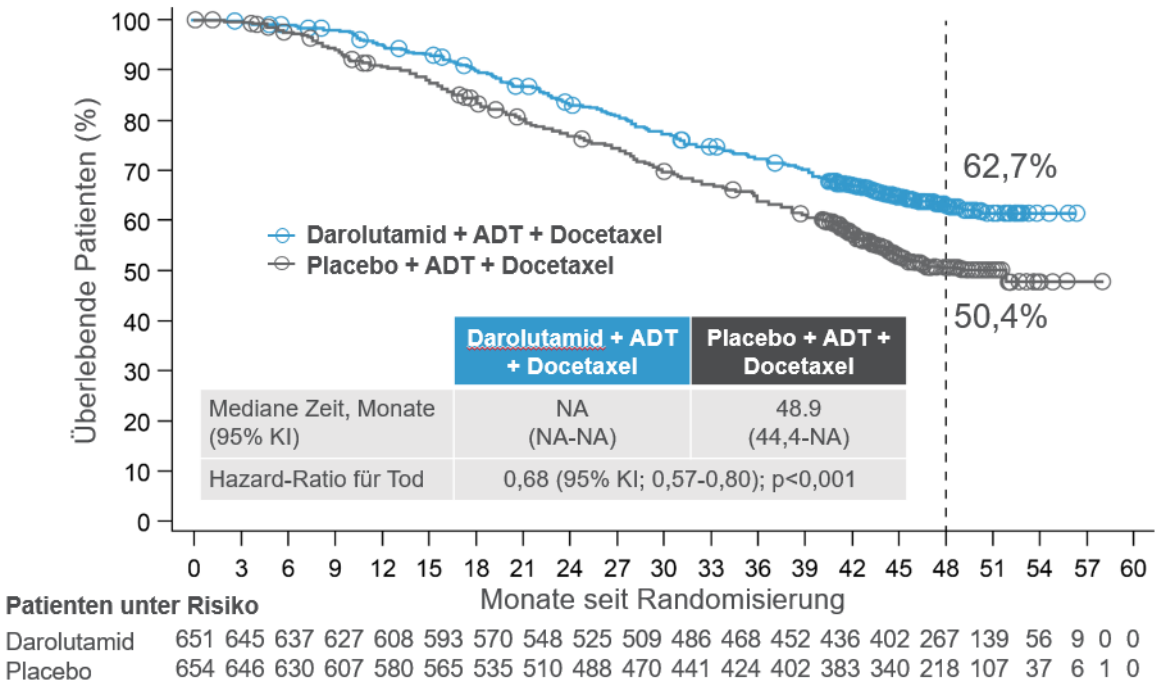
ADT + Apa

EMA-Zulassung
Januar 2020

Kommt nach der Doublette das Triplet?...

Peace-1 und ARASENS: Triple-Therapie (ADT + NHT + Doce) bei mHSPC





Fizazi et al. ESMO 2021: LBA5

Smith MR, NEJM 2022

Kommt nach der Doublette das Triplet?...

… und ist das überhaupt besser?...

Meta-Analyse Triple-Therapie (n=5.804):

Einschluss von Daten aus TITAN, ARCHES, ENZAMET, PEACE-1 und ARASENS

Overall survival

	ADT	DOC+ADT	NHT+ADT	NHT+DOC+ADT
ADT		0.79 (0.70-0.88)	0.61 (0.53-0.70)	0.59 (0.50-0.69)
DOC+ADT	1.27 (1.13-1.42)		0.77 (0.64-0.92)	0.74 (0.66-0.84)
NHT+ADT	1.65 (1.43-1.90)	1.30 (1.09-1.56)		0.97 (0.78-1.20)
NHT+DOC+ADT	1.70 (1.44-2.02)	1.35 (1.19-1.52)	1.03 (0.83-1.29)	

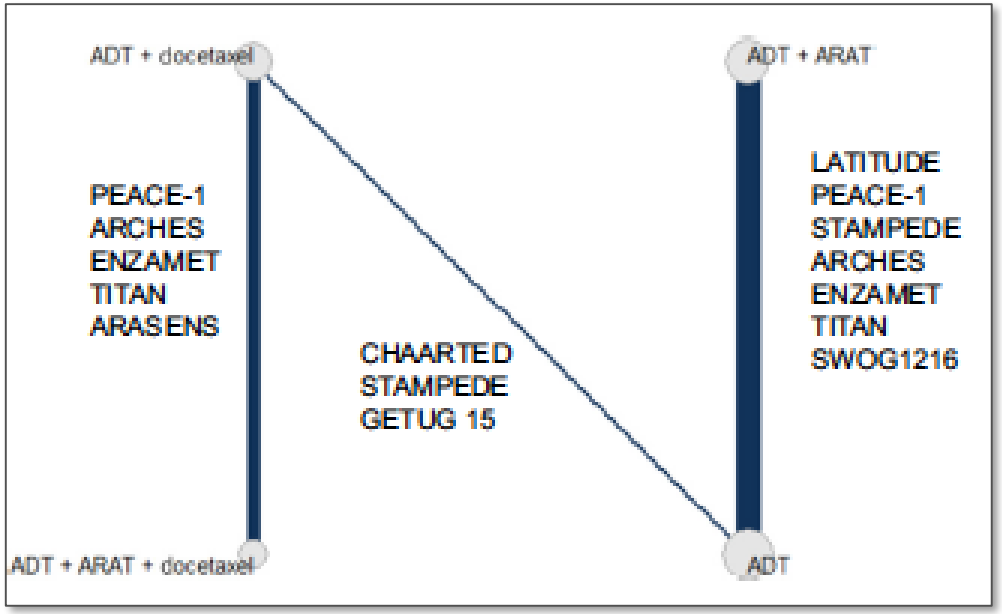
Radiographic progression free survival

	ADT	DOC+ADT	NHT+ADT	NHT+DOC+ADT
ADT		0.67 (0.60-0.75)	0.40 (0.35-0.47)	0.33 (0.26-0.41)
DOC+ADT	1.49 (1.34-1.66)		0.60 (0.50-0.72)	0.49 (0.40-0.59)
NHT+ADT	2.48 (2.14-2.87)	1.66 (1.38-1.99)		0.81 (0.63-1.05)
NHT+DOC+ADT	3.03 (2.51-3.66)	2.03 (1.74-2.37)	1.23 (0.95-1.60)	

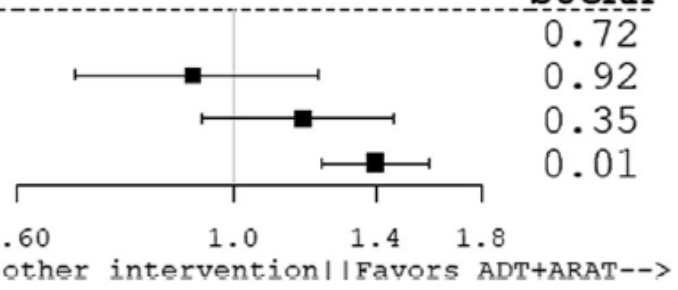
Naqvi et al., J Clin Oncol 2022 (ASCO)

Meta-Analyse Triple-Therapie:

- Elf randomisierte, kontrollierte mHSPC-Studien
- **N=11.546 Patienten**
- Standard random-effects Network-Metanalyse und Bayesian-Analyse zum Vergleich ADT/NHA vs. Triple



Treatment regimen	Hazard ratio (Bayesian)	95% Credible interval	SUCRA
ADT + ARAT	1		0.72
ADT + ARAT + docetaxel	0.91	[0.69;1.22]	0.92
ADT + docetaxel	1.18	[0.93;1.46]	0.35
ADT	1.40	[1.23;1.59]	0.01



Roy S. et al. Eur Urol Oncol 2022


SINGLE
DOUBLE
TRIPLE

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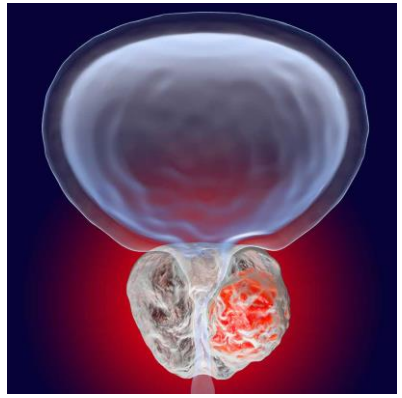
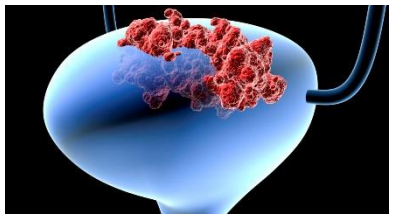
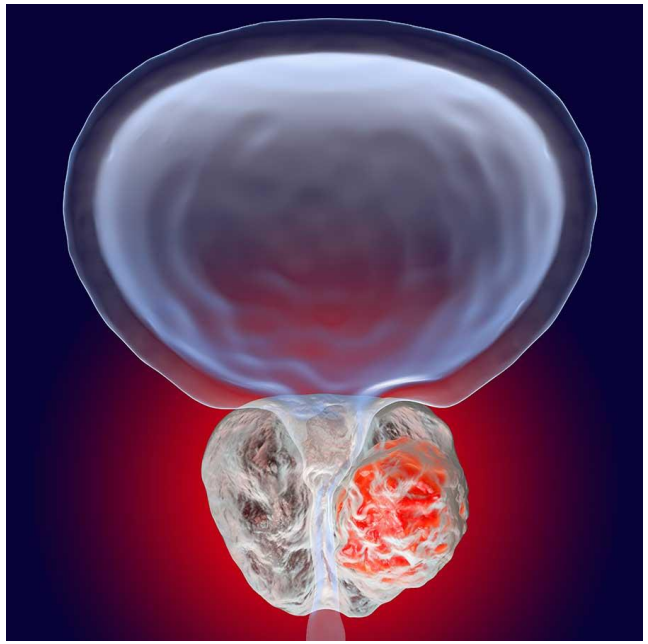


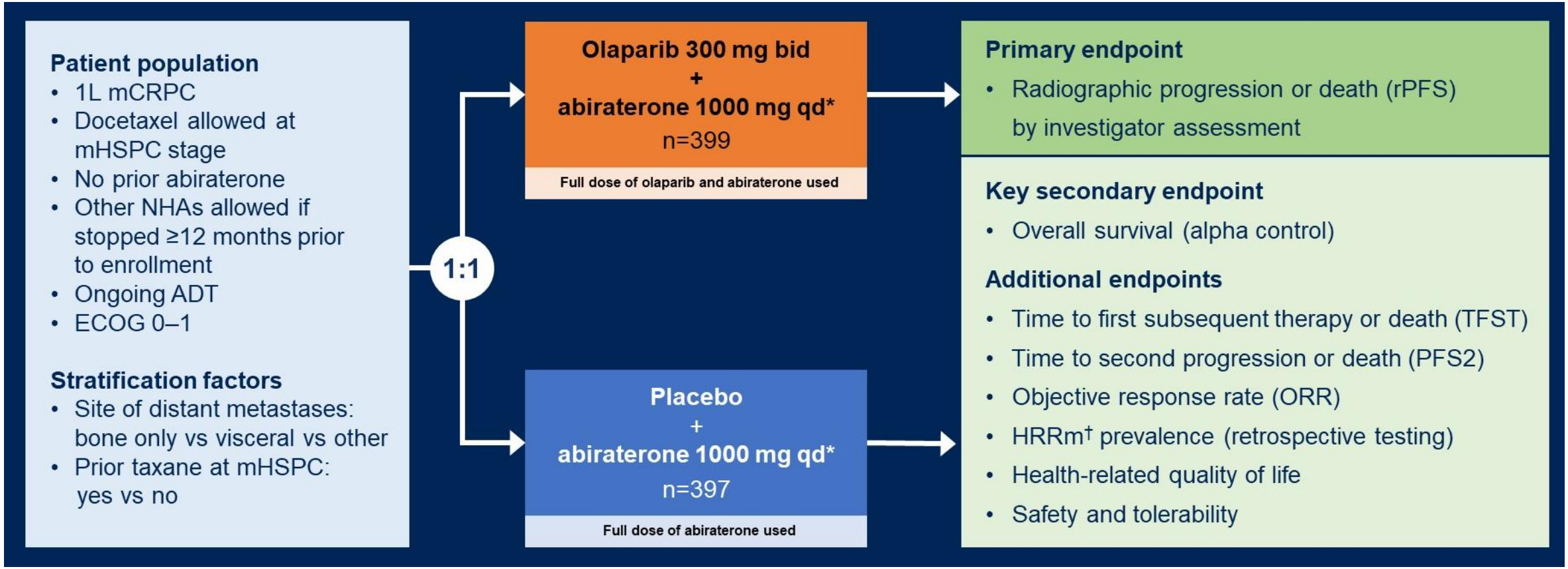


mCRPC



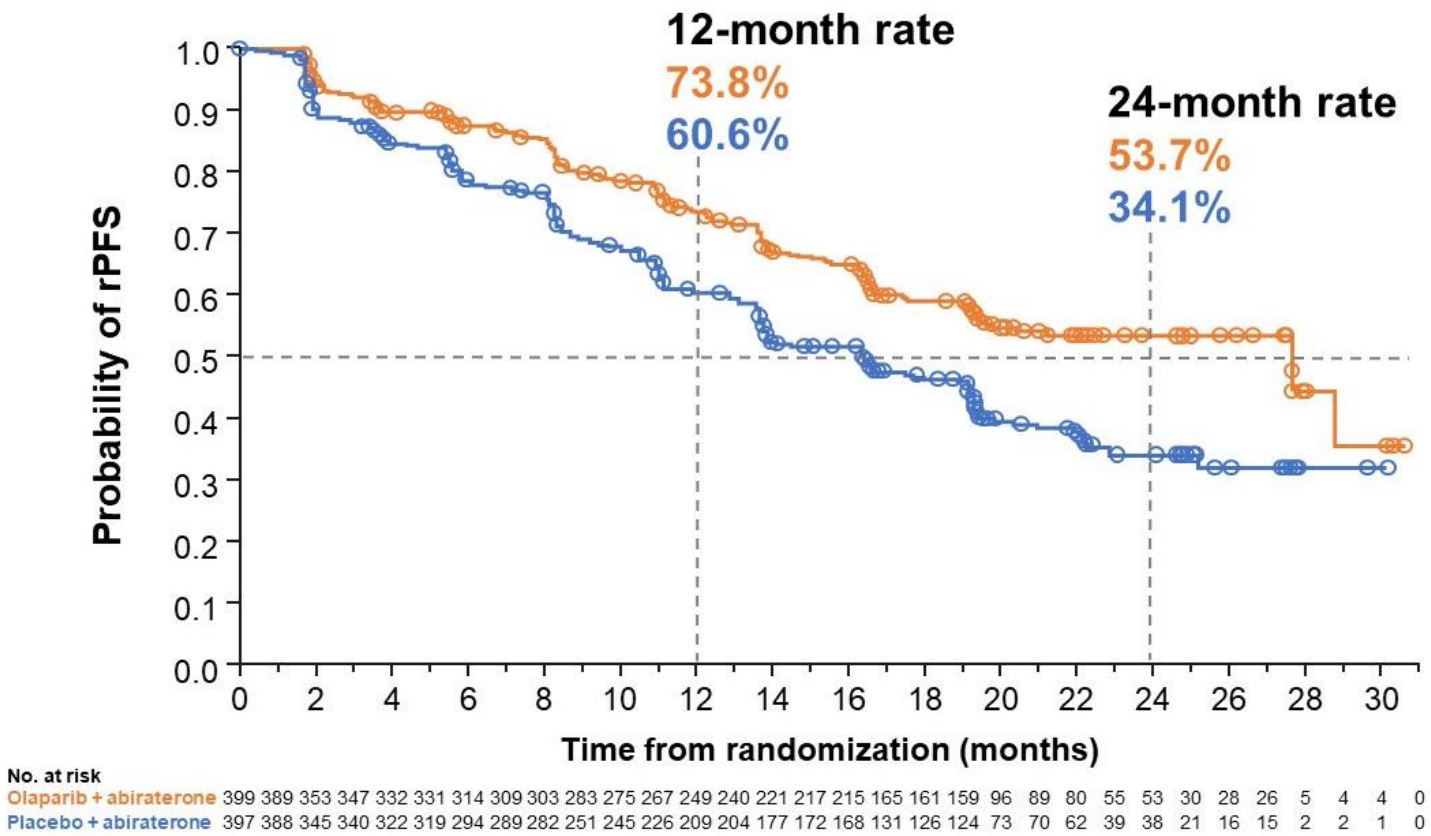
Zukünftige BRCA-Testung im Rahmen der Kombination obsolet?

PROPEL: Olaparib + Abirateron vs. Abirateron bei mCRPC



Saad F, ASCO-GU 2022

PROPEL: rPFS

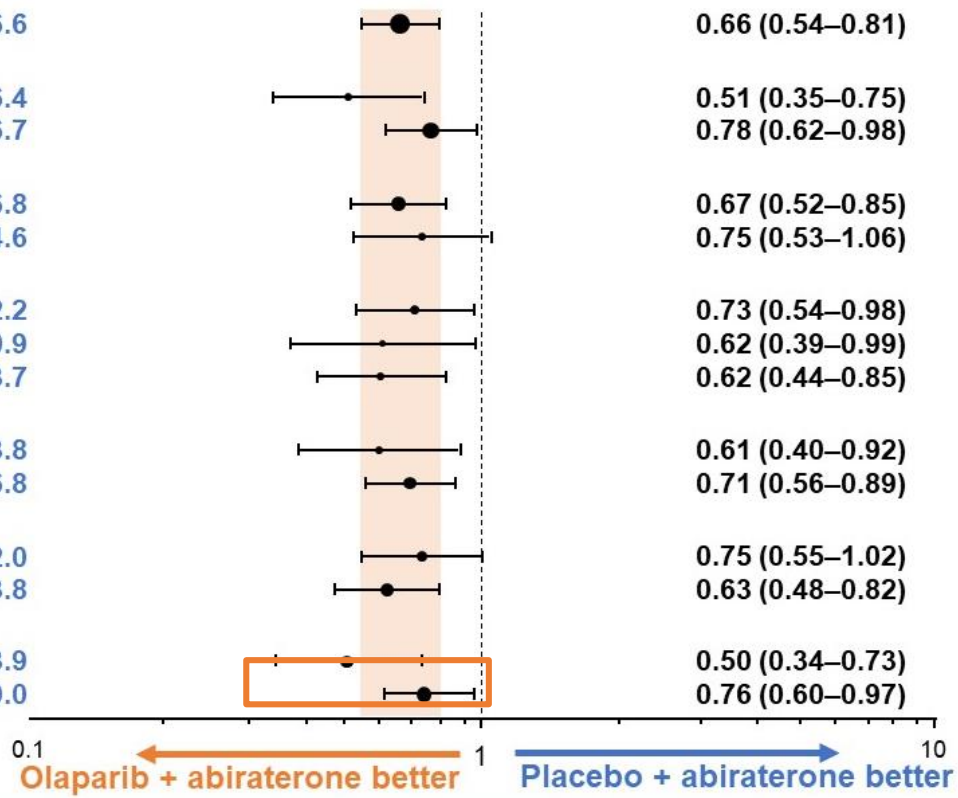


	Olaparib + abiraterone (n=399)	Placebo + abiraterone (n=397)
Events, n (%)	157 (39.3)	218 (54.9)
Median rPFS (months)	27.6	16.4
HR (95% CI)	0.61 (0.49–0.74) *P*<0.0001†	

Median rPFS improvement of 11.2 months favors olaparib + abiraterone‡

PROPEL: Subgruppenanalyse für rPFS

	Number of patients, n	Median rPFS, months		HR (95% CI)
All patients	796	24.8	16.6	**0.66 (0.54–0.81)**
Age at randomization				
<65	227	NR	16.4	**0.51 (0.35–0.75)**
≥65	569	22.0	16.7	**0.78 (0.62–0.98)**
ECOG performance status at baseline				
0	558	24.9	16.8	**0.67 (0.52–0.85)**
1	236	17.5	14.6	**0.75 (0.53–1.06)**
Site of distant metastases				
Bone only	434	27.6	22.2	**0.73 (0.54–0.98)**
Visceral	105	13.7	10.9	**0.62 (0.39–0.99)**
Other	257	20.5	13.7	**0.62 (0.44–0.85)**
Docetaxel treatment at mHSPC stage				
Yes	189	27.6	13.8	**0.61 (0.40–0.92)**
No	607	24.8	16.8	**0.71 (0.56–0.89)**
Baseline PSA				
Below median baseline PSA	396	25.2	22.0	**0.75 (0.55–1.02)**
Above or equal to median baseline PSA	397	18.5	13.8	**0.63 (0.48–0.82)**
HRRm status*				
HRRm	226	NR	13.9	**0.50 (0.34–0.73)**
Non-HRRm	552	24.1	19.0	**0.76 (0.60–0.97)**

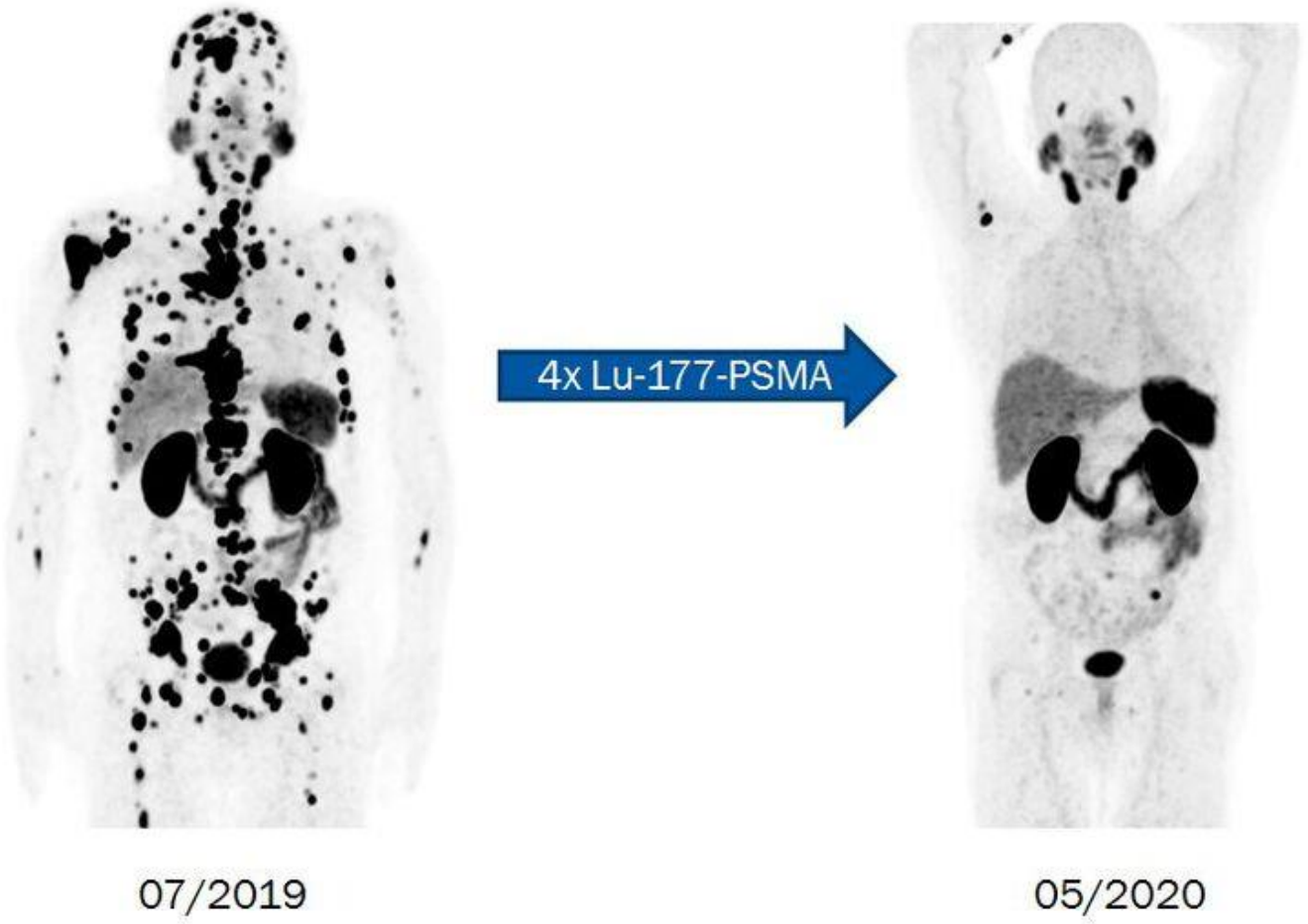


EMA-Zulassungserweiterung für Olaparib

Lynparza is indicated in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated.

PSMA-Radioligandentherapie ...

... DIE neue Drittlinientherapie?!



Open-label study of protocol-permitted standard of care ± ^{177}Lu-PSMA-617 in adults with PSMA-positive mCRPC

VISION

Eligible patients

- Previous treatment with <u>both</u>
  - ≥ 1 androgen receptor pathway inhibitor
  - 1 or 2 taxane regimens
- Protocol-permitted standard of care (SOC) planned before randomization
  - Excluding chemotherapy immunotherapy, radium-223, investigational drugs
- ECOG performance status 0–2
- Life expectancy > 6 months
- PSMA-positive mCRPC on PET/CT with ^{68}Ga-PSMA-11

2:1

Protocol-permitted SOC + ^{177}Lu-PSMA-617
7.4 GBq (200 mCi) every 6 weeks
4 cycles, increasable to 6

Protocol-permitted SOC alone

Treatment → Follow-up → Final analysis

- Randomization stratified by
  - ECOG status (0–1 or 2)
  - LDH (high or low)
  - Liver metastases (yes or no)
  - Androgen receptor pathway inhibitors in SOC (yes or no)

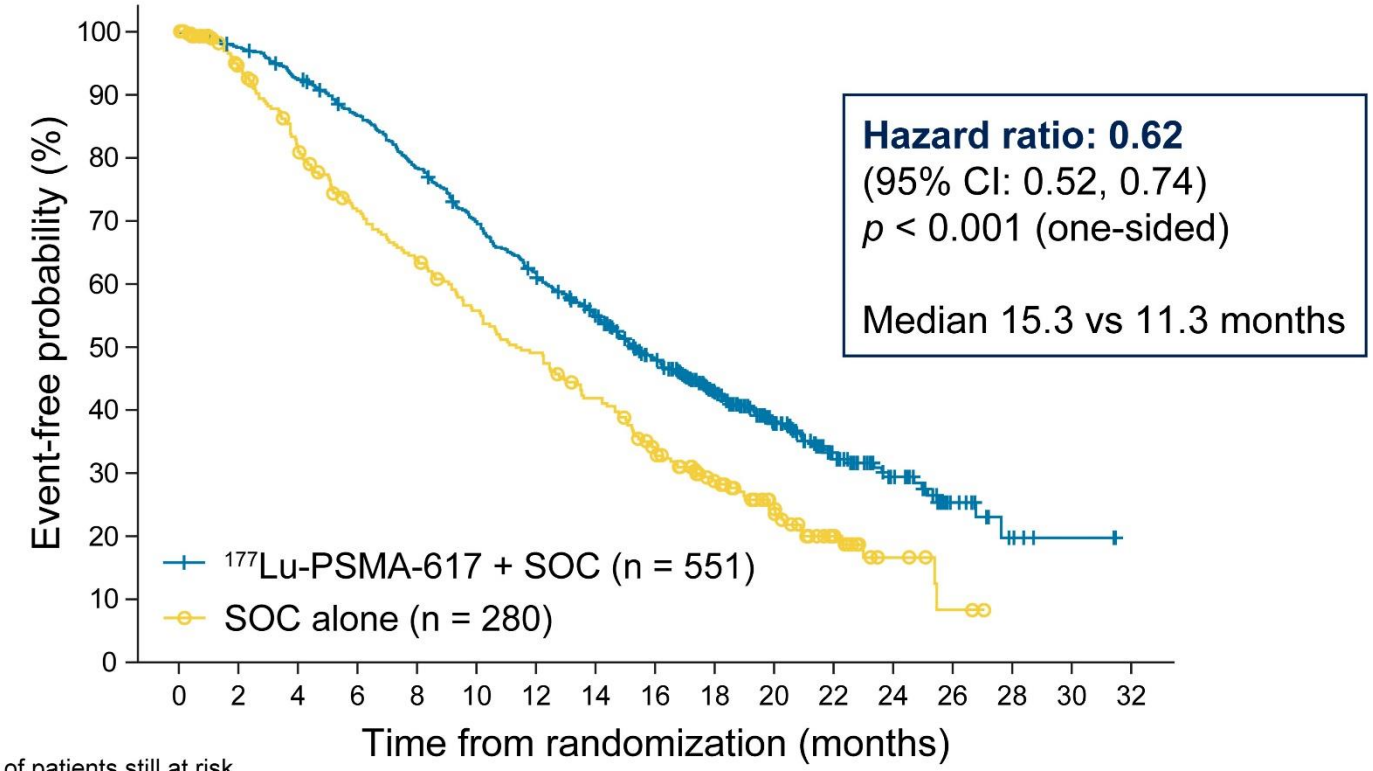
Radiographic progression-free survival (rPFS) per PCWG3

Overall survival (OS)

Primary endpoints: ^{177}Lu-PSMA-617 prolonged OS

Primary analysis

All randomized patients
(N = 831)



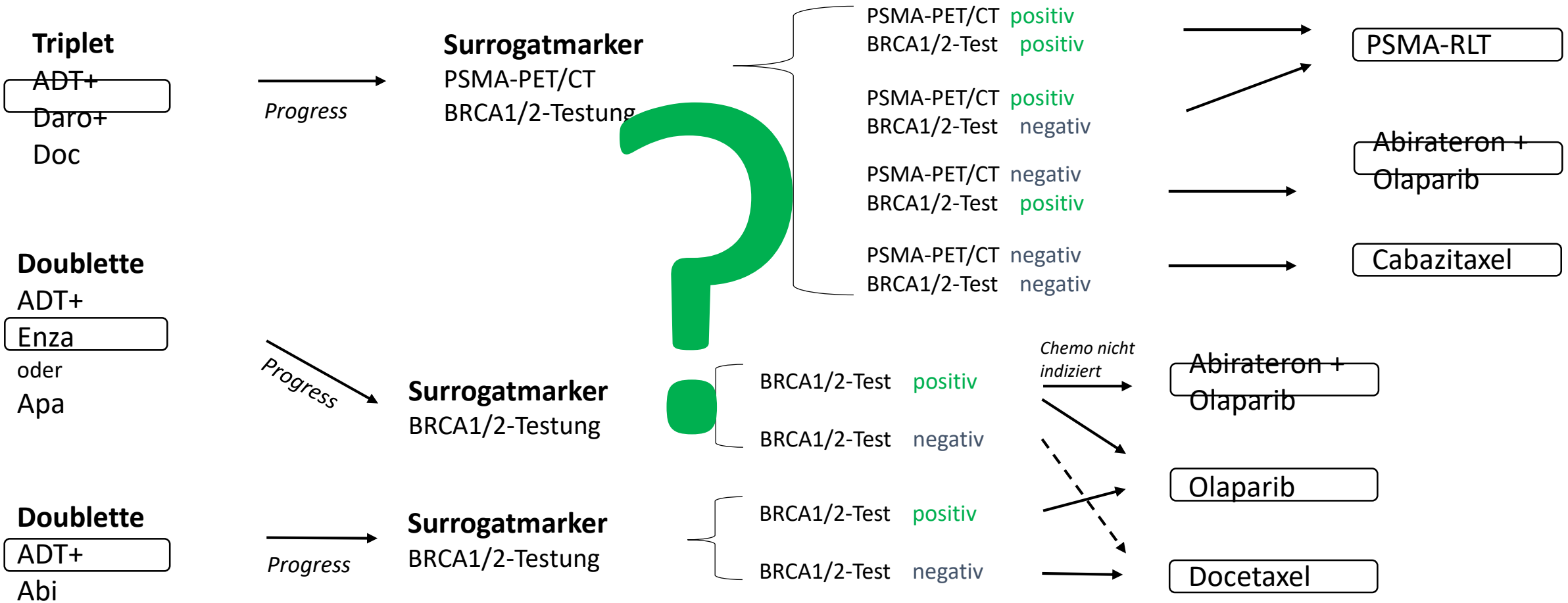
Number of patients still at risk

^{177}Lu-PSMA-617 + SOC	551	535	506	470	425	377	332	289	236	166	112	63	36	15	5	2	0
SOC alone	280	238	203	173	155	133	117	98	73	51	33	16	6	2	0	0	0

EMA-Zulassung für Pluvicto

Pluvicto in combination with androgen deprivation therapy (ADT) with or without androgen receptor (AR) pathway inhibition is indicated for the treatment of adult patients with progressive prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with AR pathway inhibition and taxane based chemotherapy.

Mögliches Flow Chart für die molekular basierte Sequenztherapie des metastasierten Prostatakarzinoms



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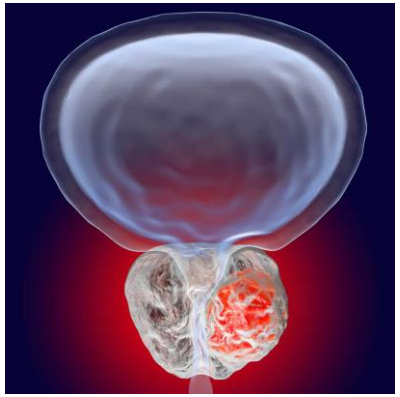
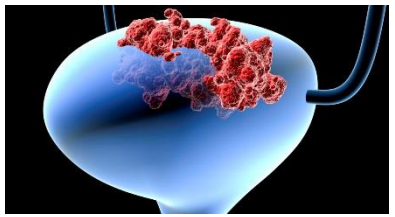




Metastasiertes RCC …

… kommt jetzt die Triple-Therapie?

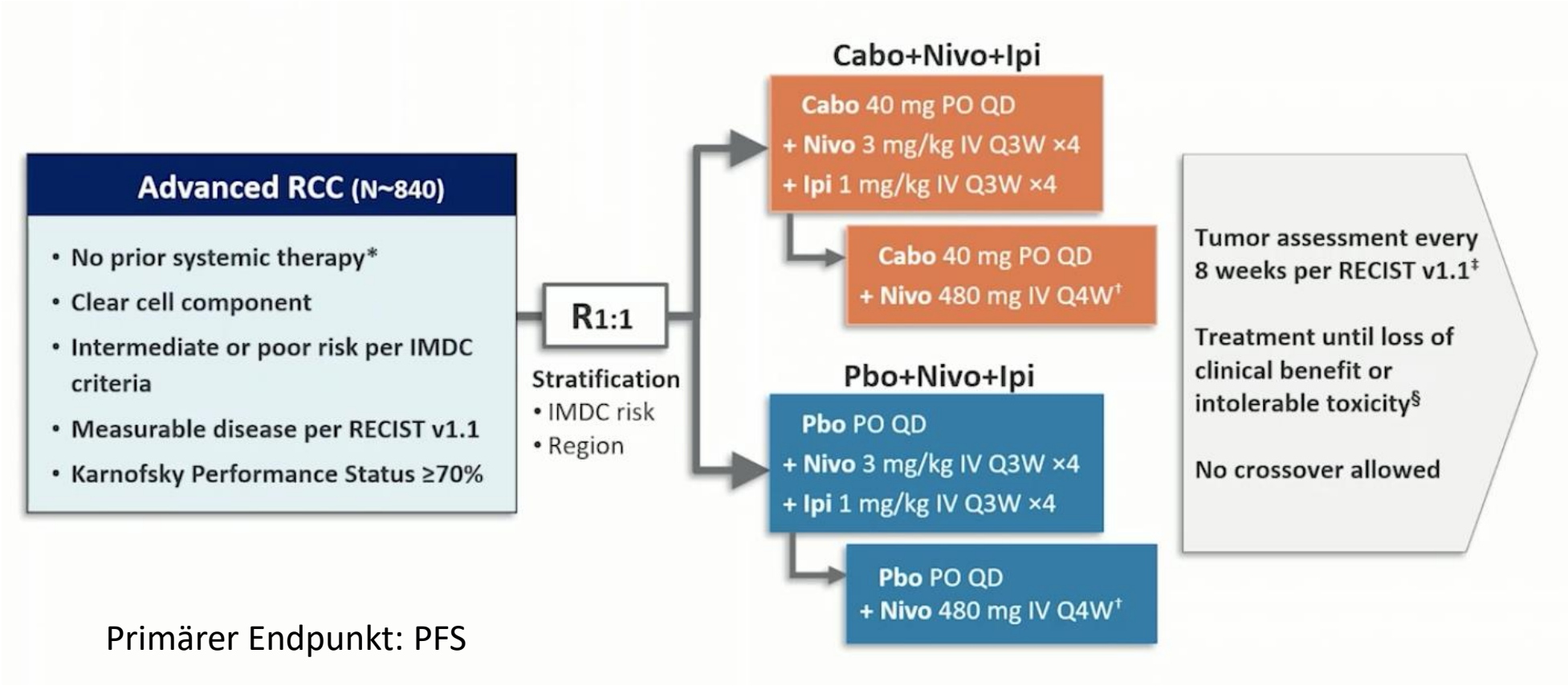
Effektivität aktueller RCC-Erstlinien-Kombinationstherapien

	Checkmate 9ER	Checkmate 214	Keynote-426	CLEAR	Javelin 101 Renal
	Cabo + Nivo (n=328) vs. **Sun** (n=328) FU 33 Monate	**Nivo + Ipi** (n=550) vs. **Sun** (n=564) FU 68 Monate	**Pem + Axi** (n=442) vs. **Sun** (n=444) FU 42 Monate	**Len + Pem** (n=335) vs. **Sun** (n=357) FU 27 Monate	**Ave + Axi** (n=444) vs. **Sun** (n=442) FU 13 Monate
OS Median, Monate HR (95% CI)	**37.7 vs. 34.3** 0.7 (0.55-0.90) p=0.0043	**47.0 vs. 26.6** 0.68 (0.58-0.81) p<0.0001	**45.7 vs. 40.1** 0.73 (0.60-0.88) p<0.001	**NR vs. NR** 0.66 (0.49-0.88) p<0.001	**NR vs. NR** 0.79 (0.61-1.03 p=0.004
PFS Median, Monate HR (95% CI)	**16.6 vs. 8.3** HR 0.56 (0.46-0.68) p<0.0001	**12.2 vs. 12.3** 0.89 (0.76-1.05) n.s.	**15.7 vs.11.1** HR 0.68 (0.58-0.8) p<0.001	**23.9 vs. 9.2** 0.39 (0.32-0.49) p<0.001	**13.8 vs. 7.2** 0.61 (0.47-0.79) p<0.001
ORR in %	**55.7 vs. 28.4** p<0.0001 CR 12.4 vs. 5.2	**42.0 vs. 27.0** p<0.0001 CR 11 vs. 2.0	**60.2 vs. 39.9** p<0.0001 CR 8.8 vs. 3	**71.0 vs. 36.1** p<0.001 CR 16.1 vs. 4.2	**52.5 vs.27.3** p<0.0001 CR 3.8 vs.2.0

Motzer R, Lancet Oncol 2022
Powels T, ASCO 2021
Motzer R, ESMO 2021

Motzer R, NEJM 2021
Choueiri TK, Ann Oncol 2020

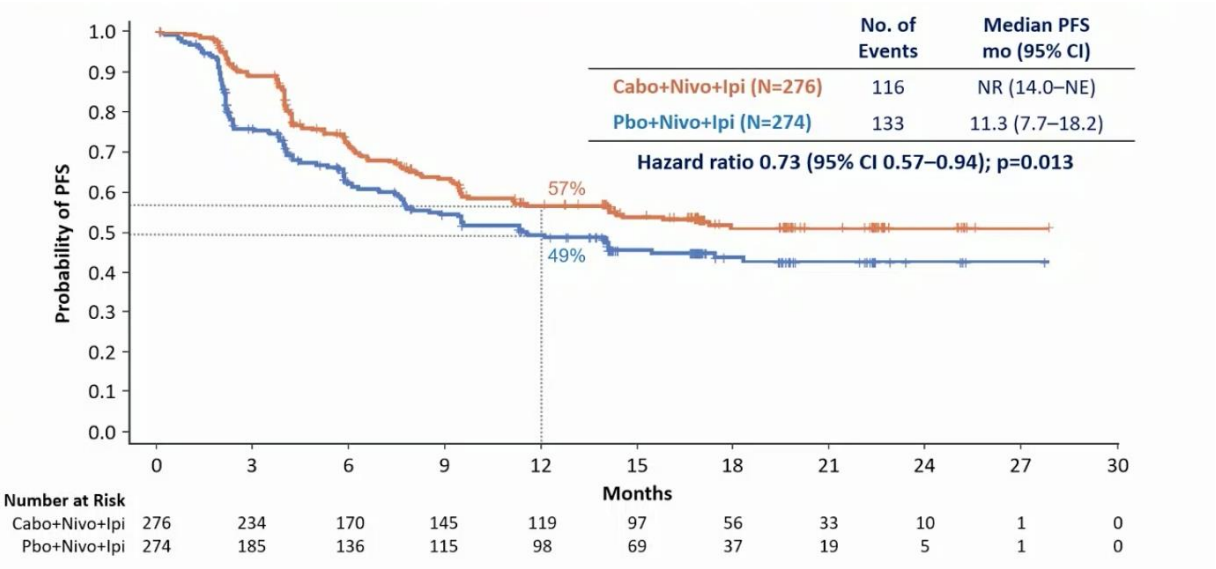
COSMIC 313:
Nivo + Ipi + Cabozantinib vs. Nivo + Ipi bei karzelligem mRCC

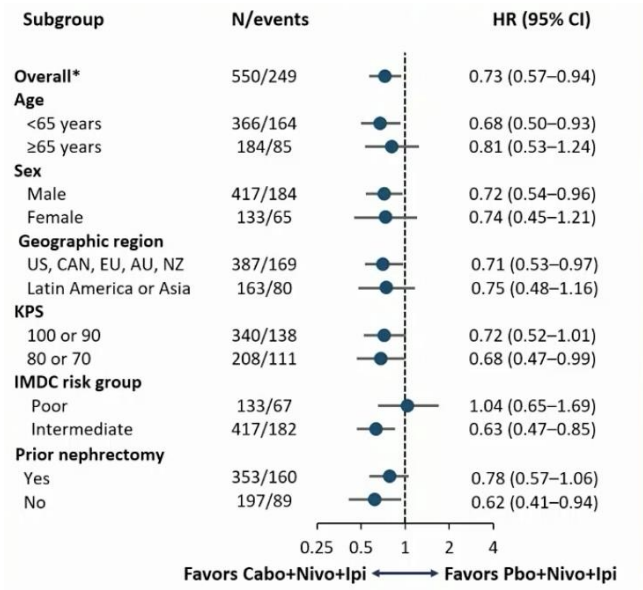


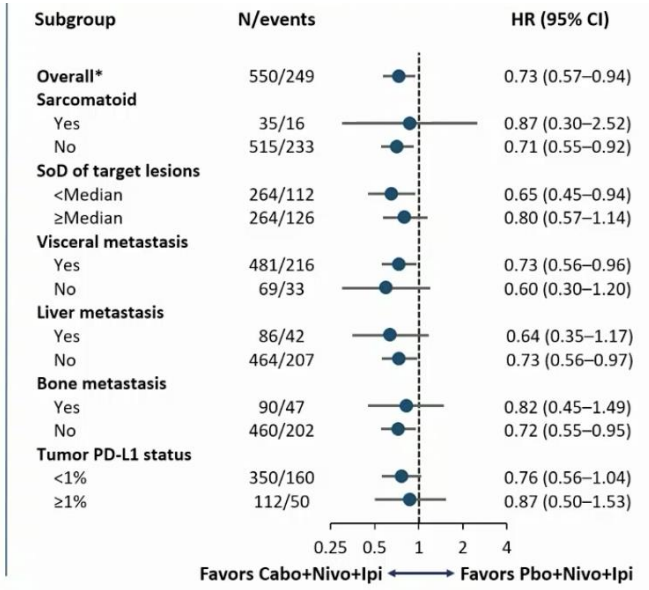
Primärer Endpunkt: PFS

Choueiri T, ESMO 2022

COSMIC 313: Ergebnisse







Choueiri T, ESMO 2022

COSMIC 313: Nebenwirkungen

	Cabo+Nivo+Ipi (N=426)		Pbo+Nivo+Ipi (N=424)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Treatment-related adverse events				
Any event,* %	99	73	91	41
Alanine aminotransferase increased	46	26	17	6
Aspartate aminotransferase increased	44	20	16	5
Diarrhea	41	4	18	3
Palmar-plantar erythrodysesthesia	28	3	4	0
Hypothyroidism	24	<1	15	0
Hypertension	23	8	5	2
Fatigue	22	2	21	1
Lipase increased	22	9	13	6
Amylase increased	20	5	12	2
Rash	20	2	20	1
Pruritus	20	0	26	<1

Choueiri T, ESMO 2022

Triple-Therapie beim mRCC:

Efficacy: **PFS-Verbesserung**

Safety: **hohe Toxizität**

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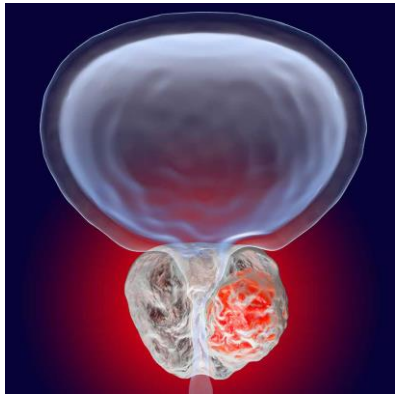
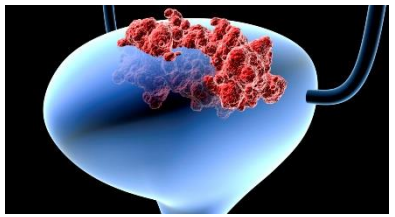
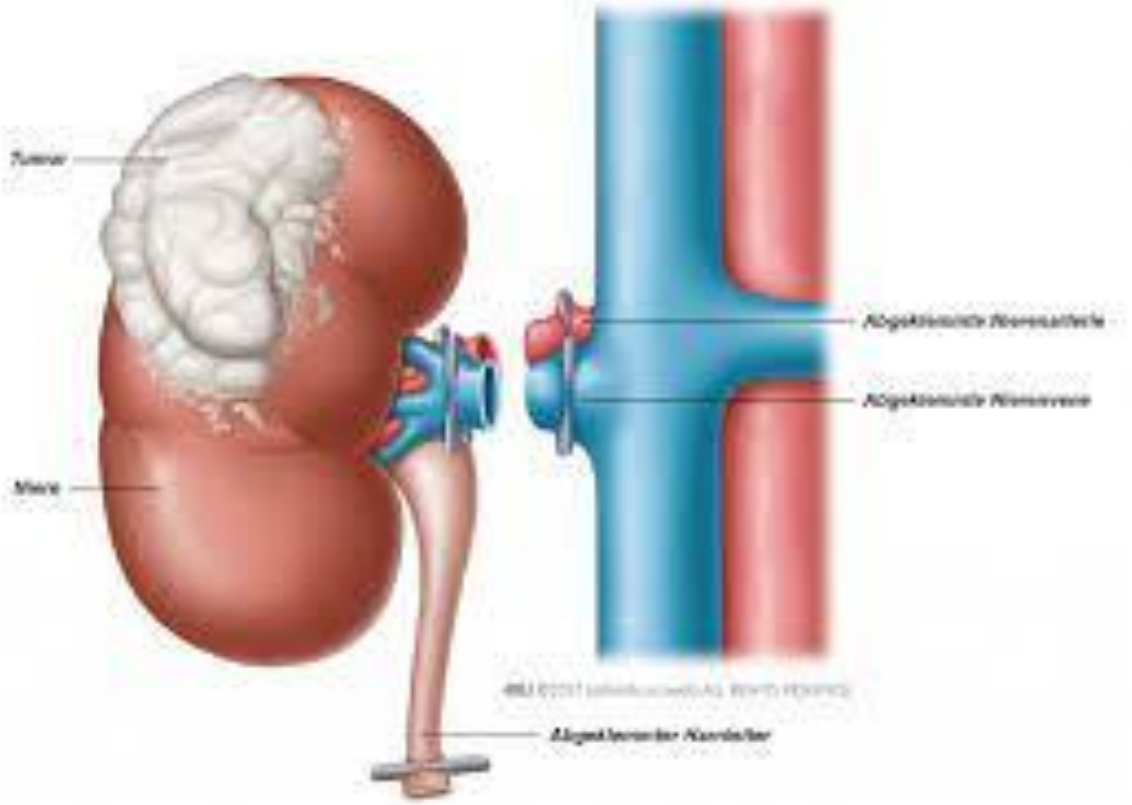




Hochrisiko-RCC nach Nephrektomie/Teilresektion ...

... gibt es ein sinnvolles Adjuvans?



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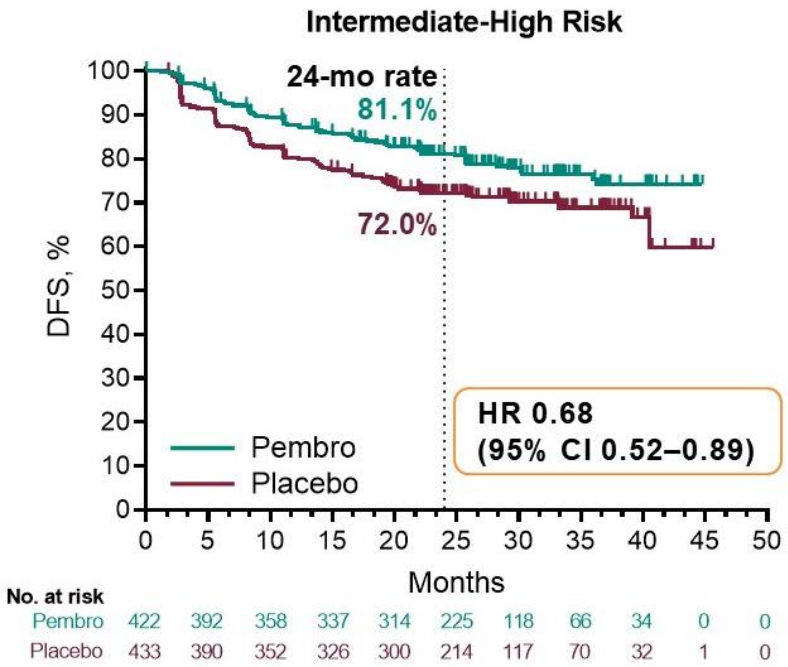
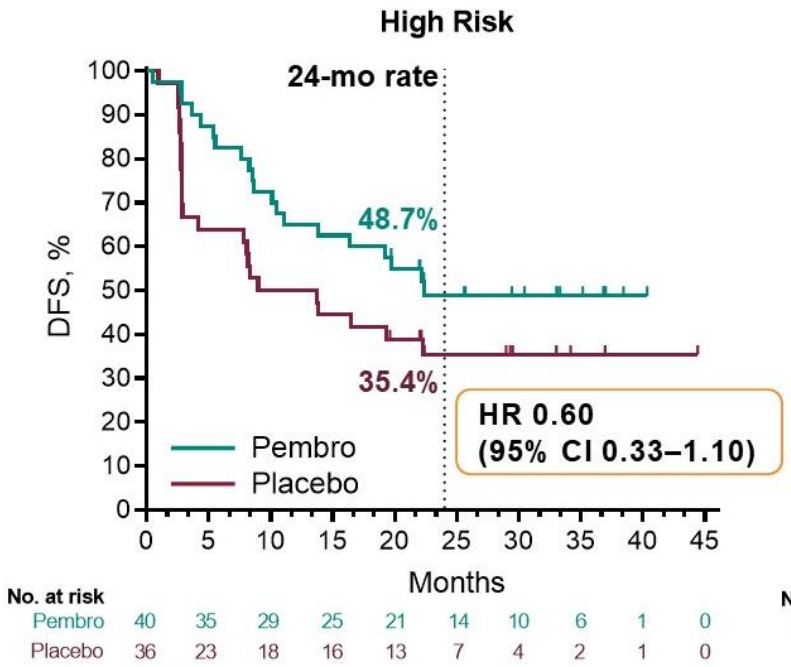
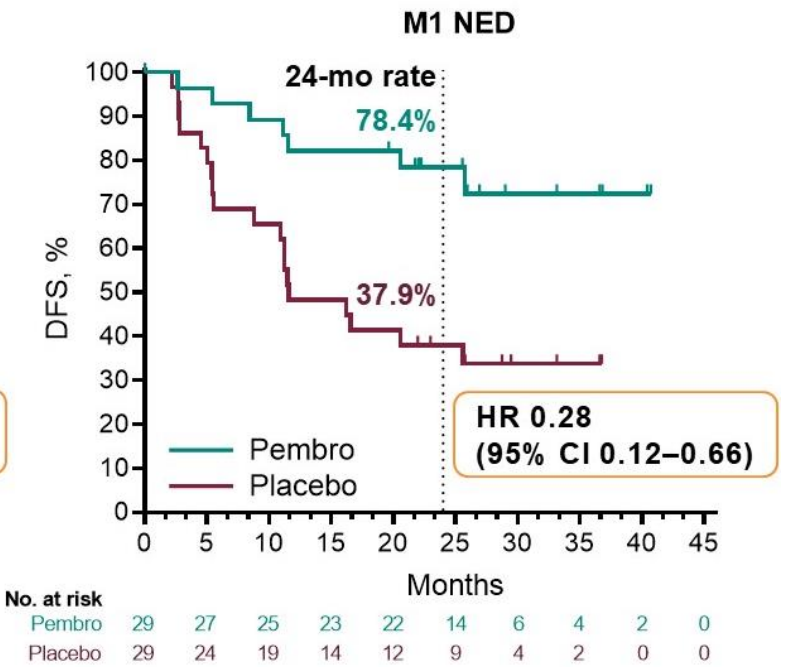
Pembrolizumab adjuvant bei Hochrisiko-RCC (Keynote-564)



	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)

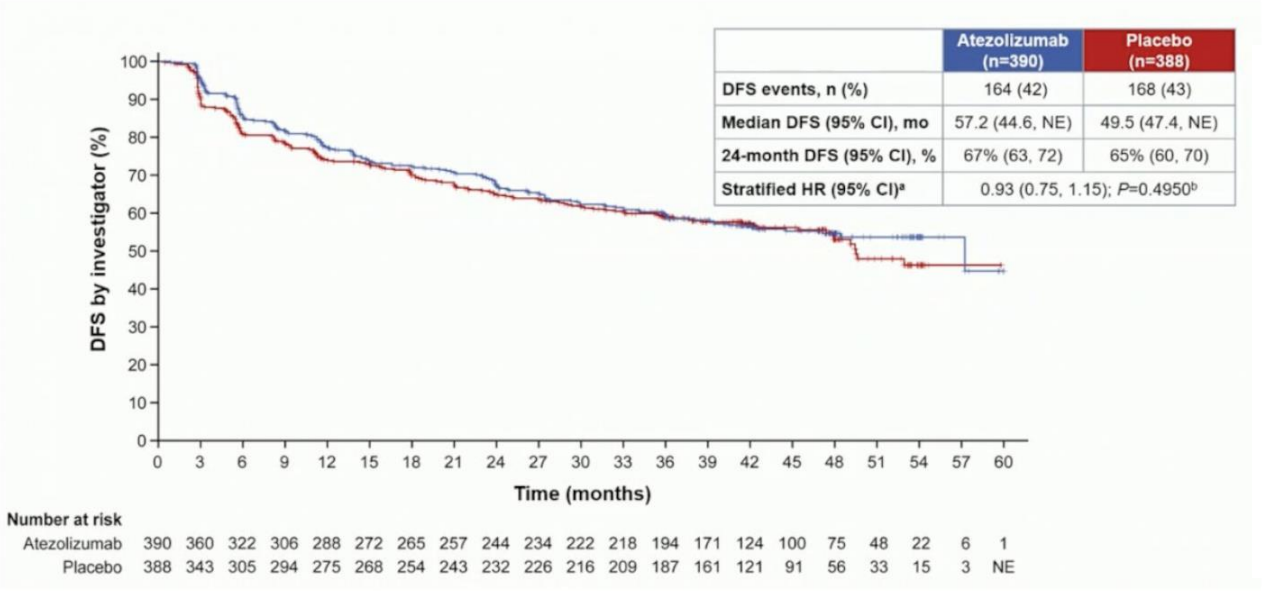


	Pts w/ Event	Median, mo (95% CI)
Pembro	7	NR (25.7–NR)
Placebo	19	11.6 (5.6–NR)

Choueiri T, ASCO GU 2022

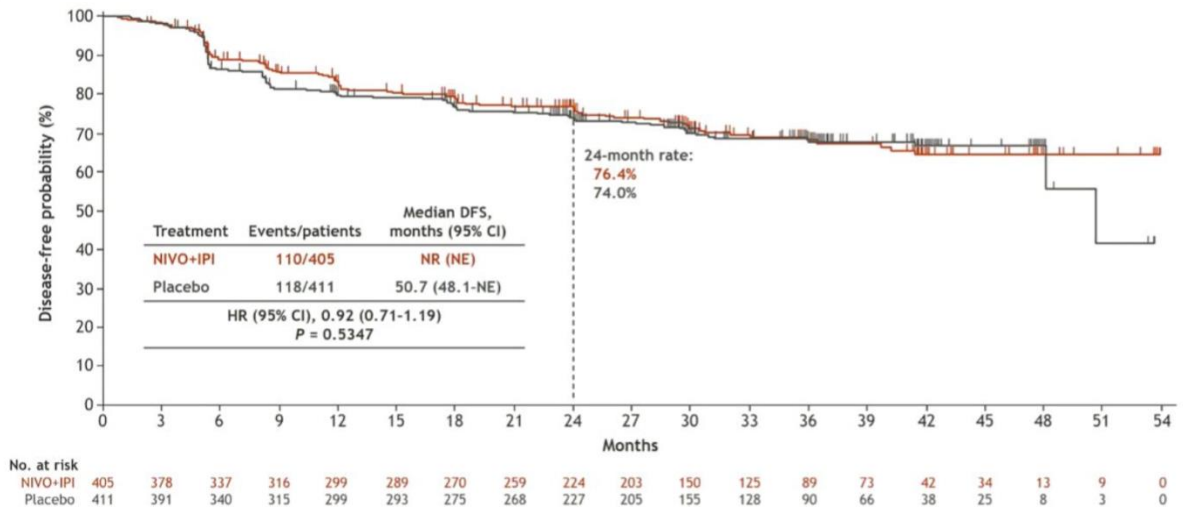
Die Daten der Konkurrenz: IMMOTION010 und Checkmate 914

IMMOTION010



Motzer RJ, ESMO 2022

Checkmate 914



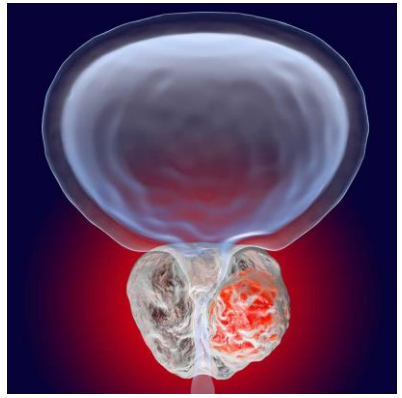
Bex A, ESMO 2022

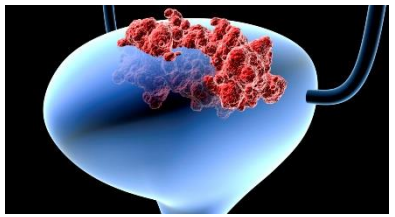
Roadmap

Prostatakarzinom
- mHSPC
- mCRPC

Nierenzellkarzinom
- Erst-Linie
- Adjuvanz

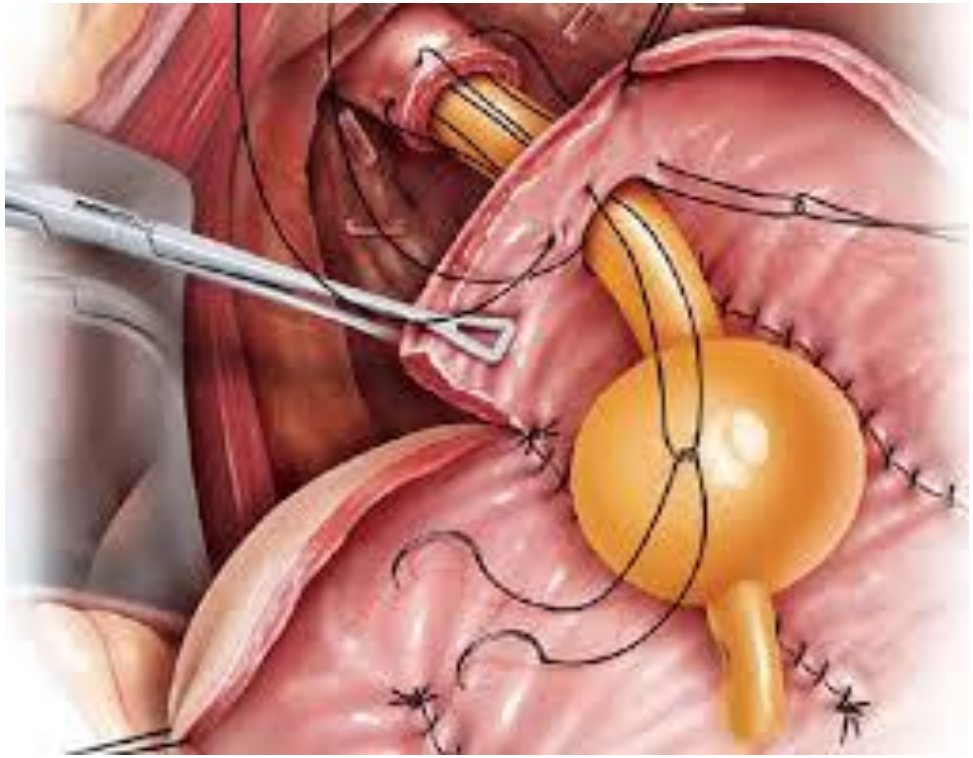
Urothelkarzinom
- **Adjuvanz**
- Dritt-Linie





Hochrisiko-MIBC (pT3/4 oder pN1) nach Zystektomie …

… gibt es zur Chemotherapie eine Alternative?



+

CheckMate 274: Phase 3, randomized, double-blind, multicenter study of adjuvant nivolumab versus placebo in patients with high-risk MIUC

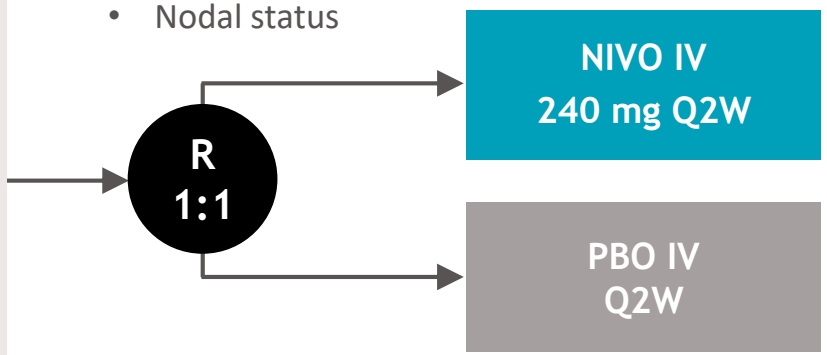
N = 709

Key inclusion criteria

- Patients with ypT2-ypT4a or ypN+ MIUC who had neoadjuvant cisplatin chemotherapy
- Patients with pT3-pT4a or pN+ MIUC without prior neoadjuvant cisplatin chemotherapy and not eligible/refuse adjuvant cisplatin chemotherapy
- Radical surgery within the past 120 days
- Disease-free status within 4 weeks of dosing

Stratification factors

- PD-L1 status (<1% vs ≥ 1%)[a]
- Prior neoadjuvant cisplatin-based chemotherapy
- Nodal status



Treat for up to 1 year of adjuvant therapy

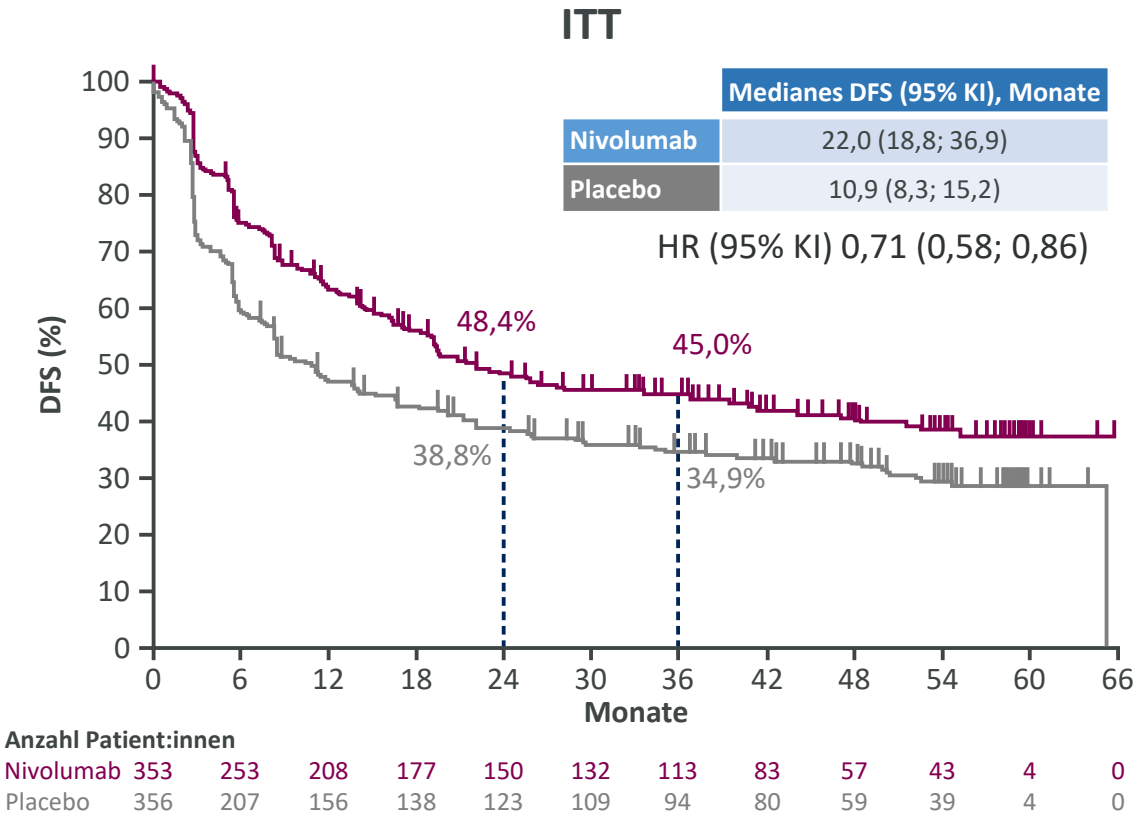
Minimum follow-up, 5.9 months
Median follow-up in ITT population, 20.9 months (NIVO) and 19.5 months (PBO)

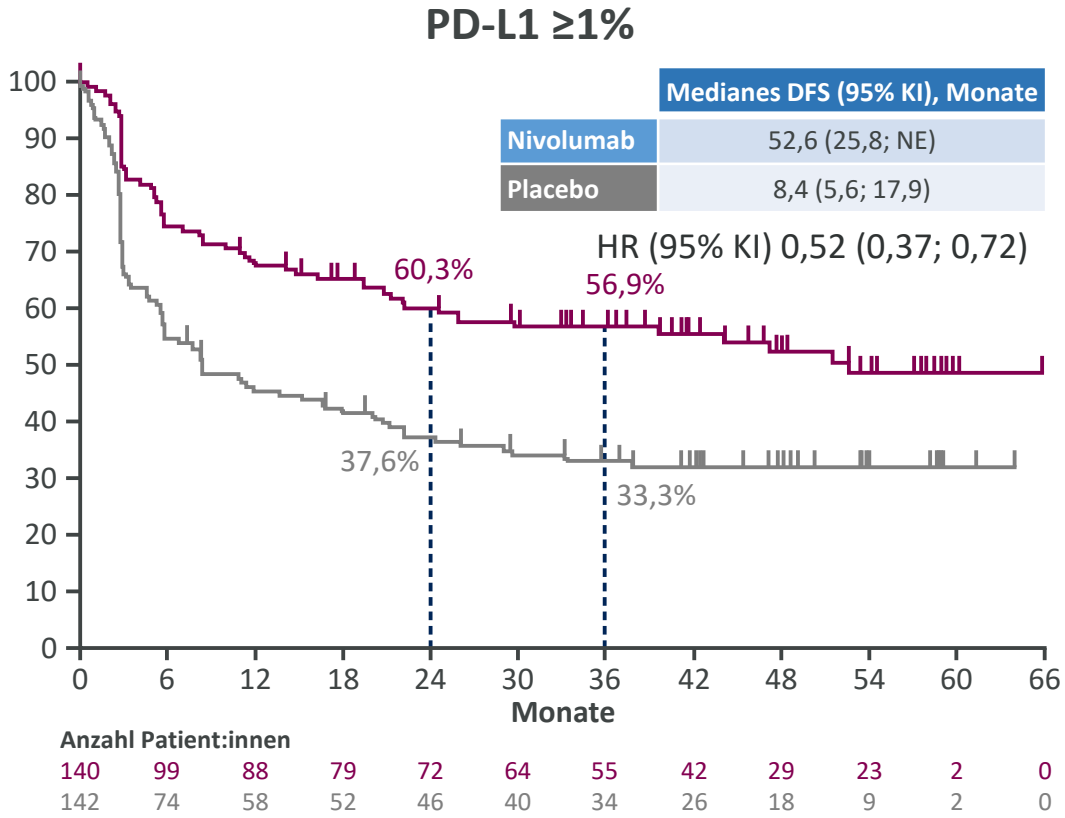
Primary endpoints: DFS in ITT population and DFS in all randomized patients with tumor PD-L1 ≥ 1%
Secondary endpoints: NUTRFS, DSS, and OS[b]
Exploratory endpoints included: DMFS, safety, HRQoL

Bajorin et al., ASCO GU 2021

CheckMate 274 – Erweitertes Follow-Up

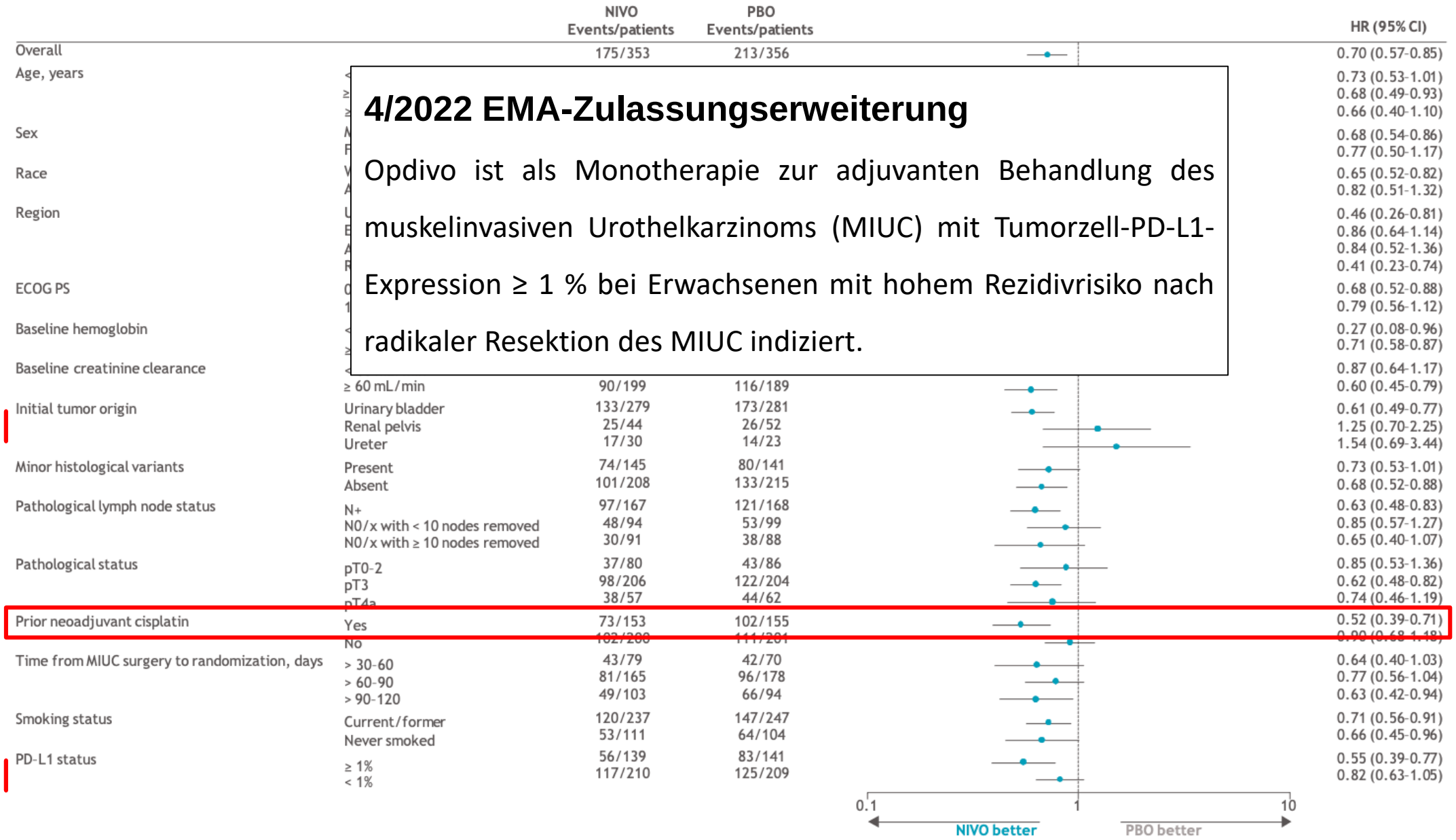
- DFS (Primärer Endpunkt)





Sowohl in der ITT- als auch in der Tumor-PD-L1-Expressionspopulation (≥1%) wurde mit Nivolumab (vs Placebo) ein anhaltender DFS-Vorteil beobachtet

Galsky et al., ASCO GU 2023



4/2022 EMA-Zulassungserweiterung

Opdivo ist als Monotherapie zur adjuvanten Behandlung des muskelinvasiven Urothelkarzinoms (MIUC) mit Tumorzell-PD-L1-Expression ≥ 1 % bei Erwachsenen mit hohem Rezidivrisiko nach radikaler Resektion des MIUC indiziert.

Nivolumab-Adjuvanz: Für wen?

- Hochrisiko-Blasenkarzinom
- Cisplatin-unfit oder –Ablehnung
- Ohne Neoadjuvanz: pT3, pT4a, or pN+
- Nach Neoadjuvanz: ypT2 to ypT4a or ypN+
- PD-L1 > 1%

Roadmap

Prostatakarzinom
- mHSPC
- mCRPC

Nierenzellkarzinom
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Urothelkarzinom
- Adjuvanz
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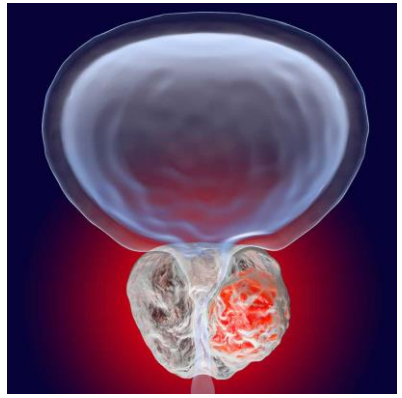
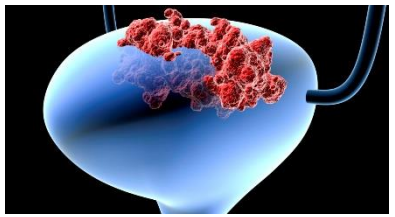
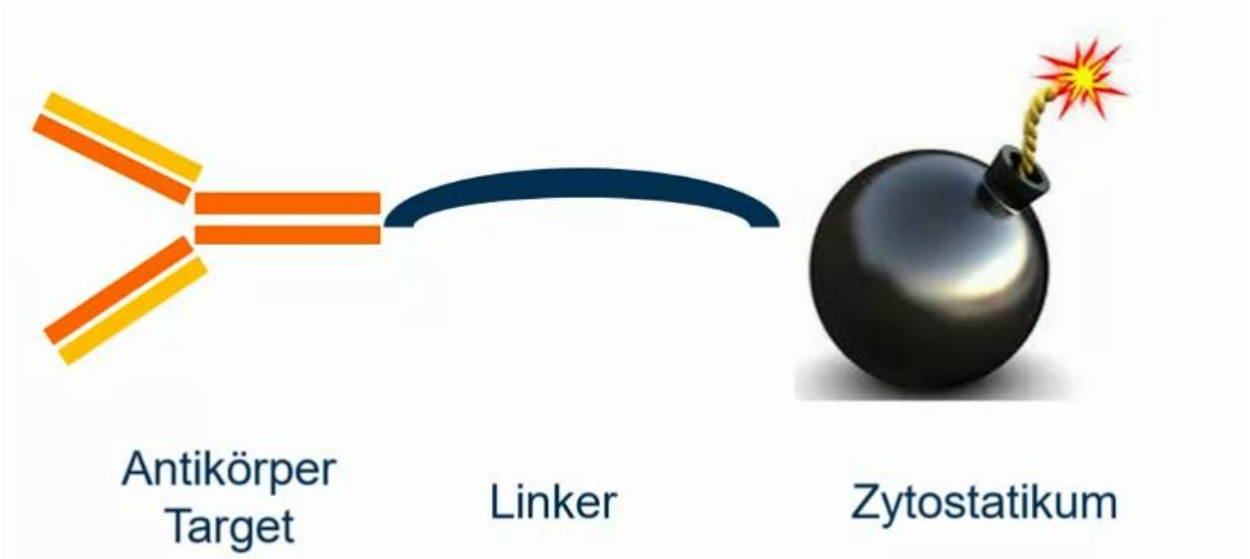




Versagen der Immuntherapie bei metastasiertem Urothelkarzinom ...

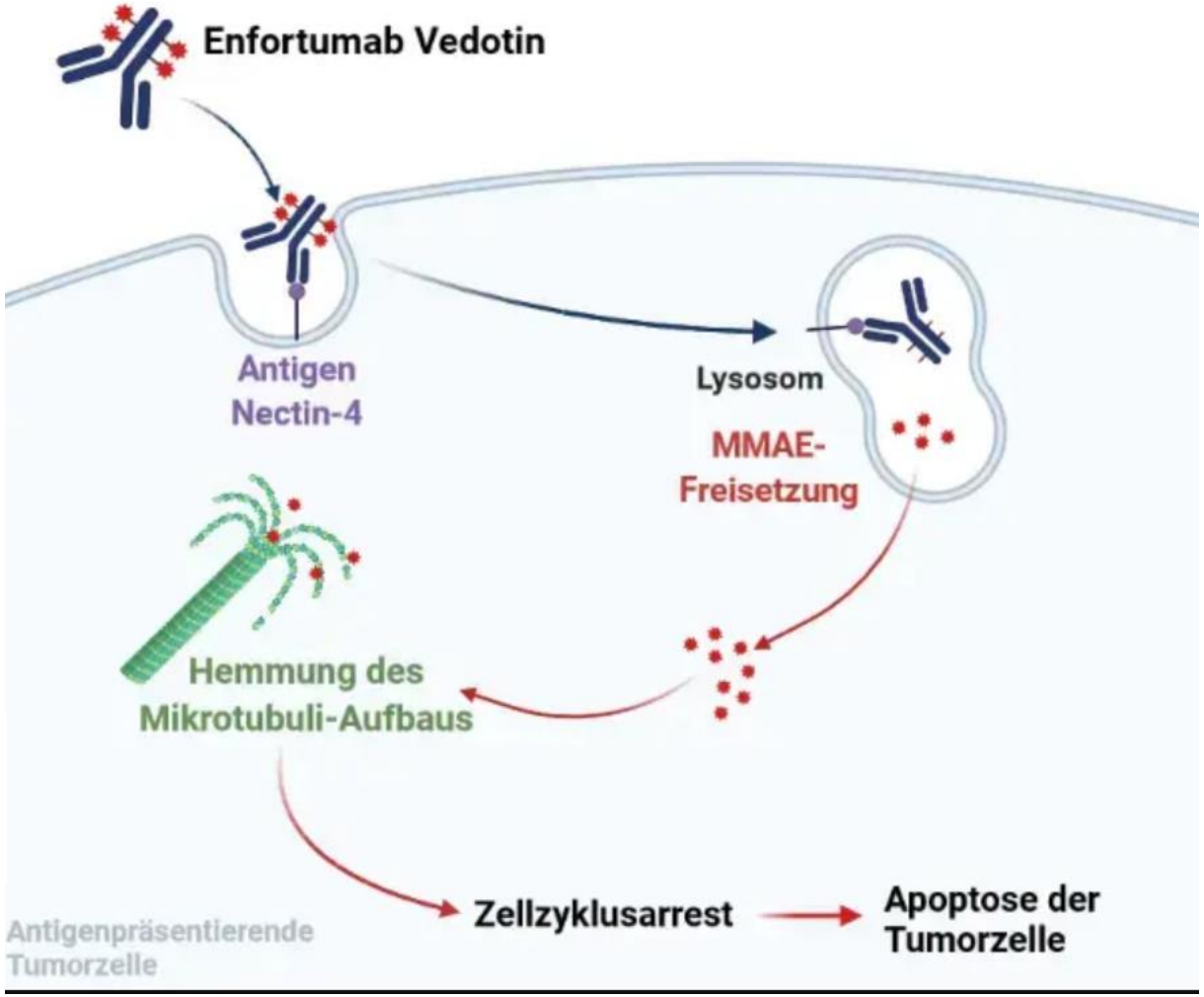
... was nun?

Enfortumab-Vedotin nach Platin- und Immuntherapie

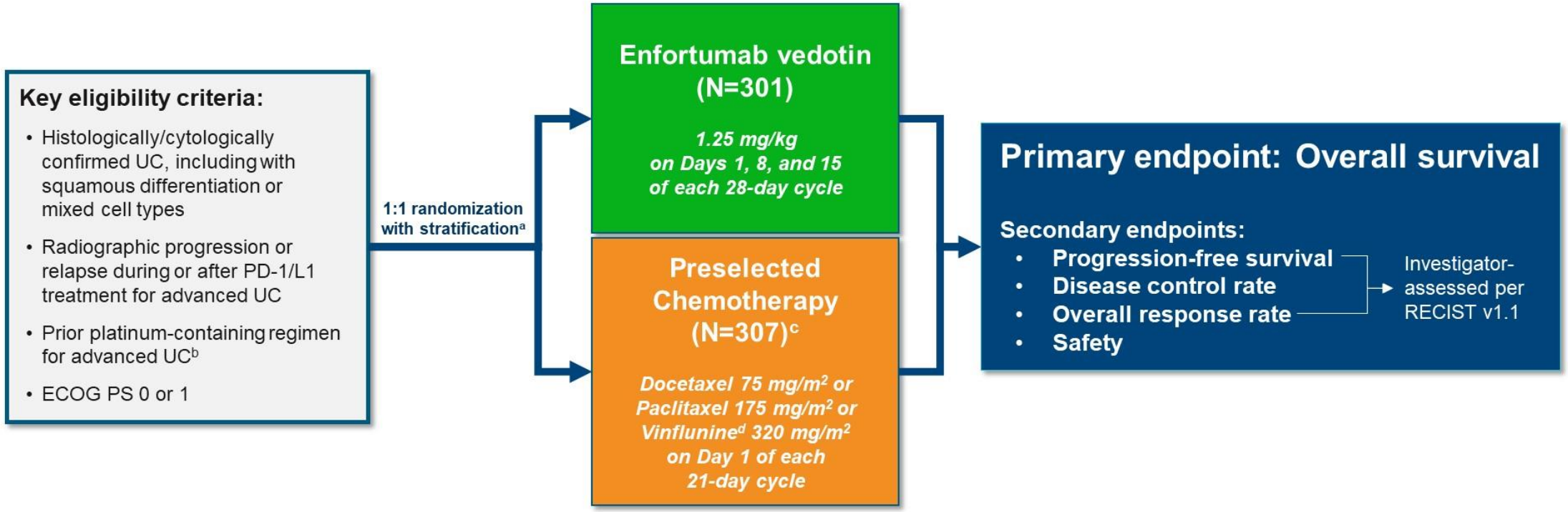


Anti-Nectin-4

Monomethyl Auristatin



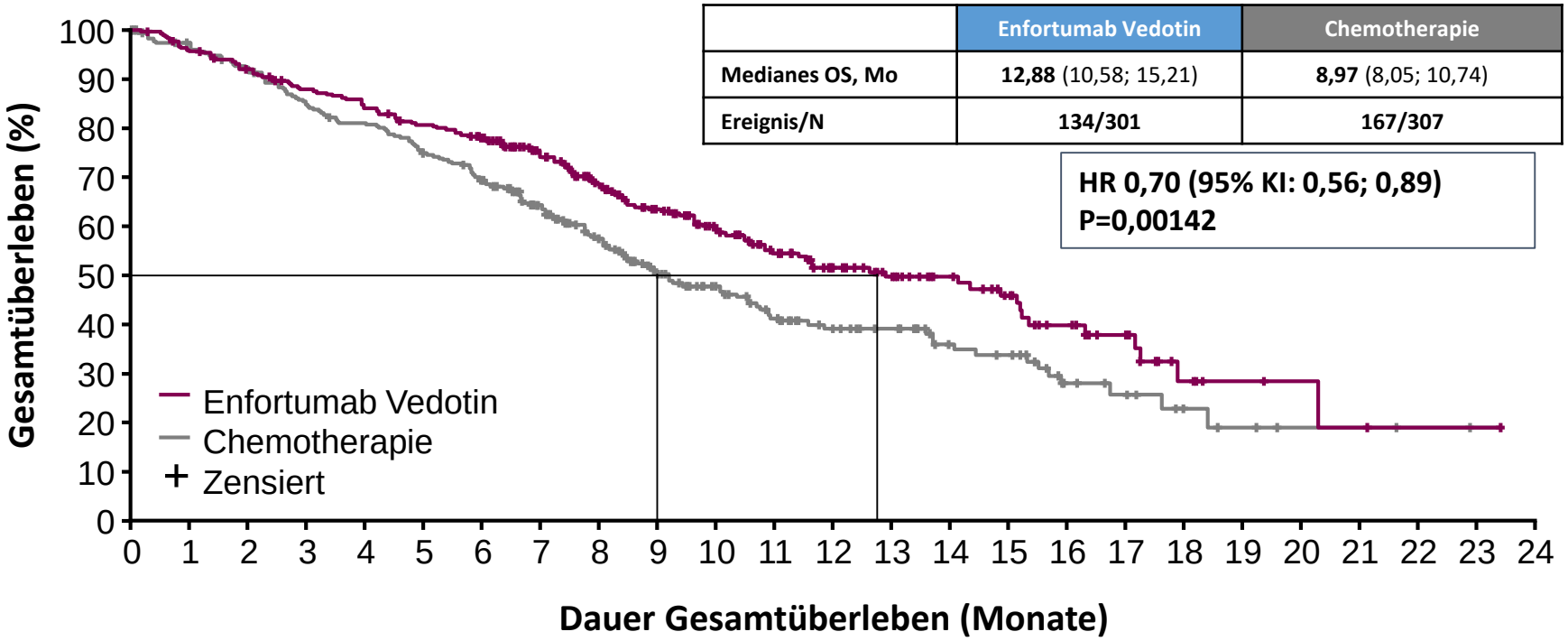
EV-301 – Therapie in der Drittlinie nach Cisplatin und CPI



[a]Stratification variables were ECOG performance status (0 or 1), regions of the world (United States, western Europe, or rest of world), liver metastasis (yes or no).
[b]If used in the adjuvant/neoadjuvant setting, progression must be within 12 months of completion.
[c]Investigator selected prior to randomization.
[d]In countries where approved; overall proportion of patients receiving vinflunine capped at 35%.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; PD-1/L1, programmed cell death protein-1/programmed death-ligand 1; RECIST, Response Evaluation Criteria in Solid Tumors; UC, advanced urothelial carcinoma.

Powles et al., ASCO GU 2021

Enfortumab-Vedotin nach Platin- und Immuntherapie



	Enfortumab Vedotin	Chemotherapie
Medianes OS, Mo	**12,88** (10,58; 15,21)	**8,97** (8,05; 10,74)
Ereignis/N	**134/301**	**167/307**

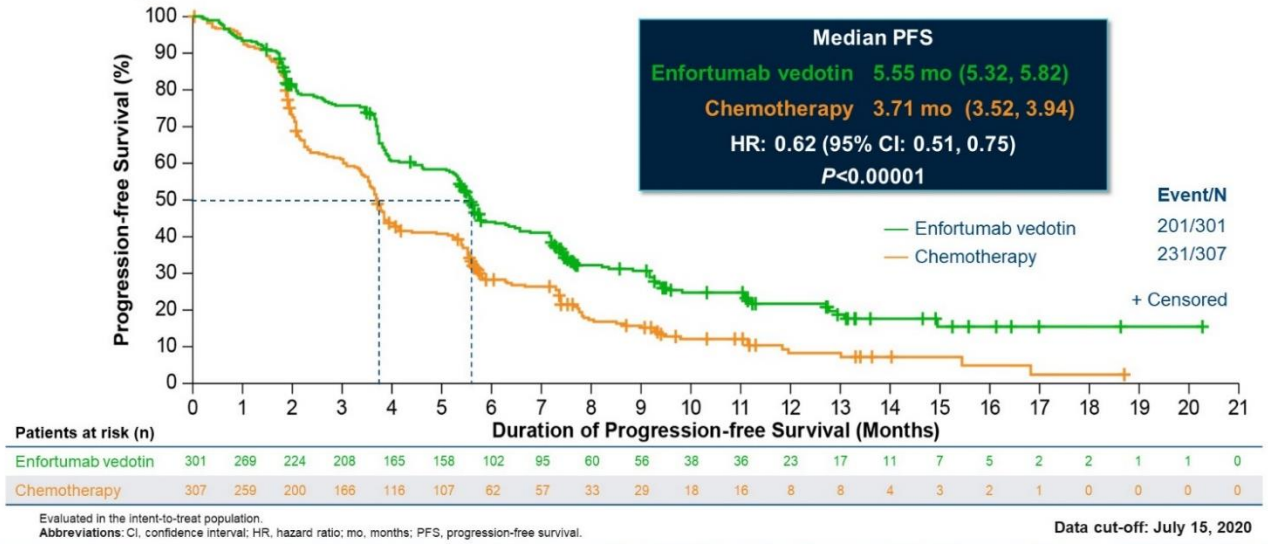
HR 0,70 (95% KI: 0,56; 0,89)
P=0,00142

Anzahl Patienten																								
Enfortumab Vedotin	301	286	272	257	246	234	222	190	158	130	105	85	63	52	42	33	23	15	7	4	3	2	1	1	0
Chemotherapie	307	288	274	250	238	219	198	163	131	101	84	66	51	44	32	29	16	11	6	4	2	2	1	0	0

Powles et al. N Engl J Med 2021

EV-301: Effektivität (PFS und ORR)

Progression-free Survival

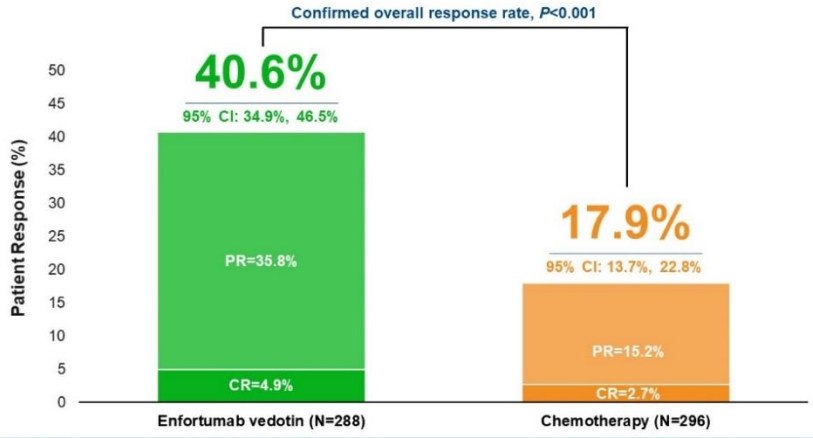


Patients at risk (n)																						
Enfortumab vedotin	301	269	224	208	165	158	102	95	60	56	38	36	23	17	11	7	5	2	2	1	1	0
Chemotherapy	307	259	200	166	116	107	62	57	33	29	18	16	8	8	4	3	2	1	0	0	0	0

Evaluated in the intent-to-treat population.
Abbreviations: CI, confidence interval; HR, hazard ratio; mo, months; PFS, progression-free survival.

Data cut-off: July 15, 2020

Investigator-Assessed Overall Response



Disease control rate,[a] % (95% CI)	**71.9 (66.3, 77.0)**	**53.4 (47.5, 59.2)**	***P*<0.001**

Evaluated in the response-evaluable population. Response is as assessed by the investigator per RECIST v1.1.
[a]Indicates the proportion of patients who had a best overall response of confirmed CR, PR, or SD (at least 7 weeks); enfortumab vedotin vs chemotherapy.
Abbreviations: CI, confidence interval; CR, complete response; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

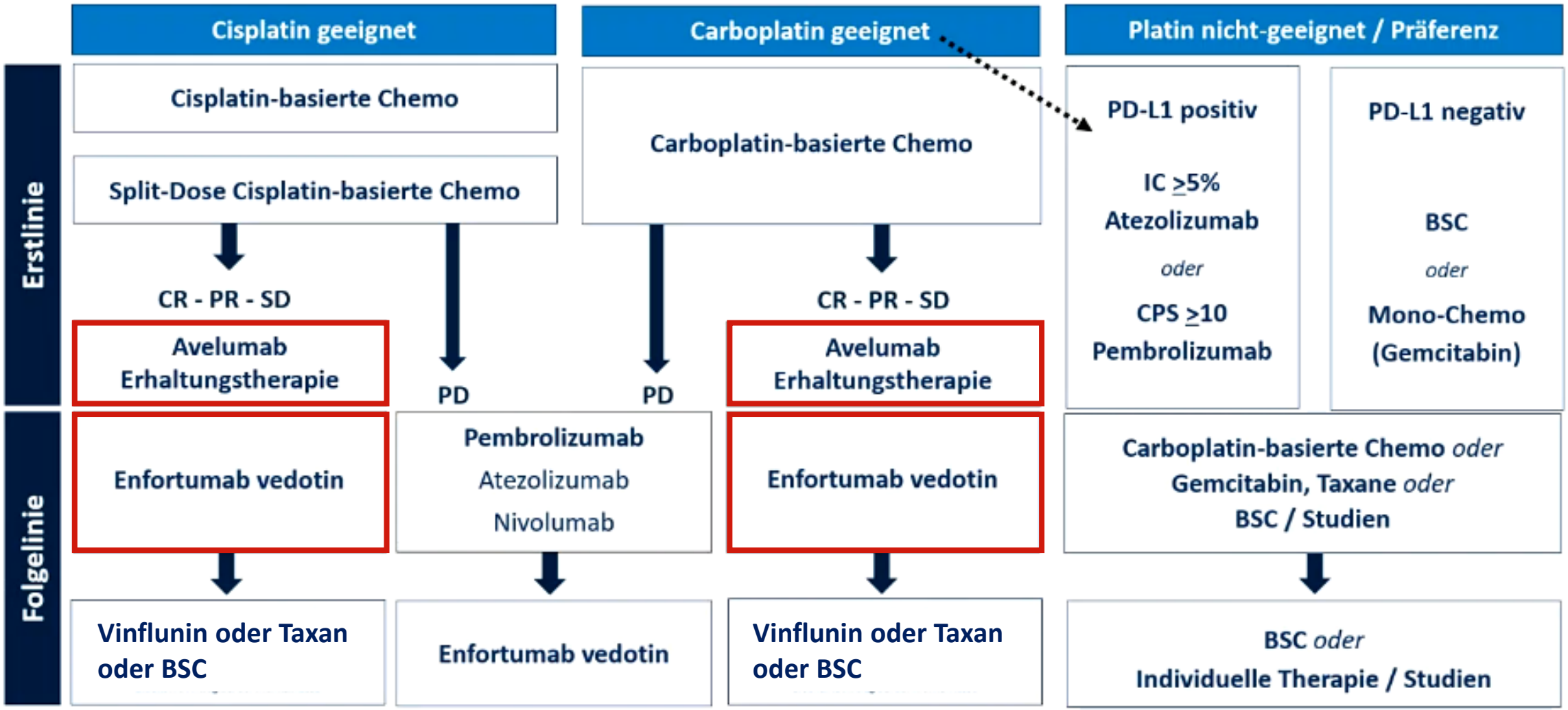
Data cut-off: July 15, 2020

Powles et al., ASCO GU 2021

4/2022 EMA-Zulassungserweiterung

Ende Dezember 2021 positives Votum des Committee for Medicinal Products for Human Use (CHMP). Am 13.04.2022 ist die Zulassung durch die Europäische Kommission erfolgt.

Therapie-Algorithmus metastasiertes Urothelkarzinom



Vielen Dank!