UPDATE – HARNBLASENKARZINOM 2023

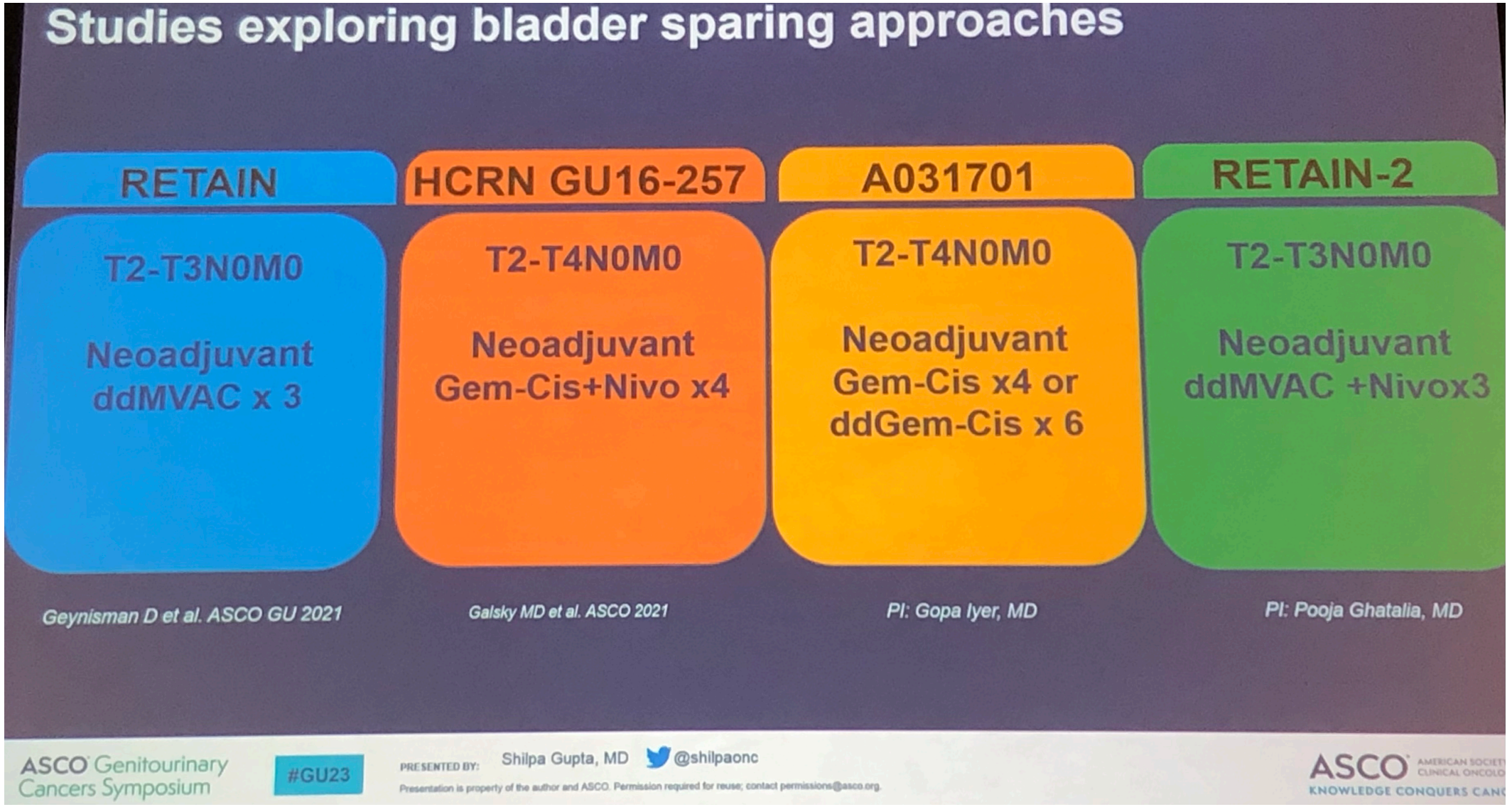
Heiko Wunderlich
Klinik für Urologie und Kinderurologie
„Prof. Dr. Maximilian Nitze“
St. Georg Klinikum Eisenach

Offenlegung potentieller Interessenkonflikte

1. **Anstellungsverhältnis oder Führungsposition**
   keine
2. **Beratungstätigkeit**
   BMS, MSD, IPSEN, Janssen, Novartis, Roche, Merck
3. **Aktienbesitz**
   keiner
4. **Honorare**
   Vorträge, Merck Healthcare, Pfizer
5. **Finanzierung wissenschaftlicher Untersuchungen**
   Studienteilnahmen, Studienleitung Cabocare
6. **Gutachtertätigkeit**
   Keine

Offenlegung potentieller Interessenkonflikte

„Sämtliche Aussagen in dieser Präsentation geben ausschließlich die persönliche und unabhängige Auffassung und Meinung des Vortragenden und Autors wider“


Studies exploring bladder sparing approaches
RETAIN
T2-T3N0M0
Neoadjuvant ddMVAC x 3
Geynisman D et al. ASCO GU 2021
HCRN GU16-257
T2-T4N0M0
Neoadjuvant Gem-Cis+Nivo x4
Galsky MD et al. ASCO 2021
A031701
T2-T4N0M0
Neoadjuvant Gem-Cis x4 or ddGem-Cis x 6
PI: Gopa Iyer, MD
RETAIN-2
T2-T3N0M0
Neoadjuvant ddMVAC +Nivox3
PI: Pooja Ghatalia, MD
ASCO Genitourinary Cancers Symposium
#GU23
PRESENTED BY: Shilpa Gupta, MD @shilpaonc
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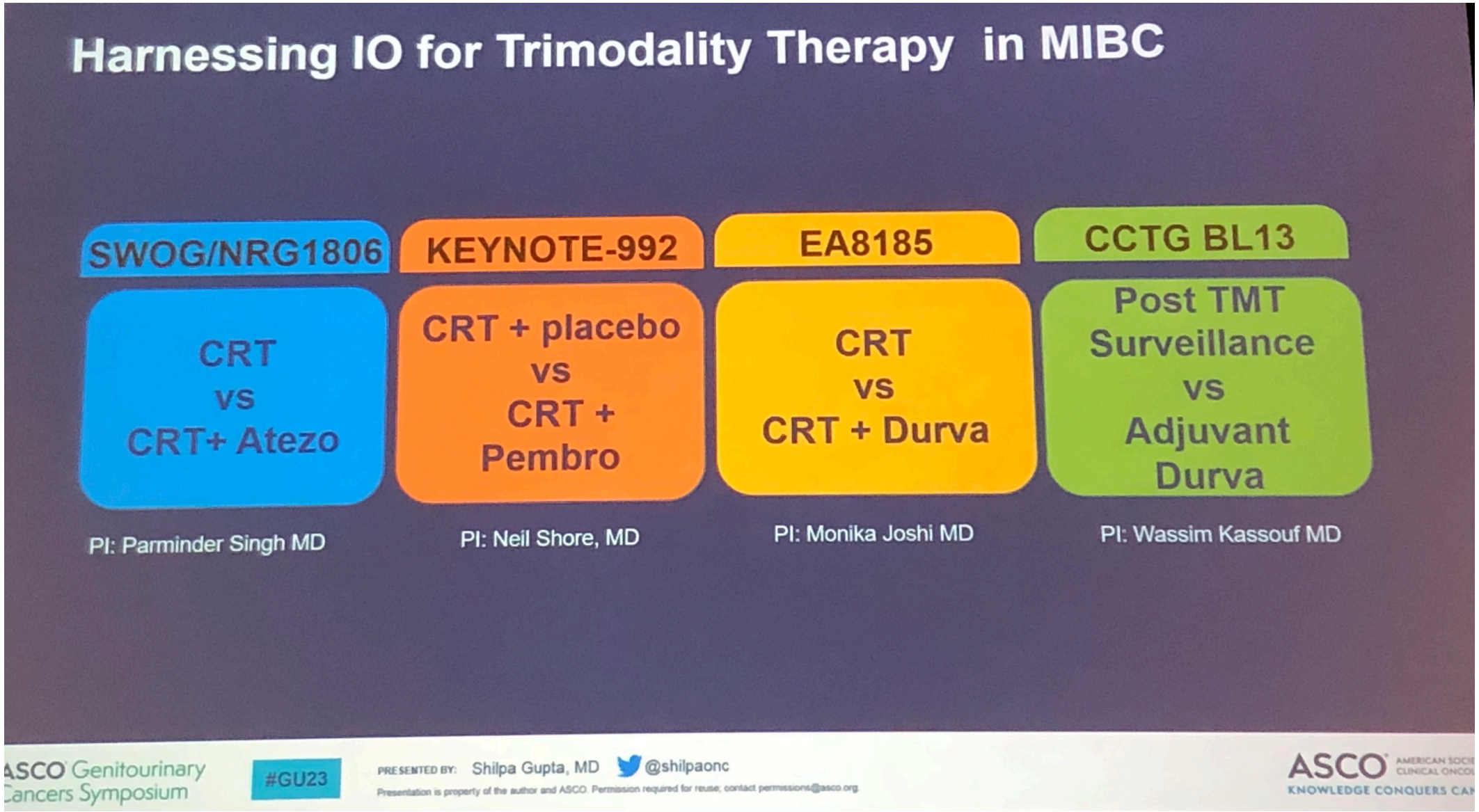
Harnessing IO for Trimodality Therapy in MIBC
SWOG/NRG1806
CRT vs CRT+ Atezo
PI: Parminder Singh MD
KEYNOTE-992
CRT + placebo vs CRT + Pembro
PI: Neil Shore, MD
EA8185
CRT vs CRT + Durva
PI: Monika Joshi MD
CCTG BL13
Post TMT Surveillance vs Adjuvant Durva
PI: Wassim Kassouf MD
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Zystektomie bei Oligometastasierung?

- Induktive Chemotherapie bei LK-pos. Befund mgl. Surrogatparameter hinsichtlich OS
- Zytoreduktive oder konsolidierende Zystektomie bei solitären Metastasen zeigt 18 Monate besseres CSS (Abufaraj et al., Euro. Urol. 2018)
- Wenn (3753 Pat.) intensive Lokaltherapie (>50 Gy Rx oder RZ) bei metast. TCC (supraregionale LK, viszeral oder Knochen) **med. OS 9,8 → 14,9 Monate** vs. keine lokale Therapie oder TuR oder Radiatio <50Gy
  Med.OS wenn induktiv Platin-Cx **17,7 Monate** (Seisen et al., J. Clin. Oncol. 2016)
- Durch Primärtumorbehandlung weniger Mts-fördernde Faktoren sezerniert (Liu et al., Mol. Cancer 2016)
- Verminderung lokaler Symptome und Komplikationen (Hämaturie, Schmerzen, Nierenversagen etc.)

Zystektomie bei Oligometastasierung?

Tab. 1 Ausgewählte klinische Studien zur Therapie beim lokal fortgeschrittenen und oligometastasierten Blasenkarzinom

Studien ID	Phase	Population	Intervention	*n*	Primärer Endpunkt
NCT03529890 (RACE IT)	2	Lokal fortgeschrittenes Urothelkarzinom der Blase	Neoadjuvant Nivolumab + Radiatio vor RZ mit pelviner Lymphadenektomie	33	Abschluss der Behandlung
NCT04047693	2	MIBC und lokal fortgeschrittenes Urothelkarzinom der Blase	Neoadjuvant dosisdicht MVAC (Methotrexat, Vinblastin, Doxorubicin + Cisplatin) + G-CSF	32	Vollständige Remissionsrate
NCT02989584	1/2	Phase 2: resezierbares Urothelkarzinom cT2-4a; N0/X; M0	Neoadjuvant Atezolizumab, Gemcitabin + Cisplatin vor RZ	54	Sicherheit
NCT04724928 (EFFORT-MIBC)	2	Nicht-metastasiertes, oligometastasiertes oder metastasiertes MIBC	Neoadjuvant Chemotherapie + RZ oder TMT ± metastasengerichtete Therapie oder Immuntherapie	156	2-Jahres-Gesamtüberleben
NCT03601455	1/2	Nicht resezierbar, lokal fortgeschritten oder metastasiertes Urothelkarzinom der Blase	Radiatio + Durvalumab	13	Sicherheit, progressionsfreies Überleben

RZ radikale Zystektomie, *TMT* trimodale Therapie, *MIBC* muskelinvasives Urothelkarzinom der Blase, *TURB* transurethrale Resektion der Blase, *MVAC* Methotrexat/Vinblastin/Adriamycin/Cisplatin, *G-CSF* granulozytenkoloniestimulierender Faktor

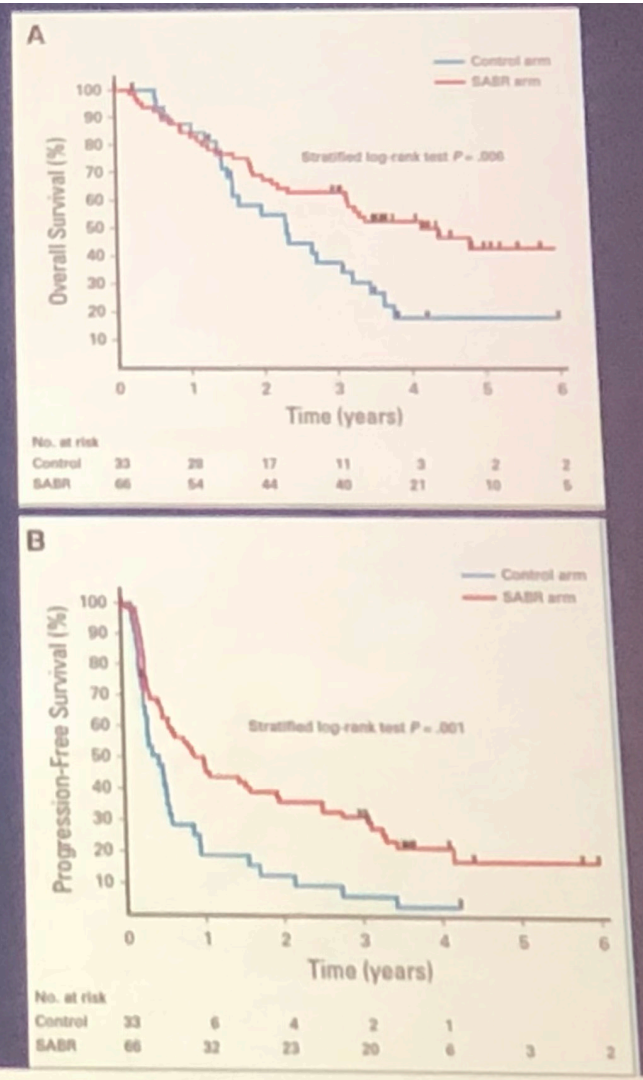
Der Urologe 12/2021, Rebhan & Gust

Operation bei Oligometastasierung?

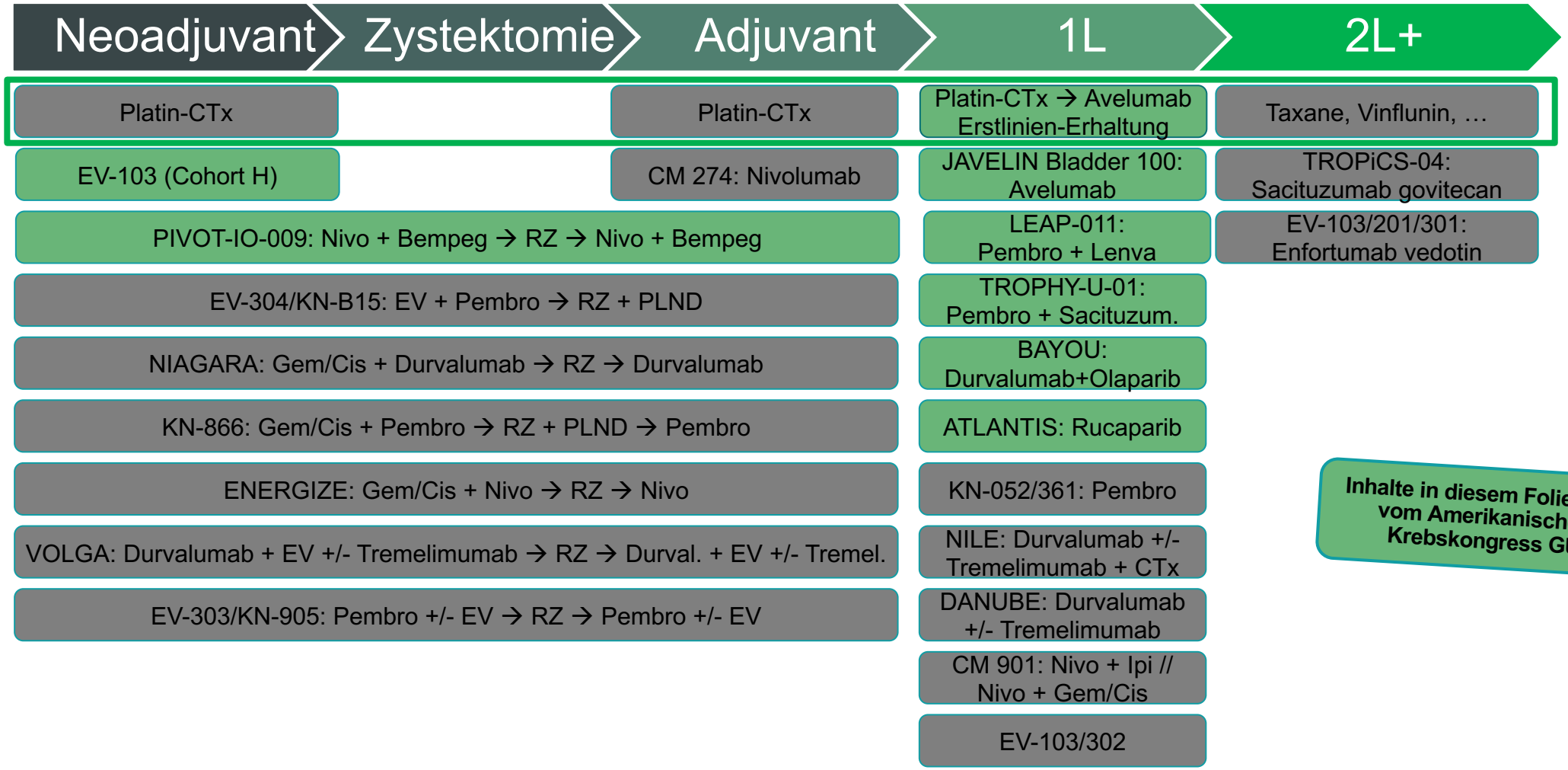
* Resektion singulärer Lungenmetastasen nach Zystektomie bei TCC steigert OS (3 Monate → 5 Jahre), 6 Patienten
  (Cowles et al., Urology 1982)
* Studie mit 32 Patienten (Matsuguma et al., Ann. Thorac. Surg. 2011) zeigt verbessertes 5-J-OS nach Resektion von Lungen-Mts. (50%), PFS (26%)
* Induktive Cx verbessert auch hier OS (Siefker.Radke et al., J. Urol. 2004)
  med. OS nach Mts-Resektion 29-42 Monate
  (Siefker.Radke et al., J. Urol. 2004; Abe et al., J. Urol. 2014; Abe et al., Eur. Urol. 2007))
* bei kleinen solitären Mts (LK, Knochen, Lunge) auch stereotaktische Rx mit > OS
  (Augugliaro et al., Neoplasma 2019)
* In Prüfung: RX und simultan bzw. folg. Immuntherapie (Pembro, Ansprechen >40%)

SABR-COMET Trial

- Randomized phase II trial of best systemic therapy +/- SBRT to all mets in patients with recurrent oligometastatic disease from solid malignancies (n=99)
- 5 yr OS 42% vs. 17% (p=0.006) in favor of SBRT
- 13 month improvement in median OS
- Urothelial patients eligible but the size of the cohort unreported



Studienlandschaft MIBC & mUC mit Fokus auf (Neo-)Adjuvanz und perioperative Konzepte*

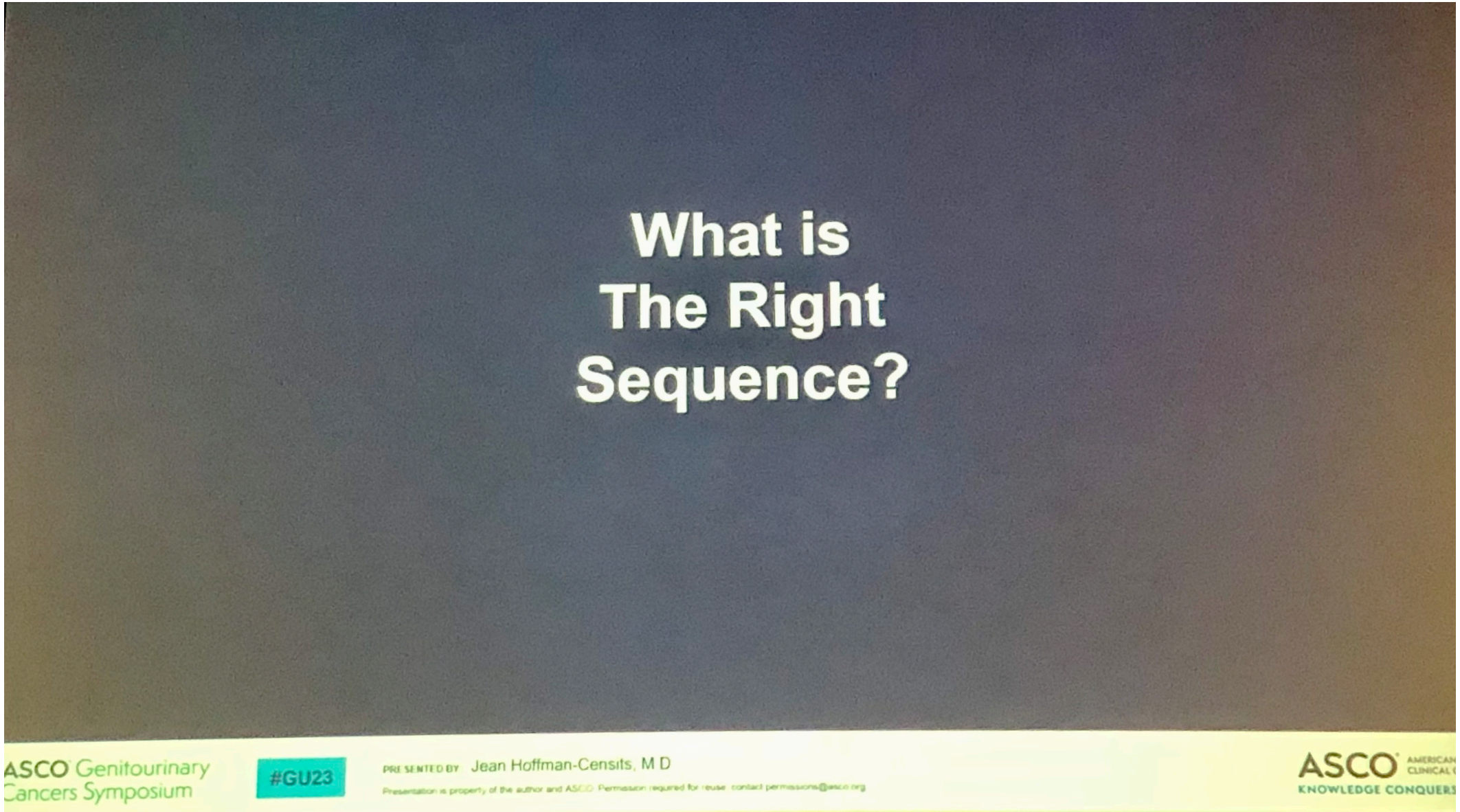


Standard of Care

Inhalte in diesem Foliensatz vom Amerikanischen Krebskongress GU

***Folie nur illustrativ: kein Anspruch auf Vollständigkeit; adaptiert nach Discussion by Rose T on "The Future Landscape of Adjuvant and Neoadjuvant Therapy in MIBC", presented at the 2022 ASCO Genitourinary Cancers Symposium, February 17-19, 2022; San Francisco, CA; Hybrid. . CM= CheckMate; KN = KEYNOTE; PLND: Dissektion des Beckenlymphknotens; RZ = Radikale Zystektomie.**

EV-103: NCT03288545; CM 274: NCT02632409; JAVELIN Bladder 100: NCT02603432; TROPiCS-04: NCT04527991; PIVOT-IO-009: NCT04209114; LEAP-011: NCT03898180; EV-103/201/301: NCT03288545/ NCT03219333/ NCT03474107; EV-304/KN-B15: NCT04700124; TROPHY-U-01: NCT03547973; EV-103/301: NCT03288545/ NCT03474107; NIAGARA: NCT03732677; BAYOU: NCT03459846; KN-866: NCT03924856; ATLANTIS: NCT03397394; ENERGIZE: NCT03661320; KN-052/361: NCT02335424/ NCT02853305; VOLGA: NCT04960709; NILE: NCT03682068; EV-303/KN-905: NCT03924895; DANUBE: NCT02516241; CM 901: NCT03036098; EV-103/302: NCT03288545/ NCT04223856.


What is
The Right
Sequence?
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Erstlinientherapie

Aktuelle Phase III Studien in der ersten Linie beim met. Urothelkarzinom

Studie	Strategie	Experimentelle(r) Arm(e)	Standard Arm	Endpunkt
CheckMate-901	PD-1 + CTLA-4	Nivolumab + Ipilimumab	Gem/Pt	OS bei cis-Uneignung, OS bei PD-L1+
	Chemo-Immuntherapie (Unterstudie)	Gem/Cis + Nivolumab	Gem/Cis	PFS, OS
NILE	PD-L1 ± CTLA-4 (+Chemo)	Durvalumab + Gem/Pt	Gem/Pt	PFS, OS
		Durvalumab + Tremelimumab + Gem/Pt		
EV-302	Enfortumab-Vedotin (EV) + PD-1	EV + Pembrolizumab	Gem/Pt	PFS/OS
MAIN-CAV Maintenance	PD-L1+VEGFR-TKI	Avelumab + Cabozantinib	Avelumab	OS
LEAP-011 Cis-ungeeignet PD-L1+, Pt-ungeeignet	PD-1 + VEGFR-TKI	Lenvatinib + Pembrolizumab	Pembrolizumab	PFS, OS

Übersicht der Phase III Studien => Eigene Darstellung

ASCO Genitourinary Cancers Symposium

IMvigor130 and the Future of Immune Checkpoint Inhibitors in the First-Line Treatment of Metastatic Urothelial Carcinoma

Andrea B. Apolo, MD

Senior Investigator and Lasker Scholar
Chief, Bladder Cancer Section
Genitourinary Malignancies Branch
Center for Cancer Research
National Cancer Institute
National Institutes of Health
February 17, 2023

Summary of Current Systemic Treatment Algorithm for Metastatic Urothelial Carcinoma

Cisplatin-eligible

- Cisplatin + gemcitabine
- Dose-dense methotrexate + vinblastine + doxorubicin + cisplatin (ddMVAC)

Cisplatin-ineligible

- Carboplatin + gemcitabine

Platinum-ineligible

- Pembrolizumab

Maintenance Checkpoint Inhibitor

- Avelumab

Second-Line and Beyond

- Pembrolizumab
- Nivolumab
- Avelumab
- Erdafitinib (FGFR2/3 genetic alteration)
- Enfortumab vedotin
- Sacituzumab govitecan

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@apolo_andrea

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Summary of Current Systemic Treatment Algorithm for Metastatic Urothelial Carcinoma

Cisplatin-eligible

- Cisplatin + gemcitabine
- Dose-dense methotrexate + vinblastine + doxorubicin + cisplatin (ddMVAC)

Maintenance Checkpoint Inhibitor

- Avelumab

Cisplatin-ineligible

- Carboplatin + gemcitabine

MAINCAV

Metastatic UC CR/PR/SD post-1st-line platinum-based chemo

R

Ongoing Study

- **Avelumab + cabozantinib**
- **Avelumab**

Alliance
PI: Dr. Gupta
Primary endpoint: OS
N=654

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@apolo_andrea

ASCO KNOWLEDGE CONQUERS CANCER

WHAT HAVE WE LEARNED?

- Chemo + CPI combos have different efficacy in a variety of solid tumors.
- The combination of chemo + CPI did not work with atezo (PD-L1 inhibitor) or with pembro (PD-1 inhibitor).
- The chemo used in the chemo + CPI combinations may make a difference. Cisplatin may be a better choice. Additional data from other trials are pending.
- Hierarchal studies limit the statistical testing of subsequent study arms if the first questions asked are negative.
- Monotherapy CPI is no longer an FDA-approved SOC option for the 1L treatment of platinum-eligible patients.
- Ongoing trials are assessing the efficacy of ADCs + CPI vs chemo in the metastatic and neoadjuvant setting.

ADC = Antibody-Drug Conjugates

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MADRID 2023 ESMO congress

Nivolumab plus gemcitabine-cisplatin versus gemcitabine-cisplatin alone for previously untreated unresectable or metastatic urothelial carcinoma: results from the phase 3 CheckMate 901 trial

Michiel S. van der Heijden,[1] Guru Sonpavde,[2a] Thomas Powles,[3] Andrea Necchi,[4b] Mauricio Burotto,[5] Michael Schenker,[6] Juan Pablo Sade,[7] Aristotelis Bamias,[8] Philippe Beuzeboc,[9] Jens Bedke,[10c] Jan Oldenburg,[11] Yüksel Ürün,[12] Dingwei Ye,[13] Zhisong He,[14] Begoña P. Valderrama,[15] Yoshihiko Tomita,[16] Jeiry Filian,[17] Daniela Purcea,[18] Federico Nasroulah,[17] Matthew D. Galsky[19]

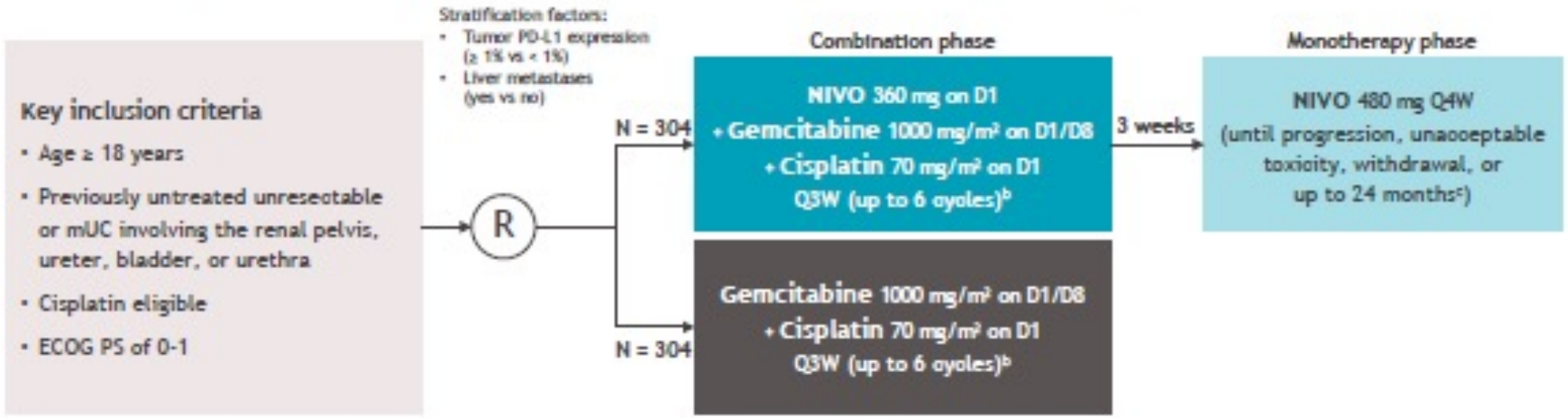
[1]Netherlands Cancer Institute, Amsterdam, the Netherlands; [2]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [3]Barts Cancer Institute, Queen Mary University of London, London, UK; [4]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [5]Bradford Hill Clinical Research Center, Santiago, Chile; [6]University of Medicine and Pharmacy, Craiova, Romania; [7]Alexander Fleming Institute, Buenos Aires, Argentina; [8]National and Kapodistrian University of Athens, ATTIKON University Hospital, Athens, Greece; [9]Hopital Foch, Suresnes, France; [10]Eberhard Karls University Tübingen, Tübingen, Germany; [11]Akershus University Hospital (Ahus), Lørenskog, Norway; [12]Ankara University, Ankara, Turkey; [13]Fudan University Shanghai Cancer Center, Shanghai, China; [14]Peking University First Hospital, Beijing, China; [15]Hospital Universitario Virgen del Rocío, Sevilla, Spain; [16]Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan; [17]Bristol Myers Squibb, Princeton, NJ, USA; [18]Bristol Myers Squibb, Boudry, Switzerland; [19]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA

[a]Current affiliation is AdventHealth Cancer Institute and University of Central Florida, Orlando, FL, USA. [b]Current affiliation is IRCCS San Raffaele Hospital, Vita-Salute San Raffaele University, Milan, Italy. [c]Current affiliation is Klinikum Stuttgart, Katharinenhospital, Stuttgart, Germany.

Presentation number LBA7

Study design

- NIVO + gemcitabine-cisplatin vs gemcitabine-cisplatin in cisplatin-eligible patients[a]



Median (range) study follow-up, 33.6 (7.4-62.4) months

Primary endpoints: OS, PFS per BICR
Key secondary endpoints: OS and PFS by PD-L1 ≥ 1%,[d] HRQoL
Key exploratory endpoints: ORR per BICR, safety

[a]Further CheckMate 901 trial design details are available at https://clinicaltrials.gov/ct2/show/NCT03036098. [b]Patients who discontinued cisplatin could be switched to gemcitabine-carboplatin for the remainder of the platinum doublet cycles (up to 6 in total). [c]A maximum of 24 months from first dose of NIVO administered as part of the NIVO + gemcitabine-cisplatin combination. [d]PD-L1 status was defined by the percentage of positive tumor cell membrane staining in a minimum of 100 tumor cells that could be evaluated with the use of the PD-L1 IHC 28-8 pharmDx immunohistochemical assay (Dako, Santa Clara, CA, USA).
BICR, blinded independent central review; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; HRQoL, health-related quality of life; ORR, objective response rate; PD-L1, programmed death ligand 1; PFS, progression-free survival; Q=W, every = weeks; R, randomization.

OS (primary endpoint)

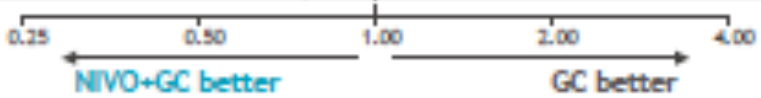
Treatment	Events/patients	Median OS (95% CI), months
NIVO+GC	172/304	21.7 (18.6-26.4)
GC	193/304	18.9 (14.7-22.4)
HR (95% CI), 0.78 (0.63-0.96) $P = 0.0171$		

No. at risk												
NIVO+GC	304	264	196	142	97	69	48	25	15	7	2	0
GC	304	242	166	122	82	49	33	17	13	4	1	0

Median (range) study follow-up was 33.6 (7.4-62.4) months. OS was estimated in all randomized patients and defined as time from randomization to death from any cause. For patients without documented death, OS was censored on the last date the patient was known to be alive. For randomized patients with no follow-up, OS was censored at randomization.

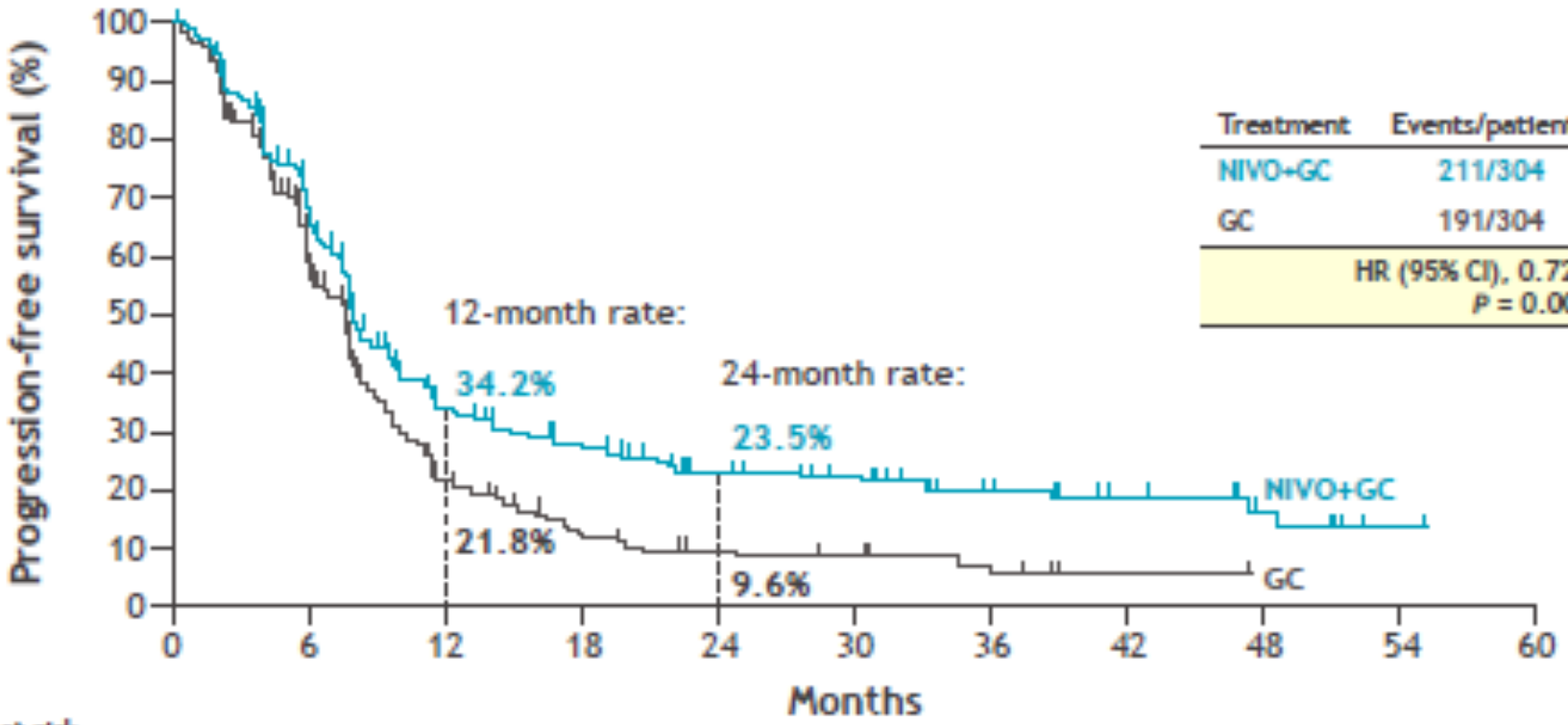
OS in subgroups

Subgroup	No. of patients	NIVO+GC No. of events/no. of patients	GC No. of events/no. of patients	Unstratified HR for death (95% CI)
Overall (N = 608)		172/304	193/304	0.78 (0.63-0.95)
Age, years				
< 65	298	85/150	100/148	0.69 (0.51-0.92)
≥ 65 and < 75	236	65/120	66/116	0.89 (0.63-1.26)
≥ 75	74	22/34	27/40	0.86 (0.49-1.52)
Sex				
Male	470	133/236	147/234	0.76 (0.60-0.97)
Female	138	39/68	46/70	0.82 (0.54-1.26)
Race				
White	436	123/211	145/225	0.80 (0.63-1.02)
Asian	138	38/75	36/63	0.71 (0.45-1.12)
Other	32	11/18	10/14	0.84 (0.35-1.97)
Region				
US	40	18/19	15/21	1.92 (0.95-3.88)
Asia	133	36/72	34/61	0.73 (0.46-1.17)
Europe	276	72/134	90/142	0.73 (0.53-0.99)
Rest of the world	159	46/79	54/80	0.73 (0.49-1.08)
ECOG PS				
0	324	74/162	87/162	0.70 (0.51-0.95)
1	282	96/140	106/142	0.85 (0.64-1.11)
PD-L1 expression				
≥ 1%	221	64/111	67/110	0.75 (0.53-1.06)
< 1% or indeterminate	387	108/193	126/194	0.80 (0.62-1.04)
Liver metastases				
Yes	128	45/64	48/64	0.77 (0.51-1.16)
No	480	127/240	145/240	0.77 (0.61-0.98)
Previous systemic anticancer therapy				
Yes	156	44/88	41/68	0.90 (0.59-1.38)
No	452	128/216	152/236	0.76 (0.60-0.96)



All randomized patients. HRs were not computed for subgroup categories (except for age, sex, race, and region) with < 10 patients per treatment group. Categories without a meaningful estimate of the HR are not shown. PD-L1 expression and liver metastases are per interactive response technology. There were no patients with indeterminate PD-L1 status. Previous systemic anticancer therapy refers to neoadjuvant/adjuvant treatments for patients undergoing radical resection or as part of a bladder-sparing approach in muscle-invasive bladder cancer.

PFS per BICR (primary endpoint)



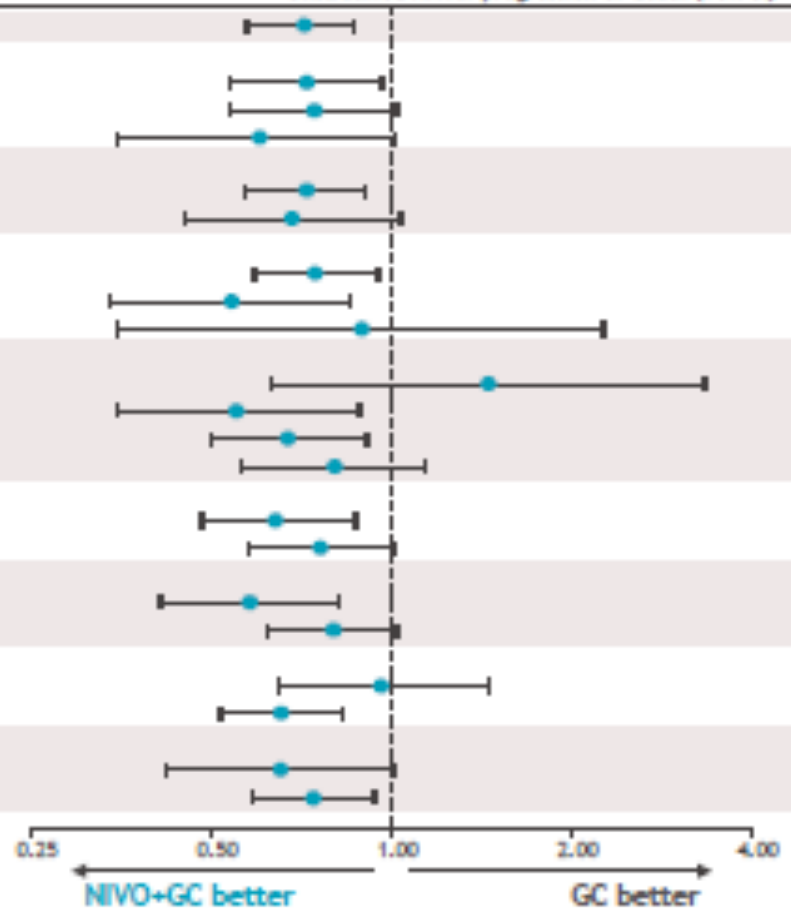
Treatment	Events/patients	Median PFS (95% CI), months
NIVO+GC	211/304	7.9 (7.6-9.5)
GC	191/304	7.6 (6.1-7.8)
HR (95% CI), 0.72 (0.59-0.88) $P = 0.0012$		

No. at risk											
NIVO+GC	304	179	82	57	41	31	19	11	6	1	0
GC	304	119	35	17	10	8	5	1	0	0	0

Median (range) study follow-up was 33.6 (7.4-62.4) months. PFS was estimated in all randomized patients and defined as time from randomization to first documented disease progression (per BICR assessments using RECIST v1.1) or death due to any cause, whichever occurred first. Patients who did not progress or die were censored at last evaluable tumor assessment. Patients without on-study tumor assessments who did not die were censored at randomization. Patients who started any subsequent anticancer therapy without prior reported progression were censored at last evaluable tumor assessment before initiation of subsequent therapy.

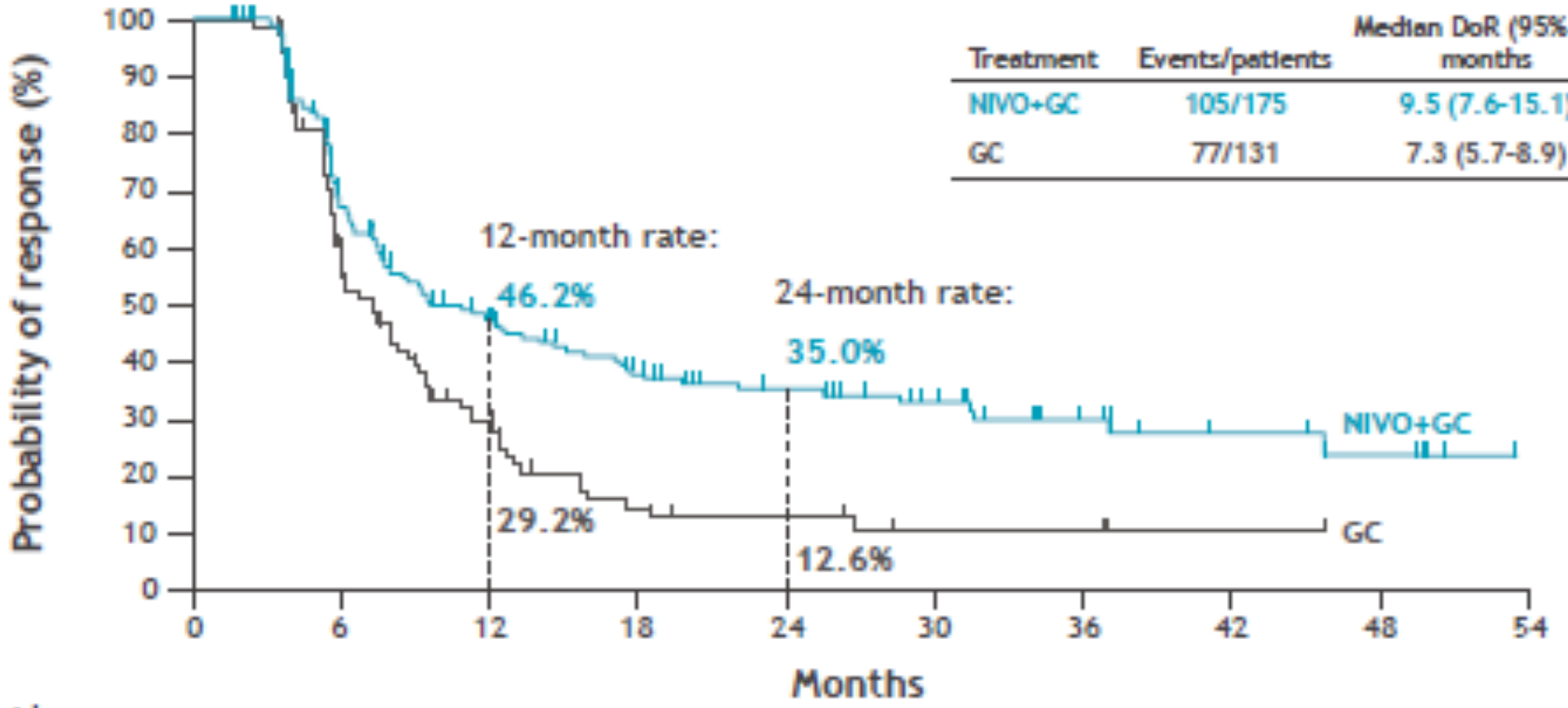
PFS per BICR in subgroups

Subgroup	No. of patients	NIVO+GC No. of events/no. of patients	GC No. of events/no. of patients	Unstratified HR for progression or death (95% CI)
Overall (N = 608)		211/304	191/304	0.71 (0.58-0.86)
Age, years				
< 65	298	102/150	90/148	0.72 (0.54-0.96)
≥ 65 and < 75	236	81/120	71/116	0.74 (0.54-1.02)
≥ 75	74	28/34	30/40	0.60 (0.35-1.01)
Sex				
Male	470	163/236	145/234	0.72 (0.57-0.90)
Female	138	48/68	46/70	0.68 (0.45-1.03)
Race				
White	436	153/211	148/225	0.74 (0.59-0.94)
Asian	138	45/75	35/63	0.54 (0.34-0.85)
Other	32	13/18	7/14	0.89 (0.35-2.25)
Region				
US	40	14/19	10/21	1.45 (0.63-3.31)
Asia	133	43/72	33/61	0.55 (0.35-0.88)
Europe	276	94/134	84/142	0.67 (0.50-0.91)
Rest of the world	159	60/79	64/80	0.80 (0.56-1.14)
ECOG PS				
0	324	97/162	90/162	0.64 (0.48-0.86)
1	282	112/140	101/142	0.76 (0.58-1.00)
PD-L1 expression				
≥ 1%	221	71/112	70/109	0.58 (0.41-0.81)
< 1% or indeterminate	387	140/192	121/195	0.80 (0.62-1.02)
Liver metastases				
Yes	124	55/62	44/62	0.97 (0.65-1.45)
No	484	156/242	147/242	0.65 (0.52-0.82)
Previous systemic anticancer therapy				
Yes	156	55/88	38/68	0.65 (0.42-1.00)
No	452	156/216	153/236	0.74 (0.59-0.93)



All randomized patients. HRs were not computed for subgroup categories (except for age, sex, race, and region) with < 10 patients per treatment group. Categories without a meaningful estimate of the HR are not shown. PD-L1 expression and liver metastases are according to the clinical report. There were no patients with indeterminate PD-L1 status. Previous systemic anticancer therapy refers to neoadjuvant/adjuvant treatments for patients undergoing radical resection or as part of a bladder-sparing approach in muscle-invasive bladder cancer.

Duration of objective response per BICR

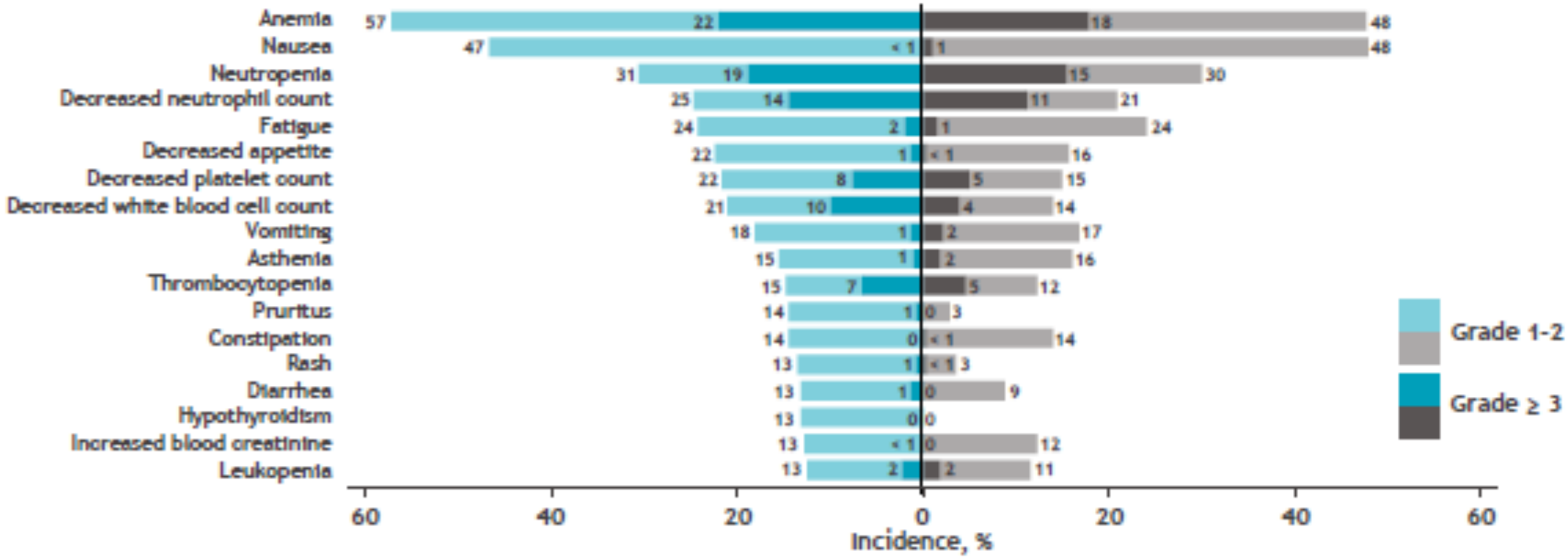


Treatment	Events/patients	Median DoR (95% CI), months
NIVO+GC	105/175	9.5 (7.6-15.1)
GC	77/131	7.3 (5.7-8.9)

No. at risk										
NIVO+GC	175	104	64	47	34	26	15	9	5	0
GC	131	49	22	9	6	3	3	1	0	0

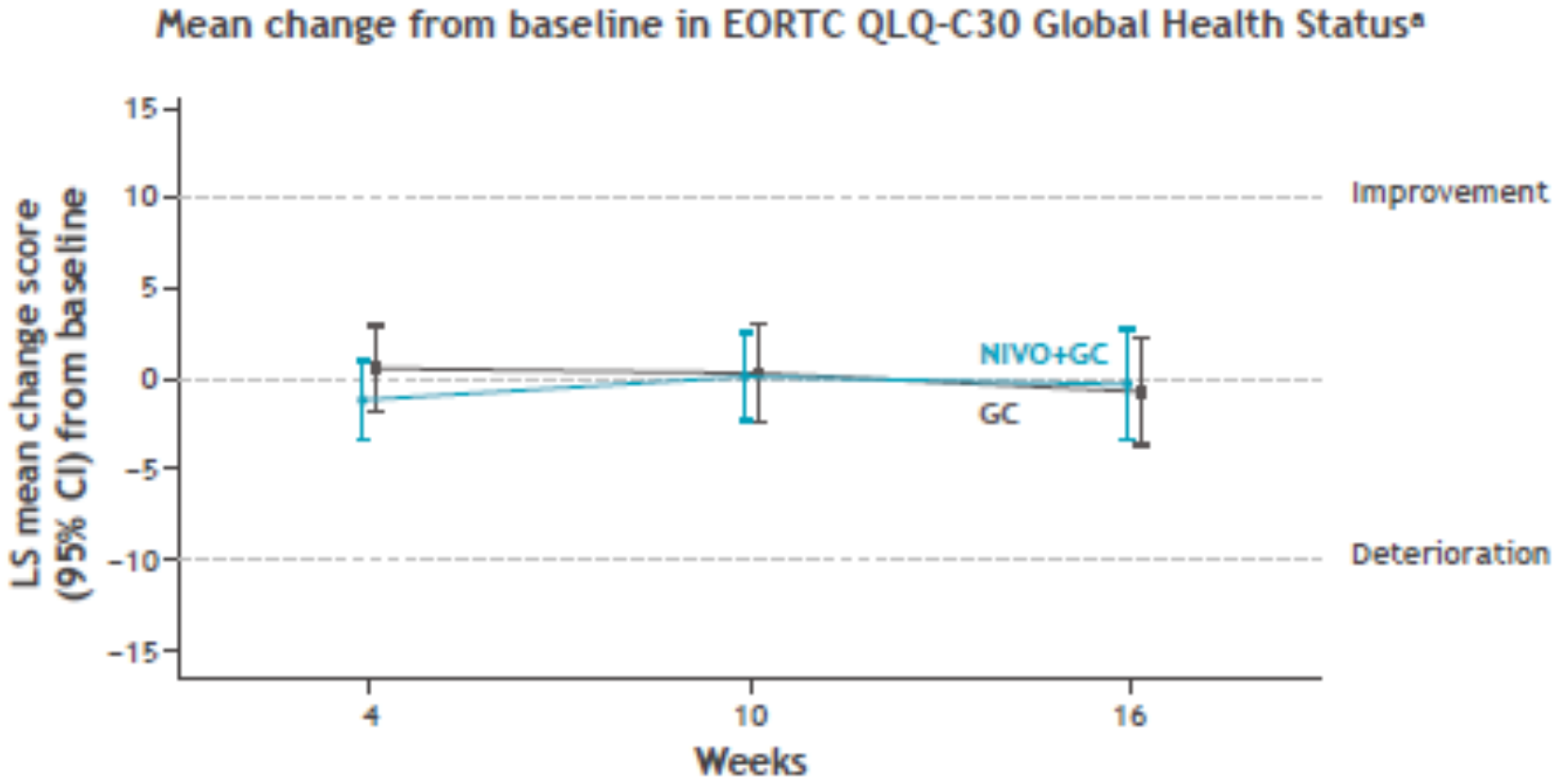
Treatment-related AEs in all treated patients

	NIVO+GC (n = 304)		GC (n = 288)	
Treatment-related AE, %[a]	Any grade	Grade ≥ 3[b]	Any grade	Grade ≥ 3[b]
Any	97	62	93	52
Leading to discontinuation	21	11	17	8



[a]Includes events that occurred in treated patients between first dose and 30 days after last dose of study therapy. Tornado plot displays individual treatment-related AEs occurring at any grade in ≥ 10% of treated patients in either arm. [b]One grade 5 event occurred in each arm (sepsis in the NIVO+GC arm and acute kidney injury in the GC arm).
AE, adverse event.

HRQoL: EORTC QLQ-C30 (secondary endpoint)



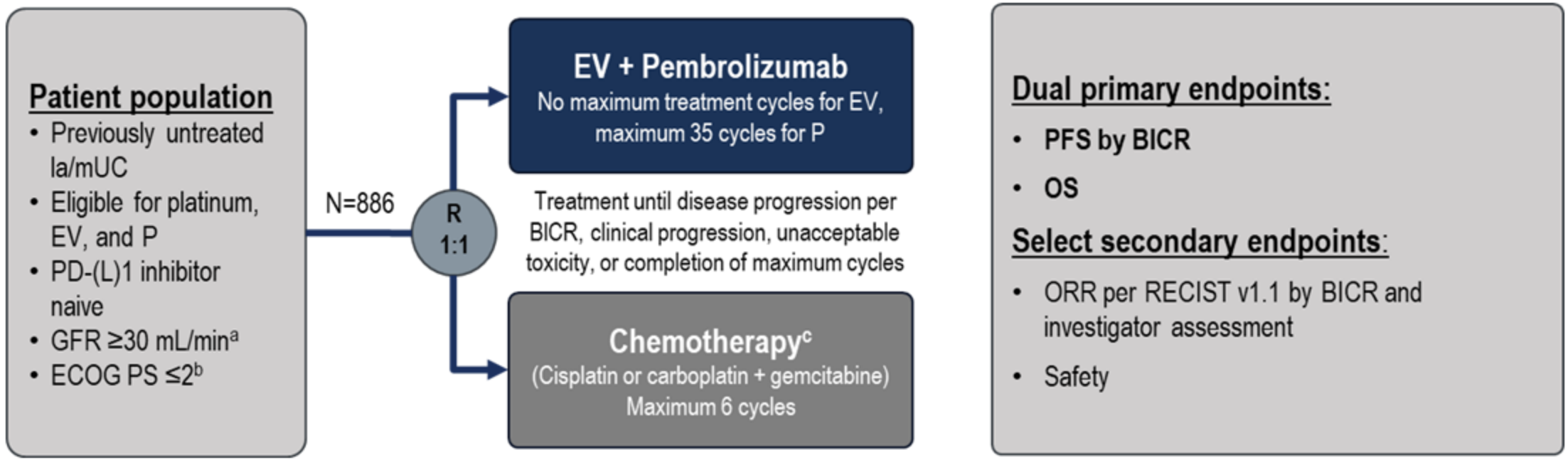
[a]In the EORTC QLQ-C30 evaluable population. Includes patients who completed ≥ 1 of the 15 domains/scales at baseline and ≥ 1 evaluable assessment at post-baseline visits based on the EORTC QLQ-C30. Changes from baseline were used as the dependent variable. Analysis used all HRQoL data assessed during the treatment period through week 16. A mixed-effects repeated measures model was used assuming unstructured covariance and included a random intercept/slope and fixed effects by treatment group, time (ie, week, as a categorical variable), PD-L1 expression, cisplatin-eligibility (ineligible vs eligible), liver metastasis (yes vs no), baseline score, and baseline score by time interaction and treatment by time interaction.
EORTC QLQ-C30, European Organisation for Research and Treatment of Care QLQ-C30 Global Health Status questionnaire; LS, least squares.

EV-302/KEYNOTE-A39: Open-Label, Randomized Phase 3 Study of Enfortumab Vedotin in Combination with Pembrolizumab vs Chemotherapy in Previously Untreated Locally Advanced or Metastatic Urothelial Carcinoma

Thomas Powles, Begona Perez-Valderrama, Shilpa Gupta, Jens Bedke, Eiji Kikuchi, Jean Hoffman-Censits, Gopa Iyer, Christof Vulsteke, Se Hoon Park, Sang Joon Shin, Daniel Castellano Gauna, Giuseppe Fornarini, Jian-Ri Li, Mahmut Gumus, Nataliya Mar, Sujata Narayanan, Xuesong Yu, Seema Gorla, Blanca Homet Moreno, Michiel Van der Heijden

Presented at the European Society for Medical Oncology Congress 2023 (ESMO 2023)
October 20 – 24, 2023
Madrid, Spain

EV-302/KEYNOTE-A39 (NCT04223856)



Stratification factors: cisplatin eligibility (eligible/ineligible), PD-L1 expression (high/low), liver metastases (present/absent)

Cisplatin eligibility and assignment/dosing of cisplatin vs carboplatin were protocol-defined; patients received 3-week cycles of EV (1.25 mg/kg; IV) on Days 1 and 8 and P (200 mg; IV) on Day 1

Statistical plan for analysis: the first planned analysis was performed after approximately 526 PFS (final) and 356 OS events (interim); if OS was positive at interim, the OS interim analysis was considered final

BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; GFR, glomerular filtration rate; ORR, overall response rate; PFS, progression-free survival; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors

[a]Measured by the Cockcroft-Gault formula, Modification of Diet in Renal Disease, or 24-hour urine.

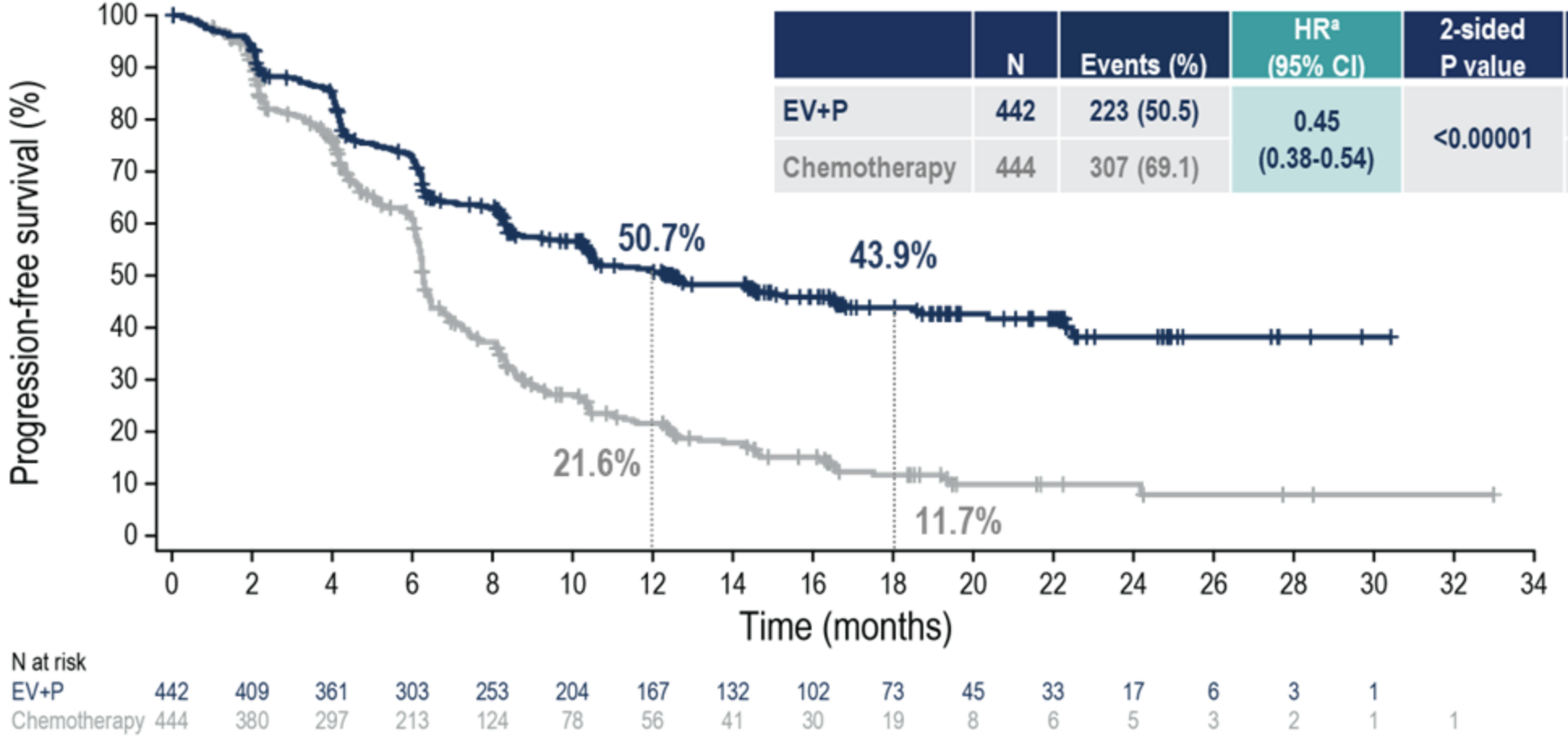
[b]Patients with ECOG PS of 2 were required to also meet the additional criteria: hemoglobin ≥10 g/dL, GFR ≥50mL/min, may not have NYHA class III heart failure.

[c]Maintenance therapy could be used following completion and/or discontinuation of platinum-containing therapy.

Progression-Free Survival per BICR

Risk of progression or death was reduced by 55% in patients who received EV+P

	N	Events (%)	HR[a] (95% CI)	2-sided P value	mPFS (95% CI), months
EV+P	442	223 (50.5)	0.45 (0.38-0.54)	<0.00001	12.5 (10.4-16.6)
Chemotherapy	444	307 (69.1)			6.3 (6.2-6.5)

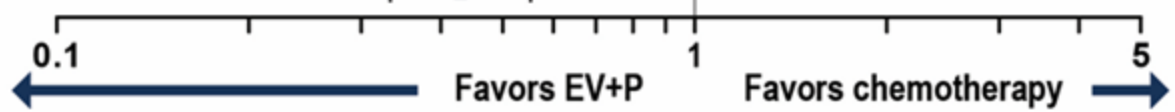


PFS at 12 and 18 months as estimated using Kaplan-Meier method
HR, hazard ratio; mPFS, median progression-free survival.
[a]Calculated using stratified Cox proportional hazards model; a hazard ratio <1 favors the EV+P arm.
Data cutoff: 08 Aug 2023.

Subgroup Analysis of PFS per BICR

PFS benefit in select pre-specified subgroups was consistent with results in overall population

Subgroup	Events/N EV+P	Events/N Chemotherapy	Hazard Ratio (95% CI)
Overall	223/442	307/444	0.45 (0.38-0.54)
Age			
<65 years	75/144	88/135	0.45 (0.32-0.62)
≥65 years	148/298	219/309	0.45 (0.36-0.56)
Sex			
Female	55/98	74/108	0.49 (0.34-0.71)
Male	168/344	233/336	0.44 (0.36-0.54)
ECOG PS			
0	93/223	146/215	0.36 (0.28-0.48)
1-2	130/219	161/227	0.53 (0.42-0.68)
Primary disease site of origin			
Upper tract	69/135	70/104	0.50 (0.35-0.71)
Lower tract	152/305	236/339	0.44 (0.35-0.54)
Liver metastases			
Present	66/100	78/99	0.53 (0.38-0.76)
Absent	157/342	229/345	0.43 (0.35-0.52)
PD-L1 expression			
Low (CPS <10)	105/184	127/185	0.50 (0.38-0.65)
High (CPS ≥10)	116/254	176/254	0.42 (0.33-0.53)
Cisplatin eligibility			
Eligible	117/244	149/234	0.48 (0.38-0.62)
Ineligible	106/198	158/210	0.43 (0.33-0.55)



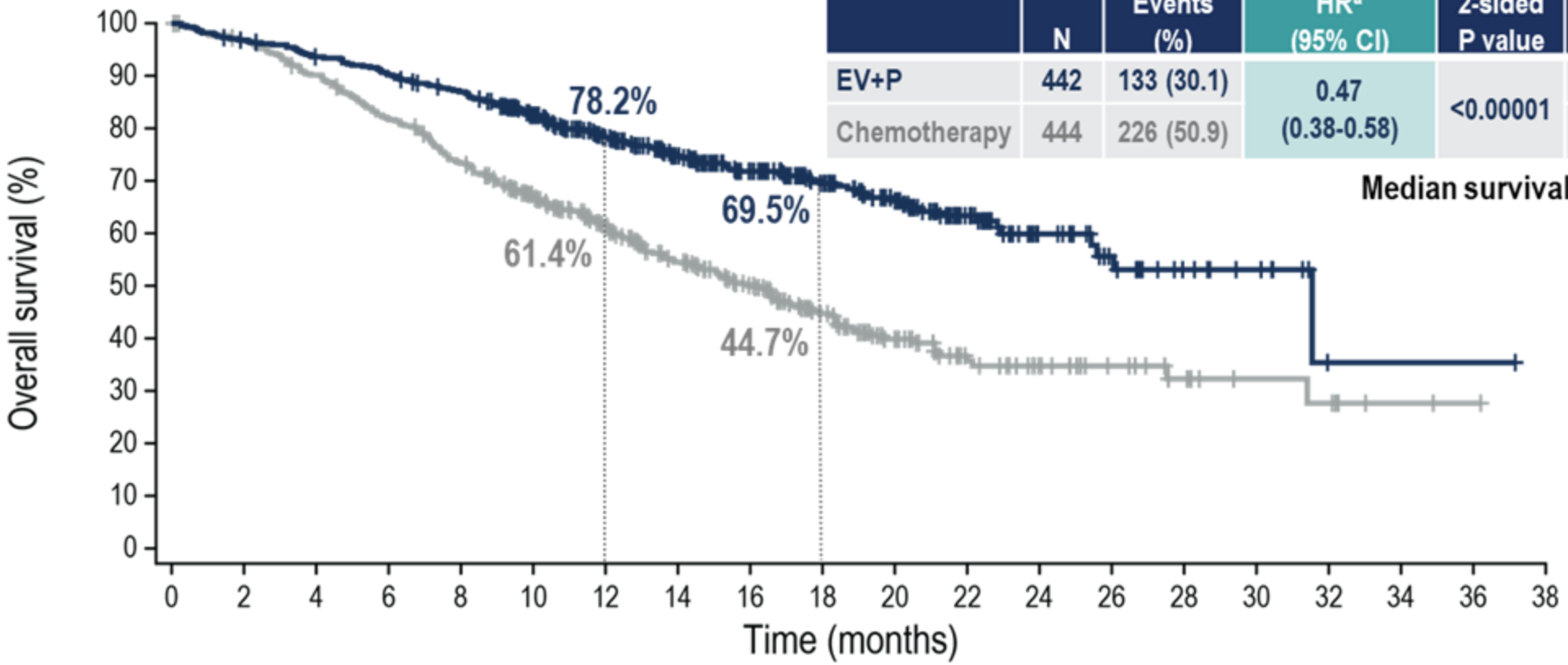
Data cutoff: 08 Aug 2023.

Overall Survival

Risk of death was reduced by 53% in patients who received EV+P

	N	Events (%)	HR[a] (95% CI)	2-sided P value	mOS (95% CI), months
EV+P	442	133 (30.1)	0.47 (0.38-0.58)	<0.00001	31.5 (25.4-NR)
Chemotherapy	444	226 (50.9)			16.1 (13.9-18.3)

Median survival follow-up: 17.2 months



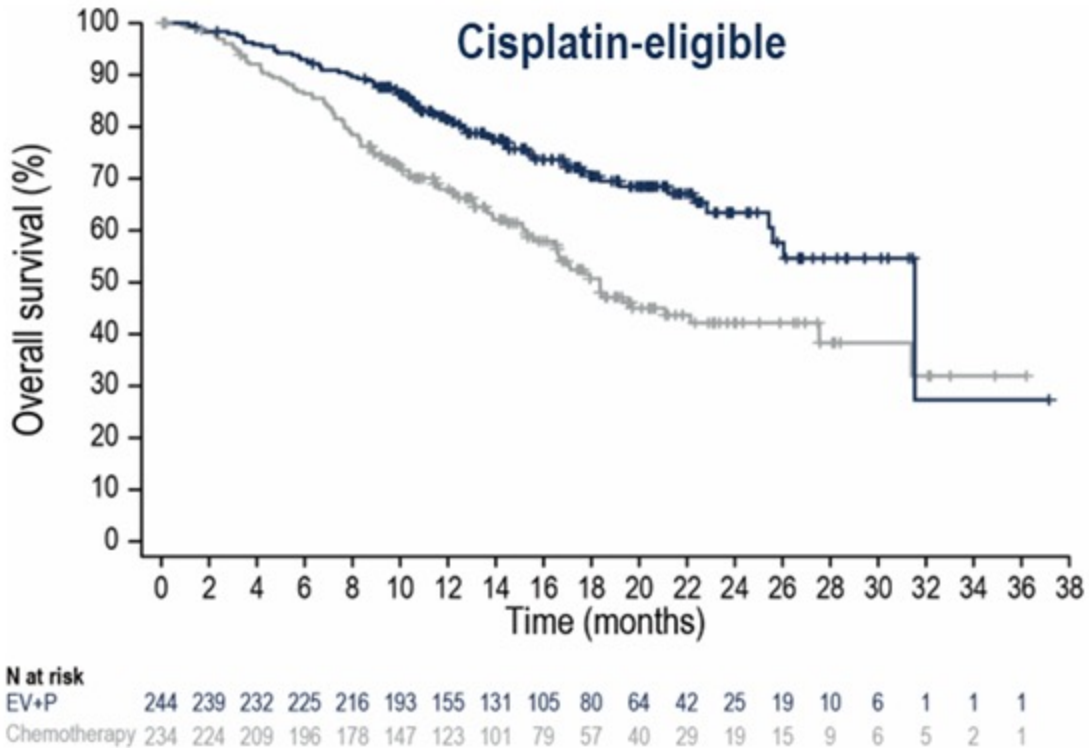
N at risk

EV+P	442	426	409	394	376	331	270	222	182	141	108	67	36	22	12	8	1	1	1
Chemotherapy	444	423	393	356	317	263	209	164	125	90	60	37	25	18	12	7	6	2	1

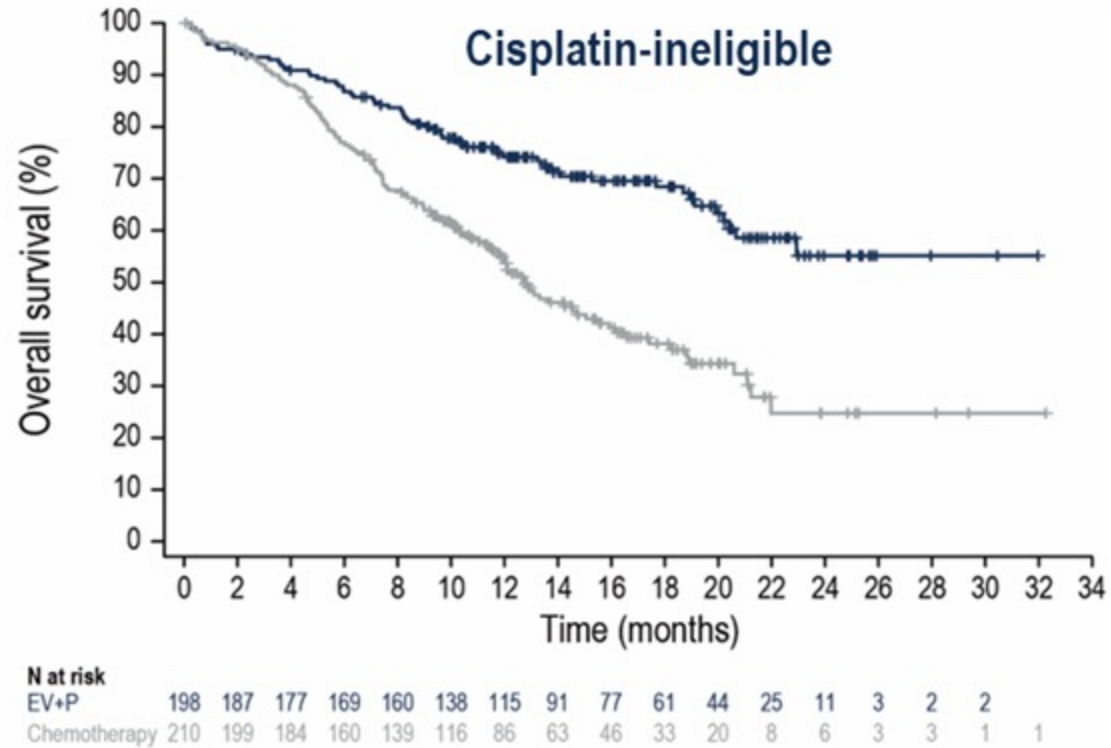
OS at 12 and 18 months was estimated using Kaplan-Meier method.
mOS, median overall survival; NR, not reached.
[a]Calculated using stratified Cox proportional hazards model. A hazard ratio <1 favors the EV+P arm.
Data cutoff: 08 Aug 2023.

OS Subgroup Analysis: Cisplatin Eligibility

OS benefit was consistent with overall population regardless of cisplatin eligibility



	Events, n	HR (95% CI)	mOS (95% CI), months
EV+P	69	0.53 (0.39-0.72)	31.5 (25.4-NR)
Chemotherapy	106		18.4 (16.4-27.5)

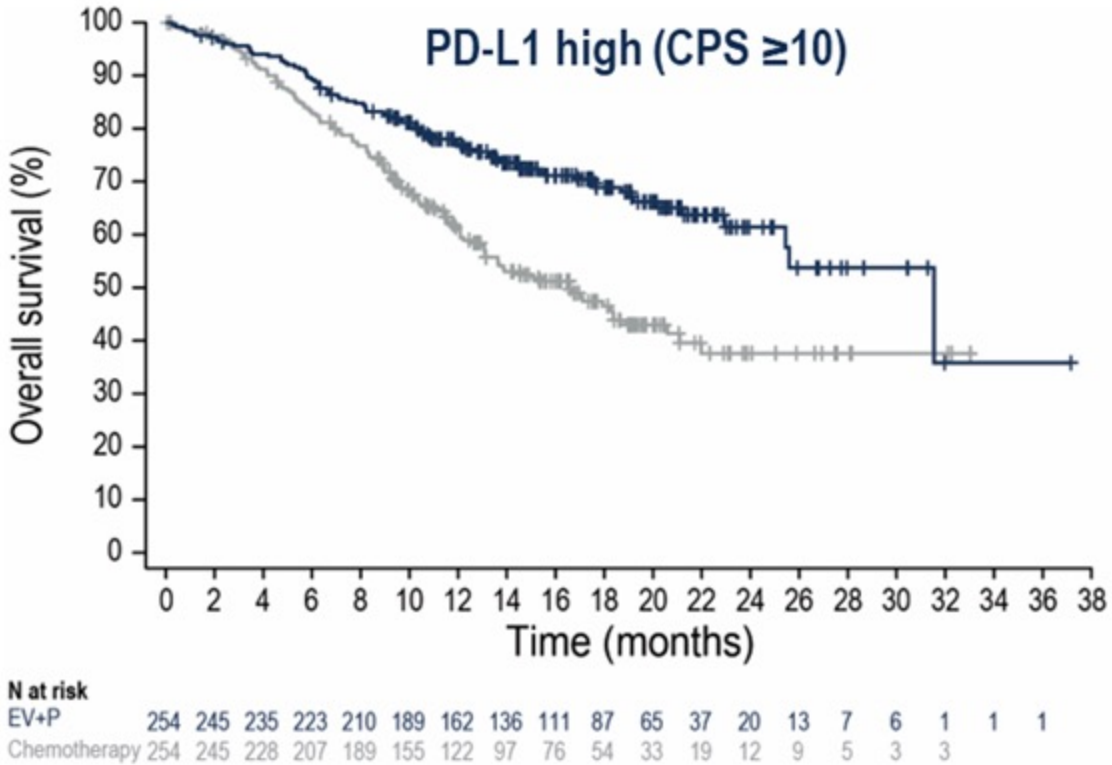


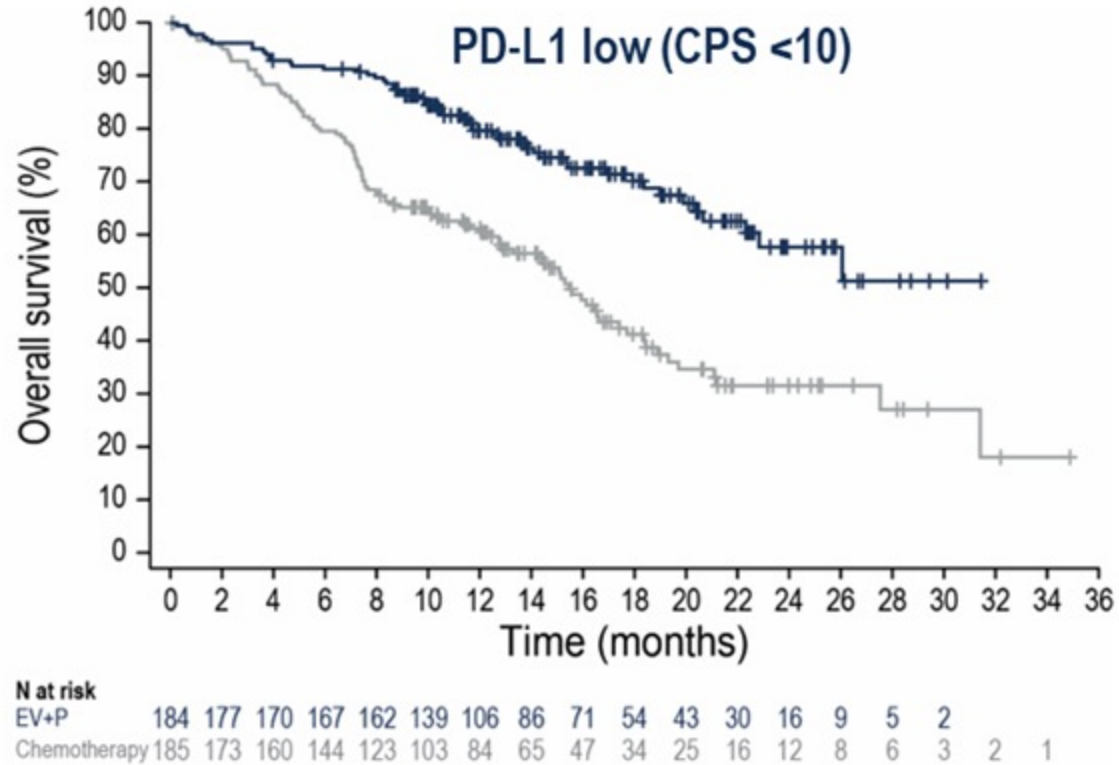
	Events, n	HR (95% CI)	mOS (95% CI), months
EV+P	64	0.43 (0.31-0.59)	NR (20.7-NR)
Chemotherapy	120		12.7 (11.4-15.5)

Data cutoff: 08 Aug 2023.

OS Subgroup Analysis: PD-L1 Expression

OS benefit was consistent with overall population regardless of PD-L1 expression status





	Events, n	HR (95% CI)	mOS (95% CI), months
EV+P	79	0.49 (0.37-0.66)	31.5 (25.4-NR)
Chemotherapy	125		16.6 (13.1-20.6)

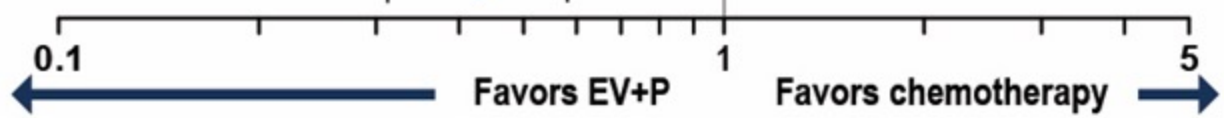
	Events, n	HR (95% CI)	mOS (95% CI), months
EV+P	53	0.44 (0.31-0.61)	NR (22.3-NR)
Chemotherapy	99		15.5 (12.9-17.7)

Data cutoff: 08 Aug 2023.

Subgroup Analysis of OS

OS benefit in select pre-specified subgroups was consistent with results in overall population

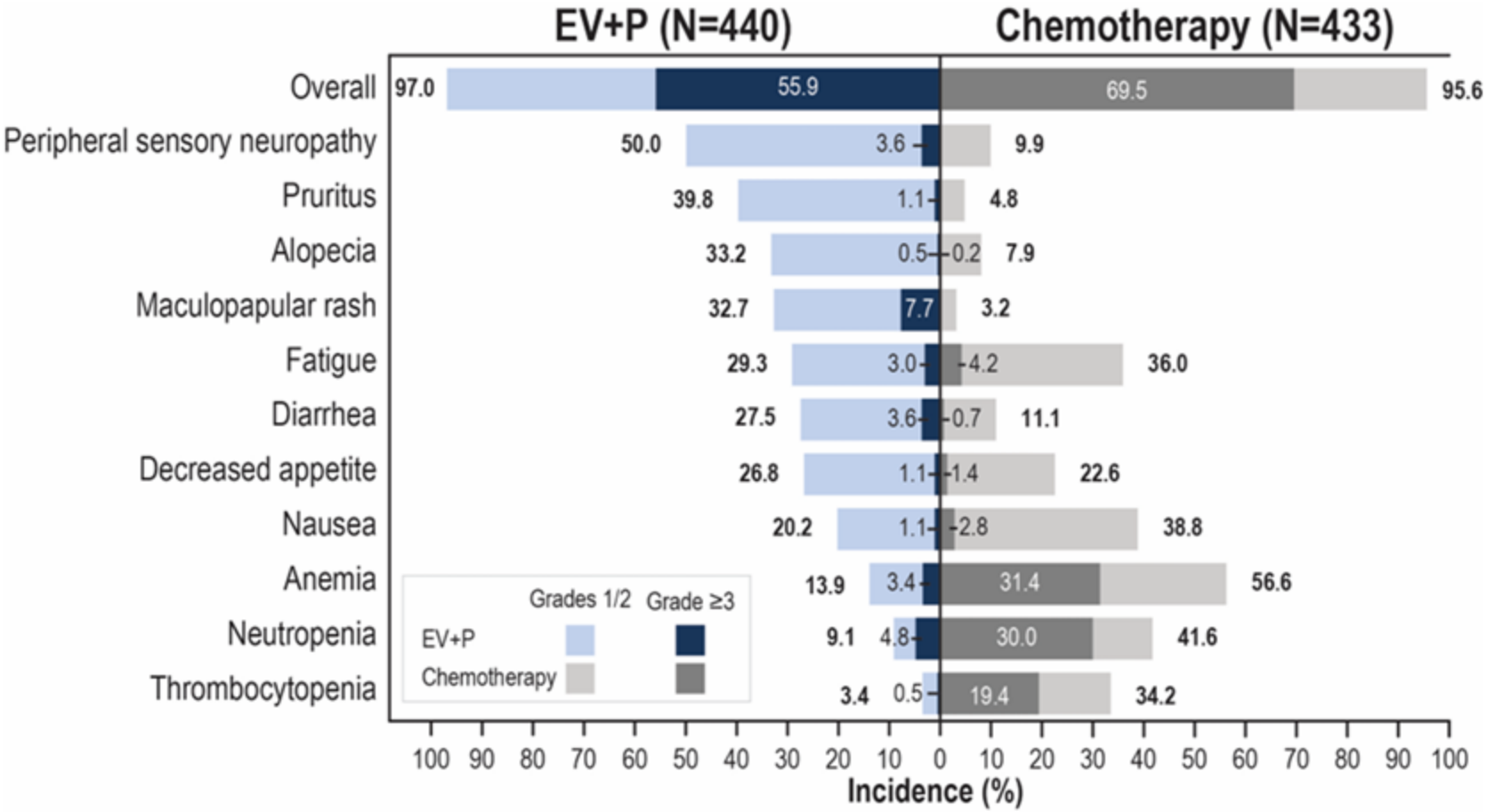
Subgroup	Events/N EV+P	Events/N Chemotherapy	Hazard Ratio (95% CI)
Overall	133/442	226/444	0.47 (0.38-0.58)
Age			
<65 years	39/144	58/135	0.46 (0.30-0.71)
≥65 years	94/298	168/309	0.48 (0.38-0.63)
Sex			
Female	32/98	54/108	0.51 (0.32-0.80)
Male	101/344	172/336	0.47 (0.36-0.60)
ECOG PS			
0	44/223	94/215	0.36 (0.25-0.53)
1-2	89/219	131/227	0.54 (0.41-0.72)
Primary disease site of origin			
Upper tract	38/135	45/104	0.53 (0.34-0.83)
Lower tract	94/305	180/339	0.46 (0.36-0.59)
Liver metastases			
Present	43/100	67/99	0.47 (0.32-0.71)
Absent	90/342	159/345	0.47 (0.36-0.61)
PD-L1 expression			
Low (CPS <10)	53/184	99/185	0.44 (0.31-0.61)
High (CPS ≥10)	79/254	125/254	0.49 (0.37-0.66)
Cisplatin eligibility			
Eligible	69/244	106/234	0.53 (0.39-0.72)
Ineligible	64/198	120/210	0.43 (0.31-0.59)



Data cutoff: 08 Aug 2023.

Treatment-Related Adverse Events

Grade ≥3 events were 56% in EV+P and 70% in chemotherapy



Serious TRAEs:
- 122 (27.7%) EV+P
- 85 (19.6%) chemotherapy

TRAEs leading to death (per investigator):
EV+P: 4 (0.9%)
- Asthenia
- Diarrhea
- Immune-mediated lung disease
- Multiple organ dysfunction syndrome

Chemotherapy: 4 (0.9%)
- Febrile neutropenia
- Myocardial infarction
- Neutropenic sepsis
- Sepsis

- **Median number of cycles (range): 12.0 (1,46) for EV+P; 6.0 (1,6) for chemotherapy**

TRAEs shown in figure are any grade by preferred term in ≥20% of patients for any grade in either arm.
TRAEs, treatment-related adverse events.
Data cutoff: 08 Aug 2023.

ST. GEORG KLINIKUM EISENACH

Zusammenfassung

- Keine Empfehlung mehr für CPI-Mono in der 1. Linie
- Kombination CPI und Chemo mit unterschiedlichem Ansprechen
- Chemo-Partner möglicherweise entscheidend
- Neue Substanzgruppen wie ADC im Kommen
- wie sich EV 302 im Gesamtkonzept einordnet bleibt abzuwarten
    - Alle Patienten der Verumgruppe waren behandlungsnaiv
    - Kein Vergleich zu Gem/Cis und Erhaltung
- Entscheidend wird neoadjuvante Behandlungssituation