Current State of Immunotherapy in RCC and TCC

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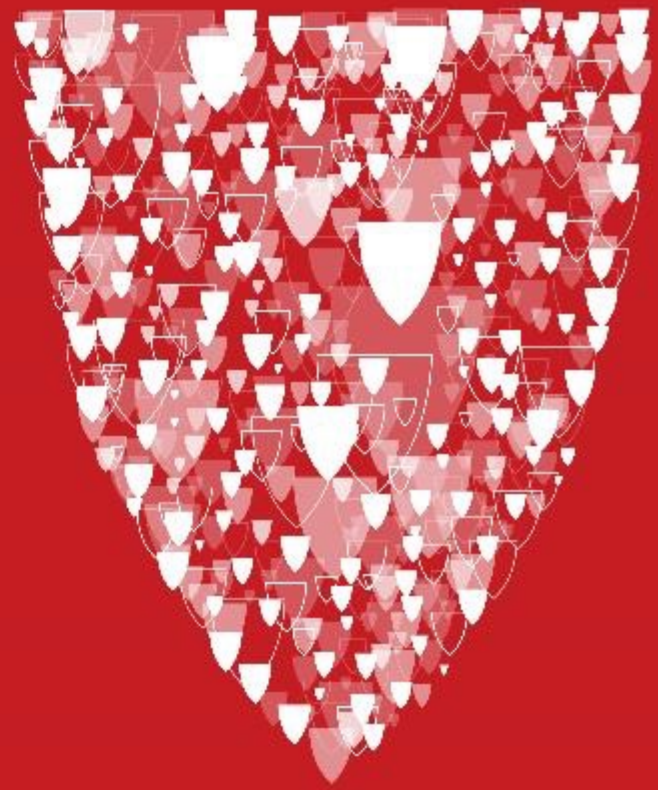
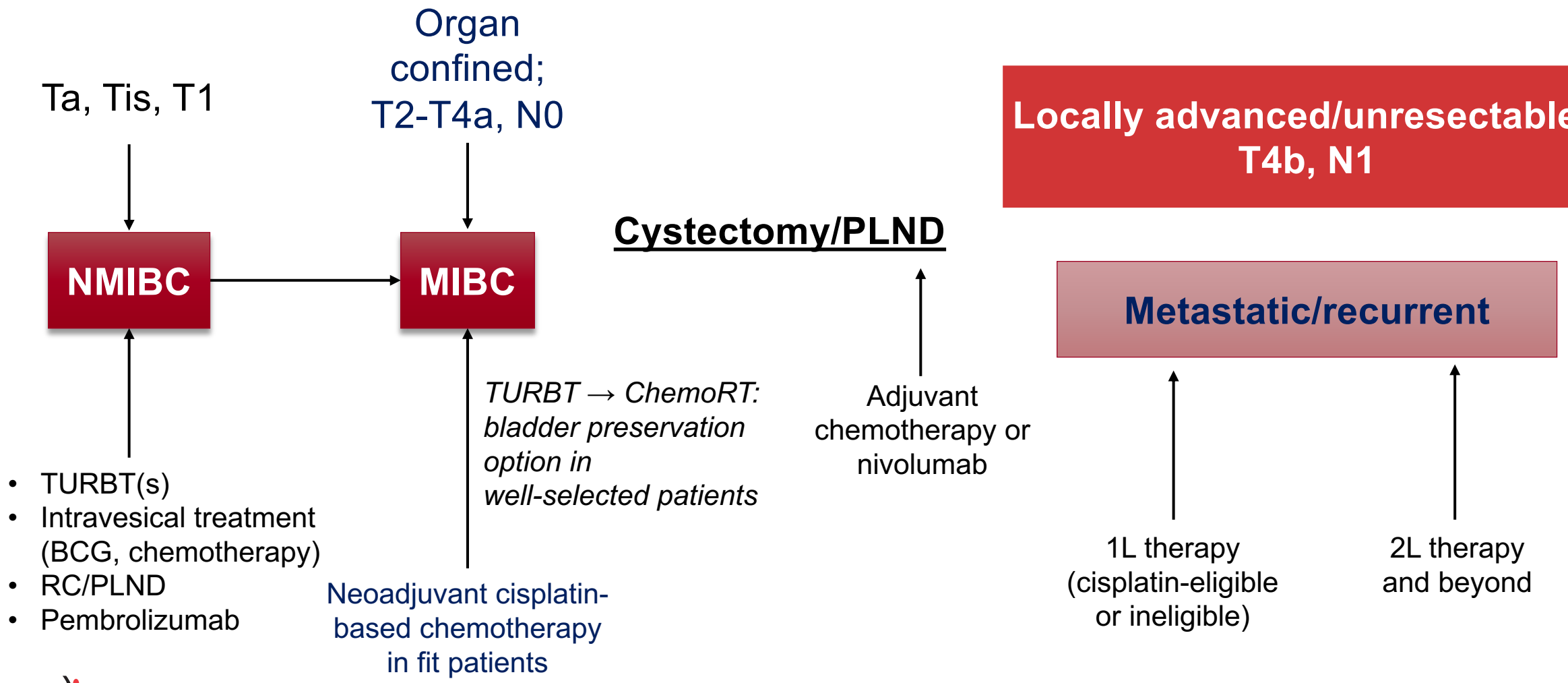
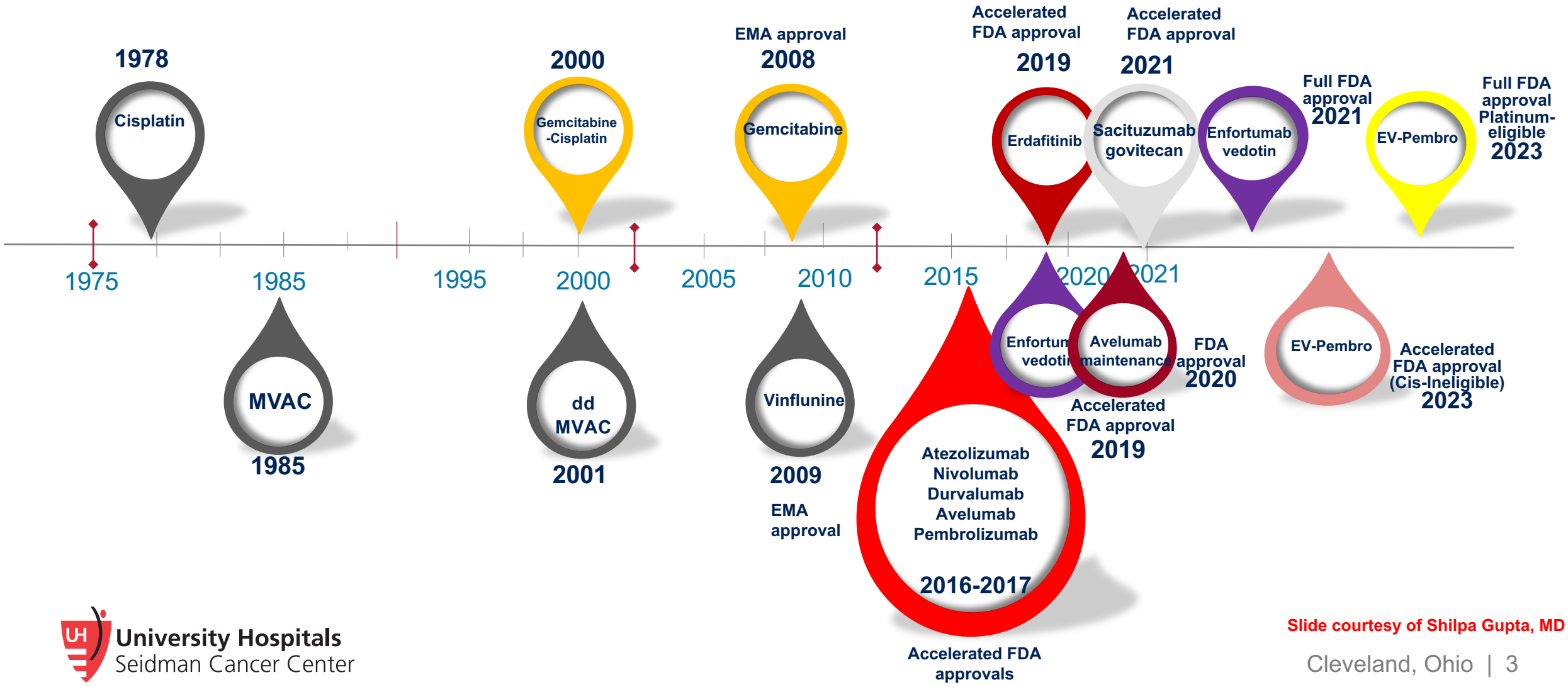


San Juan, Puerto Rico – March 2024

When Thinking of Urothelial Transitional Cell Cancer



Finally Progress is Seen: Drug Development in Bladder Cancer



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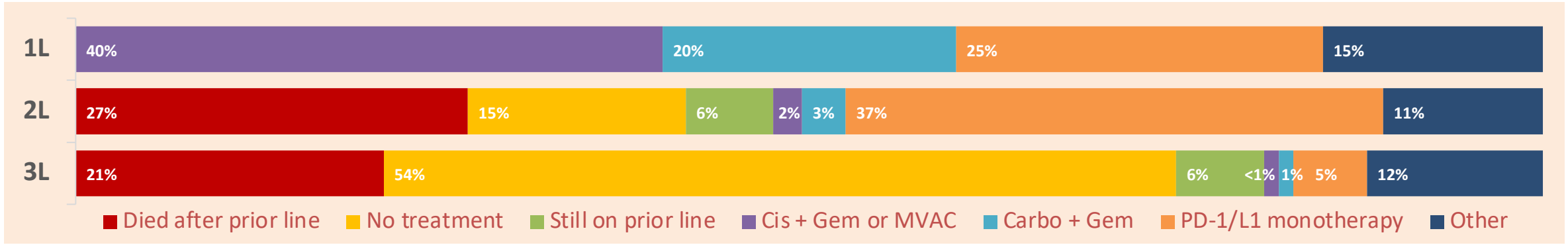
Slide courtesy of Shilpa Gupta, MD

Our biggest Challenge as Medical Oncology Community

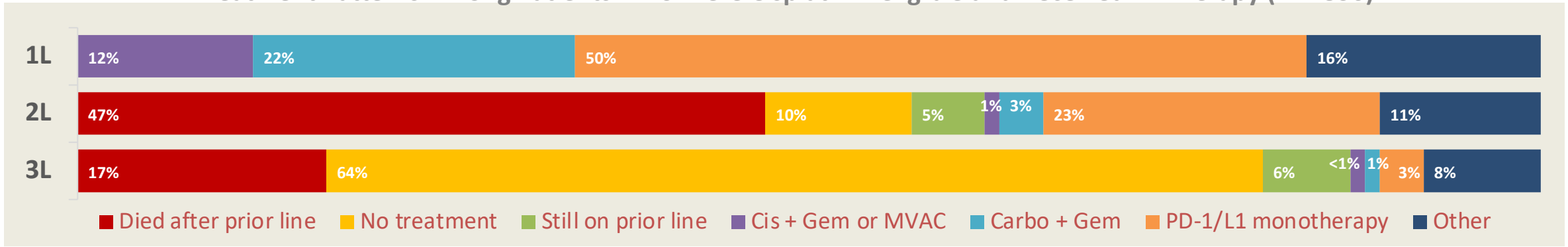
~One-Quarter of Patients Did Not Receive 1L Therapy;
~Half of Patients Did Not Receive 2L Therapy

- **Of 4300 patients who met inclusion criteria, 23% did not receive 1L therapy**

Treatment Patterns Among Patients Who Were Cisplatin Eligible and Received 1L Therapy (N=1475)



Treatment Patterns Among Patients Who Were Cisplatin Ineligible and Received 1L Therapy (N=1836)



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Patients aged ≥18 years diagnosed with Ia/mUC from May 2016 to October 2020 in the Flatiron Health database.
Patients were followed until death or end of data availability in June 2021.
Other therapies included PD-1/L1 combination therapy, mono-chemotherapy (taxanes, gemcitabine, cisplatin monotherapy, carboplatin monotherapy), and other off-label treatments.
Sonpavde GP, et al. ASCO 2022. Poster 56.

Chemotherapy Perspectives in Bladder Cancer

- Gemcitabine-Cisplatin (GC): Median OS ~ 14 months, ORR 49%
- ddMVAC: Median OS ~ 15 months, ORR 70%
- Gemcitabine-Carboplatin: Recent Trials show median OS~ 13 months ORR 43%
- Only a minority of patients receive 2nd-line therapy for mUC
- An unmet need to improve survival with 1st-line treatment

Von der Maase H et al. JCO 2005 Sternberg CN Eur J Cancer 2006, Galsky MD Lancet 2020, Flannery K et al. Future Oncol 2019, Powles T ASC) GU 2021

Role of Pembrolizumab in Front-line Therapy: mTCC

KEYNOTE-361 Study Design (NCT02853305)

Key Eligibility Criteria
- UC of renal pelvis, ureter, bladder or urethra
- Locally advanced unresectable or metastatic disease
- No prior systemic therapy for advanced disease
- ECOG PS 0, 1 or 2
- Tissue sample for PD-L1 assessment[a]

Stratification Factors
- PD-L1 expression[a] (CPS ≥10 vs <10)
- Choice of platinum

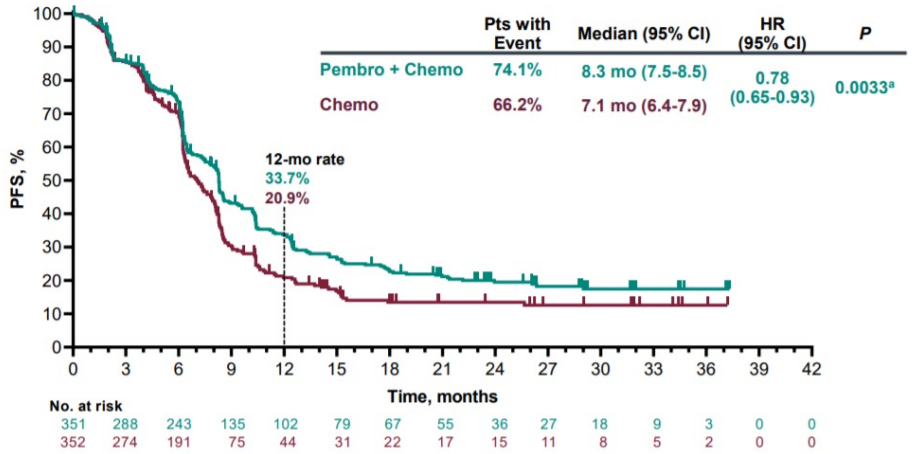
R (1:1:1)

- Pembrolizumab 200 mg Q3W + Gemcitabine 1000 mg/m² + Cisplatin 70 mg/m² *OR* Carboplatin AUC 5 for ≤6 cycles → Pembrolizumab 200 mg Q3W for ≤29 cycles
- Pembrolizumab 200 mg Q3W for ≤35 cycles
- Gemcitabine 1000 mg/m² on days 1 and 8 Q3W + Cisplatin 70 mg/m² *OR* Carboplatin AUC 5 on day 1 Q3W for ≤6 cycles

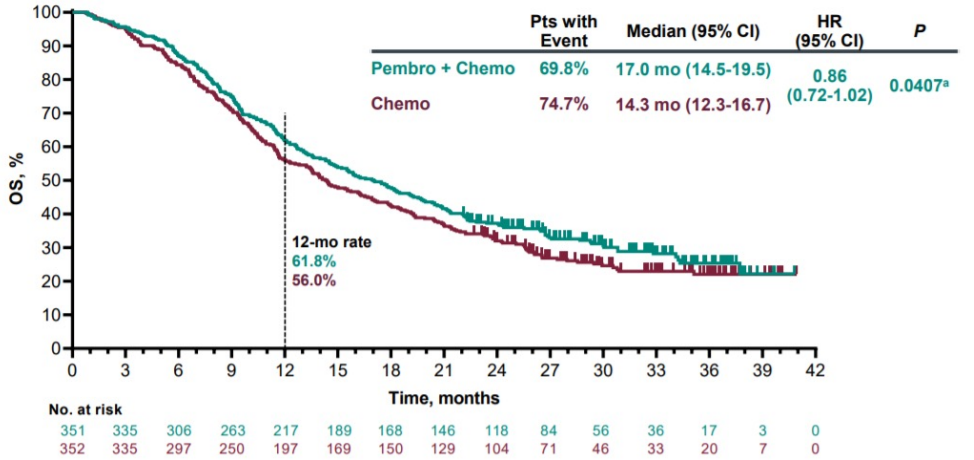
- Dual primary endpoints: PFS per RECIST v1.1 by BICR and OS
- Secondary endpoints: ORR, DCR, and DOR by BICR per RECIST v1.1, safety

n=1010

PFS by BICR: Pembro + Chemo vs Chemo, ITT Population (Primary Endpoint)



OS: Pembro + Chemo vs Chemo, ITT Population



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Ajjai Alva ESMO 2020, Powles T et al. Lancet 2021

Atezolizumab with or without chemotherapy in mUC (IMvigor130)

IMvigor130 study design

- Locally advanced or mUC
- No prior systemic therapy in the metastatic setting
- ECOG PS ≤ 2
- 1L platinum-eligible
- N = 1200
- Randomised 1:1:1

Arm A Atezo + plt/gem

Arm B Atezo monotherapy

Arm C Placebo + plt/gem

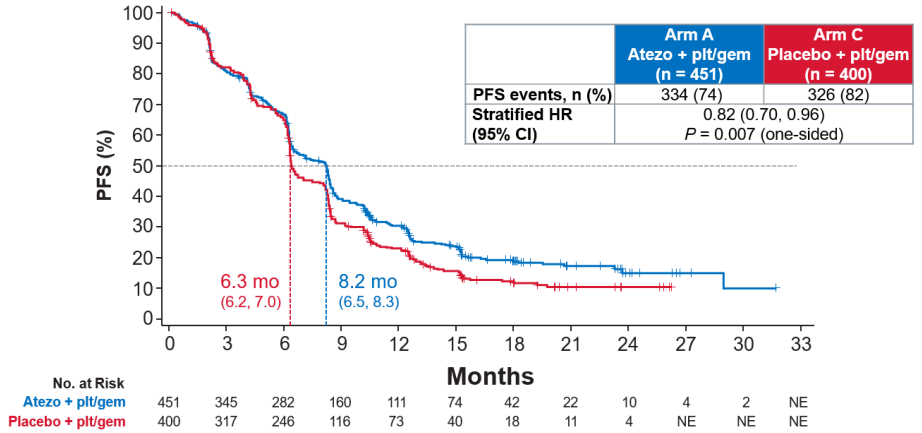
Stratification factors:
- PD-L1 IC status (IC0 vs IC1 vs IC2/3)
- Bajorin risk factor score including KPS < 80% vs ≥ 80% and presence of visceral metastases (0 vs 1 vs 2 and/or patients with liver metastases)
- Investigator choice of plt/gem (cisplatin + gem or carboplatin + gem)

Co-primary endpoints:
- INV-assessed PFS[a] and OS (Arm A vs C)
- OS (Arm B vs C, hierarchical approach)

Key secondary endpoints:
- INV-ORR[a] and DOR
- PFS[a] and OS (Arm B vs C; PD-L1 IC2/3 subgroup)
- Safety

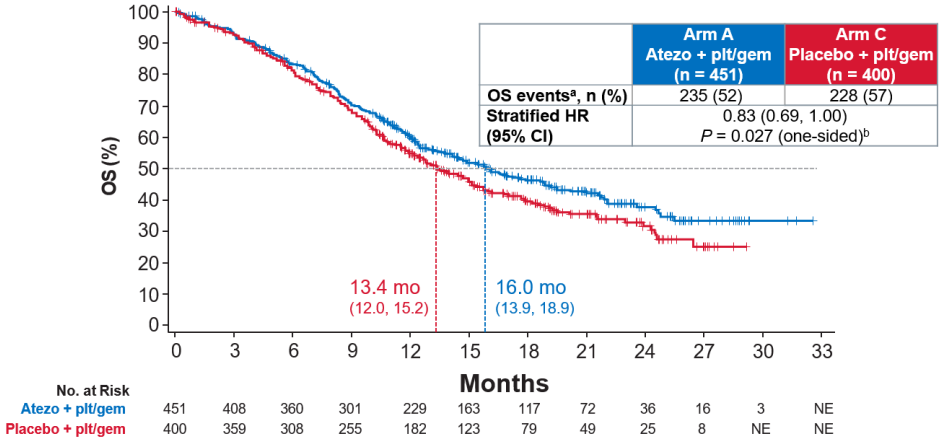
[a] per RECIST 1.1.

Final PFS: ITT (Arm A vs Arm C)



	Arm A Atezo + plt/gem (n = 451)	Arm C Placebo + plt/gem (n = 400)
PFS events, n (%)	334 (74)	326 (82)
Stratified HR (95% CI)	0.82 (0.70, 0.96) *P* = 0.007 (one-sided)	

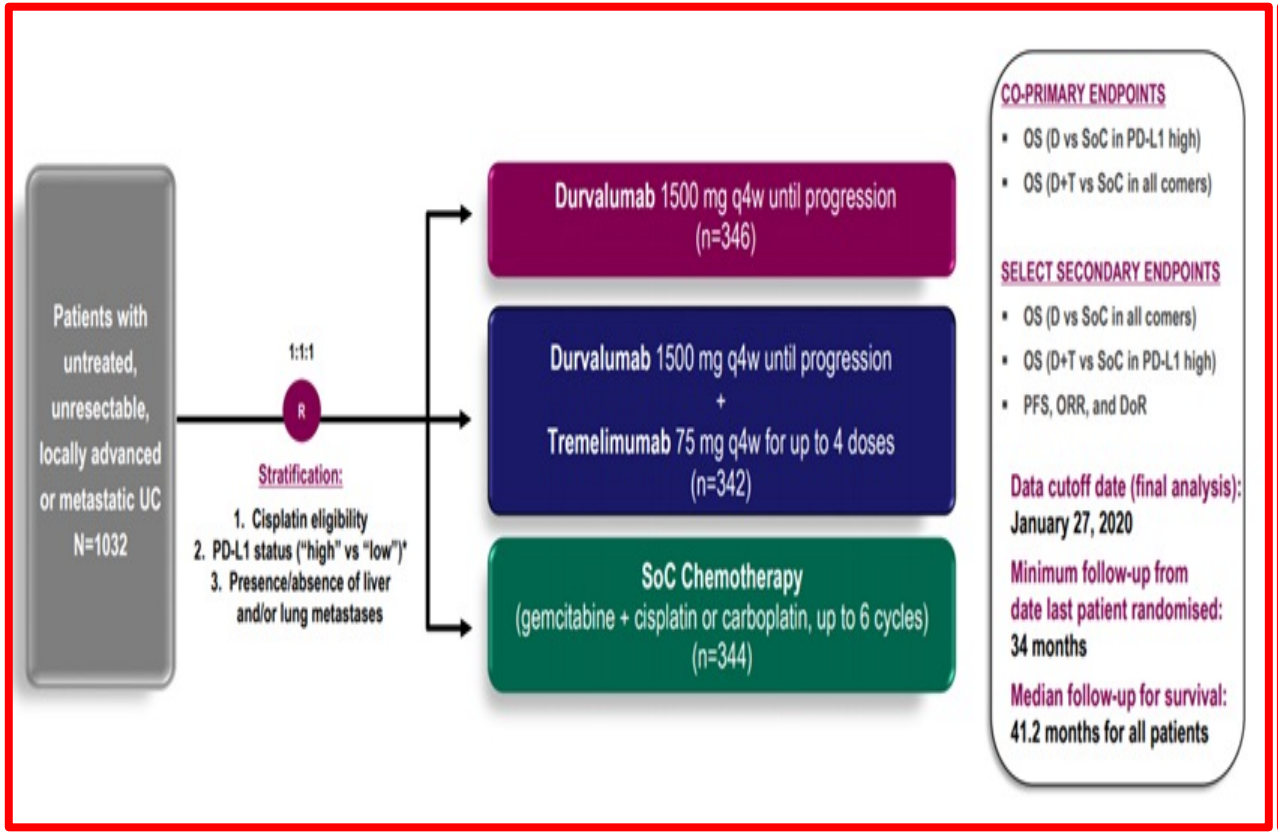
Interim OS: ITT (Arm A vs Arm C)

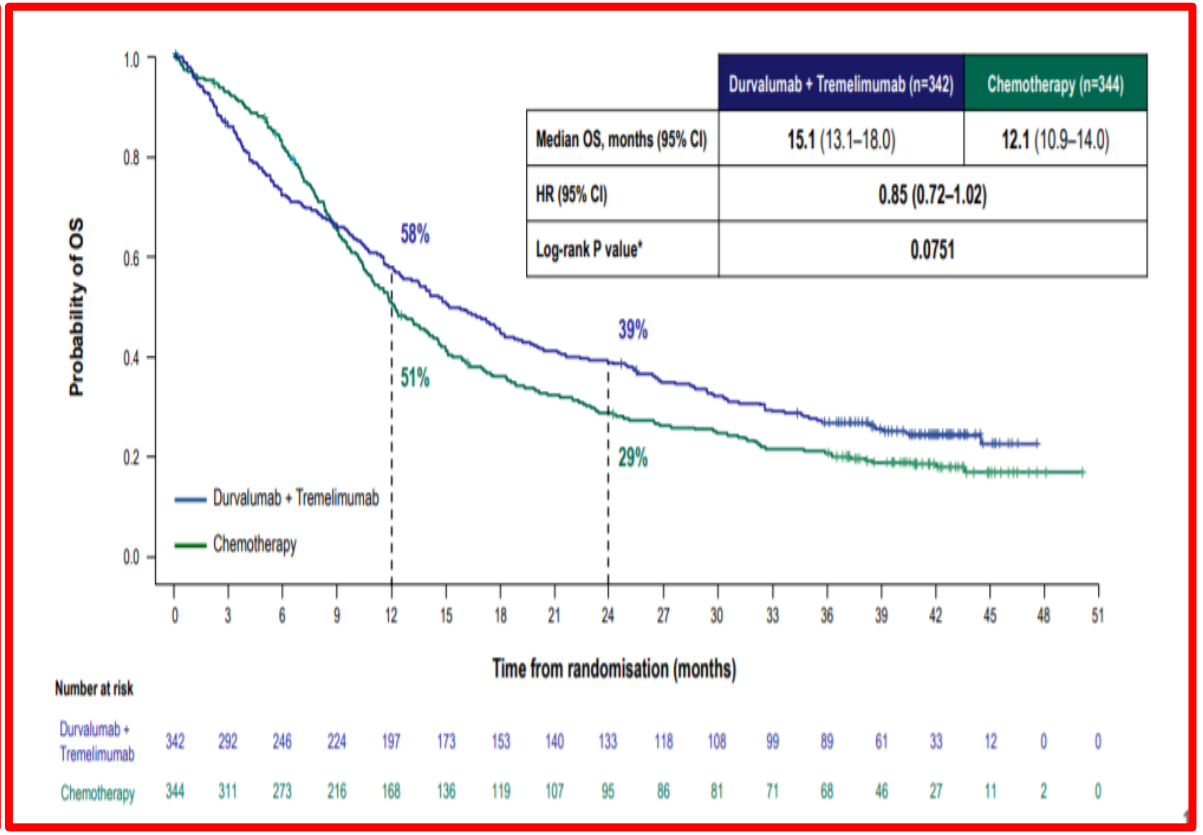


	Arm A Atezo + plt/gem (n = 451)	Arm C Placebo + plt/gem (n = 400)
OS events[a], n (%)	235 (52)	228 (57)
Stratified HR (95% CI)	0.83 (0.69, 1.00) *P* = 0.027 (one-sided)[b]	

Galsky MD et et al. Lancet Oncology 2020

1L durvalumab with or without tremelimumab vs SOC chemotherapy in patients with mUC (DANUBE)

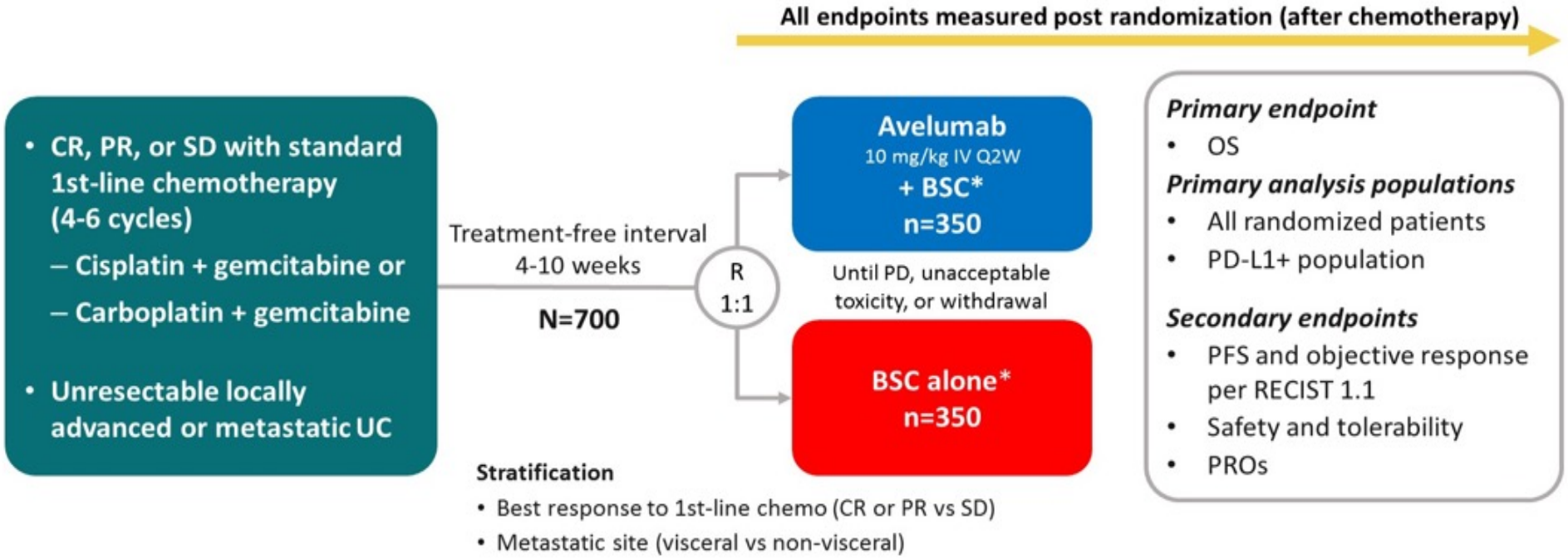




Powles T et al. Lancet. 2020

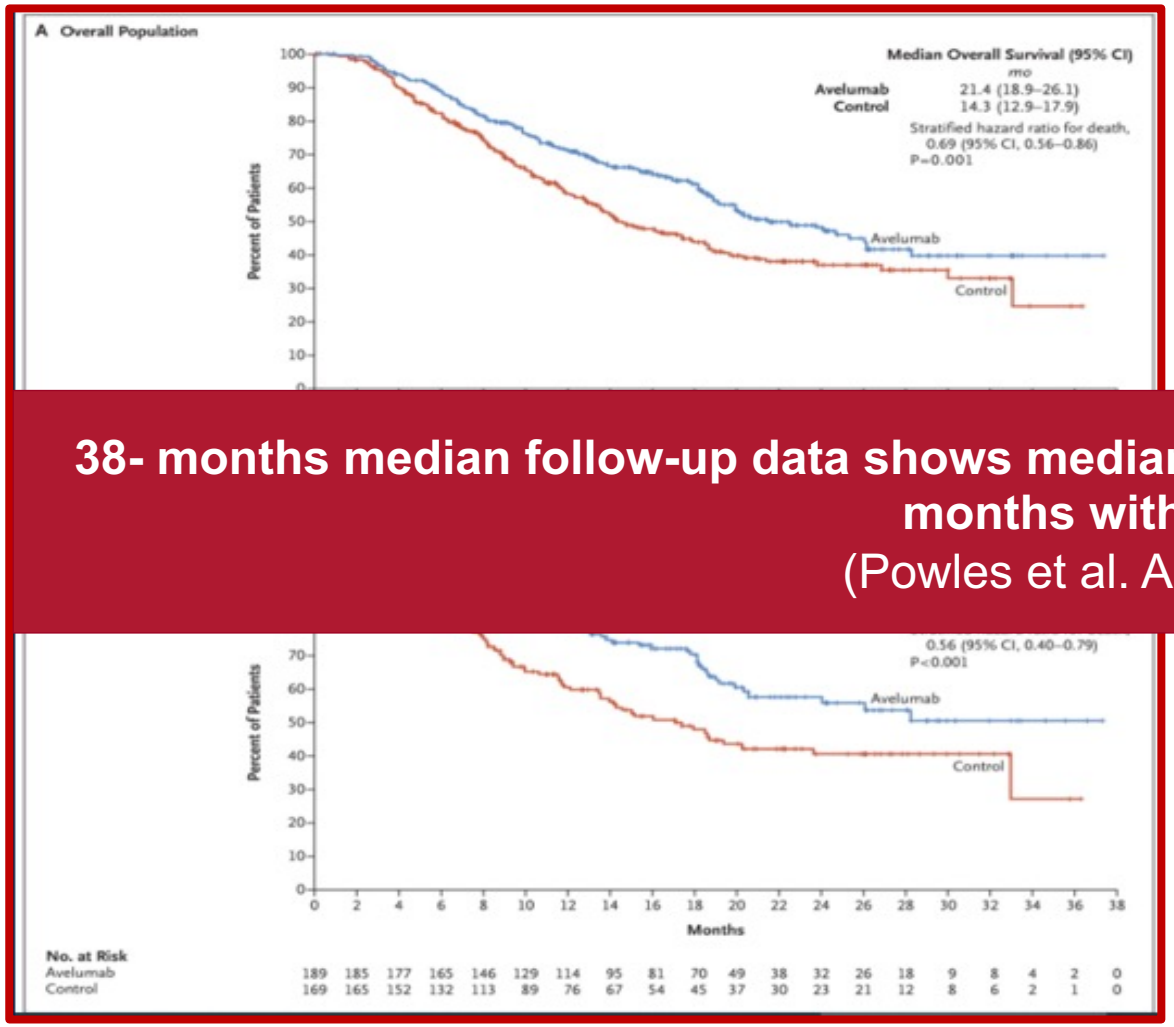
JAVELIN Bladder 100- "Maintenance" Strategy after 1L platinum-based chemotherapy

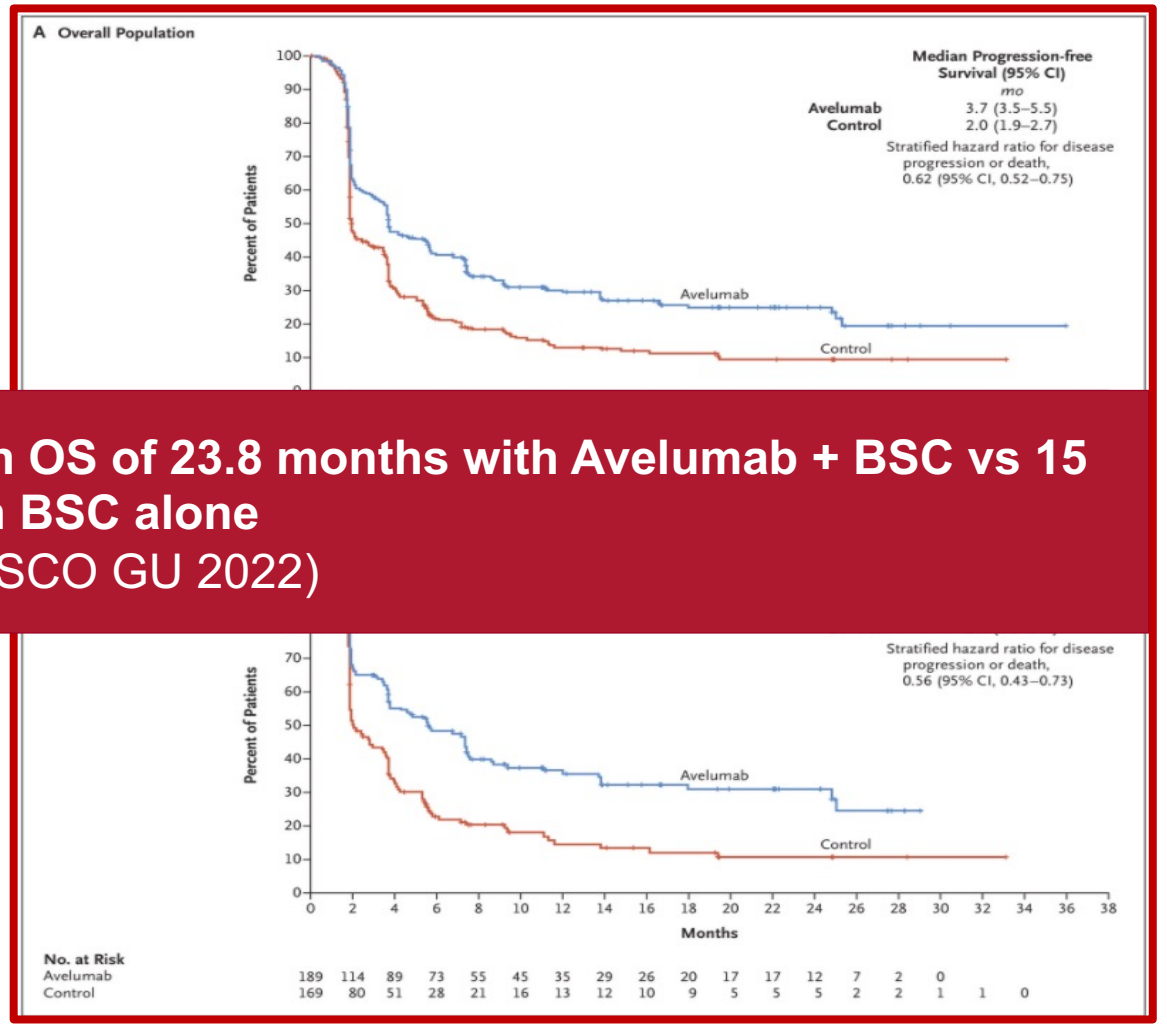
JAVELIN Bladder 100 study design (NCT02603432)



PD-L1+ status was defined as PD-L1 expression in ≥25% of tumor cells or in ≥25% or 100% of tumor-associated immune cells if the percentage of immune cells was >1% or ≤1%, respectively, using the Ventana SP263 assay; 358 patients (51%) had a PD-L1–positive tumor

Maintenance Avelumab improves OS and PFS





38- months median follow-up data shows median OS of 23.8 months with Avelumab + BSC vs 15 months with BSC alone
(Powles et al. ASCO GU 2022)

Thomas Powles et al. NEJM 2020

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

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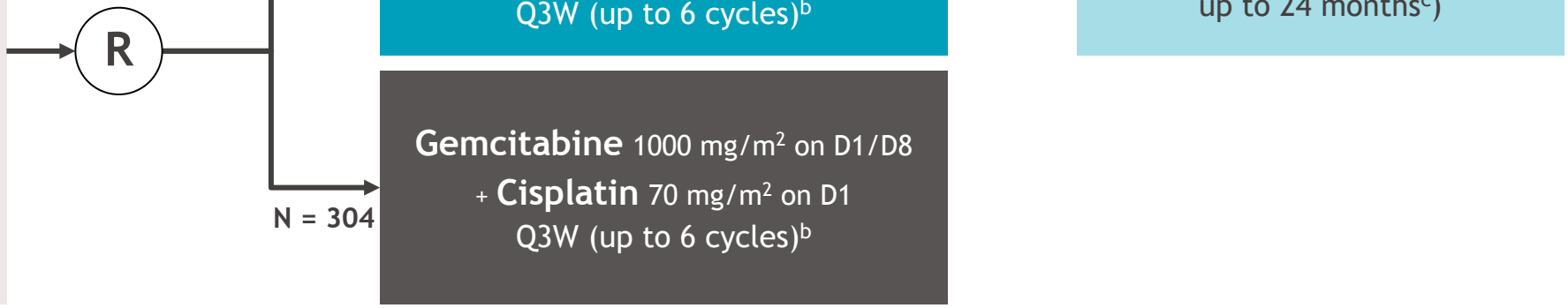
[a]Current affiliation is AdventHealth Cancer Institute and University of Central Florida, Orlando, FL, USA. [b]Current affiliation is IRCCS San Raffaele Hospital, Vita-Salute San Raffaele University, Milan, Italy. [c]Current affiliation is Klinikum Stuttgart, Katharinenhospital, Stuttgart, Germany.

Key inclusion criteria

- Age ≥ 18 years
- Previously untreated unresectable or mUC involving the renal pelvis, ureter, bladder, or urethra
- Cisplatin eligible
- ECOG PS of 0-1

Stratification factors:
- Tumor PD-L1 expression (≥ 1% vs < 1%)
- Liver metastases (yes vs no)

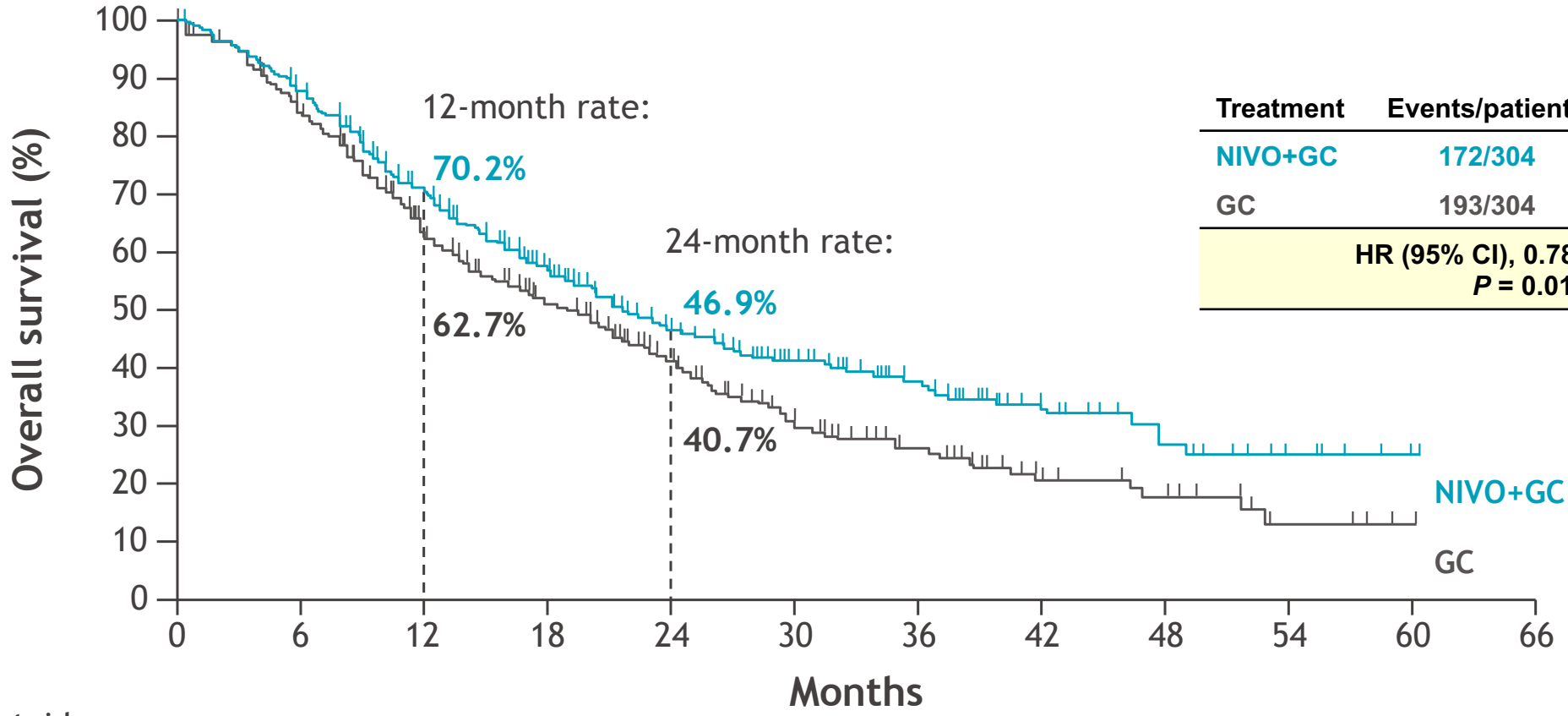


Median (range) study follow-up, 33.6 (7.4-62.4) months

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)

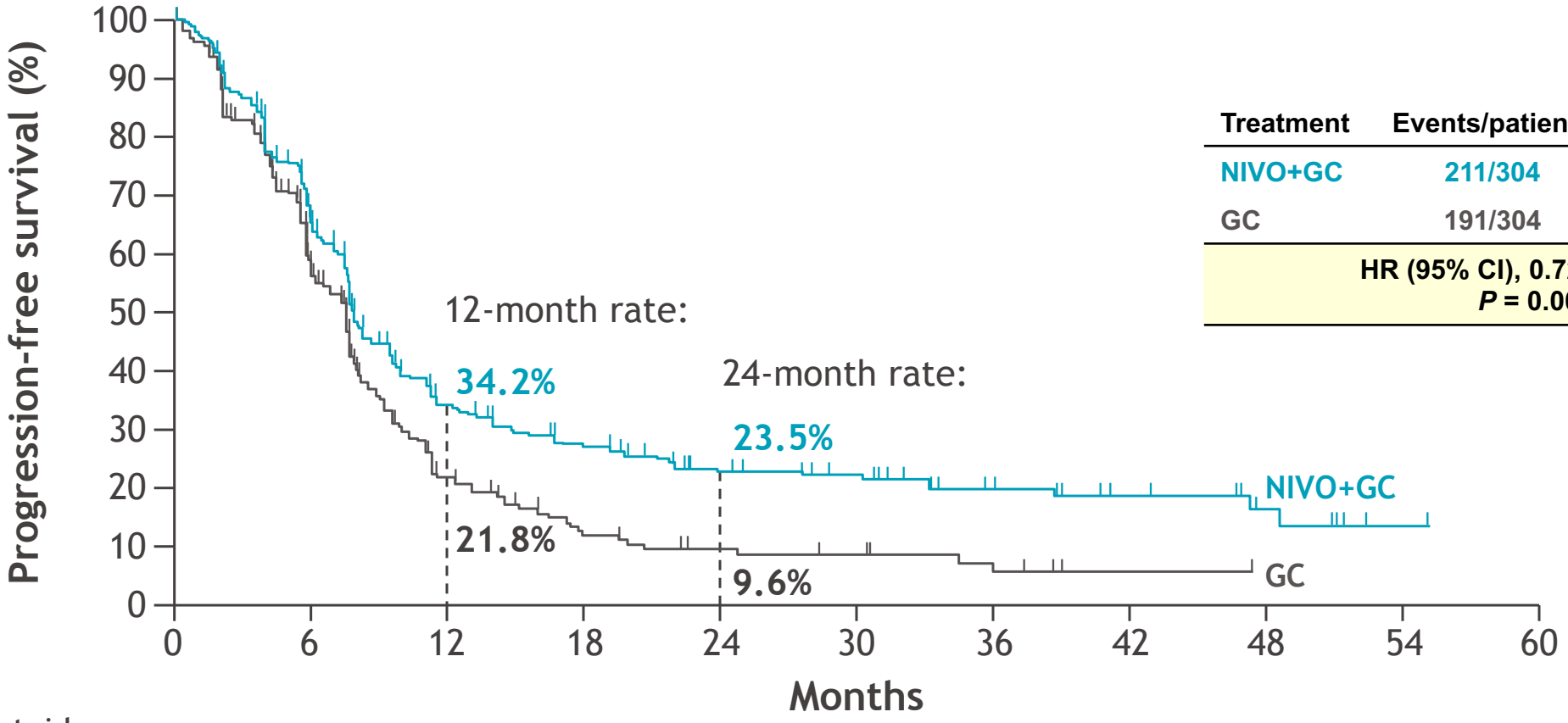


Treatment	Events/patients	Median OS (95% CI), months
NIVO+GC	172/304	21.7 (18.6-26.4)
GC	193/304	18.9 (14.7–22.4)
HR (95% CI), 0.78 (0.63–0.96) *P* = 0.0171		

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.

PFS per BICR (primary endpoint)



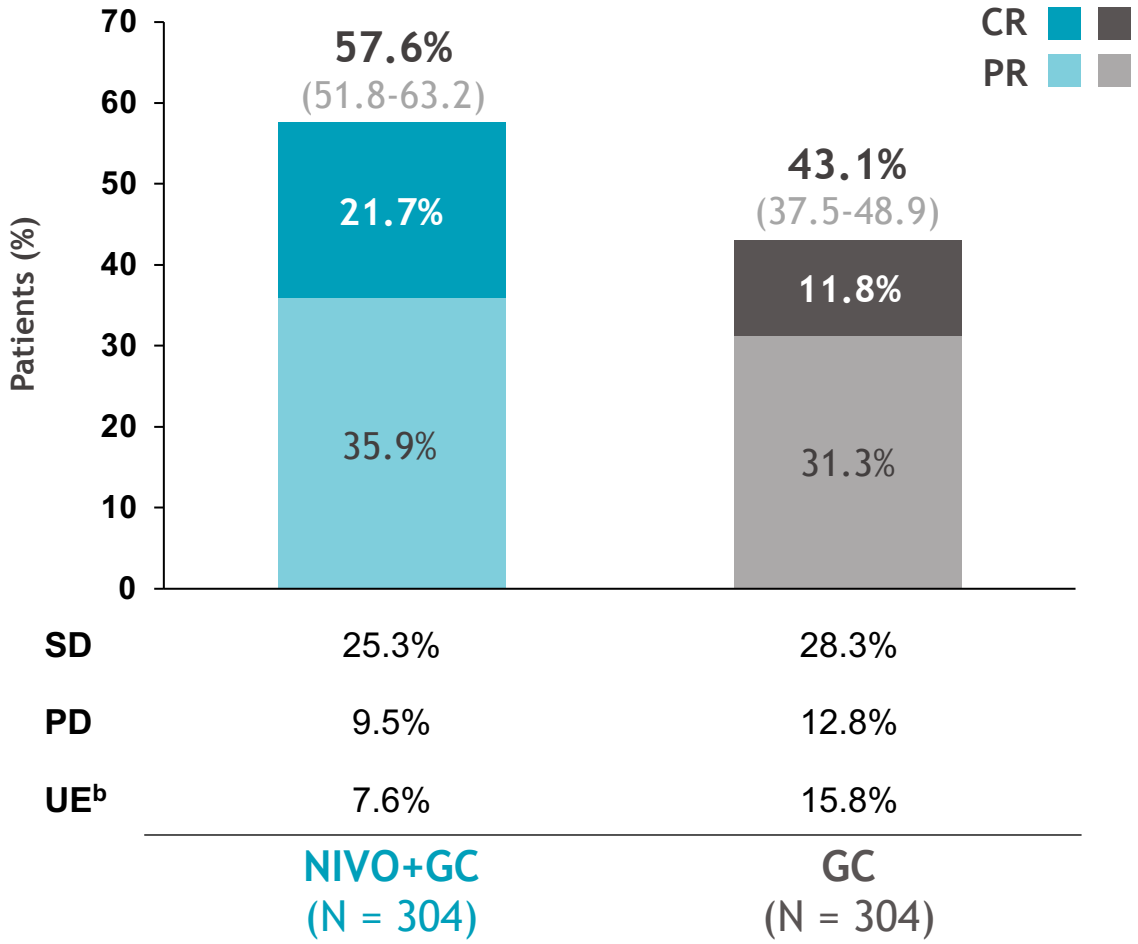
Treatment	Events/patients	Median PFS (95% CI), months
NIVO+GC	211/304	7.9 (7.6-9.5)
GC	191/304	7.6 (6.1–7.8)
HR (95% CI), 0.72 (0.59–0.88) *P* = 0.0012		

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.**

Objective response outcomes (exploratory endpoints)

ORR (95% CI) and BOR per BICR[a]



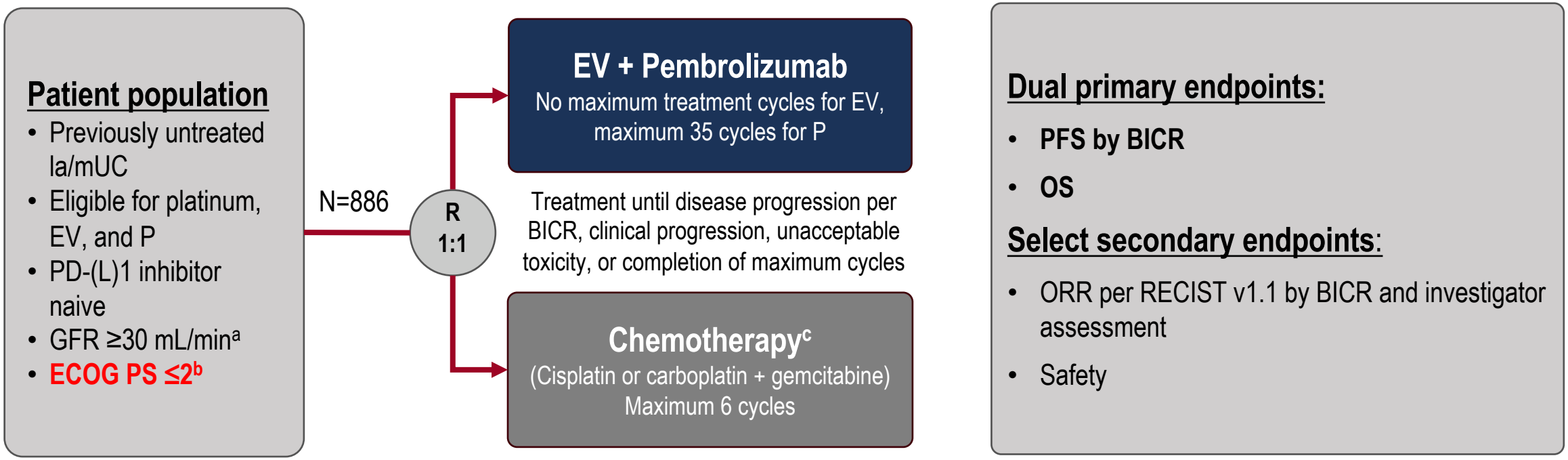
Time to and duration of responses

Any objective response[c]	NIVO+GC (n = 175)	GC (n = 131)
Median TTR (Q1-Q3), months	2.1 (2.0–2.3)	2.1 (2.0–2.2)
Median DoR (95% CI), months	9.5 (7.6–15.1)	7.3 (5.7–8.9)

Complete response[d]	NIVO+GC (n = 66)	GC (n = 36)
Median TTCR (Q1-Q3), months	2.1 (1.9-2.2)	2.1 (1.9-2.2)
Median DoCR (95% CI), months	37.1 (18.1-NE)	13.2 (7.3-18.4)

[a]In all randomized patients. [b]The most common reasons for UE response included death before first tumor assessment, withdrawal of consent, treatment stopped due to toxicity, patient never treated, and receipt of subsequent anticancer therapy before first tumor assessment. [c]Based on patients with an objective response per BICR (PR or CR as BOR). [d]Based on patients with a CR per BICR.
BOR, best overall response; CR, complete response; DoCR, duration of complete response; DoR, duration of objective response; NE, not estimable; PD, progressive disease; PR, partial response; Q, quartile; SD, stable disease; TTCR, time to complete response; TTR, time to objective response; UE, unevaluable.

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

Data cutoff: 08 Aug 2023; FPI: 7 Apr 2020, LPI: 09 Nov 2022

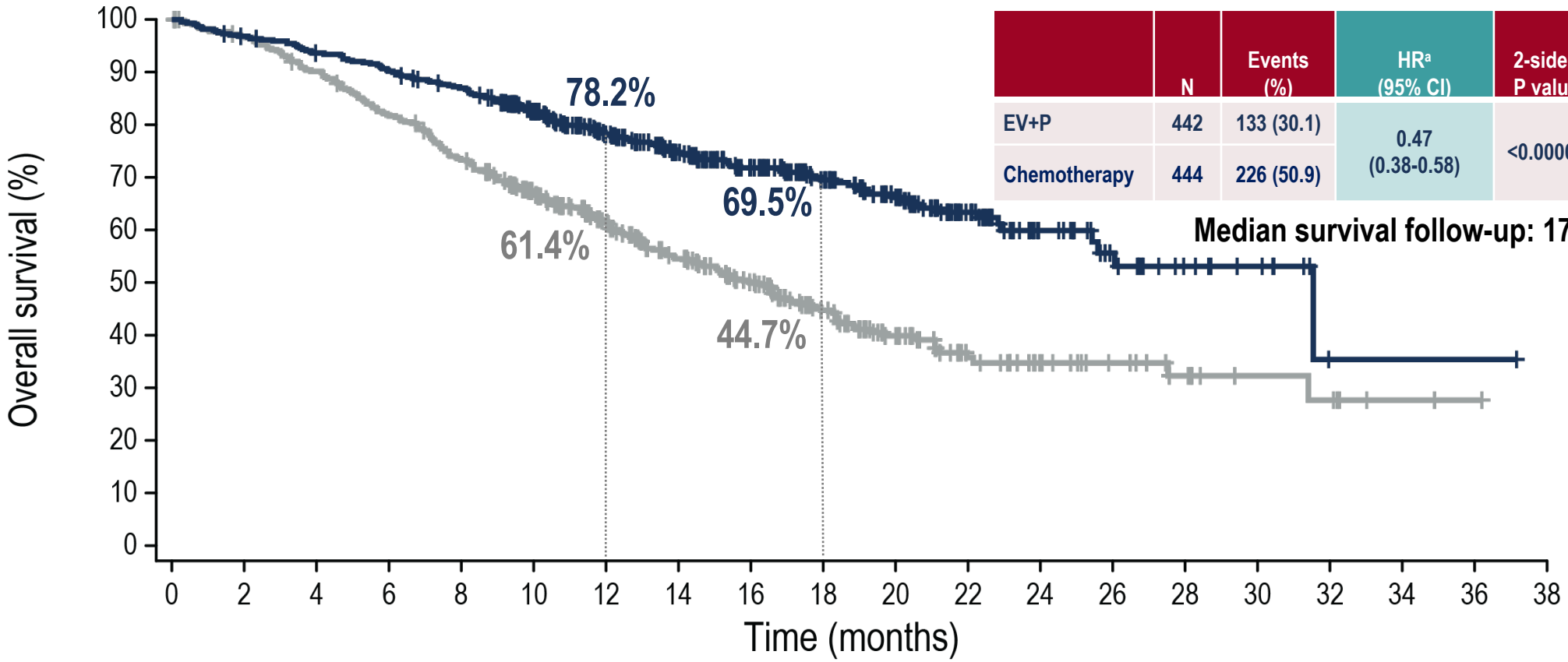
BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; GFR, glomerular filtration rate; ORR, overall response rate; PFS, progression-free survival; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors

[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

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

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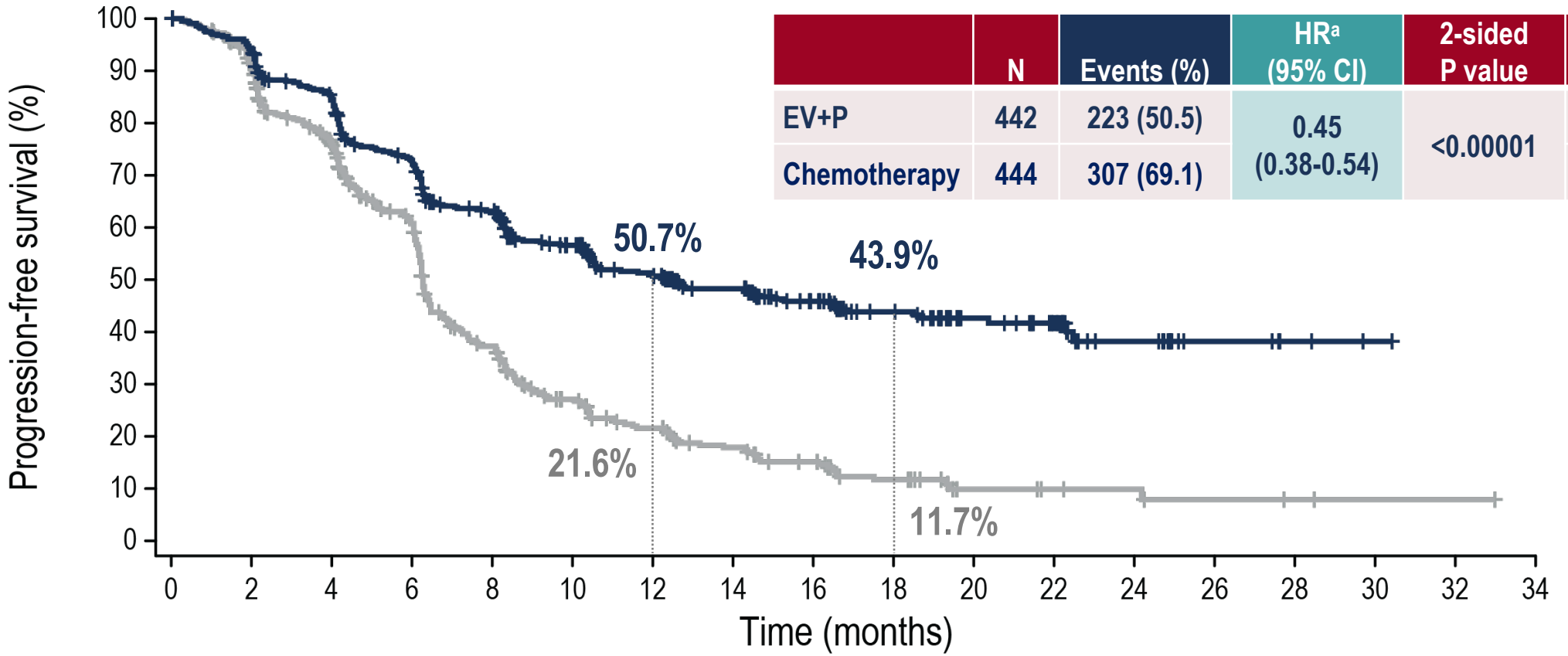
Data cutoff: 08 Aug 2023

Powles et al.

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

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)



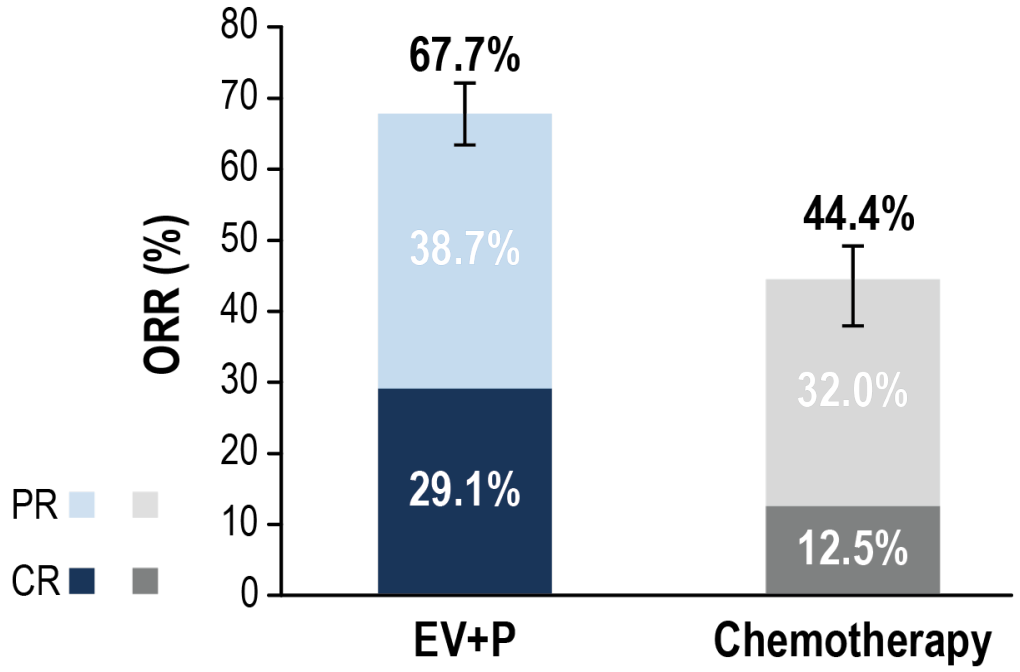
N at risk

EV+P	442	409	361	303	253	204	167	132	102	73	45	33	17	6	3	1
Chemotherapy	444	380	297	213	124	78	56	41	30	19	8	6	5	3	2	1	1

Data cutoff: 08 Aug 2023

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

Significant improvement in objective response rate was observed with EV+P



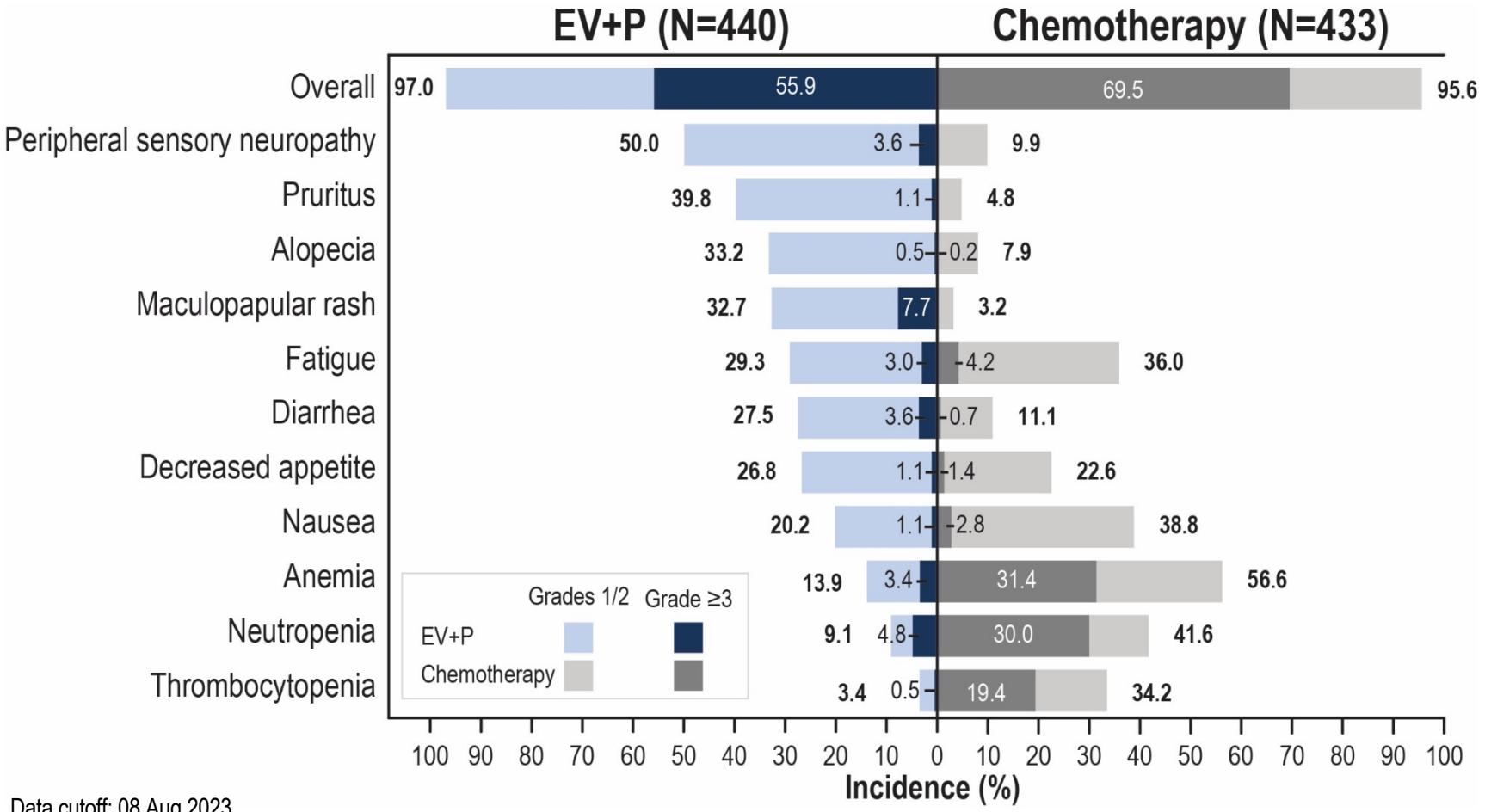
	EV+P (N=437)	Chemotherapy (N=441)
Confirmed ORR, n (%) (95% CI)	**296 (67.7) (63.1-72.1)**	**196 (44.4) (39.7-49.2)**
2-sided P value	<0.00001	
Best overall response[a], n (%)		
Complete response	127 (29.1)	55 (12.5)
Partial response	169 (38.7)	141 (32.0)
Stable disease	82 (18.8)	149 (33.8)
Progressive disease	38 (8.7)	60 (13.6)
Not evaluable/No assessment[b]	21 (4.8)	36 (8.2)

Median DOR (95% CI)	NR (20.2, NR)	7.0 (6.2, 10.2)

Data cutoff: 08 Aug 2023

CR, complete response; DOR, duration of response; PR, partial response
[a]Best overall response according to RECIST v1.1 per BICR. CR or PR was confirmed with repeat scans ≥28 days after initial response
[b]Patients had either post-baseline assessment and the best overall response was determined to be not evaluable per RECIST v1.1 or no response assessment post-baseline

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

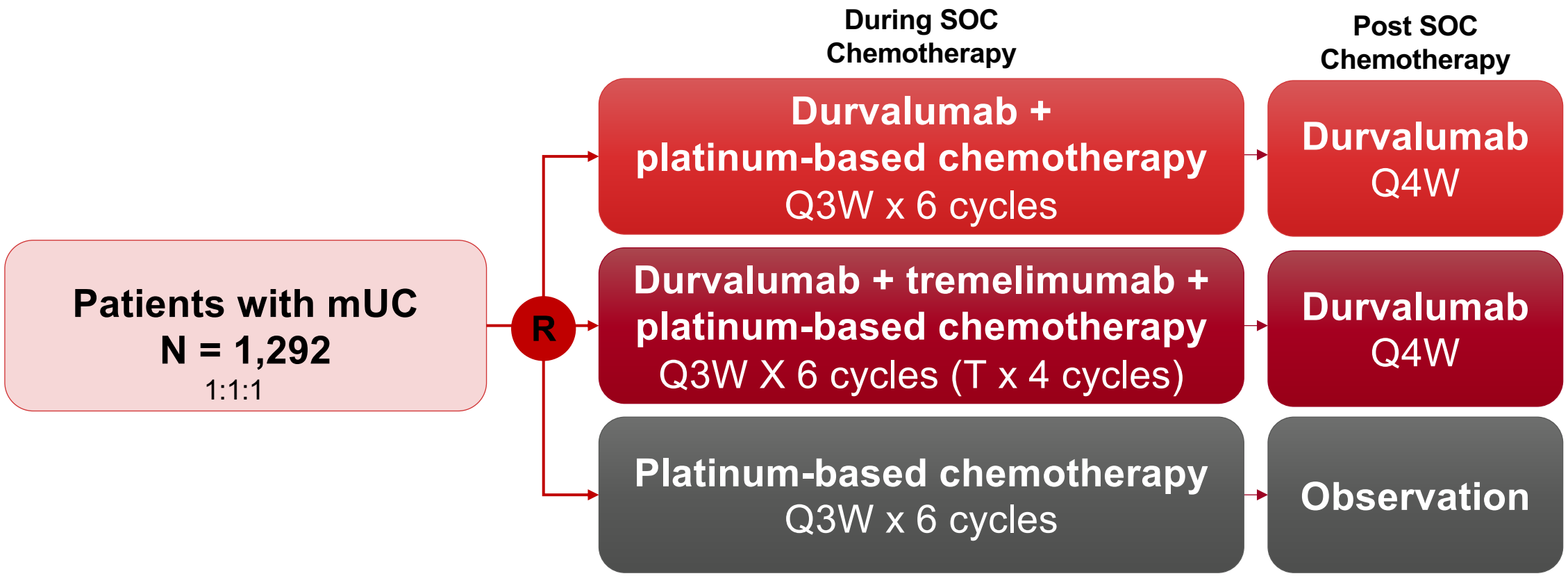
Data cutoff: 08 Aug 2023

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

Powles et al.

Ongoing Phase 3 NILE: IO Plus Chemo in 1L mUC



- **Co-primary endpoints:** OS in PD-L1+ (arm 1 vs arm 3)
- **Select secondary endpoints:** OS, OS 24 mo, PFS, ORR

Pembrolizumab is the preferred IO in patients with platinum-refractory la/mUC (KEYNOTE-045)

Initial efficacy was maintained at 2-, 3-, and 5-years follow-up

5-year follow-up	Pembrolizumab ITT n = 270	Chemotherapy ITT n = 272
ORR, % (95% CI)	21.9 (17.1-27.3)	11.0 (7.6-15.4)
Best response, n (%)		
CR	27 (10.0)	8 (2.9)
PR	32 (11.9)	22 (8.1)
SD	47 (17.4)	92 (33.8)
PD	129 (47.8)	90 (33.1)
NA[a]	31 (11.5)	51 (18.8)
NE[b]	4 (1.5)	9 (3.3)

Pembrolizumab vs Investigator's choice chemotherapy
OS: 10.1 mo vs 7.2 mo
DOR: 29.7 mo vs 4.4 mo

Nivolumab and Avelumab are also approved in this setting and are alternative options

Bellmunt J et al. N Engl Med. 2017;Fradet Y et al. Ann Oncol. 2019; Necchi A et al. Ann Oncol. 2019; Bellmunt J et al. ASCO 2021 Abstract 4532

Neoadjuvant Single-agent IO also effective in MIBC

	PURE-01[1]	ABACUS[2]	NABUCCO[3]	AURA[4]	MDACC[5]	DUTRENEO[6]
N	114	95	24 (14)	28	28	23
Immunotherapy	Pembrolizumab	Atezolizumab	Ipi/Nivo	Avelumab	Durval/Tremi	Durva/Tremi
Cisplatin eligible	✓	✓	✗	✗	✗	✗
pCR rates with single-agent IO similar to NAC						
PFS	91% (1yr)	79% (1yr)	92% (1yr)	Not reported	82.8% (1yr)	Not reported

1Necchi et al, Eur Urol 2022, 2 Powles et al, Nat Med 2019, 3Van Dijk et al, ASCO Annual Mtg 2020;abstr 5020, 4 Kaimakliotis et al, ASCO Annual Mtg 2020;abstr 5019
5Gao J et al Nature Med 2020 6. Grande E et al. J Clin Oncol Suppl 5012

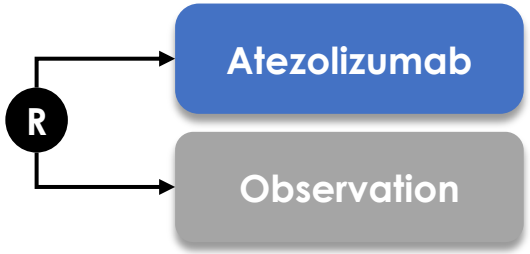
Ongoing Phase 3 Neoadjuvant IO-based Trials in MIBC

	Clinical Trial	N	Treatment Arms
CISPLATIN ELIGIBLE	KEYNOTE-866	870	Pembro + GC vs GC
	KEYNOTE-B15/EV-304	784	Pembro +EV vs GC
	NIAGARA	1050	Durva+ GC vs GC
	ENERGIZE	1200	Nivo + GC vs GC ~~GC+ Nivo + Linrodostat~~
CISPLATIN-INELIGIBLE	KEYNOTE-905/ EV-303	836	RC vs Pembro+EV vs Pembro
	VOLGA	830	RC vs Druva/Tremi+EV vs Durva+EV
	SWOG GAP	196	Surgery vs Gem-Carbo+ Avelumab

Adjuvant IO trials in high-risk MIUC

High risk MIUC: if received NAC- ypT2-T4a/ypN+ or pT3-T4a/pN+ if not eligible for or declined adjuvant cisplatin-based chemotherapy

IMvigor010

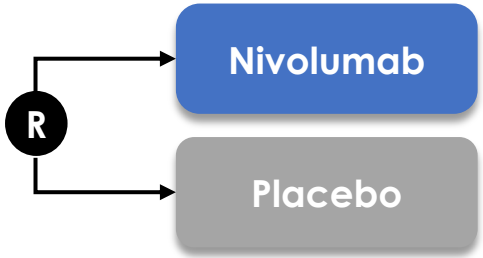


Primary endpoint:
DFS

Key secondary endpoints:
OS, DSS, distant metastasis-free survival, NUTRFS

No DFS or OS improvement

CheckMate -274



Primary endpoint:
DFS

Key secondary endpoints:
OS, NUTRFS, DSS

DFS Improvement Waiting for OS

AMBASSADOR

Coprimary endpoints:
DFS and OS

Key secondary endpoints:
OS and DFS in PD-L1–positive and PD-L1–negative patients

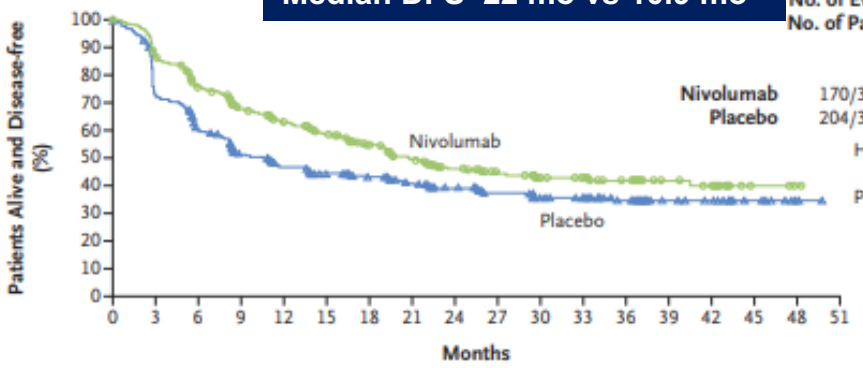
DFS Improvement

PI Andrea Apolo MD

Checkmate 274: DFS improvement with nivolumab

Intention-to-Treat Population

Median DFS 22 mo vs 10.9 mo

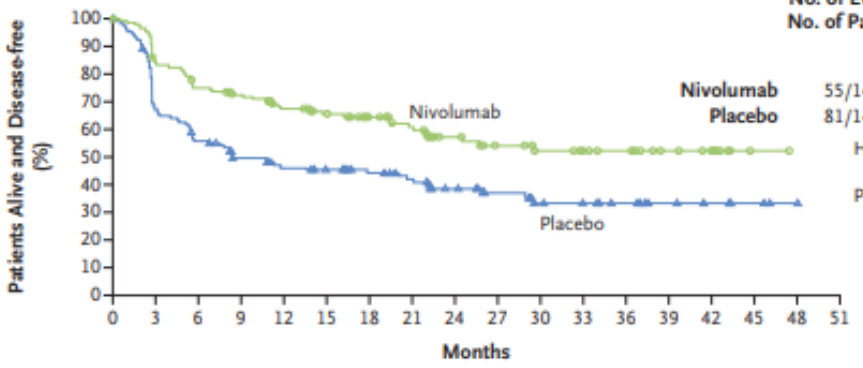


	No. of Events/ No. of Patients	Disease-free Survival at 6 Mo (95% CI)	Disease-free Survival at 12 Mo (95% CI)
		%	
Nivolumab	170/353	74.9 (69.9–79.2)	62.8 (57.3–67.8)
Placebo	204/356	60.3 (54.9–65.3)	46.6 (41.1–51.9)

Hazard ratio for disease recurrence or death, 0.70 (98.22% CI, 0.55–0.90)
P<0.001

No. at Risk																		
Nivolumab	353	296	244	212	178	154	126	106	85	68	57	51	36	23	20	3	1	0
Placebo	356	248	198	157	134	121	105	94	80	65	54	50	37	22	19	10	2	0

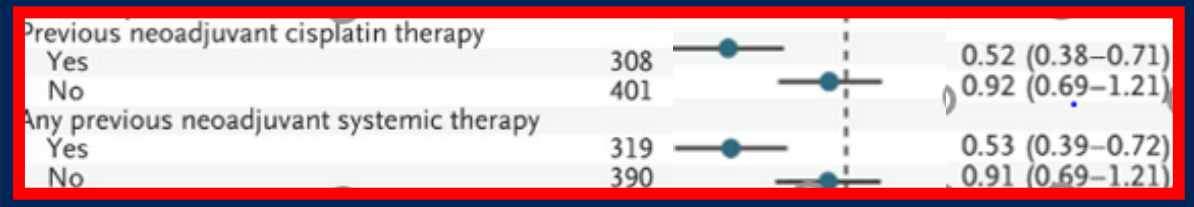
Patients with a PD-L1 Expression Level of ≥1%



	No. of Events/ No. of Patients	Disease-free Survival at 6 Mo (95% CI)	Disease-free Survival at 12 Mo (95% CI)
		%	
Nivolumab	55/140	74.5 (66.2–81.1)	67.2 (58.4–74.5)
Placebo	81/142	55.7 (46.8–63.6)	45.9 (37.1–54.2)

Hazard ratio for disease recurrence or death, 0.55 (98.72% CI, 0.35–0.85)
P<0.001

No. at Risk																		
Nivolumab	140	113	98	91	76	68	58	50	38	31	27	24	21	12	10	1	0	0
Placebo	142	90	73	59	53	49	42	37	28	22	17	16	12	7	5	3	1	0



What about OS?

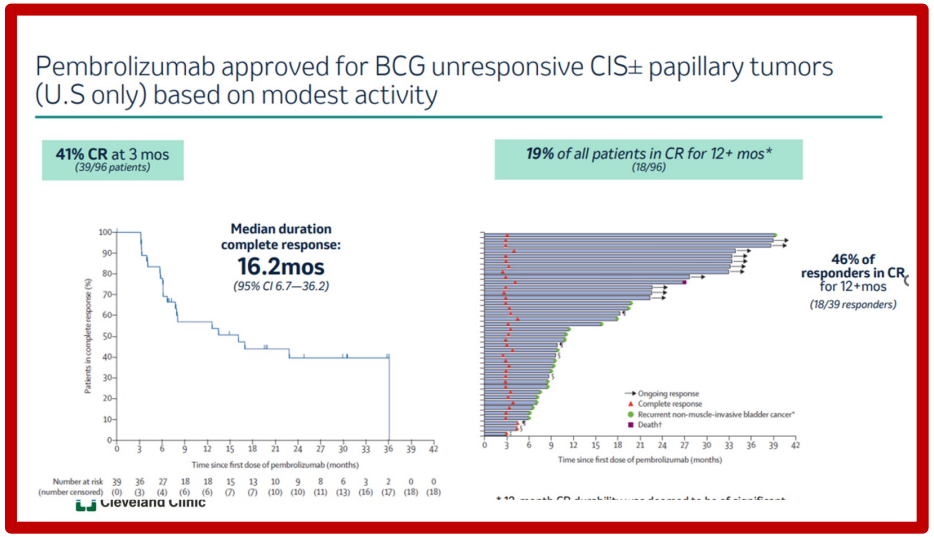
Bajorin, DF et al. NEJM 2021

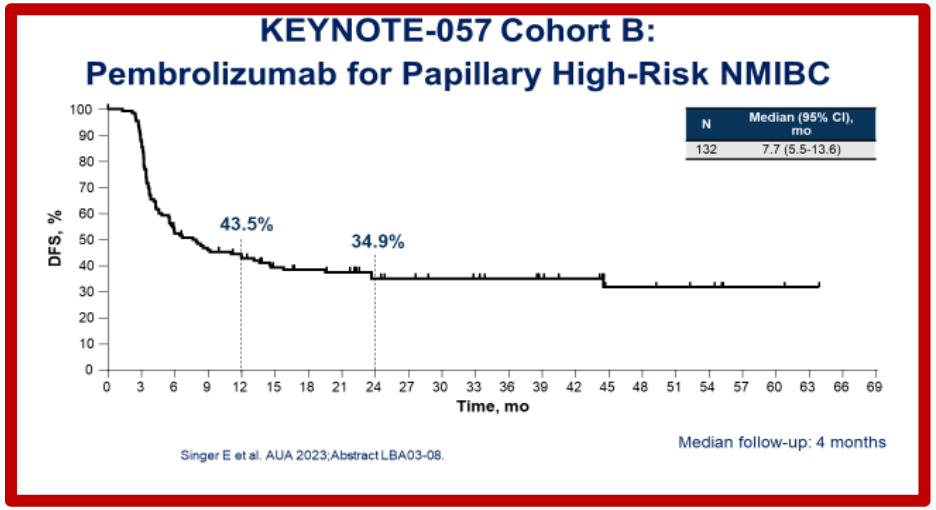
Pembrolizumab in NMITCC- NCG refractory

KEYNOTE-057

- Pembrolizumab in BCG-unresponsive NMIBC
  - Phase II (N = 320)
- **Cohort A** (CIS ± papillary tumors) (n = 101)
- Median follow-up: 36.4 mo[1]
- 41% (39/96) of evaluable patients had CR at 3 mo
- Median DoR: 16.2 mo
- 19% of all patients in CR at 12+ months
- No new safety signals

Pembrolizumab is approved by FDA for patients with BCG-unresponsive, high-risk NMIBC with CIS (± papillary tumors) who are ineligible or have elected not to undergo cystectomy





Summary Statements

- Enfortumab Vedotin in combination with Pembrolizumab has become the new SOC for patients with mUC entering first-line therapy
- No role of Chemo + IO regimens or maintenance IO based approaches
- Very small role of Monotherapy with IO based approaches
- Adjuvant IO: Pt selection important while waiting for OS data
- Second-line Therapy will likely include Chemo vs. other ADCs or FGFR inhibitors (FGRF mutant)
- Awareness of unique AEs important but not the reason for early termination
    - AEs are very manageable – worth in the setting of durable responses and OS benefits across different settings in disease natural history

Renal Cell Carcinoma: Role of Immunotherapy

Immunotherapy in Renal Cell Carcinoma: An "Old" SOC

- Front-line therapy for Clear Cell Met RCC remains IO-based
  - CTLA-4 + PD1 followed by PD1 maintenance
  - PD1 + VEGF-TKI (three regimens)

- Risk-Prognostic Classification clinically important for counseling
  - Presence of Absence of Primary Tumor
  - Symptomatic disease or Not
  - Patient Preference and QOL concerns

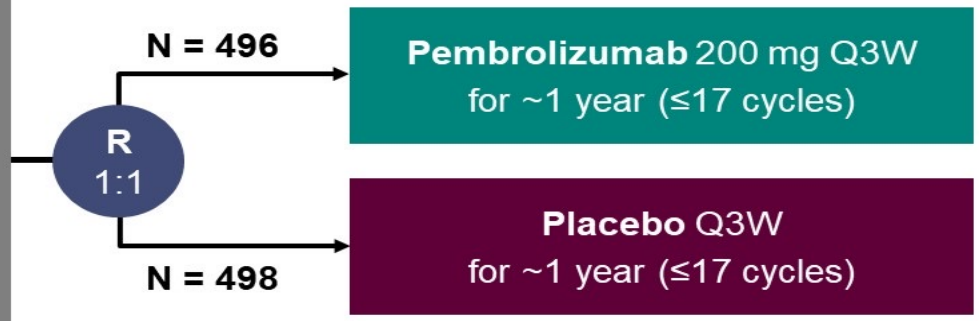
- Developing understanding and comfort level (Clinical care team) critical

- Biomarkers for treatment selection will eventually arrive

KEYNOTE-564 Study (NCT03142334)

Key Eligibility Criteria

- Histologically confirmed clear cell RCC with no prior systemic therapy
- Surgery ≤12 weeks prior to randomization
- Postnephrectomy intermediate-high risk of recurrence (M0):
  - pT2, grade 4 or sarcomatoid, N0
  - pT3, any grade, N0
- Postnephrectomy high risk of recurrence (M0):
  - pT4, any grade, N0
  - Any pT, any grade, N+
- Postnephrectomy + complete resection of metastasis (M1 NED)
- ECOG PS 0 or 1



Stratification Factors

- M stage (M0 vs. M1 NED)
- M0 group further stratified:
  - ECOG PS 0 vs. 1
  - US vs. non-US

Primary Endpoint

- Disease-free survival by investigator

Key Secondary Endpoint

- Overall survival

Other Secondary Endpoints

- Safety

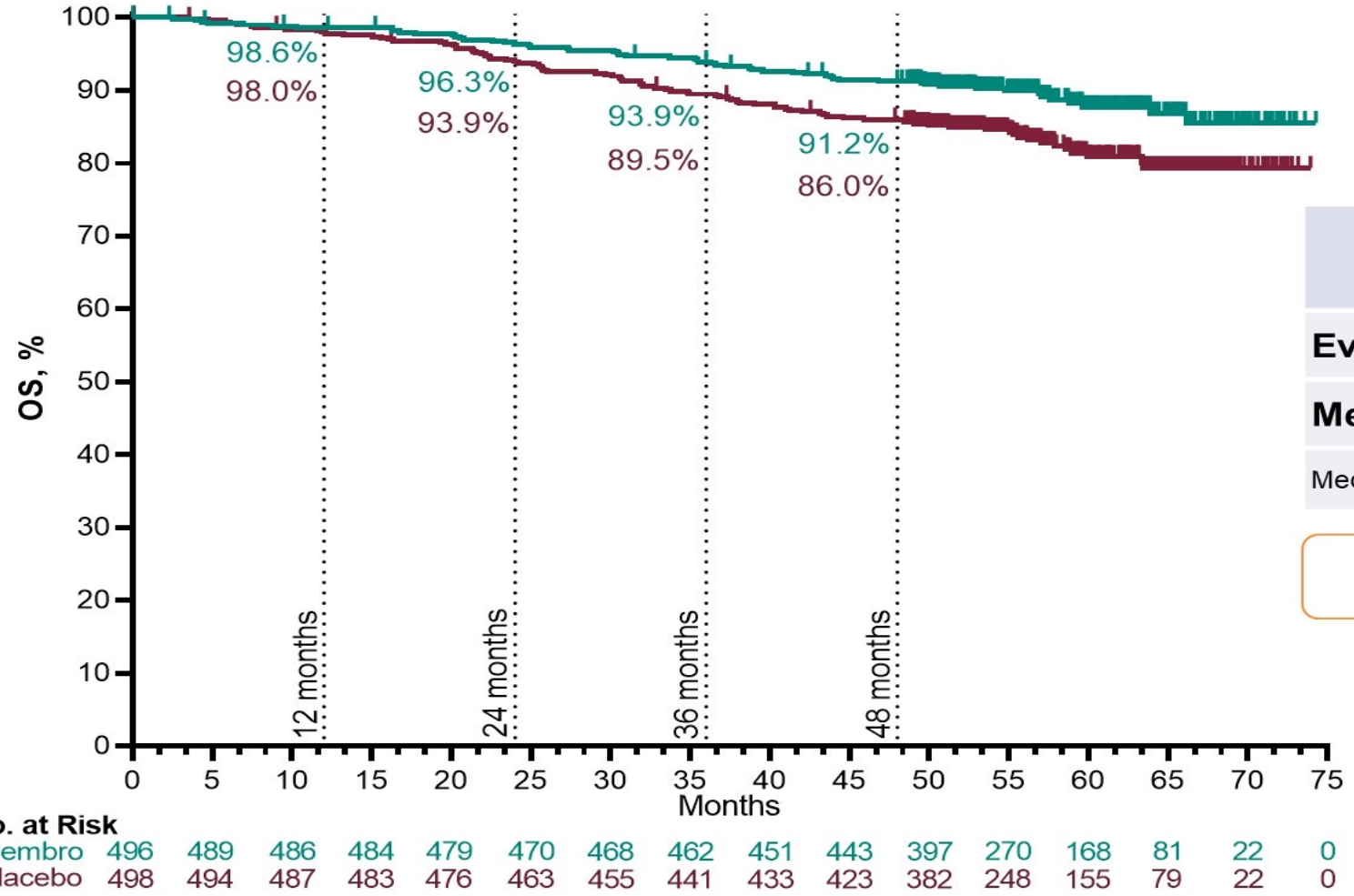
NED, no evidence of disease.

Baseline Characteristics

	Pembrolizumab (N = 496)	Placebo (N = 498)
Age, median (range), yrs	60 (27–81)	60 (25–84)
Male	70.0%	72.1%
ECOG performance status of 0	84.9%	85.5%
Region		
United States (US)	23.0%	23.5%
Outside US	77.0%	76.5%
M stage		
M0	94.2%	94.4%
M1	5.8%	5.6%
Disease risk category[a]		
M0 intermediate-high risk	85.1%	86.9%
M0 high risk	8.1%	7.4%
M1 NED	5.8%	5.6%
Sarcomatoid features		
Present	10.5%	11.8%
Absent	83.5%	83.3%
Unknown	6.0%	4.8%
PD-L1 status[b]		
CPS <1	25.0%	22.7%
CPS ≥1	73.6%	76.9%
Missing	1.4%	0.4%

[a]Another 1.0% of pts in the pembro group and 0% in the placebo group had T2 (grade ≤3) N0 M0 or T1 N0 M0 disease (protocol violations). [b]Assessed with PD-L1 IHC 22C3 pharmDx. PD-L1 combined positive score (CPS) is the # of PD-L1–staining cells (tumor cells, lymphocytes, and macrophages) divided by the total # of viable tumor cells, multiplied by 100. Data cutoff date: September 15, 2023.

Overall Survival, Intention-to-Treat Population



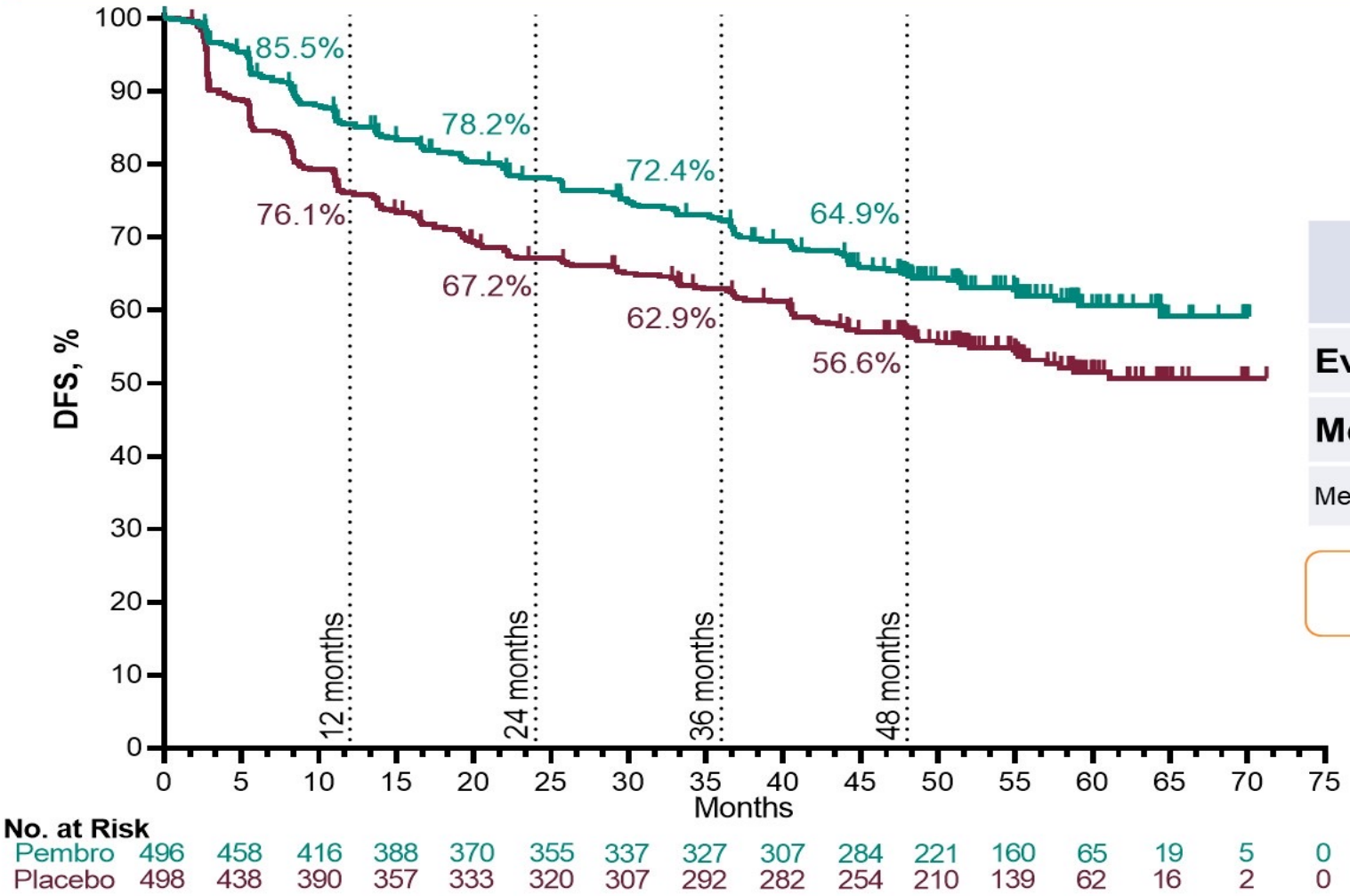
	Pembro (N = 496)	Placebo (N = 498)
Events, n	55	86
Median, mo (95% CI)	NR (NR–NR)	NR (NR–NR)
Median follow-up was 57.2 months (range, 47.9–74.5)		

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

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

Data cutoff date: September 15, 2023.

Updated Disease-Free Survival by Investigator, Intention-to-Treat Population



	Pembro (N = 496)	Placebo (N = 498)
Events, n	174	224
Median, mo (95% CI)	NR (NR–NR)	NR (54.9–NR)

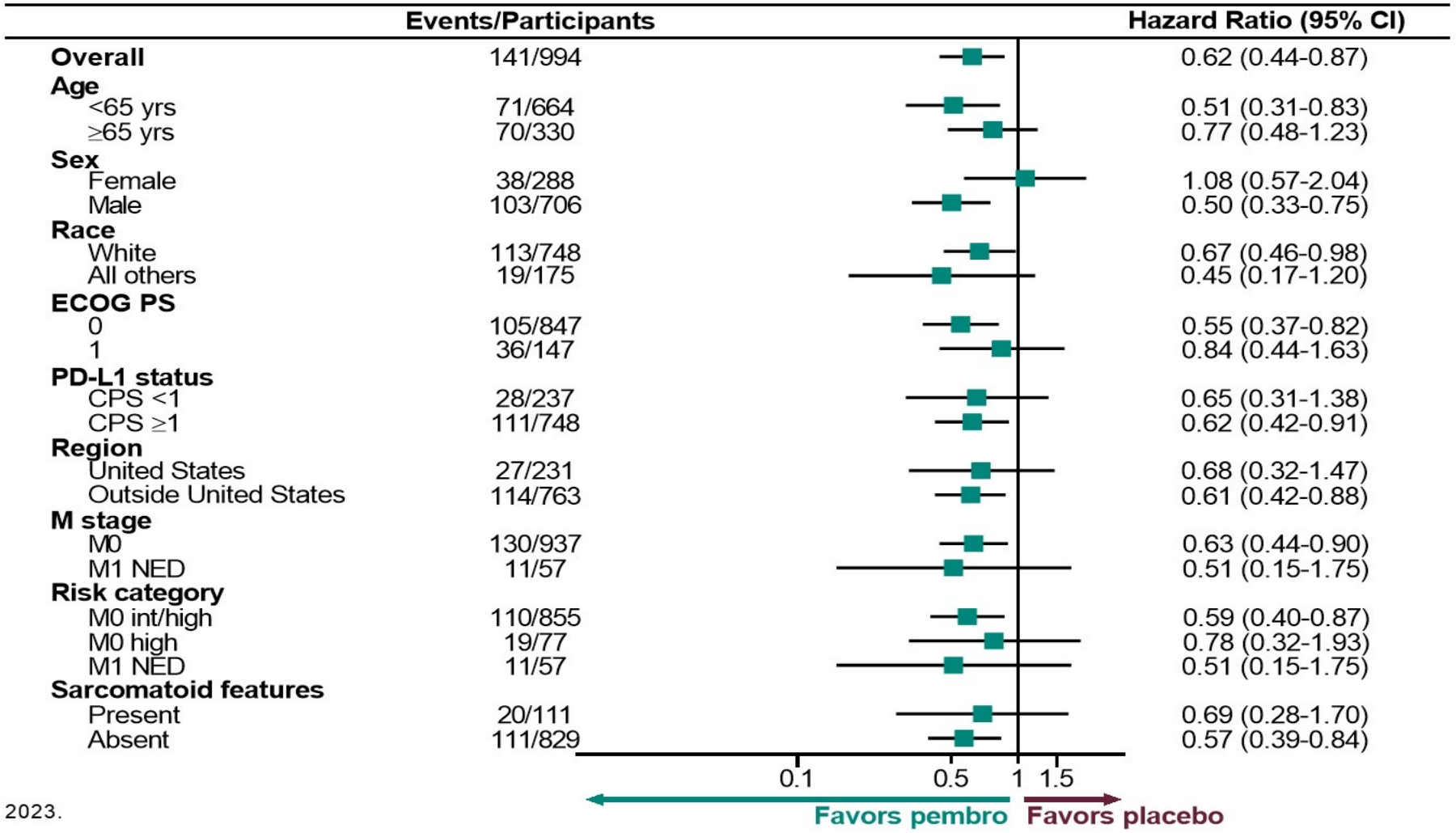
Median follow-up was 57.2 months (range, 47.9–74.5)

HR 0.72 (95% CI 0.59–0.87)

Primary DFS endpoint was met at IA1 and was not formally statistically tested thereafter.

Data cutoff date: September 15, 2023.

Overall Survival by Subgroups



Data cutoff date: September 15, 2023.

Subsequent Therapies, Intention-to-Treat Population

	Participants with Documented Recurrence	
	Pembrolizumab (N = 161)	Placebo (N = 210)
Received any subsequent therapy[a,b]	128/161 (79.5%)	171/210 (81.4%)
Received systemic anticancer drug therapy Anti–PD-(L)1 therapy[c] VEGF/VEGFR inhibitor[d] Other[e]	102/128 (79.7%) 42/102 (41.2%) 94/102 (92.2%) 32/102 (31.4%)	145/171 (84.8%) 101/145 (69.7%) 123/145 (84.8%) 60/145 (41.4%)
Received radiation therapy	31/128 (24.2%)	33/171 (19.3%)
Received surgery	35/128 (27.3%)	50/171 (29.2%)
No subsequent therapy	28/161 (17.4%)	28/210 (13.3%)
No subsequent therapy data available	5/161 (3.1%)	11/210 (5.2%)

[a]An additional 4 and 1 pts respectively in the pembro and placebo arms who are not included in the figure received subsequent therapy without documented recurrence. [b]Pts could have multiple subsequent anticancer therapies for RCC; each pt is counted once in each applicable category. [c]Atezolizumab, avelumab, durvalumab, nivolumab, pembrolizumab. [d]Axitinib, bevacizumab, cabozantinib, lenvatinib, pazopanib, sorafenib, sunitinib, tivozanib. [e]Included but was not limited to belzutifan, everolimus, and ipilimumab.
Data cutoff date: September 15, 2023.

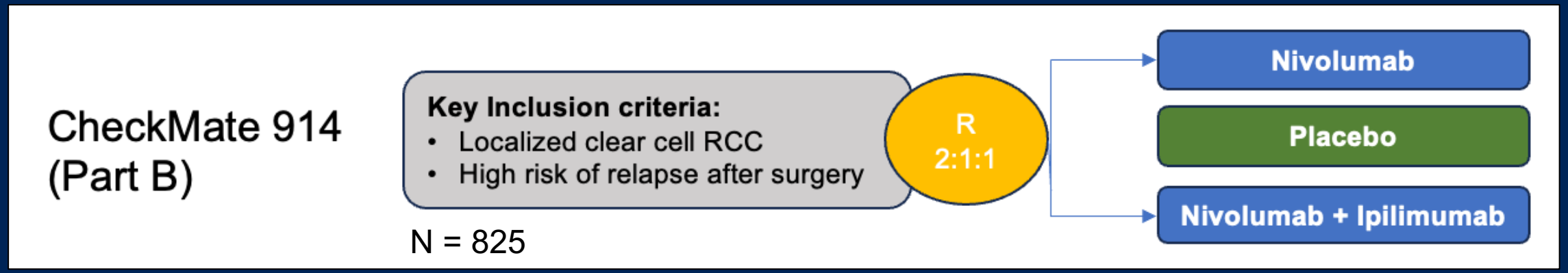
Summary of Updated Safety Findings, As-Treated Population

	Prior Analysis (30.1 mo follow-up)		IA3 (57.2 mo follow-up)	
	Pembrolizumab (N = 488)	Placebo (N = 496)	Pembrolizumab (N = 488)	Placebo (N = 496)
Duration of therapy, median (range), months	11.1 (0.03–14.3)	11.1 (0.03–15.4)	11.1 (0.03–14.3)	11.1 (0.03–15.4)
Any-cause AEs[a]	470 (96.3%)	453 (91.3%)	470 (96.3%)	453 (91.3%)
Grade 3 to 5	157 (32.2%)	88 (17.7%)	156 (32.0%)	88 (17.7%)
Led to treatment discontinuation	103 (21.1%)	11 (2.2%)	103 (21.1%)	11 (2.2%)
Led to death	2 (0.4%)	1 (0.2%)	2 (0.4%)	1 (0.2%)
Serious AEs[a]	101 (20.7%)	57 (11.5%)	101 (20.7%)	57 (11.5%)
Led to treatment discontinuation	49 (10.0%)	5 (1.0%)	49 (10.0%)	5 (1.0%)
Treatment-related AEs[a]	386 (79.1%)	265 (53.4%)	386 (79.1%)	263 (53.0%)
Grade 3 to 4	91 (18.6%)	6 (1.2%)	91 (18.6%)	6 (1.2%)
Led to treatment discontinuation	89 (18.2%)	4 (0.8%)	89 (18.2%)	4 (0.8%)
Led to death	0	0	0	0
Immune-mediated AEs and infusion reactions[b]	174 (35.7%)	34 (6.9%)	178 (36.5%)	36 (7.3%)
Grade 3 to 4	45 (9.2%)	3 (0.6%)	46 (9.4%)	3 (0.6%)
Led to death	0	0	0	0
Required high-dose (≥40 mg/day) systemic corticosteroids	37 (7.6%)	3 (0.6%)	37 (7.6%)	3 (0.6%)

[a]AEs were graded per the NCI CTCAE v4.0 and reported from randomization to 30 days (90 days for serious AEs) after study therapy discontinuation. [b]Based on a list of preferred terms intended to capture known risks of pembro and were considered regardless of attribution to study treatment by the investigator.
Data cutoff date: September 15, 2023.

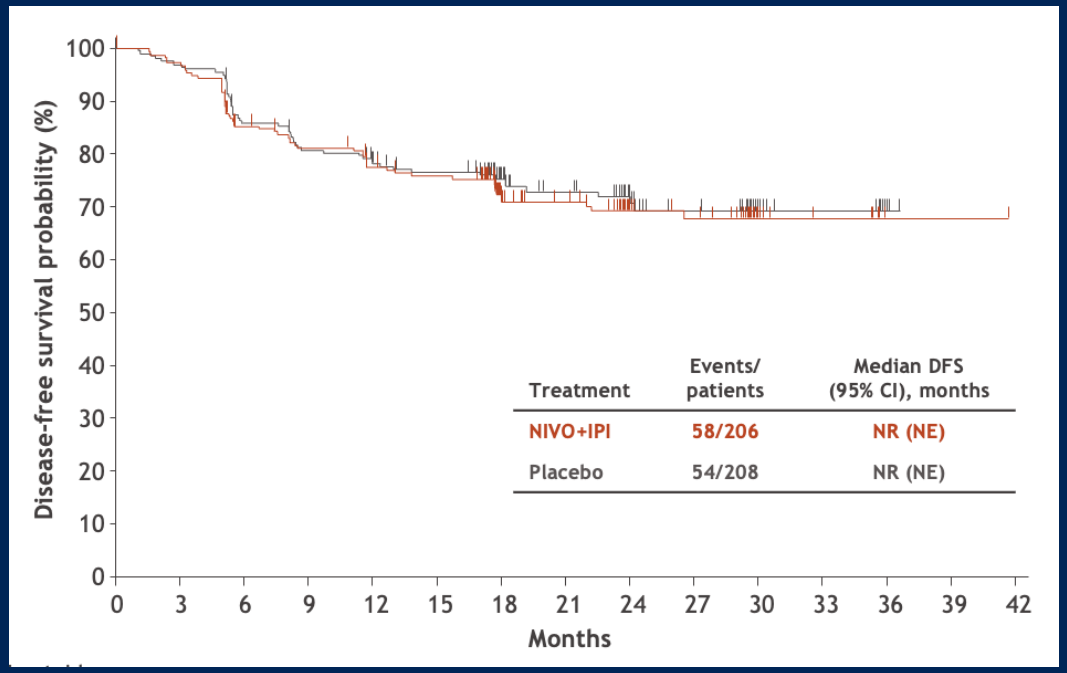
CheckMate 914 Is An Important Adjuvant Study

- Tests the activity of an active regimen (Ipi/Nivo)
- Evaluates the individual contribution of Nivolumab and Ipilimumab
- Explores shorter duration (6 months) of immunotherapy
- Complements PROSPER data (peri-operative nivolumab)

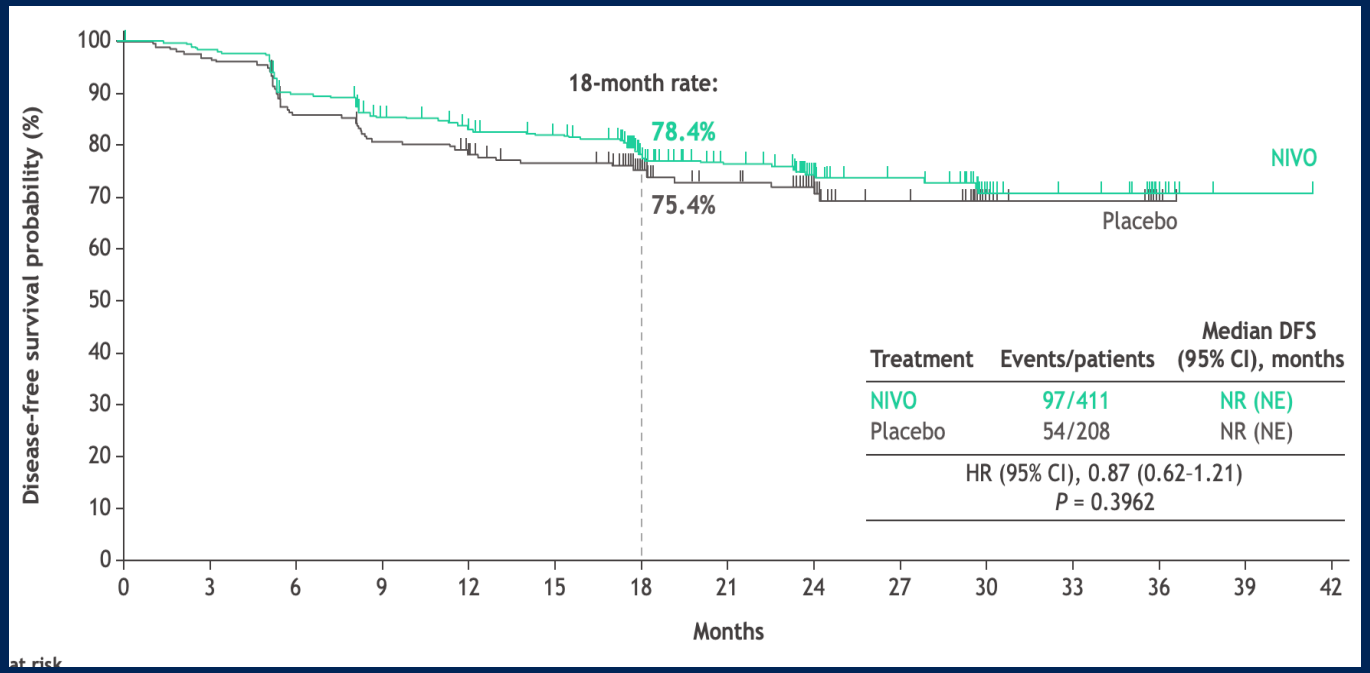


CheckMate 914: PART A and B

- Clear lack of benefit with shorter duration of nivolumab +- ipilimumab
- 2-Year DFS with control ~73% (*vs.* ~68% DFS KN564)
- Ipi/nivo: Increase G3/4 toxicity / HD steroids / 25% ≤ 3 months tx cycles and D/C rates – impact on efficacy of most active regimen?

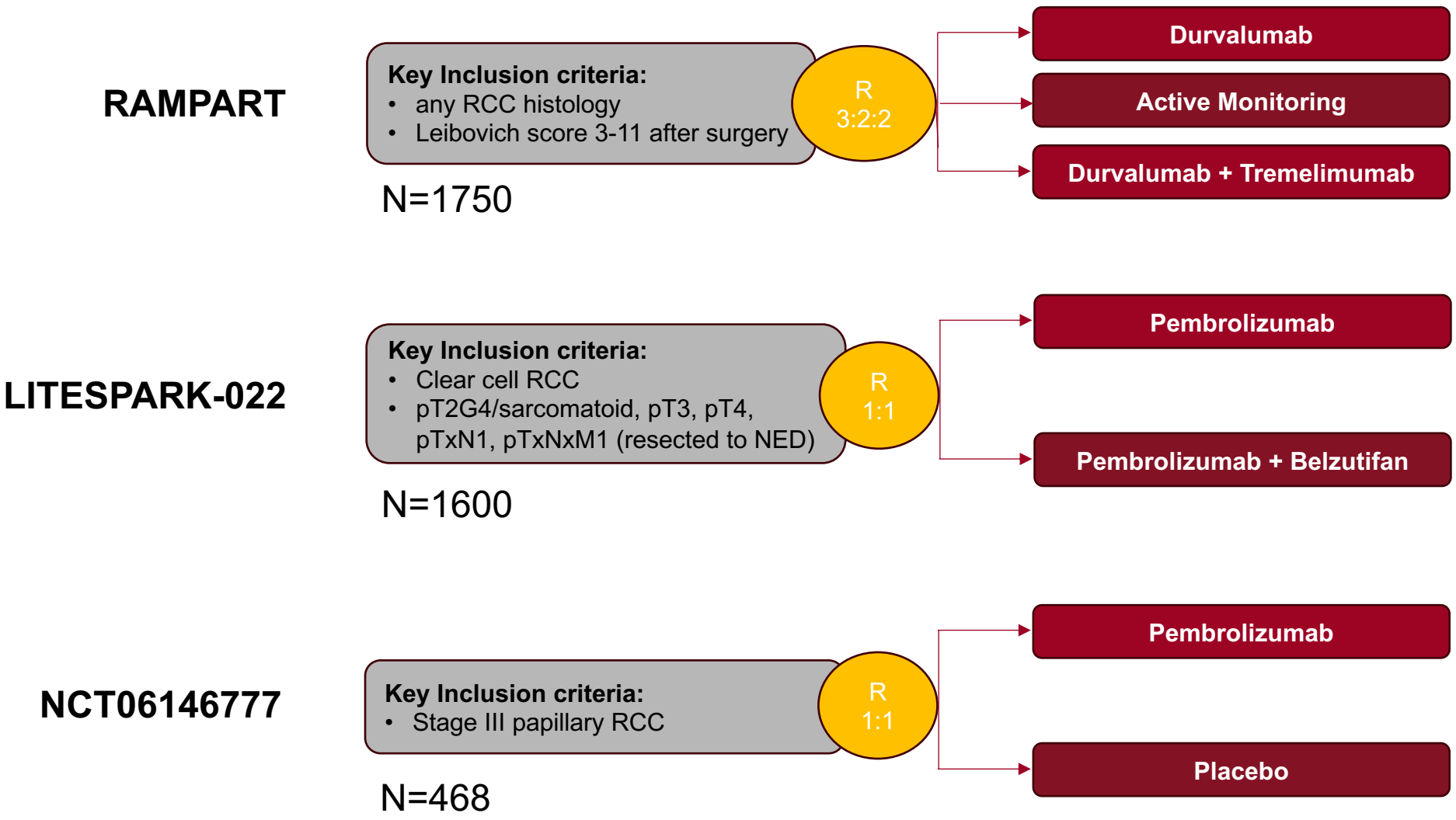


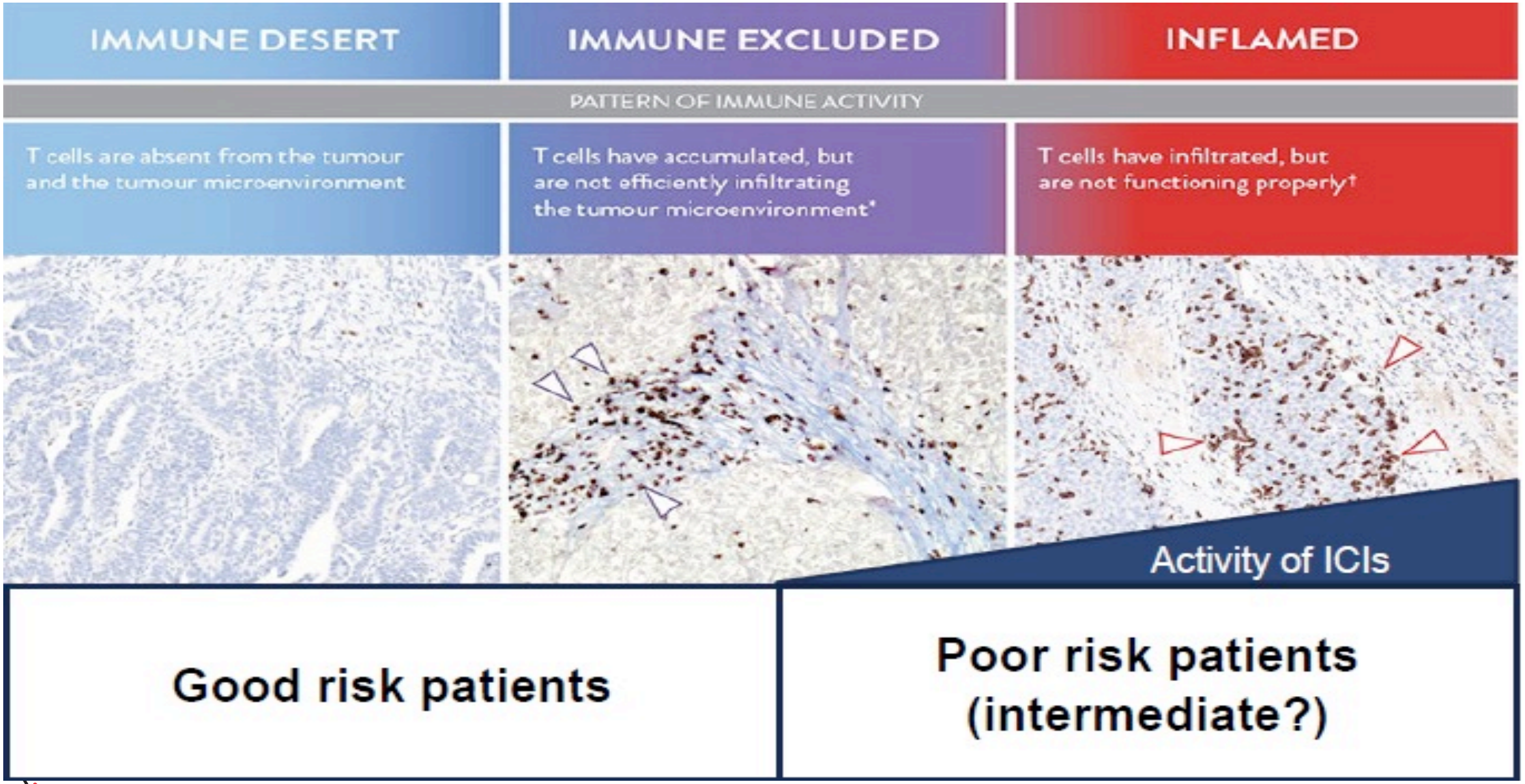
Checkmate 914 (Part B), Motzer et al, Lancet 2023



Checkmate 914 (Part B), Motzer et al, ASCO GU 2024

Upcoming Trials in the Adjuvant Space: High-risk RCC




IMMUNE DESERT
IMMUNE EXCLUDED
INFLAMED
PATTERN OF IMMUNE ACTIVITY
T cells are absent from the tumour and the tumour microenvironment
T cells have accumulated, but are not efficiently infiltrating the tumour microenvironment*
T cells have infiltrated, but are not functioning properly†
Activity of ICIs
Good risk patients
Poor risk patients (intermediate?)

Summary Statements

- Adjuvant Pembrolizumab is SOC for pts with high-risk cc RCC

- SOC entering front-line
  - Good-risk disease: observation vs. treatment
  - Sarcomatoid Hx = Ipi/Nivo
  - Long natural history = Ipi/Nivo
  - Need for rapid response and PFS = TKI/IO (Axi/Pembro vs. Cabo/Nivo vs. Len/Pembro

- Responses greater for TKI/IO but durability and tail of the curve favor IO/IO

- Newer trials including biomarkers/novel agents (HIF inhibitors and novel IOs)


Seidman Cancer Center
University Hospitals