UKE HAMBURG

II. Medizinische Klinik, UCCH, Universitätsklinikum Hamburg – Eppendorf

II MARTINI-KLINIK

Perioperative Systemtherapie des Urothelkarzinoms- Was und wann?

Gunhild von Amsberg

DGHO Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie
ÖGHO SSMO SSOM SGMO SGH+SSH

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2023 13.–16. Okt. Hamburg

Hubertus Wald Tumorzentrum
Universitäres Cancer Center Hamburg
Ein Kompetenznetzwerk des UKE

Offenlegung Interessenskonflikte

1. Anstellungsverhältnis oder Führungsposition: nein

2. Beratungs- bzw. Gutachtertätigkeit: Advisory Boards: Roche, BMS, Astellas, Sanofi, Janssen, MSD, Ipsen, Pfizer, AstraZeneca, Merck, EISAI

3. Besitz von Geschäftsanteilen, Aktien oder Fonds: nein

4. Patent, Urheberrecht, Verkaufslizenz: nein

5. Honorare / Vorträge / Reisekosten/ Kongressunterstützung: Roche, BMS, Astellas, Sanofi, Ipsen, EISAI, Pierre Fabre, MSD, Astra Zeneca, Janssen, Pfizer

6. Finanzierung wissenschaftlicher Untersuchungen: im Rahmen Industrie-gesponserter Studien (Roche, BMS, MSD, Astra Zeneca, Sanofi, Pfizer, AvenCell, Lilly, Amgen)

7+8. Andere finanzielle Beziehungen und immaterielle Interessenkonflikte: nein

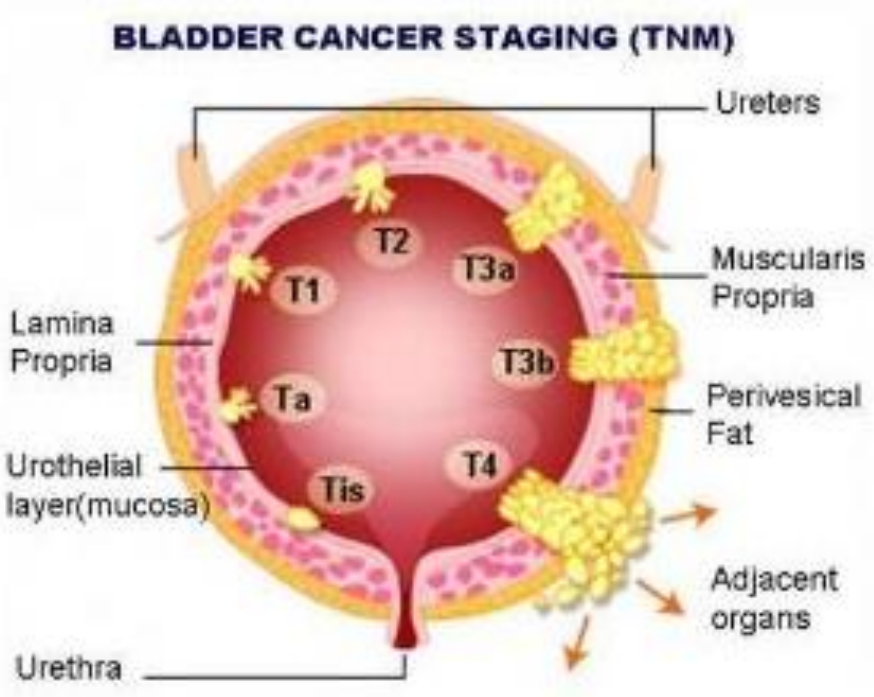
MUSKELINVASIVES UROTHELKARZINOM DER BLASE

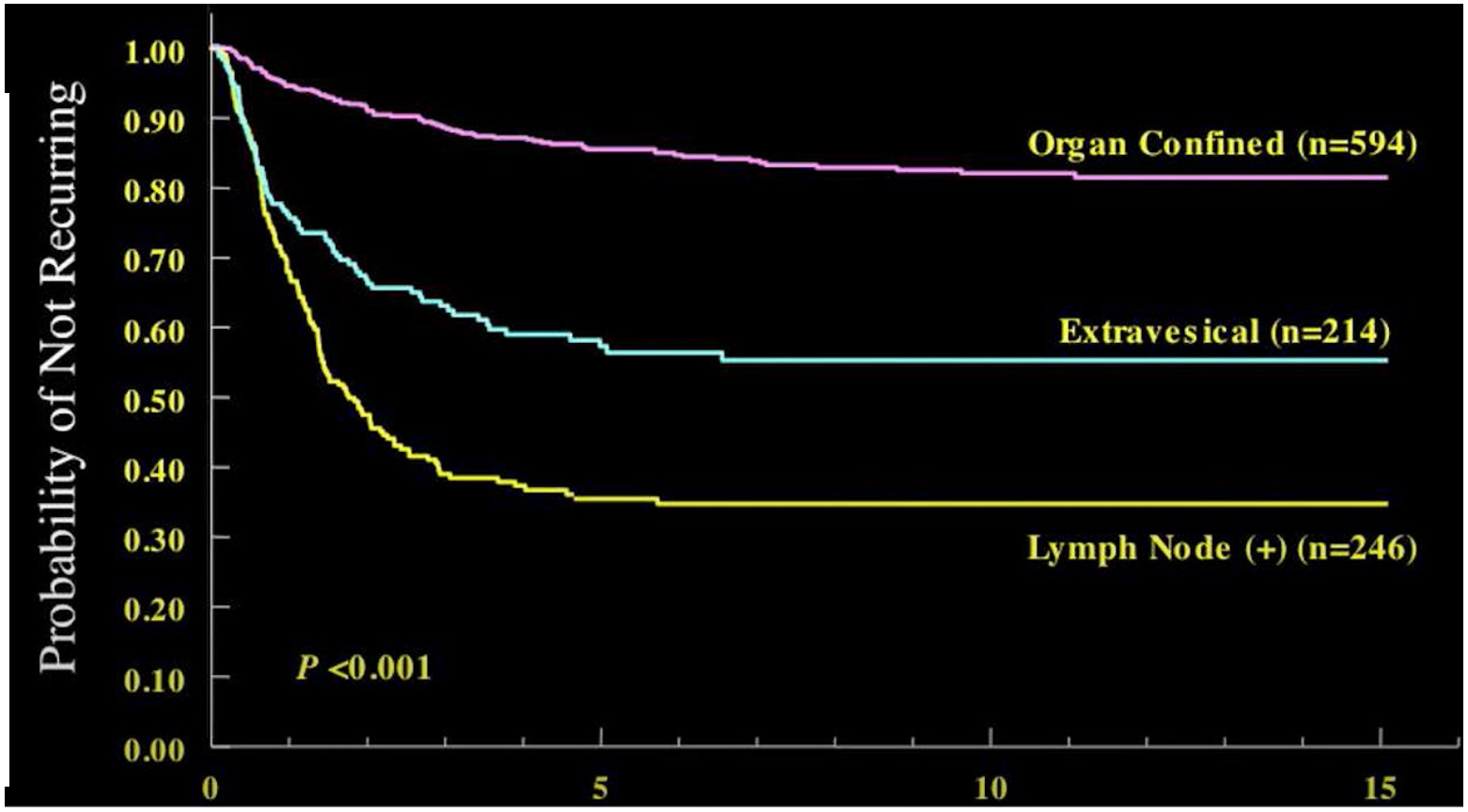
Neoadjuvante und adjuvante Chemotherapie

Gunhild von Amsberg

Warum brauchen wir perioperative Behandlungskonzepte beim Urothelkarzinom?

Risiko für Krankheitsrezidiv in Abhängigkeit der Tumorausdehnung





Stein JP JCO 2001;19: 666-75

Vorteile und Nachteile der neoadjuvanten Chemotherapie

- ☺ Durchführung der Chemotherapie zum frühestmöglichen Zeitpunkt (geringe Belastung durch mikrometastatische Erkrankungen)
- ☺ Bessere Verträglichkeit der Chemotherapie und höhere Compliance der Patient:innen vor der Zystektomie
- ☺ Ansprechen auf NAC als Indikator für In-vivo-Chemosensitivität (günstiges pathologisches Ansprechen mit ypT0, ≤ ypT1, ypN0 und negativen chirurgischen Schnitträndern)

- ☹ Negative Auswirkung für Patienten mit fehlendem Ansprechen durch verzögerte Zystektomie
- ☹ Negativer Einfluss der NAC auf das chirurgische Ergebnis
- ☹ Klinische Stadieneinteilung durch bimanuelle Abtastung, CT oder MRT mit Risiko des Over- oder Understaging (Staging-Genauigkeit nur ca. 70%)

J.A. Witjes et al. EAU guidelines

Onkologischer Benefit der NAC
SWOG-8710

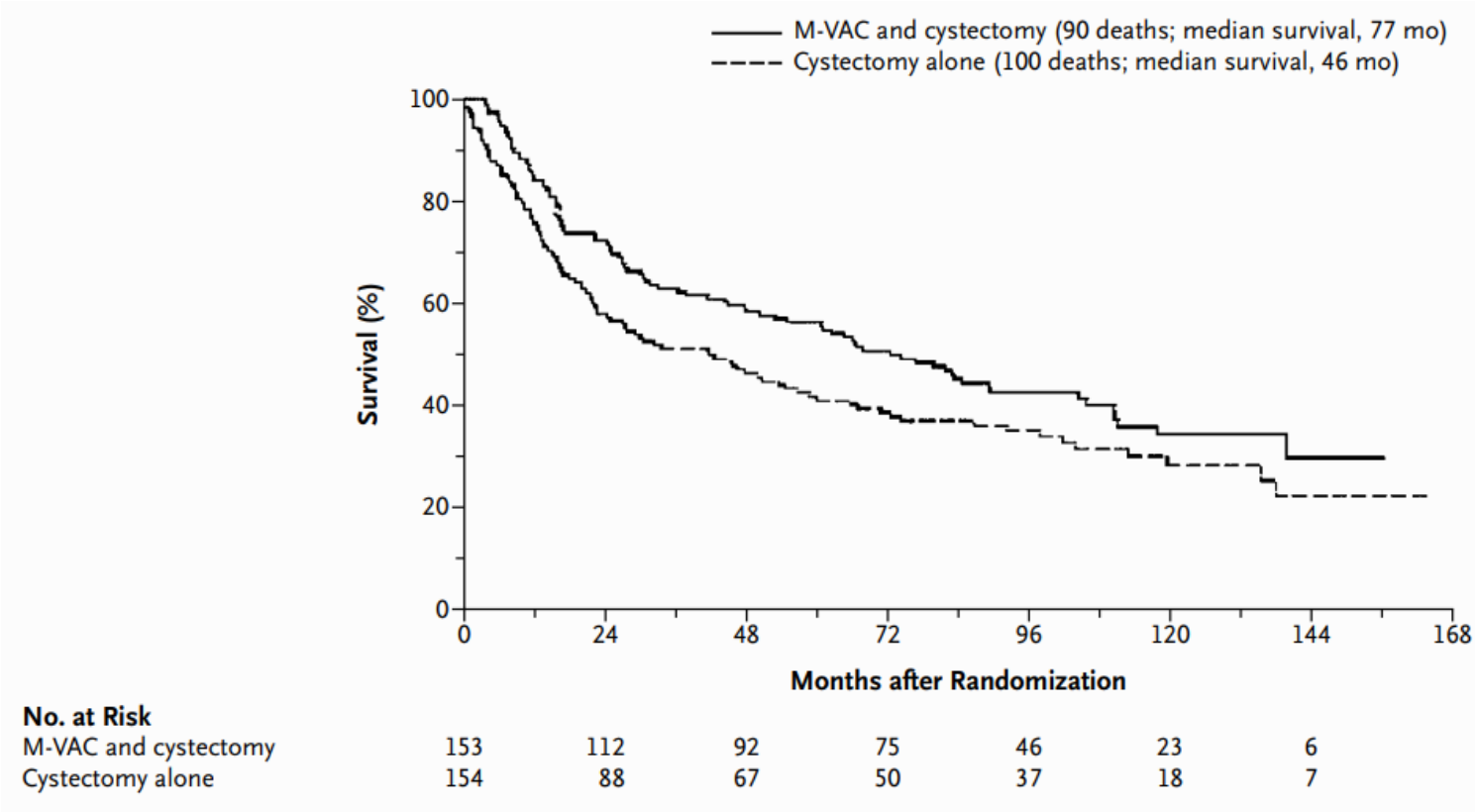


Table 1. Base-Line Characteristics of the Patients.*

Characteristic	Total (N=307)	Cystectomy Alone (N=154)	M-VAC and Cystectomy (N=153)
Age — yr			
Median	63	63	63
Range	39–84	39–84	36–79
Sex — no. (%)			
Male	251 (82)	124 (81)	127 (83)
Female	56 (18)	30 (19)	26 (17)
Age and tumor stage — no. (%)			
<65 yr and T2	61 (20)	35 (23)	26 (17)
<65 yr and T3 or T4a	111 (36)	52 (34)	59 (39)
≥65 yr and T2	61 (20)	26 (17)	35 (23)
≥65 yr and T3 or T4a	74 (24)	41 (27)	33 (22)

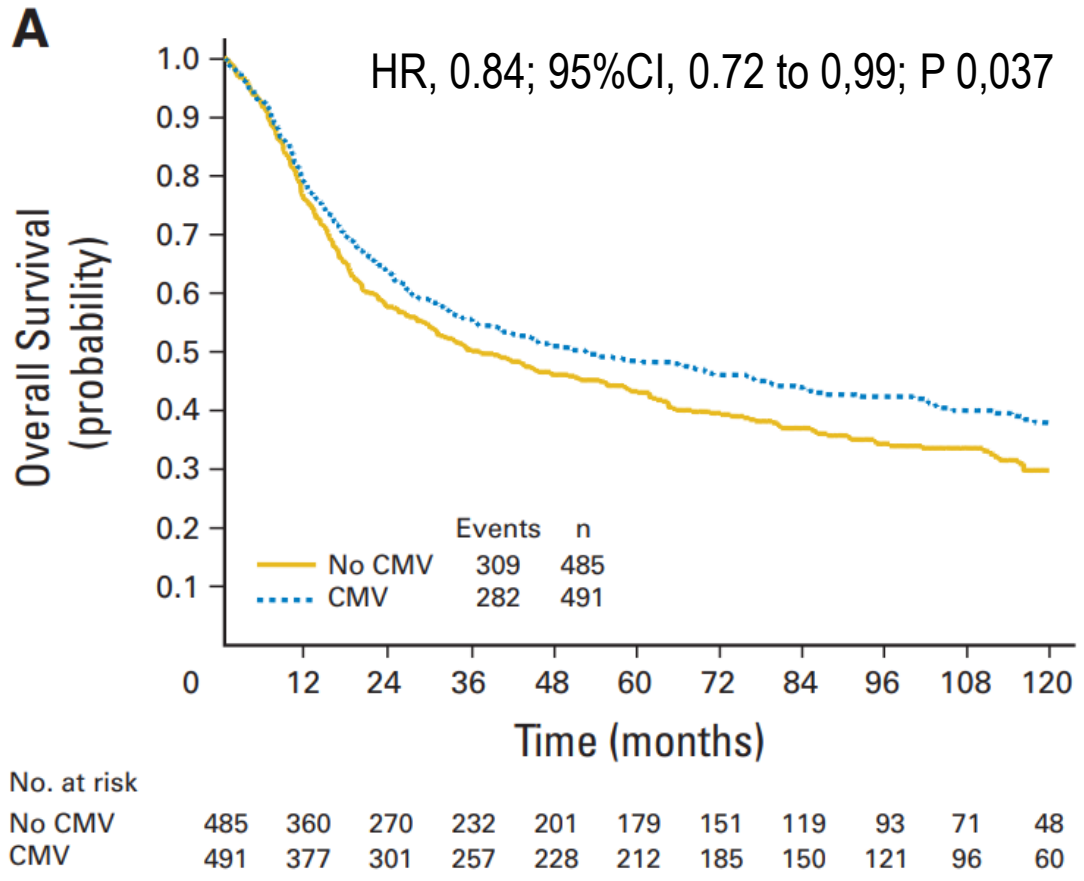
* Of the 317 patients who underwent randomization, 10 (5 in each group) were found to be ineligible and were excluded from the analysis. M-VAC denotes methotrexate, vinblastine, doxorubicin, and cisplatin.

	MVAC + Surgery	Surgery alone
5-J-Überleben	57%	43%

MVAC	all patients	cT2	cT3/4
ypT0	38% (48/126)	50% (26/52)	30% (22/74)

Grossmann et al. N Engl J Med 2003;349:859-66

Onkologischer Benefit der NAC
BA06 30894



	CMV + Surgery	Surgery alone
5-yr survival	49%	43%
10-yr survival	36%	30%

International Collaboration of Trialists; J Clin Oncol . 2011 Jun 1;29(16):2171-7

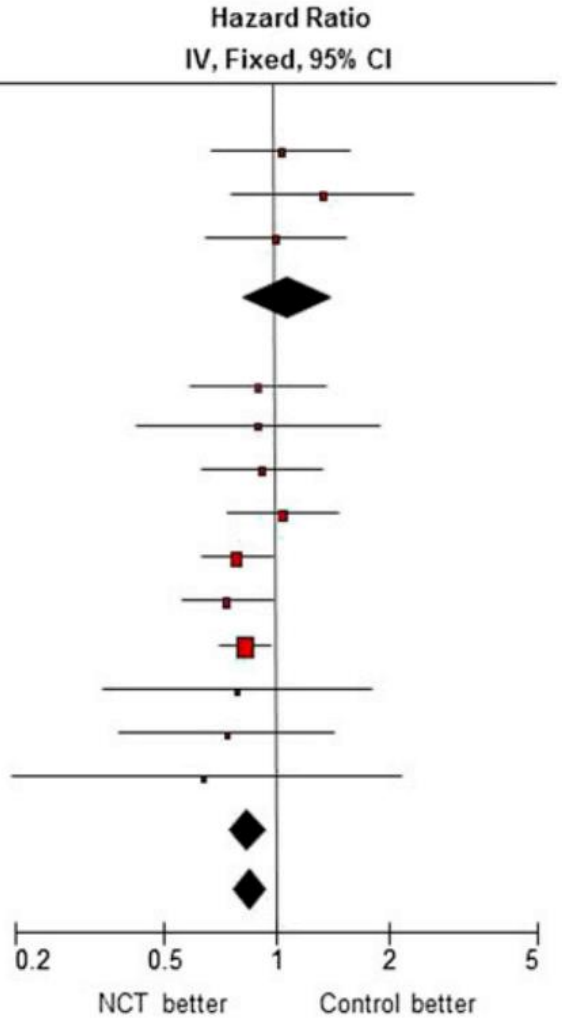
Oncologischer Benefit der NAC
Meta-Analysen zur NAC

Year of publication	No. of trials	No. of pts	Results	Reference
2003	10	2,688	Overall survival benefit (HR 0.87; 0.78–0.98, p=0·016) Reduction Risk of Death: 13% Absolute survival benefit at 5yrs: 5%	ABC MA Collaboratorium Vale et al.Lancet 2003; 361, P1927-1934
2004	11 (8 Cisplatin containing)	2,605	Overall survival benefit (HR 0.90; 0.82 to 0.99, p = 0.02) Only Cisplatin containing trials: Overall survival benefit (HR 0.87; 0.78 to 0.96, p = 0.006)) Absolute Survival Benefit: 6.5%	Winquist et al. J Urol. 2004 Feb;171:p561-9.
2005	11	3,005	Overall survival benefit (HR 0.86, 0.77–0.95, *p* = 0.003) Absolute survival benefit at 5yrs: 5% Disease free survival benefit at 5 yrs: 9%	ABC MA Collaboratorium Vale et al. Europ Urol. 2005 (48) P202-206
2016	15	3,285	Overall survival benefit (HR 0.87, 0.79–0.96; p= 0.004).	Yin et al. The Oncologist 2016; 21:708–715

Gibt es einen überlegenen Behandlungsansatz?

Platin-Monotherapie versus Kombination?

Study	NCT	Control	Weight	Hazard Ratio IV, Fixed, 95% CI
Single platinum				
Wallace et al. 1991 [23]	59/83	50/76	4.9%	1.05 [0.69, 1.60]
Wallace et al. 1991 [23]	34/41	37/55	2.8%	1.36 [0.78, 2.38]
Martinez-Piñerio et al. 1995 [24]	43/62	38/59	4.7%	1.02 [0.66, 1.57]
Subtotal				**1.10 [0.84, 1.44]**
Combination platinum				
Cortesi (unpublished)	43/82	41/71	4.9%	0.91 [0.60, 1.39]
Shipley et al. 1998 [25]	31/61	31/62	1.6%	0.91 [0.43, 1.92]
Bassi et al. 1999 [26]	53/102	60/104	6.3%	0.93 [0.64, 1.35]
Sengeløv et al. 2002 [27]	70/78	60/75	7.3%	1.06 [0.75, 1.50]
Sherif et al. 2004 [16]	145/306	173/314	18.4%	0.80 [0.64, 0.99]
Grossman et al. 2003 [4]	90/153	100/154	11.1%	0.75 [0.57, 0.99]
BA06 30894 2011 [5]	282/491	309/485	34.5%	0.84 [0.72, 0.98]
Osman et al. 2014 [28]	11/30	15/30	1.3%	0.80 [0.35, 1.83]
Khaled et al. 2014 [30]	NA/59	NA/55	2.0%	0.75 [0.39, 1.46]
Kitamura et al. 2014 [29]	NA/64	NA/66	0.6%	0.65 [0.19, 2.20]
Subtotal				**0.84 [0.76, 0.93]**
Total			**100.0%**	**0.87 [0.79, 0.96]**



Yin et al. The Oncologist 2016; 21:708–715

Gibt es einen überlegenen Behandlungsansatz?
Die VESPER-Studie

500 Patient:innen aus 28 Zentren, eingeschlossen in den Jahren 2013-2018

Einschlusskriterien:

- Reines oder gemischtes Urothelkarzinom (exkl. neuroendokrine Differenzierung)
- ECOG PS <2
- Alle Kriterien für Cisplatin-Eignung erfüllt
- Schriftliche Einverständniserklärung

UND

- ≥T2, N0 (LN ≤10 mm im CT-Scan), M0 (neoadjuvante Chemotherapie)
- <pT2 oder pN+ und M0 (adjuvante Chemotherapie)

N=493
Adjuvant (N=56)
Neoadjuvant (N=437)

R

Chemotherapie:

4 Zyklen GC:
Gemcitabin 1250 mg/m² an Tagen 1 und 8
Cisplatin 70 mg/m² an Tag 1

alle drei Wochen

6 Zyklen dd-MVAC:
Methotrexat 30 mg/m² an Tag 1
Vinblastin 3 mg/m² an Tag 2
Doxorubicin 30 mg/m² an Tag 2
Cisplatin 70 mg/m² an Tag 2
+G-CSF unterstützend an den Tagen 3-9

alle 2 Wochen

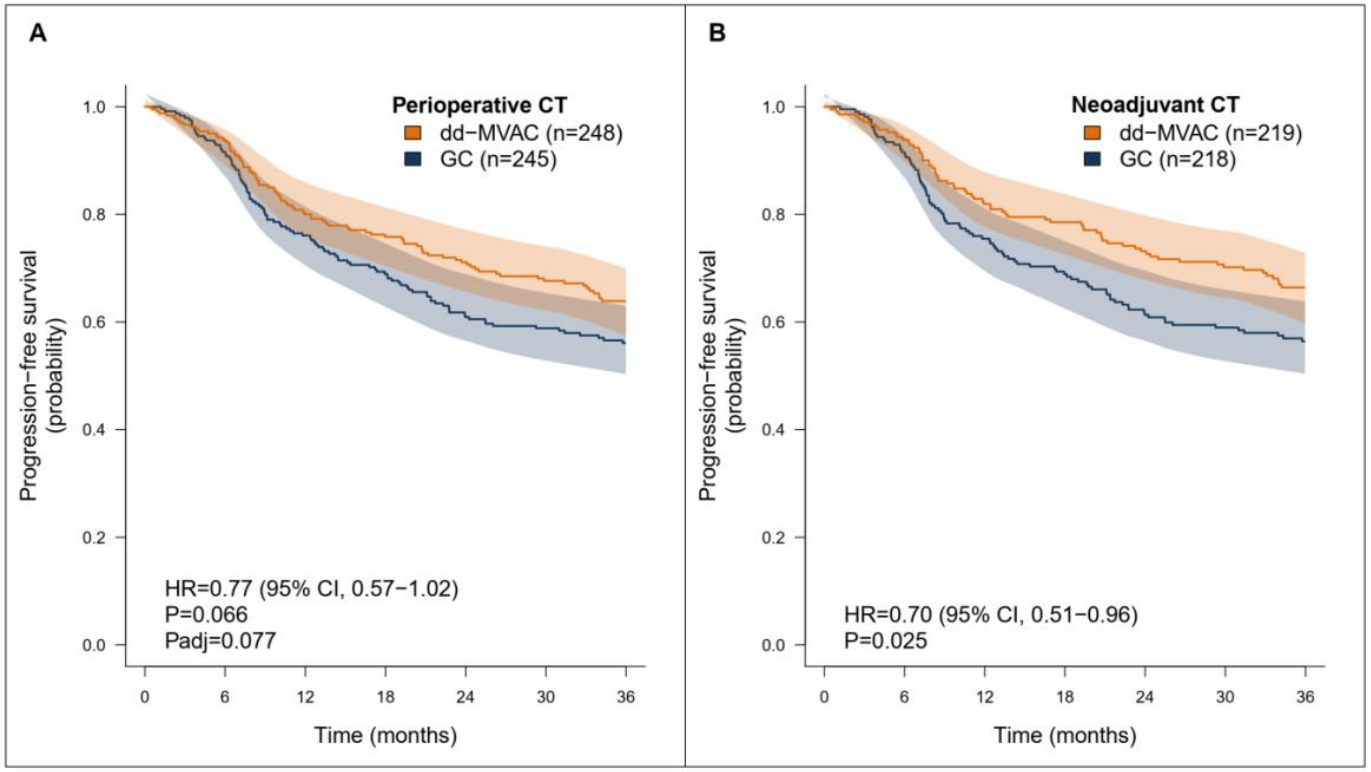
Primärer Endpunkt:
- Progressionsfreies Überleben (PFS) nach 3 Jahren

Finale Analyse:
- Gesamtüberleben (OS)
- krankheitsspezifisches Überleben (DSS) nach 5 Jahren

Pfister Ch, et al. ESMO 2021; P6520; 2021 Feb;79(2):214-221; Contemp Clin Trials Commun. 2020; Grande E; invited Discussant P6520 ESMO2021 ; ASCO 2023 LBA 4507

Gibt es einen überlegenen Behandlungsansatz?

Die VESPER-Studie: Ergebnisse

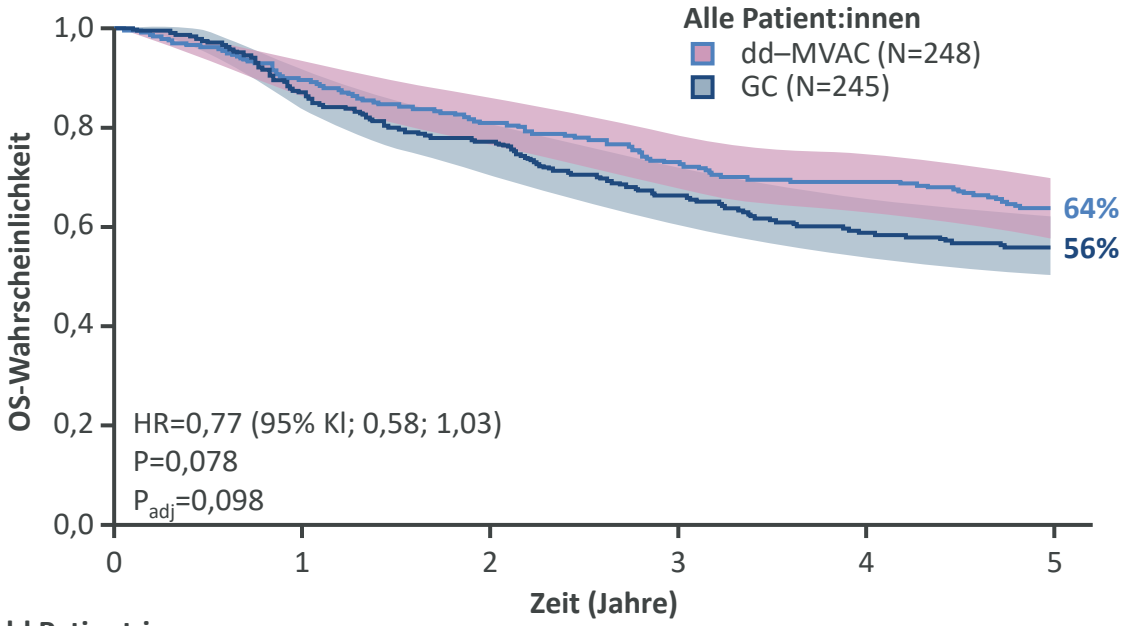


	GC	DD-MVAC
Patients enrolled	N=245	N=248
Peri-operative Chemotherapy	11	12
Adjuvant (%)	89	88
Neoadjuvant (%)		
NAC Subgroup		
Pathological Resonse (%)		
ypT0N0	36	42
ypTIS,Ta or T1 and ypN0	14	21
ypT2N0	13	14
≥ ypT3 or ypN+	37	22
Uncertain staiging	1	2
3yr PFS (%)	56	64

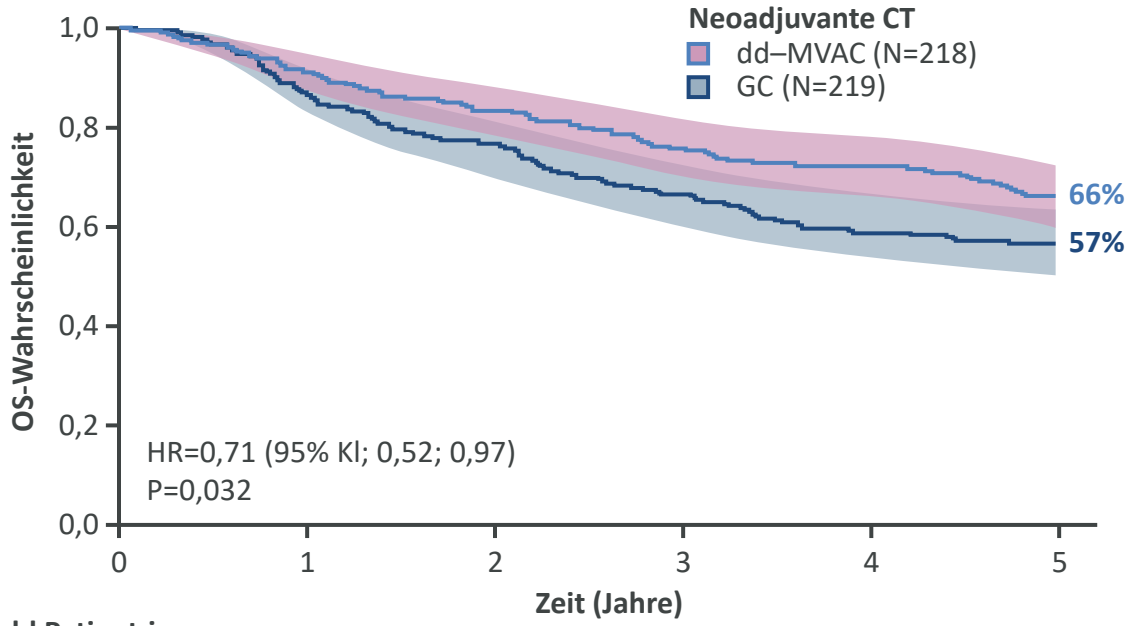
Pfister Ch, et al. DOI: 10.1200/JCO.21.02051 *Journal of Clinical Oncology* 40, no. 18 (June 20, 2022) 2013-2022;
ESMO 2021; P6520; 2021 Feb;79(2):214-221; Contemp Clin Trials Commun. 2020; Grande E; invited Discussant P6520 ESMO2021

Gibt es einen überlegenen Behandlungsansatz?

Die VESPER-Studie: 5-Jahres Überleben



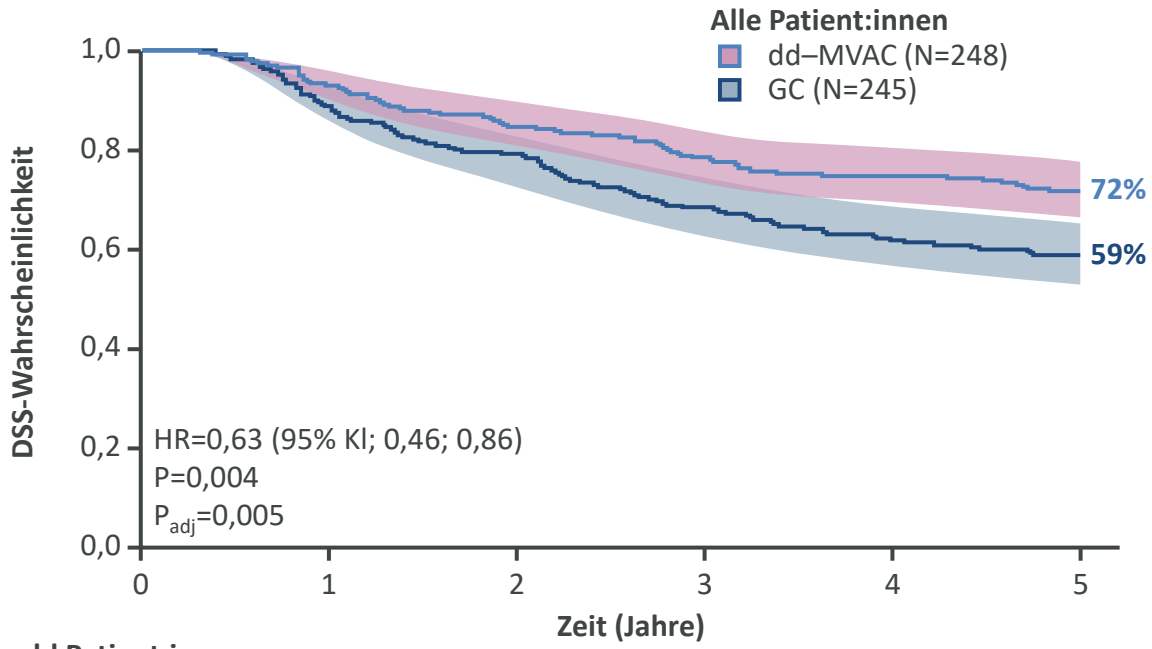
Anzahl Patient:innen						
dd–MVAC	248	217	193	171	157	126
GC	245	207	184	157	134	112



Anzahl Patient:innen						
dd–MVAC	218	193	174	156	144	116
GC	219	184	163	140	119	100

Gibt es einen überlegenen Behandlungsansatz?

Die VESPER-Studie: 5-Jahres Krankheitsspezifisches Überleben



Anzahl Patient:innen						
dd–MVAC	248	217	193	171	157	126
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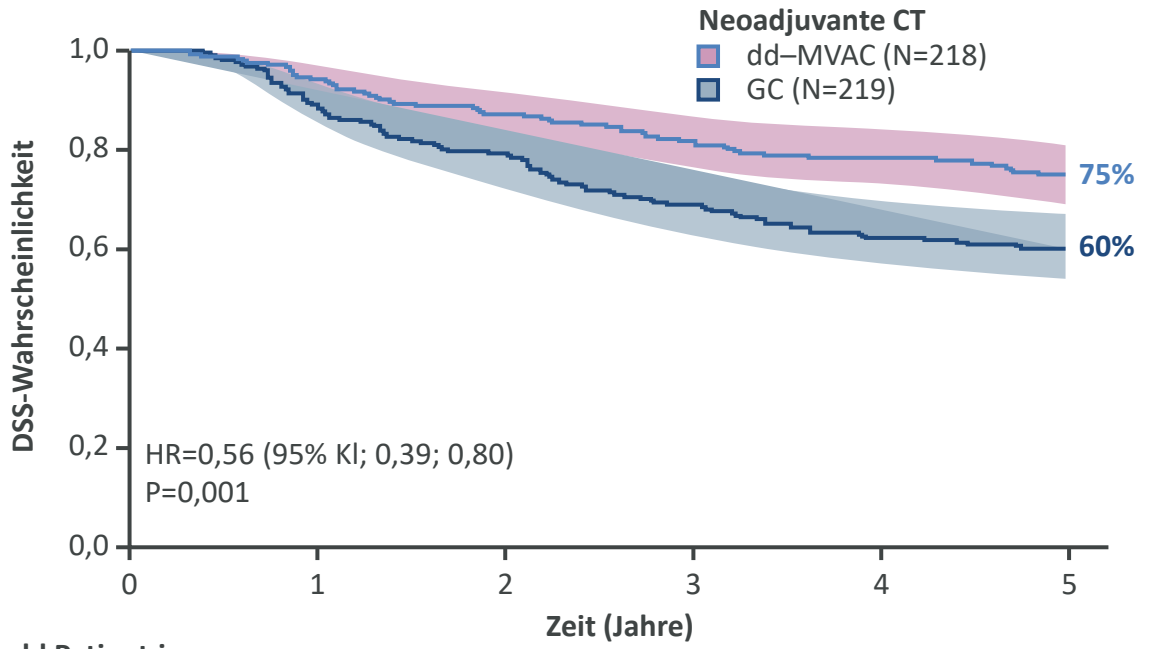
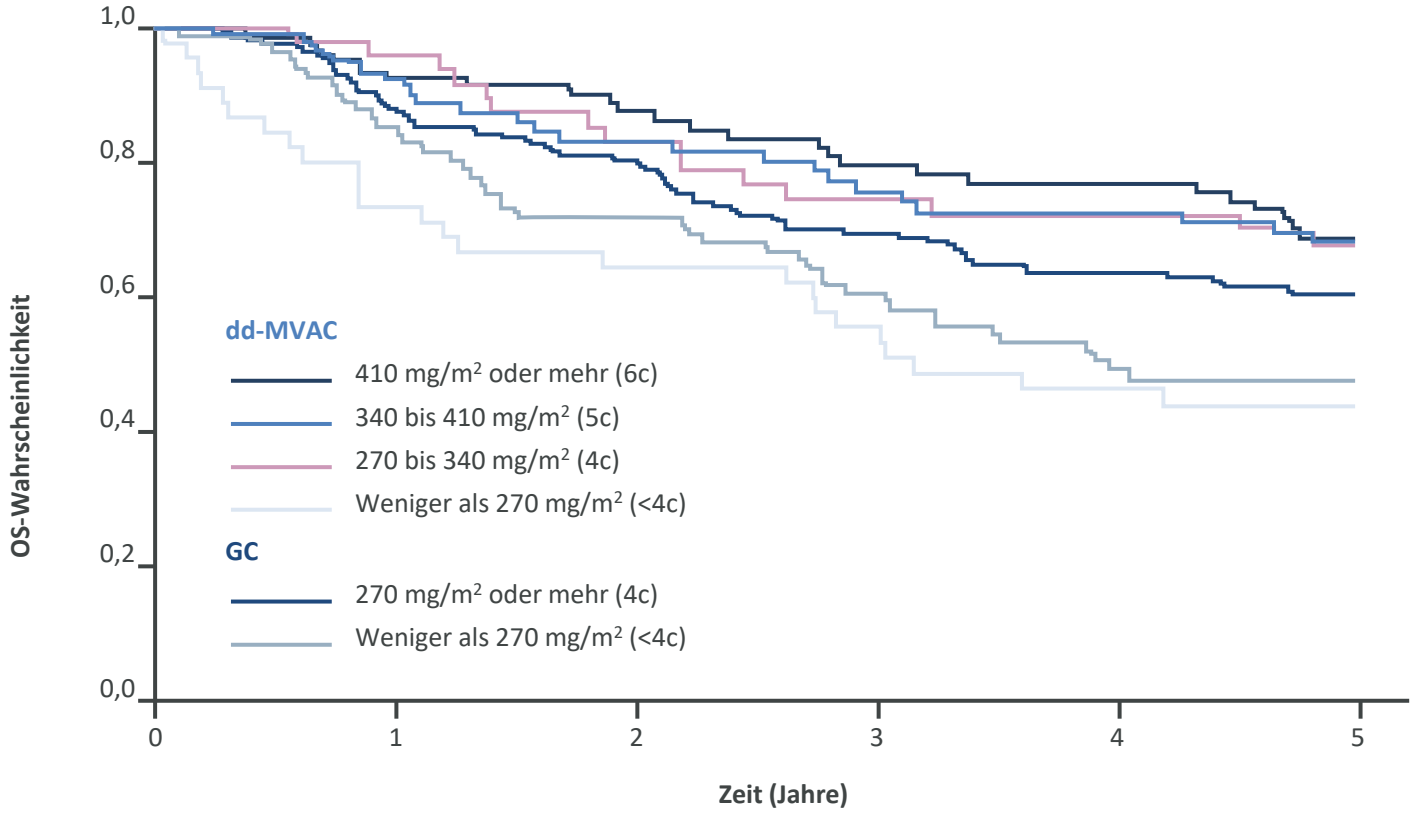


Anzahl Patient:innen						
dd–MVAC	218	193	174	156	144	116
GC	219	184	163	140	119	100

Pfister C | Abstract LBA4507 | ASCO 2023

Gibt es einen überlegenen Behandlungsansatz?

Die VESPER-Studie: Gesamtüberleben nach Chemotherapiearm und Zyklenzahl



Anzahl Patient:innen

ddMVAC	6c	79	73	68	61	58	47
	5c	71	66	57	51	47	38
	4c	47	45	39	35	33	26
	<4c	51	33	29	24	19	15
GC	4c	159	138	126	108	96	82
	<4c	86	69	58	49	38	30

Wichtigkeit kumulativer Cisplatin-Dosis

- *Schlechtes OS:*
  <4 volle Dosen Cisplatin
- *Medianes OS:*
  GC-Arm: 4 volle Dosen Cisplatin
- *Hohes OS:*
  dd-MVAC-Arm: >4 volle Dosen Cisplatin

Pfister C | Abstract LBA4507 | ASCO 2023

Gibt es einen überlegenen Behandlungsansatz?

Die VESPER-Studie: Machbarkeit und Toxizität

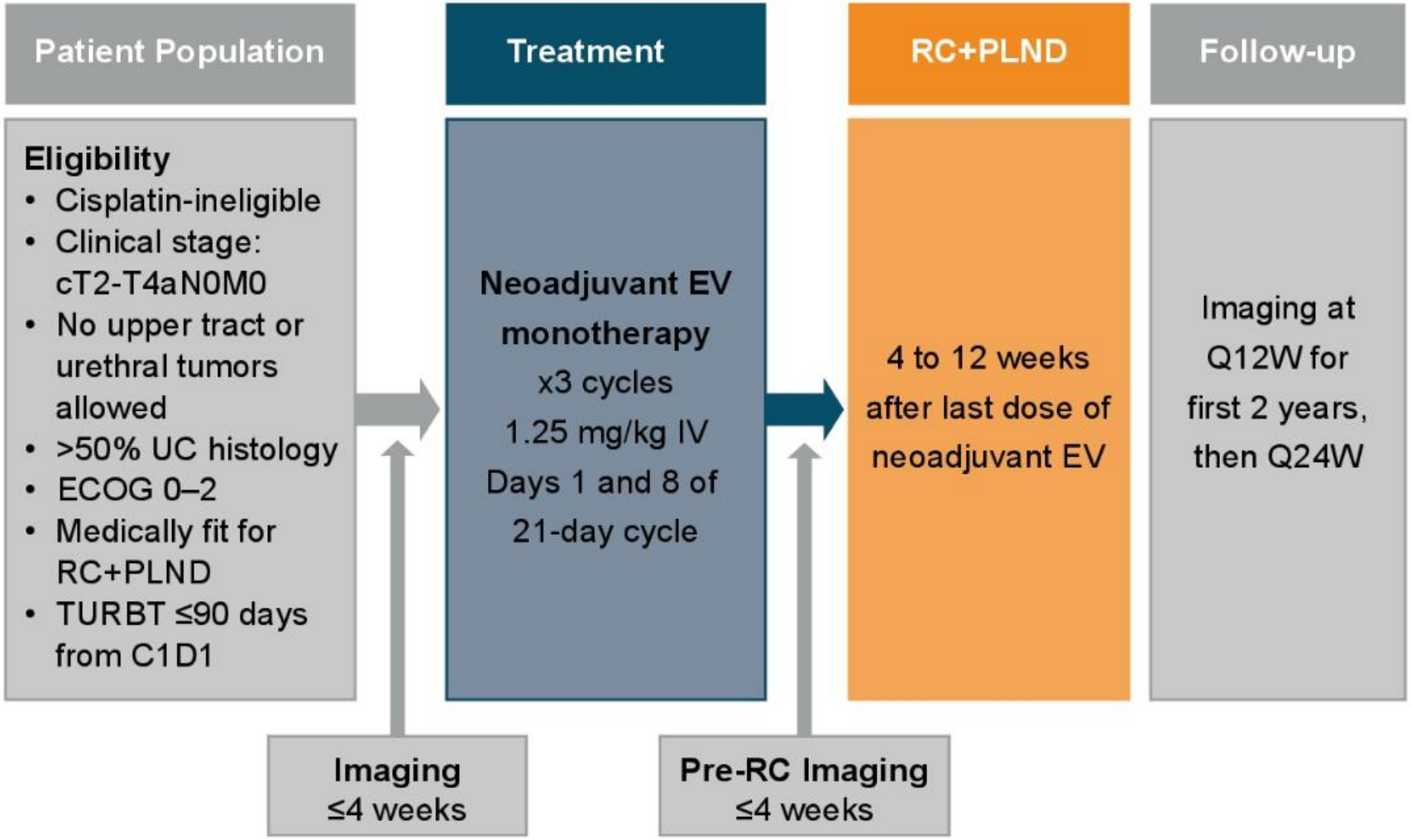
Neoadjuvant Subgroup	GC	DD-MVAC
Treatment Delivery of pre-planned cycles (%)	84	60
Radical Cystectomy performed (%)	90	91
Delay of Surgery (days)	48	51

	GC (N=245)	dd-MVAC (N=248)	P value
Nausea/vomiting	7 (2.9%)	24 (9.7%)	0.003
Diarrhea	2 (0.81%)	3 (1.2%)	-
Asthenia	10 (4.1%)	35 (14%)	<0.001
Cardiovascular	17 (6.9%)	16 (6.5%)	>0.9
Kidney	13 (5.3%)	15 (6.0%)	0.9
Liver	13 (5.3%)	7 (2.8%)	0.2
Neuropathy	0	2 (0.81%)	-
Anemia	19 (7.8%)	54 (22%)	<0.0001
Neutropenia	113 (46%)	97 (39%)	0.14
Febrile neutropenia	6 (2.4%)	16 (6.5%)	0.053
Thrombopenia	41 (17%)	49 (20%)	0.5
Chemotherapy-related deaths	1	3	-

Pfister Ch, et al. ESMO 2021; P6520; 2021 Feb;79(2):214-221; Contemp Clin Trials Commun. 2020; Grande E; invited Discussant P6520 ESMO2021

Was tun bei Cisplatin- ungeeigneten Patient:innen? EV-103 Kohorte H: Enfortumab Vedotin Monotherapie

Studiendesign



Petrylak et al. ASCO 2022; J Clin Oncol 40, 2022 (suppl 16; abstr 4582)

Was tun bei Cisplatin- ungeeigneten Patient:innen? EV-103 Kohorte H

Baseline Charakteristika

Characteristic	Patients (N=22)
Median age (range), years	74.5 (56, 81)
Male sex, n (%)	20 (90.9)
White race, n (%)	22 (100.0)
Current or former smoker, n (%)	21 (95.5)
Median enrollment time from diagnosis (range), months	1.6 (1, 3)
ECOG performance status, n (%)	
0	13 (59.1)
1	8 (36.4)
2	1 (4.5)
Current stage, n (%)	
cT2N0	15 (68.2)
cT3N0	6 (27.3)
cT4aN0	1 (4.5)
Histology type, n (%)	
TCC only	15 (68.2)
TCC with squamous differentiation	3 (13.6)
TCC with other histologic variants	4 (18.2)
TCC+adenocarcinoma	1 (4.5)
TCC+micropapillary	2 (9.1)
TCC+sarcomatoid	1 (4.5)

	Patients (N=22) n (%)
Patients meeting at least one of the following Galsky criteria	22 (100.0)
Reason for cisplatin-ineligibility[a]	
Creatinine clearance <60 mL/min and ≥30 mL/min[b]	11 (50.0)
ECOG PS of 2	1 (4.5)
Grade ≥2 hearing loss	9 (40.9)
Creatinine clearance <60 mL/min and ≥30 mL/min and Grade ≥2 hearing loss	1 (4.5)

Petrylak et al. ASCO 2022; J Clin Oncol 40, 2022 (suppl 16; abstr 4582)

Was tun bei Cisplatin- ungeeigneten Patient:innen? EV-103 Kohorte H

Ergebnisse

	EV Monotherapy (N=22)
Duration of neoadjuvant treatment[a] (months)	Median (Range) 2.1 (0.7–2.3)
Patients treated at[b]	n (%)
Neoadjuvant Cycle 1	22 (100.0)
Neoadjuvant Cycle 2	20 (90.9)
Neoadjuvant Cycle 3	19 (86.4)
Time from end of neoadjuvant EV to RC+PLND[c] (months)	Median (Range) 1.8 (1.0–2.7)
Bladder surgery not performed or delayed due to to TEAEs[d]	0
Patients on study	19 (86.4)
Patients off study	3 (13.6)
Reason off study: Death	3 (13.6)

Pathological Response	Central Pathology Results (N=22) n (%) [95% Confidence Interval]
Pathological Complete Response Rate (defined as absence of any viable tumor tissue; ypT0 and N0)	8 (36.4) [17.2–59.3]
Pathological Downstaging Response Rate (defined as presence of ypT0, ypTis, ypTa, ypT1, and N0)	11 (50.0) [28.2–71.8]

Petrylak et al. ASCO 2022; J Clin Oncol 40, 2022 (suppl 16; abstr 4582)

Vorteile und Nachteile der adjuvanten Chemotherapie (AC)

- ☺ Therapie auf der Grundlage des pathologischen Stadiums (T3/4 und/oder N+)
- ☺ Sofortige Behandlung des Primarius mit Entfernung der größten und chemoresistentesten (?) Tumorlast
- ☺ Behandlung von Mikrometastasen, wenn das Tumorvolumen gering ist

- ☹ Unnötige Exposition von Patienten, die bereits durch Zystektomie geheilt sind
- ☹ Fehlende Möglichkeit der Sensitivitätsprüfung für die Chemotherapie
- ☹ Fehlende Eignung einer signifikanten Anzahl von Patienten für die Durchführung der AC

J.A. Witjes EAU Guidelines

Onkologischer Benefit der AC

Meta-Analyse: AC + lokale Tx vs. lokale Tx alleine

Trial	Accrual years	Number of participants	Stage	Treatment details	Control treatment details	Reason for trial stopping early	Median follow-up (yr)
Trial randomised between local treatment plus adjuvant chemotherapy or local treatment alone							
Skinner [19]	1980–1988	102	pT3-pT4, pN+, M0	Cystectomy + 4 cycles of CAP: Cisplatin 100 mg/m^2 Cyclophosphamide 600 mg/m^2 Doxorubicin 60 mg/m^2	Cystectomy	Benefit of treatment seen in trial	14.5
Bono [20]	1984–1987	90 [a]	pT2-pT4a, pN0, M0	Cystectomy + 4 cycles of: Cisplatin 70 mg/m^2 Methotrexate 40 mg/m^2	Cystectomy	Did not stop early	3.4
Studer [21]	1984–1989	91	pT1 (grade 2)-pT4, pN1–2, M0	Cystectomy + 3 cycles of cisplatin 90 mg/m^2	Cystectomy	Smaller difference than expected seen between treatments at interim analysis	6.4
Stöckle [23], Lehmann [24]	1987–1990	49	pT3b-pT4a, pN+, M0	Cystectomy + 3 cycles of MVEC or MVAC: Cisplatin 70 mg/m^2 Methotrexate 30 mg/m^2 Vinblastine 3 mg/m^2 Adriamycin 30 mg/m^2 Epirubicin 45 mg/m^2	Cystectomy	Benefit of treatment seen in trial at interim analysis	14.8
Otto [25]	1993–1999	108	pT3, N1–2, M0	Cystectomy + 3 cycles of MVEC: Cisplatin 70 mg/m^2 Methotrexate 30 mg/m^2 Vinblastine 3 mg/m^2 Epirubicin 45 mg/m^2	Cystectomy	Did not stop early	3.9
Stadler [3]	1997–2006	114	pT1-pT2, pN0, M0 (all p53+)	Cystectomy + 3 cycles of MVAC: Cisplatin 70 mg/m^2 Methotrexate 30 mg/m^2 Vinblastine 3 mg/m^2 Doxorubicin 30 mg/m^2	Cystectomy	Smaller difference than expected seen between treatments at interim analysis	5.4

Advanced Bladder Cancer (ABC) Meta-analysis Collaborators Group EUROPEAN UROLOGY 81 (2022) 50–61

Onkologischer Benefit der AC

Meta-Analyse: AC + lokale Tx vs. lokale Tx alleine

Trial	Accrual years	Number of participants	Stage	Treatment details	Control treatment details	Reason for trial stopping early	Median follow-up (yr)
Trial randomised between local treatment plus adjuvant chemotherapy or local treatment plus chemotherapy on relapse							
Freiha [22]	1986–1993	51 [b]	pT3b-pT4, any pN, M0	Cystectomy + 4 cycles of CMV: Cisplatin 100 mg/m^2 Methotrexate 30 mg/m^2 Vinblastine 4 mg/m^2	Cystectomy + (same) chemotherapy on relapse	Smaller difference than expected seen between treatments	5.1
Cognetti [4]	2001–2007	194	pT2 (grade 3) pT3-pT4, pN0–2, M0	Cystectomy + 4 cycles of: Cisplatin 70 mg/m^2 Gemcitabine 1000 mg/m^2 *Cisplatin given on day 2 or day 15*	Cystectomy + (same) chemotherapy on relapse	Accrual slower than expected	4.5
Sternberg [5]	2002–2014	284	pT3-pT4 or pN1–3, M0	Cystectomy + choice of 4 cycles of either: (1) MVAC (28-d cycle), (2) high-dose MVAC (14-d cycle), or (3) GC: Cisplatin 70 mg/m^2 Methotrexate 30 mg/m^2 Vinblastine 3 mg/m^2 Adriamycin 30 mg/m^2 Gemcitabine 1000 mg/m^2	Cystectomy + 6 cycles (same) chemotherapy on relapse	Accrual slower than expected	6.9
Zhegalik [6]	2007–2013	100	pT3-pT4 and/or pN+, M0	Cystectomy + 2 cycles of: Cisplatin 75 mg/m^2 Gemcitabine 1000 mg/m^2	Cystectomy + (same) chemotherapy on relapse	Did not stop early	7.3

CAP = cyclophosphamide, doxorubicin, and cisplatin; CMV = cisplatin, methotrexate, and vinblastine; GC = gemcitabine and cisplatin; MVAC = methotrexate, vinblastine, doxorubicin, and cisplatin; MVEC = methotrexate, vinblastine, epirubicin, and cisplatin.

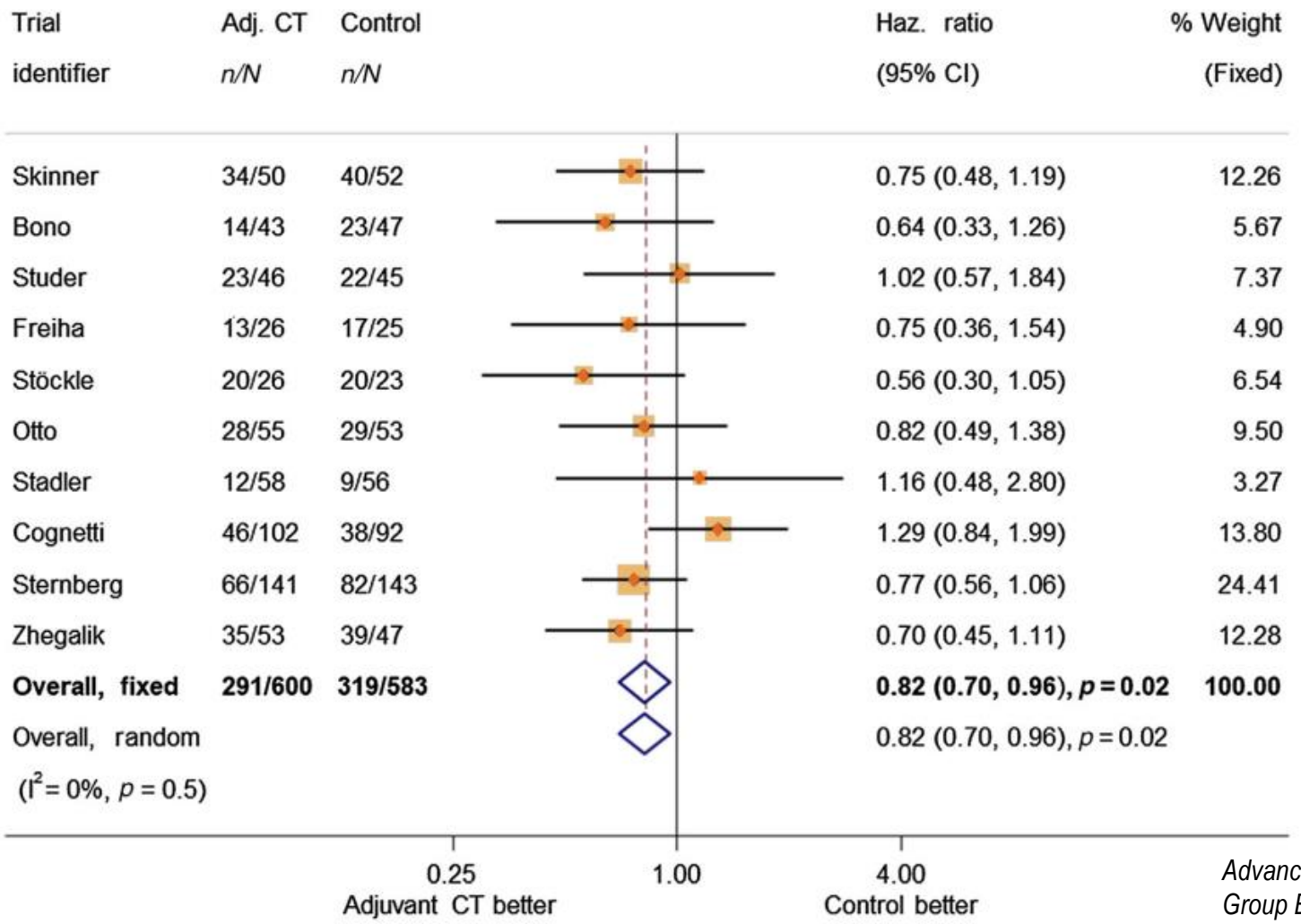
[a] Ninety participants supplied and used in 2005 analysis.

[b] Fifty-five randomised and 51 supplied.

Advanced Bladder Cancer (ABC) Meta-analysis Collaborators Group EUROPEAN UROLOGY 81 (2022) 50–61

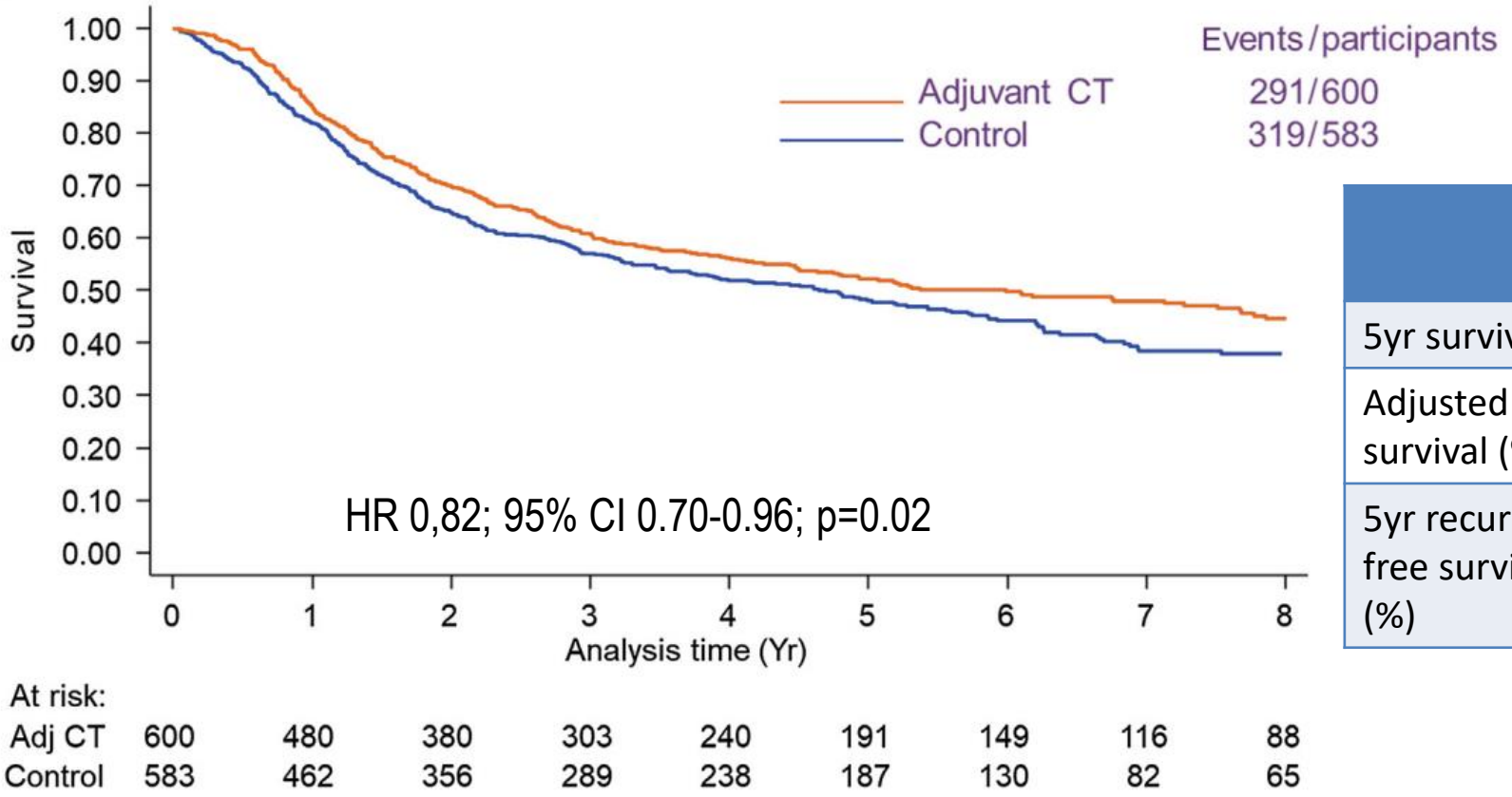
Onkologischer Benefit der AC

Meta-Analyse: AC + lokale Tx vs. lokale Tx alleine



Advanced Bladder Cancer (ABC) Meta-analysis Collaborators Group EUROPEAN UROLOGY 81 (2022) 50–61

Onkologischer Benefit der AC
Meta-Analyse



	local Tx + AC	Local Tx alone +/- CTX on relapse
5yr survival (%)	56	50
Adjusted 5yr survival (%)	59	50
5yr recurrence free survival** (%)	61	50

*Adjusted for age, sex, pT stage and N stage
** based on 1075 participants (9RCTs)

Advanced Bladder Cancer (ABC) Meta-analysis Collaborators Group EUROPEAN UROLOGY 81 (2022) 50–61

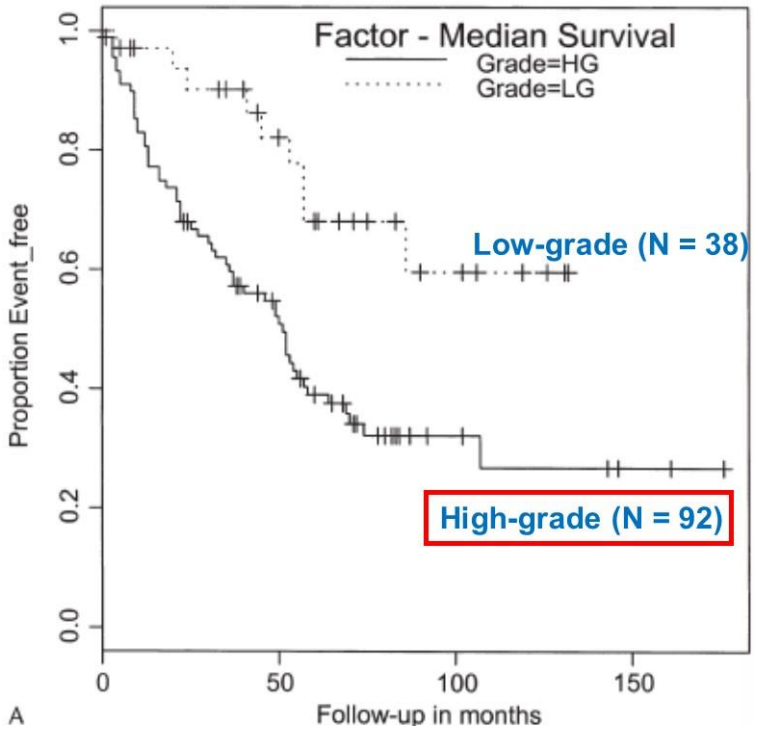
UROTHELKARZINOM DES OBEREN HARNTRAKTS (UTUC)

Neoadjuvante und adjuvante Chemotherapie

Gunhild von Amsberg

Urothelkarzinom des oberen Harntrakts

Selten aber tödlich…

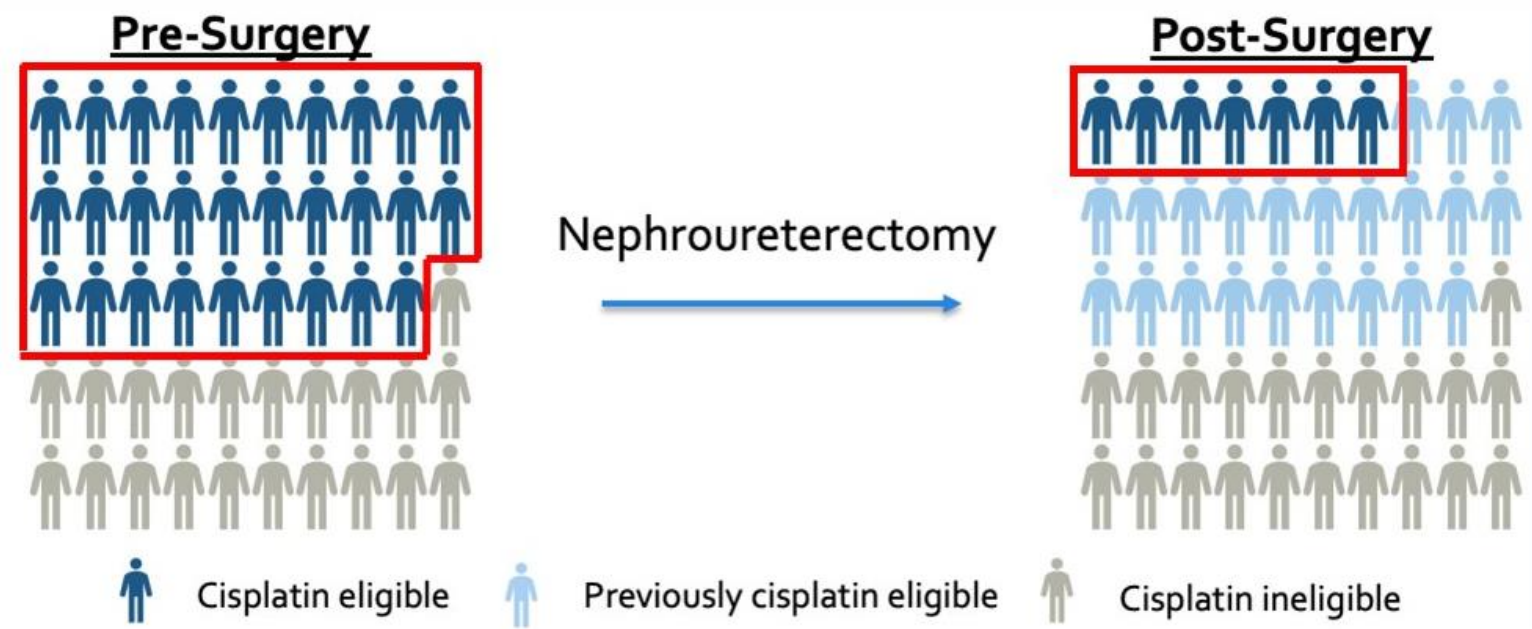


5-year cancer specific mortality:

pT2: 21%

pT3: 35%

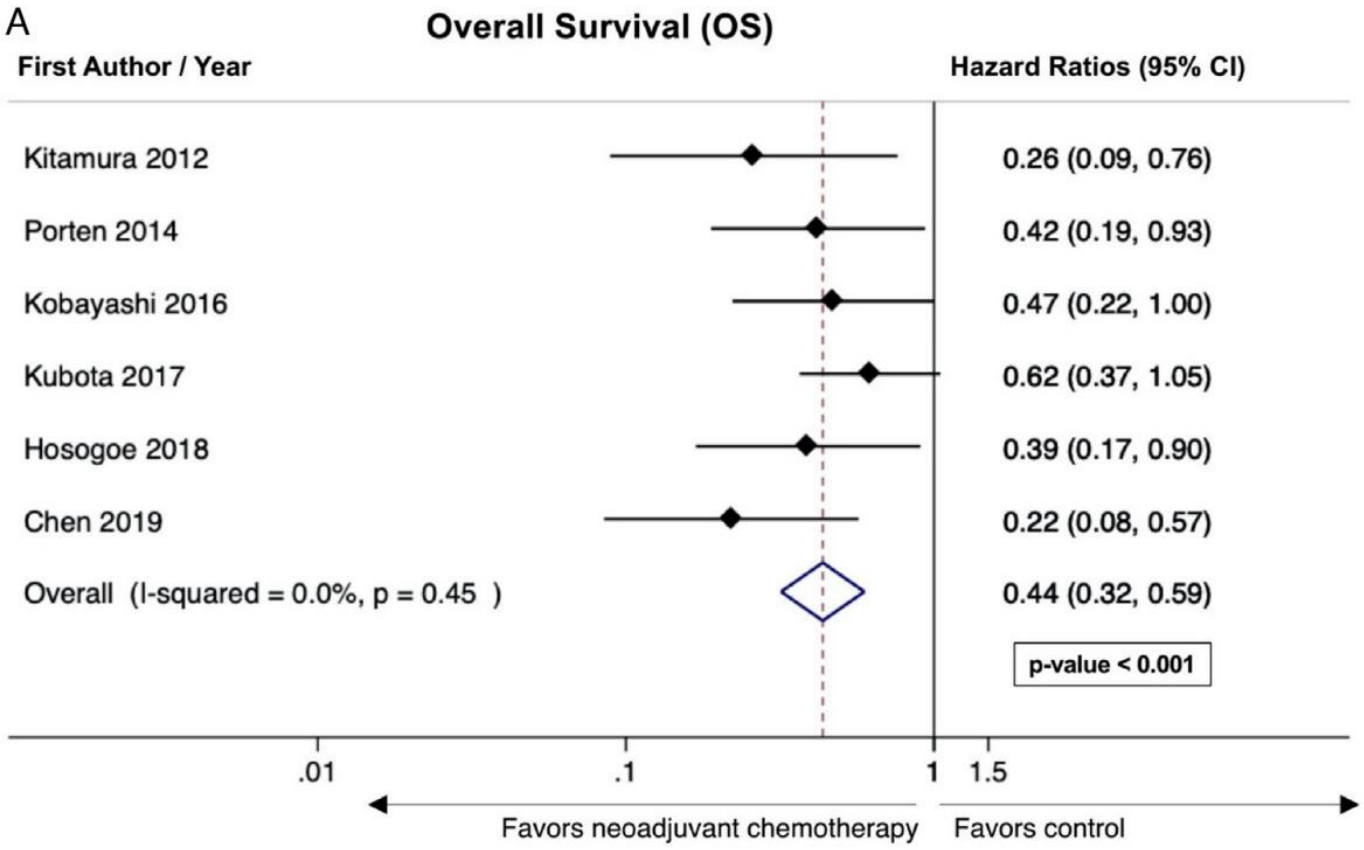
pT4: 59%



Cisplatin eligibility declines from neoadjuvant 58% to adjuvant 15%

Leow et al. Eur Urol 2014 P529-541

Urothelkarzinom des oberen Harntrakts
Neoadjuvante Therapie- Metaanalyse



- Seven retrospective trials with comparison to RNU
- 14 studies with 811 patients for pathological response:
  - ypT0: 11% (95% CI 8-15%)
  - < ypT2: 43% (95% CI 34-52%)

Leow et al. Eur Urol 2020; DOI:https://doi.org/10.1016/j.eururo.2020.07.003

Urothelkarzinom des oberen Harntrakts

Prospektive, nicht-randomisierte Phase 2-Studie

Key inclusion criteria

High-risk UTUC

High-grade biopsy and/or imaging (cT2-T4a) and positive selective cytology

No metastases

eGFR ≥55ml/min by CKD-EPI formula.

Karnofsky performance status ≥70%.

→

Gemcitabin
1000 mg/m^2 d 1, 8

Cisplatin
35 mg/m^2 d1, 8

→

Radical nephroureterectomy or ureterectomy with lymph node resection

→

Follow-up according to standardized protocol

Cytology and cytoscopy Q3M x 18Mo, Q6M x 18Mo, then Q1Y

Imaging Q6M x 18Mo, then Q1Y

Primary endpoint

pathological response rate (<ypT2N0)

Secondary endpoints

Pathologic complete response rate (ypT0N0)

time to disease progression

Overall survival

Safety and tolerabilit

Simon's Minimax 2-Stage Design

Promising at >60% pathologic response rate

Unacceptable at <40% pathological response rate

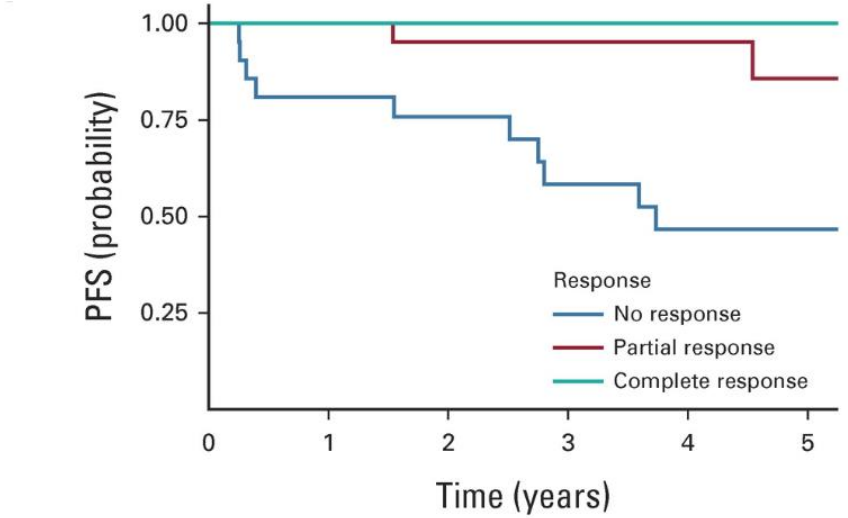
Yip W, et al. ASCO GU 2022 J Clin Oncol 40, 2022 (suppl 6; abstr 440;

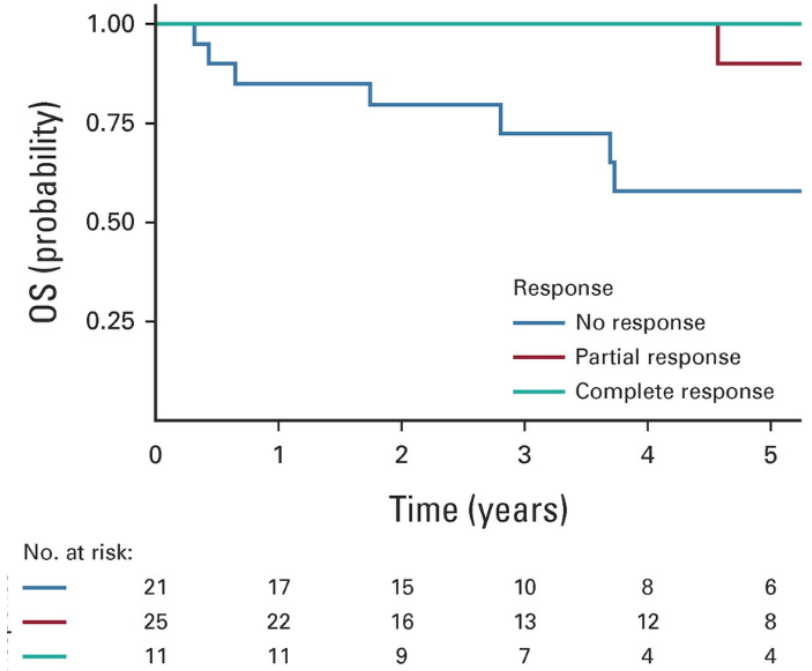
Urothelkarzinom des oberen Harntrakts

Prospektive, nicht-randomisierte Phase 2-Studie

Pathologic Response		N = 57
Responders (<ypT2N0)		36 (63%)
	T0	11 (19%)
	Ta	10 (18%)
	Tis	7 (12%)
	T1	8 (14%)
Non-Responders (≥ypT2Nany)		21 (37%)
	T2	5 (9%)
	T3	9 (16%)
	TanyN+	7 (12%)
Progression prior to surgery		0 (0%)

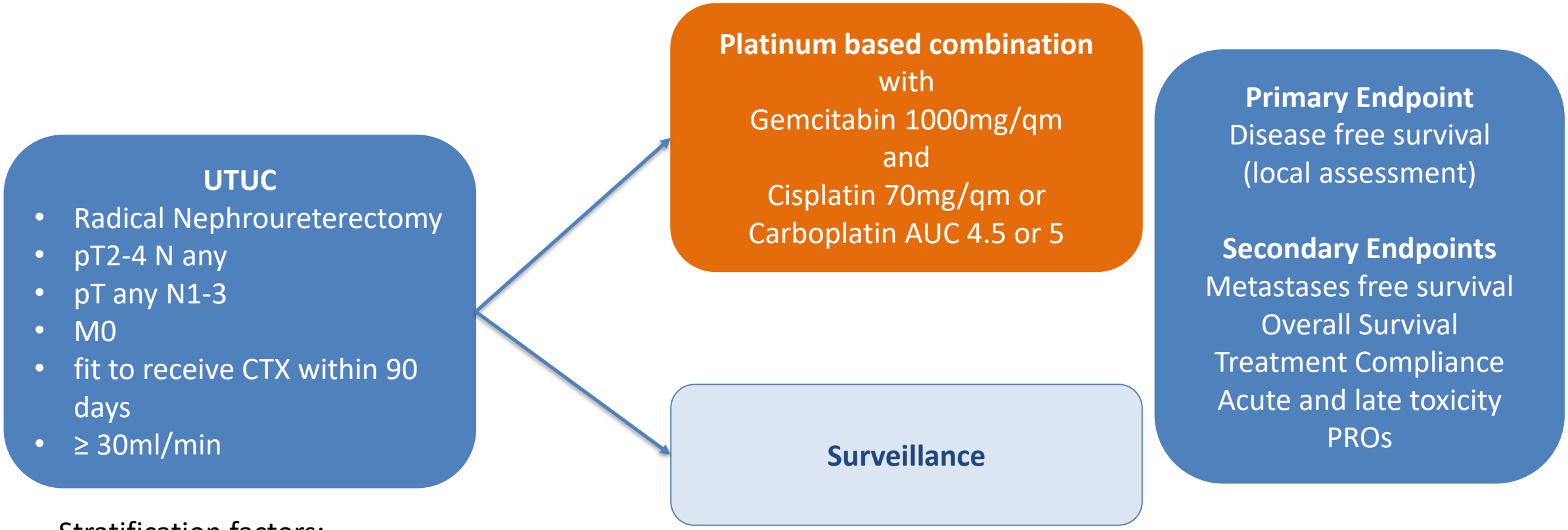
	2 years	5 years
PFS	78%	65%
OS	93%	79%





Yip W, et al. ASCO GU 2022 J Clin Oncol 40, 2022 (suppl 6; abstr 440);
Coleman et al. 2023 Mar 10;41(8):1618-1625. doi: 10.1200/JCO.22.00763

Urothelkarzinom des oberen Harntrakts
Adjuvante Therapie: POUT-Studie



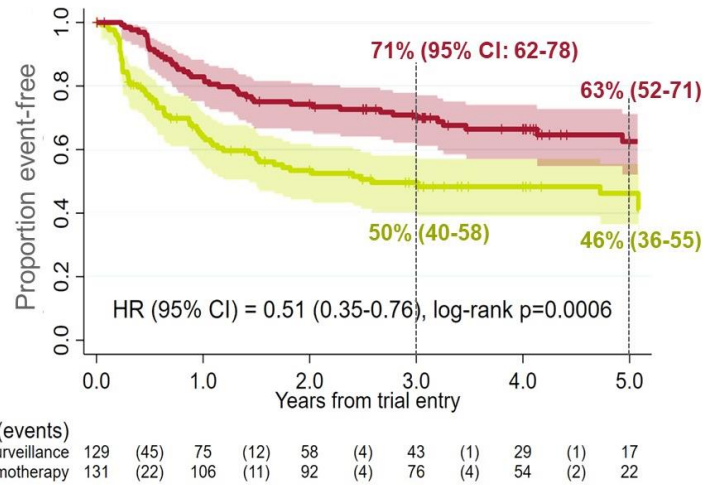
Stratification factors:
Cisplatin vs. Carboplatin
N0 vs. N1 vs. N2 vs. N3
Positive or negative margins

Birtle A et al. Lancet 2020; 395: 1268–77

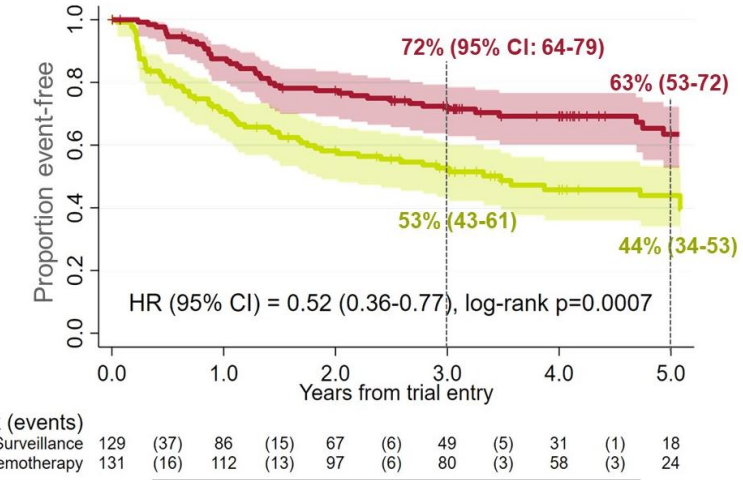
Urothelkarzinom des oberen Harntrakts

Adjuvante Therapie: POUT-Studie

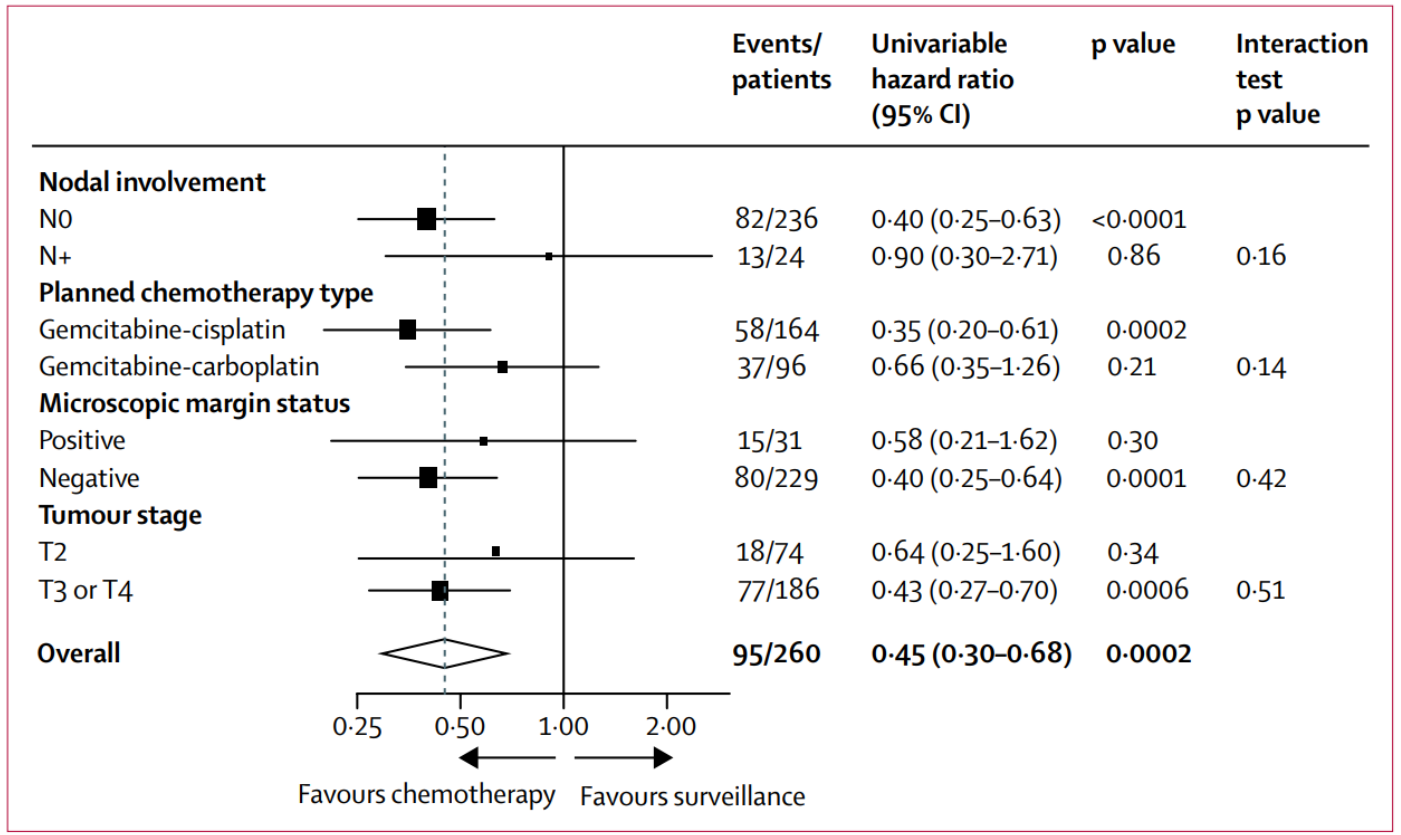
Disease-free survival

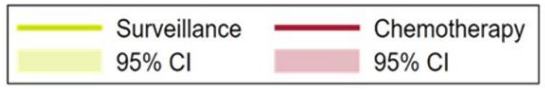


Metastasis-free survival



3 year DFS: CTX 71% (95% CI 61-78); surveillance 46% (95%CI 36-56)



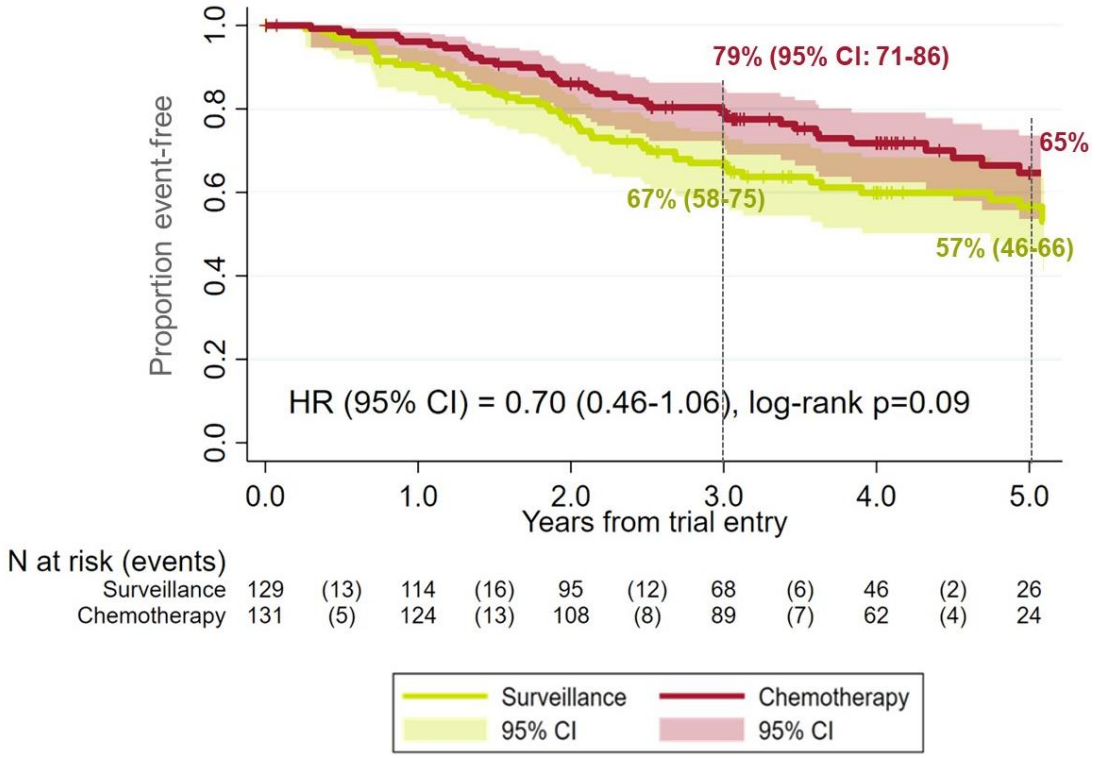


Birtle A et al. Lancet 2020; 395: 1268–77; ASCO GU 2021,# 455

Urothelkarzinom des oberen Harntrakts

Adjuvante Therapie: POUT-Studie

Overall Survival



	Surveillance	Chemotherapy
Death	52/129	41/131
Post-recurrence systemic therapy	41/63 (65.1%)	18/40 (45.0%)

Birtle A et al. Lancet 2020; 395: 1268–77; ASCO GU 2021,# 455

IMMUNTHERAPEUTISCHE KONZEPTE

Neoadjuvant und Adjuvant

Gunhild von Amsberg

Neoadjuvante Immuntherapie des Urothelkarzinoms-Studienübersicht

Study	Phase	Treatment	Patients Included	pCR	Survival
PURE-01 [1] [21]	2	PEM	80	39%	-
PURE-01 (VH)	2	PEM	19	16%	-
PANDORE [30]	2	PEM	34	29.4%	-
ABACUS	2	AZ	95	31%	1 y RFS: 79%
AURA (Cohort 2)	2	A; PG + A	56	36% (A) vs. 18% (PG + A)	-
NABUCCO (cohort 1)	2	N + IPI	24	46%	-
NABUCCO (cohort 2)	2	2a: N (1) + IPI (3) 2b: N (3) + IPI (1)	15 15	43% 7%	
MDACC	2	DU + TRE	28	37.5%	1 y RFS: 82.8% 1 y OS: 88%
MDACC (VH)	2	DU + TRE	7	57%	-
DUTRENEO	2	DU +TRE, PG	61	"Hot" arm: 34.8% (DU + TRE) vs. 36.4 (PG) "Cold" arm: 68.8% (PG)	-
CA209-9DJ	2	Cohort 1: N (3)/Cohort 2: N(1) + I(3)	30	Cohort 1: 13% Cohort 2: 7%	12 m RFS C1: 77% 12 m RFS C2: 68%.
ABACUS-2 (VH)	2	Atezolizumab	-	-	-
NCT02845323	2	N ± Urelumab	-	-	-
NCT03532451	1b	N ± Lirilimab	-	-	-
PIVOT-IO 009	3	N ± Bempegaldesleukin	-	-	-
OPTIMUS	2	Retifanlimab, Epacadostat, INCAGN02385, INCAGN02390	-	-	-
BLASST-2	2	PEM + Oleclumab	-	-	-

A: Avelumab
AZ: Atezolizumab
DU: Durvalumab
I: Ipilimumab
N: Nivolumab
pCR: pathological complete response
PG: Cisplatin/Gemcitabin
PEM: Pembrolizumab
OS: Overall Survival
RFS Recurrence free survival
TRE: Tremeliumab

Esteban-Villarrubia et al. Cancers 2023, 15, 566 https://doi.org/10.3390/cancers15030566.

Checkmate-274: Nivolumab adjuvant

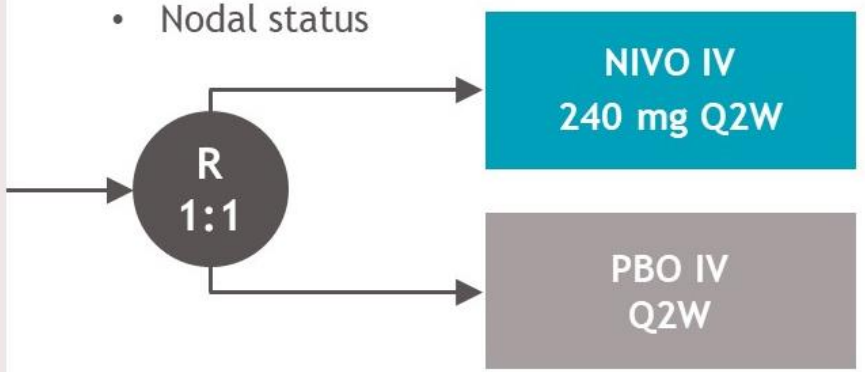
N = 709

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

[a]Defined by the percent of positive tumor cell membrane staining in a minimum of 100 evaluable tumor cells using the PD-L1 IHC 28-8 PharmDx immunohistochemistry assay.
[b]OS data were not mature at the time of the first planned interim analysis. OS and DSS data are not presented.
DFS, disease-free survival; DMFS, distant metastasis-free survival; DSS, disease-specific survival; HRQoL, health-related quality of life; IHC, immunohistochemistry; ITT, intent-to-treat; NUTRFS, non-urothelial tract recurrence-free survival; OS, overall survival; PD-L1, programmed death ligand 1; Q2W, every 2 weeks; R, randomized.

Galsky et al. ASCO GU 2023; LBA 443Bajorin et al ASCO GU 2021; N Engl J Med 2021; 384:2102-2114;

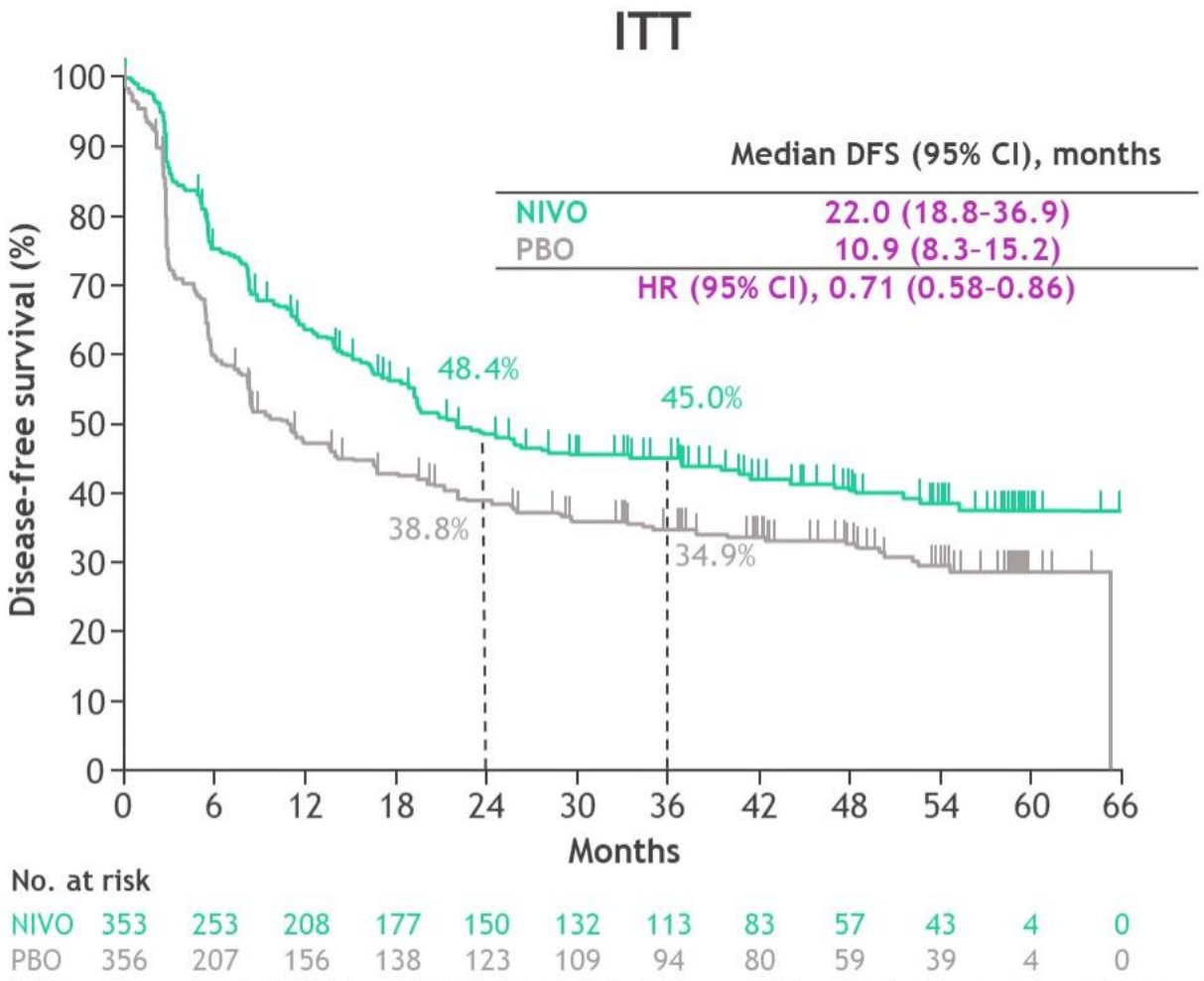
Checkmate-274: Nivolumab adjuvant

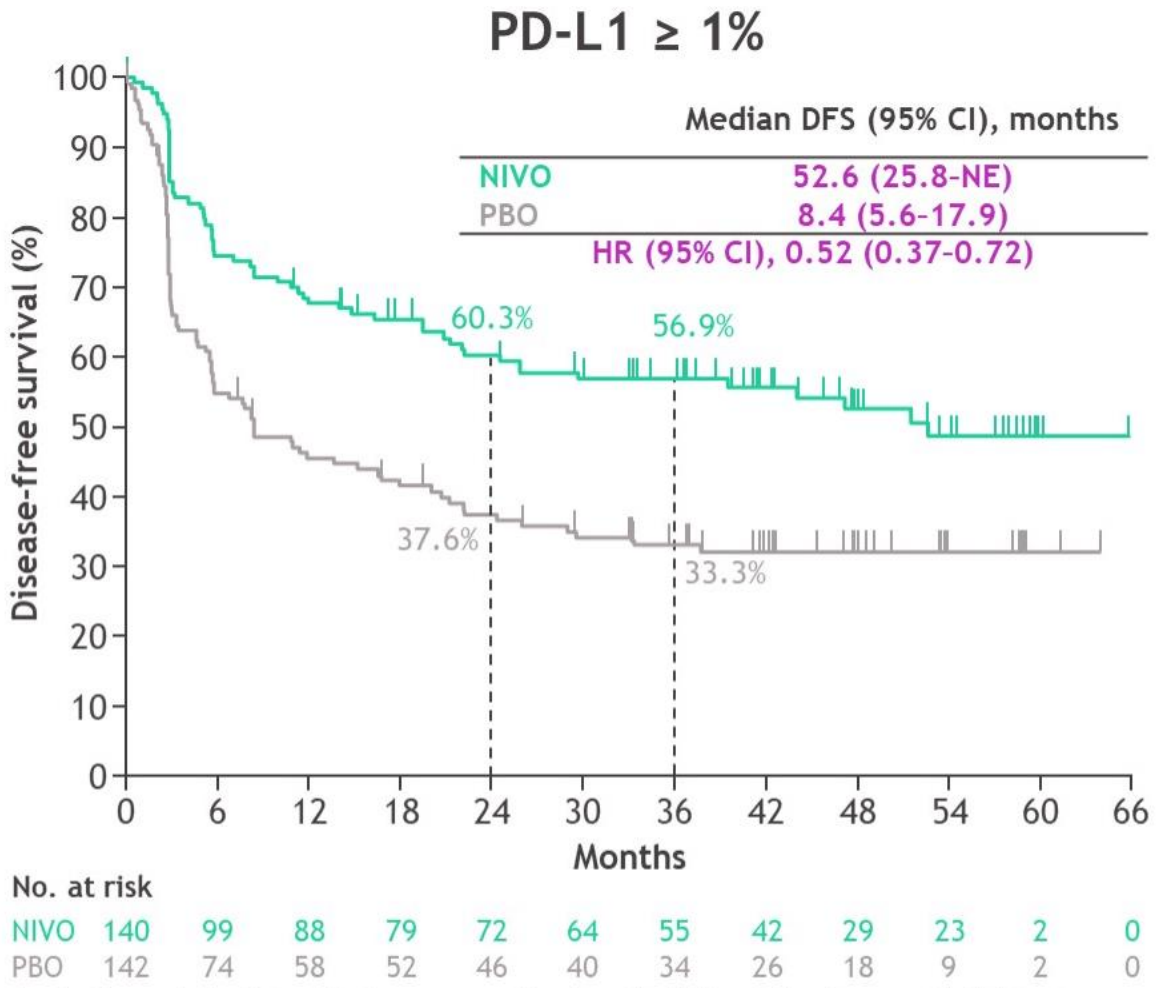
	NIVO (N = 353)	PBO (N = 356)
Mean age (range), years	65.3 (30-92)	65.9 (42-88)
Male, %	75	77
Race or ethnic group, %		
White	75	76
Asian	23	21
Black	1	1
Other/unreported	2	2
ECOG PS,[a] %		
0	63	62
1	35	35
2	2	3
Tumor origin at initial diagnosis, %		
Urinary bladder	79	79
Renal pelvis	12	15
Ureter	8	6
Tumor PD-L1 ≥ 1% as recorded at randomization by IVRS, %	40	40
Prior neoadjuvant cisplatin, %	43	44
Pathologic T stage at resection,[b,c] %		
pT0-2	23	24
pT3	58	57
pT4a	16	17
Nodal status at resection,[c] %		
N+	47	47
N0/x with < 10 nodes removed	27	28
N0 with ≥ 10 nodes removed	26	25

[a]Not reported for 1 patient in the PBO arm. [b]pTX in 1% of patients in the NIVO arm; pTis in 1% of patients in the NIVO arm and 1% of patients in the PBO arm. [c]Not reported for 1 patient each in the NIVO and PBO arm.
ECOG PS, Eastern Cooperative Oncology Group performance status; IVRS, interactive voice-response system.
1. Bajorin DF, et al. *N Engl J Med* 2021;384:2102-2114.

Galsky et al. ASCO GU 2023; LBA 443Bajorin et al ASCO GU 2021; N Engl J Med 2021; 384:2102-2114;

Checkmate-274: Krankheitsfreies Überleben





Minimum follow-up in the ITT population, 31.6 months. DFS was defined as the time between the date of randomization and the date of first recurrence (local urothelial tract, local non-urothelial tract or distant) or death.
NE, not estimable.

Galsky et al. ASCO GU 2023; LBA 443Bajorin et al ASCO GU 2021; N Engl J Med 2021; 384:2102-2114;

Checkmate-274: Krankheitsfreies Überleben

Subgruppenanalyse

	NIVO Events/patients	PBO Events/patients	HR for DFS (95% CI)
Overall	195/353	233/356	0.71 (0.58-0.86)
Age			
< 65 years	81/155	81/136	0.74 (0.54-1.01)
≥ 65 and < 75 years	76/131	112/164	0.68 (0.50-0.92)
≥ 75 years	38/67	40/56	0.64 (0.39-1.04)
Sex			
Male	148/265	184/275	0.69 (0.56-0.87)
Female	47/88	49/81	0.79 (0.52-1.20)
Region			
USA	26/49	38/53	0.52 (0.30-0.89)
Europe	102/170	113/171	0.84 (0.64-1.10)
Asia	37/80	39/74	0.77 (0.48-1.24)
Rest of the world	30/54	43/58	0.51 (0.30-0.89)
Baseline ECOG PS			
0	121/224	143/221	0.67 (0.53-0.86)
1	72/122	82/125	0.81 (0.58-1.12)
Initial tumor origin			
Urinary bladder	152/279	190/281	0.63 (0.51-0.78)
Renal pelvis	26/44	28/52	1.22 (0.69-2.15)
Ureter	17/30	15/23	1.41 (0.65-3.06)

Galsky et al. ASCO GU 2023; LBA 443Bajorin et al ASCO GU 2021; N Engl J Med 2021; 384:2102-2114;

Checkmate-274: Krankheitsfreies Überleben

Subgruppenanalyse

	Events/patients		
Minor histologic variants			
Presence	85/145	88/141	0.78 (0.58-1.07)
Absence	110/208	145/215	0.68 (0.53-0.88)
Pathologic lymph node status			
N+	109/167	134/168	0.62 (0.48-0.81)
N0/x with < 10 nodes removed	50/94	56/99	0.84 (0.57-1.24)
N0 with ≥ 10 nodes removed	36/91	42/88	0.75 (0.47-1.18)
Pathologic status			
pT0-2	42/80	48/86	0.91 (0.59-1.42)
PT3	113/206	132/204	0.64 (0.50-0.83)
PT4a	38/57	49/62	0.68 (0.43-1.08)
PD-L1 expression			
≥ 1	61/140	87/141	0.53 (0.38-0.73)
< 1	132/210	141/209	0.84 (0.66-1.06)
Previous neoadjuvant cisplatin			
Yes	81/153	110/155	0.54 (0.40-0.72)
No	114/200	123/201	0.91 (0.70-1.17)

Galsky et al. ASCO GU 2023; LBA 443Bajorin et al ASCO GU 2021; N Engl J Med 2021; 384:2102-2114;

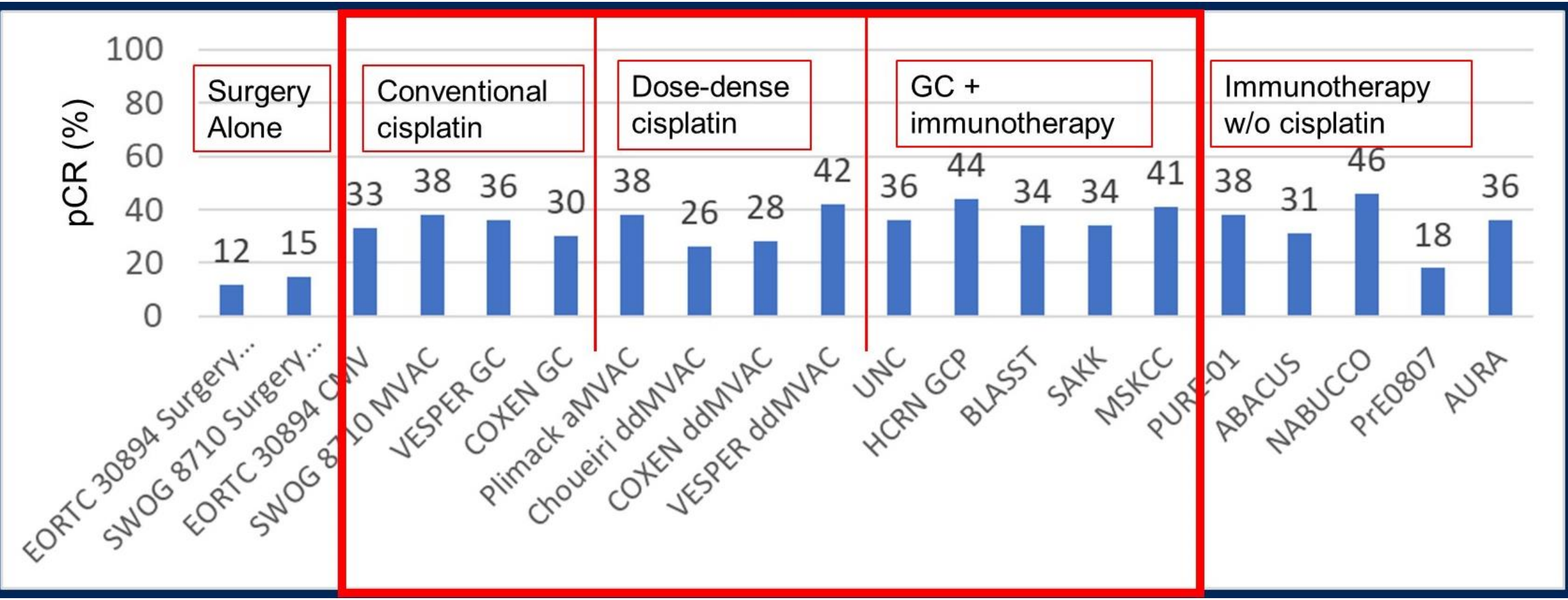
Neoadjuvante Chemoimmuntherapie -Studienübersicht

Study	Phase	Treatment	Patients Included	pCR	Survival
HCRN GU 114-88 (Cohort 1)	1b/2	CG + PEM	43	44.4%	Estimated 36 m RFS: 63% Estimated 36 m OS: 82%
HCRN GU 114-88 (Cohort 2)	1b/2	G + PEM	37	45.2%	Estimated 12 m RFS: 74.9% Estimated 12 m OS: 93.8%
Iccc1520 trial	2	C (35)G + PEM	39	36%	-
BLASST-1	2	CG + N	41	65.8 (≤ypT1N0)	12 m PFS: 85.4%
SAKK 06/17	2	CG + DUR	61	34%	OS at 2 years: 87.3%
NCT02989584	2	AZ → CG + AZ → AZ	44	41%	No relapse in <ypT2N0 patients.
AURA (cohort 1)	2	CG + Av vs. dd-MVAC +Av	28 28	32% 43%	- -
NIAGARA	3	CG + DUR → DUR	1050 to include	-	-
KEYNOTE 866	3	PG + PEM → PEM	870 to include	-	-
ENERGIZE	3	PG + N ± LM	1200 to include	-	-
SWOG-GAP	2	Ca + G + Av	196 to include	-	-
NEMIO	2	ddMVAC + DUR	120 to include	-	-
RETAIN-2	2	AMVAC + N	71 to include	-	-
NCT04383743	2	MVAC + PEM	17 to include	-	-

Av: avelumab
AMVAC: accelerated MVAC
C: cisplatin
Ca carboplatin
ddMVAC: dose-dense MVAC,
DUR: durvalumab
G: gemcitabine
LM: linrodostat mesylate
N: nivolumab
OS: overall survival
pCR: pathological complete response
PEM: pembrolizumab
RFS: recurrence-free survival

Esteban-Villarrubia et al. Cancers 2023, 15, 566 https://doi.org/10.3390/cancers15030566.

Neoadjuvante Therapien im Vergleich: Was bringt die Therapieintensivierung?



Posterdiskussion Milowsky ASCO 2022; Rose et al JCO 2021; Hoimes et al. ESMO 2018 abstr. 5681;
Gupta et al. JCO 38,6supp Feb 2020: Cathomas ASCO 2022 Abstr 4515; Funt et al JCO 2022;
Grossmann NEJM 2003; Necchi JCO 2018; Grivas et al. ASCO 2021; Kaimakliotis ASCO 2020; Pfister Europ Urol 2021;

Perioperative Therapie – Take Home Message

MIBC

- Neoadjuvante, Cisplatin-basierte ChT ist Standard für Cisplatin-geeignete Patienten!
- Schwächere Evidenz für die adjuvanten Cisplatin-basierten ChT für Pt ohne vorherige neoadjuvante ChT
- Eine adjuvante ChT für cisplatin-ungeeigntete Patienten kann nicht empfohlen werden.

UTUC

- Schwache Evidenz für den Einsatz der adjuvanten Cisplatin-basierten ChT (POUT; OS Metaanalysen)
- Unklare Rolle der adjuvanten Carboplatin-basierten ChT (limitierte Power der POUT Subgruppen).

IMMUNTHERAPIE

- Zulassung von Nivoumab für PD-L1+ Patienten (Cisplatin-ungeeignet oder nach NAC)
- Therapiekonzepte zur Immunchemotherapie bislang ohne wesentliche Verbesserung der cpRR, Einsatz im Rahmen klinischer Studien!
- Neue perioperative Konzepte werden im Rahmen klinischer Studien evaluiert (z.B. mit Enfortumab Vedotin: VOLGA (mit Duvalumab/ Tremelimumab) oder Keynote-905 (mit Pembrolizumab)

Vielen Dank für Ihre Aufmerksamkeit

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