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Updates in Kidney and Bladder Cancers

- Renal Cell Carcinoma

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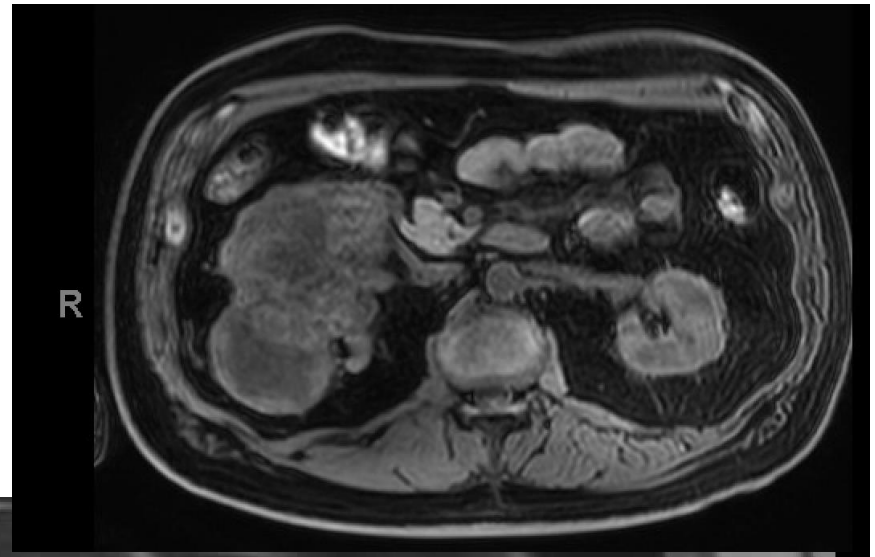
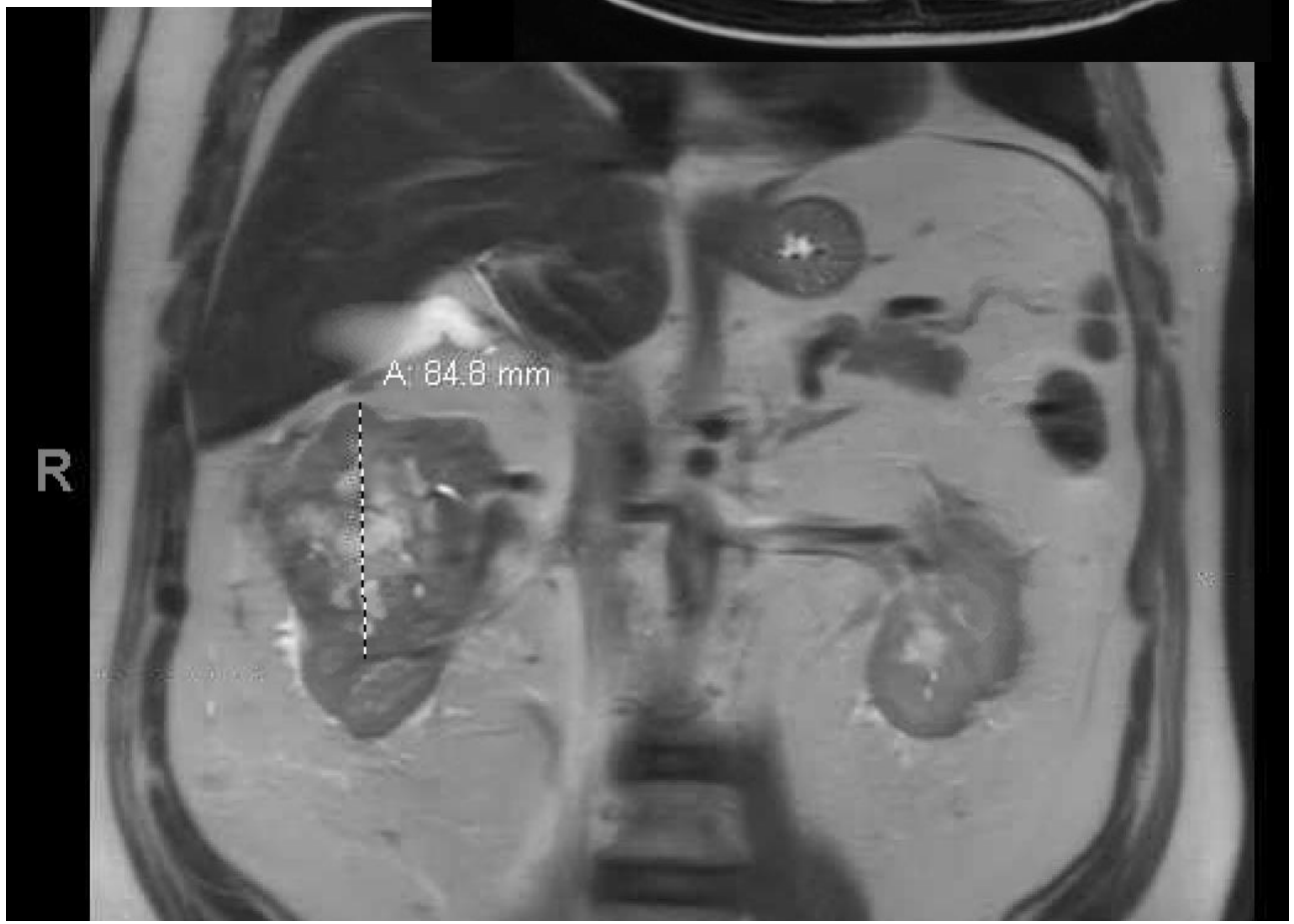
Clinical Case:

70-year-old man presented with gross hematuria

- CT shows 13cm R renal mass with hemorrhage into ureter and bladder
- R radical nephrectomy: pathology showed clear cell RCC, 11cm, extensive involvement of renal vein, renal sinus fat, rhabdoid and focal sarcomatoid differentiation, multifocal tumor necrosis; margins negative pT3aNxMx



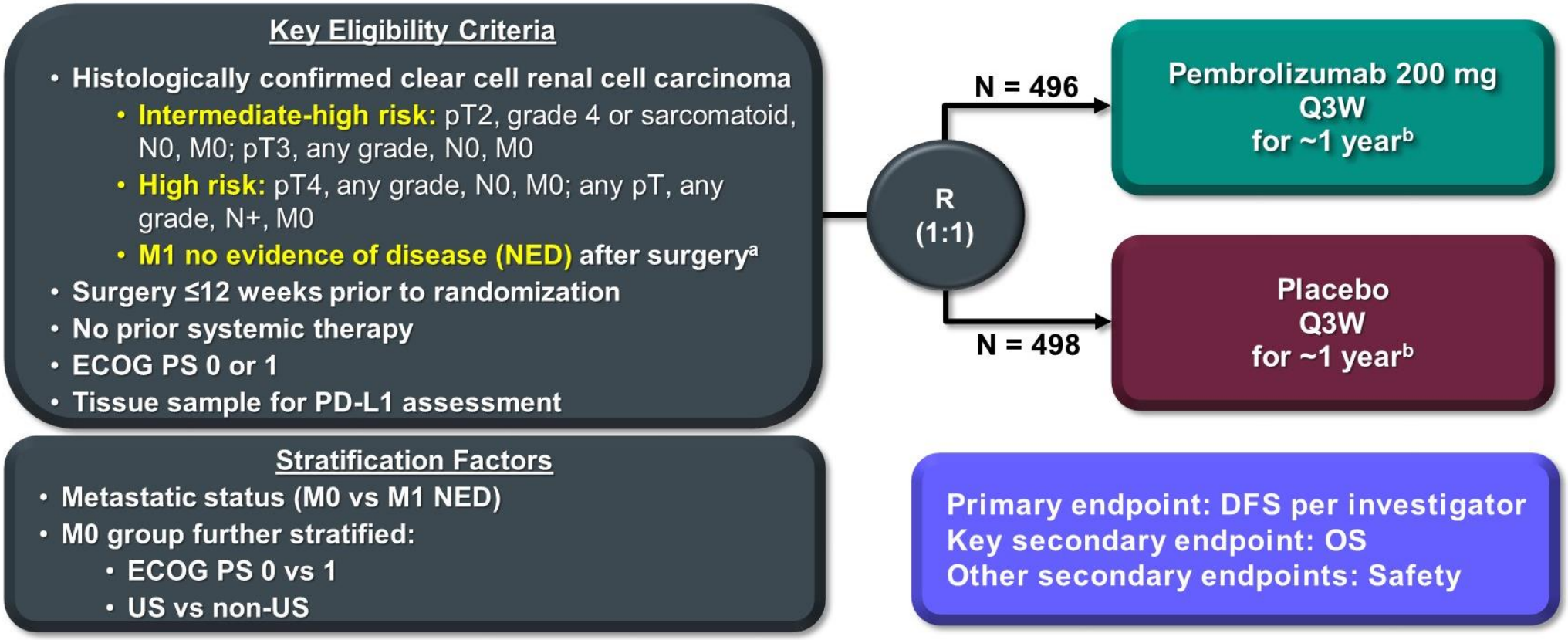


Different Models Predict Risk of Recurrence

- ~50% of post-nephrectomy patients with high-risk features will eventually recur;
- Factors such as disease stage, size, nuclear grade, regional LN involvement are associated with disease recurrence and survival.

Model	RCC subtype	Factors
Kattan, Kattan M et al, J Urol 2001	Any	TNM, tumor size, histology, symptoms
SSIGN/Mayo, Frank I et al, J Urol 2002	Clear cell	TNM, tumor size, grade, tumor necrosis
Leibovich, Leibovich et al, Cancer 2003	Clear cell	TNM, N+, size, grade, tumor necrosis
UCLA/UISS, Patard JJ et al, JCO 2004	Any	TNM, grade, ECOG PS
MSKCC, Sorbellini et al, J Urol 2005	Clear cell	TNM, tumor size, grade, tumor necrosis, vascular invasion, symptoms
Karakiewicz, Karakiewicz et al, JCO 2007	Any	TNM, tumor size, grade, histology, age, symptoms
GRANT, Buti S et al, ESMO 2017	Any	Grade, age, Nodes, tumor size
VENUSS, Klatte T et al, BMC Med 2019	Papillary	TNM, Venous tumor thrombus, grade, size

KEYNOTE-564 (NCT03142334) Study Design



- Median (range) time from randomization to cutoff: 30.1 (20.8–47.5) months

Q3W, every 3 weeks.
[a]M1 NED: no evidence of disease after primary tumor + soft tissue metastases completely resected ≤1 year from nephrectomy; [b]≤17 cycles of treatment were equivalent to ~1 year.
Data cutoff date: June 14, 2021.

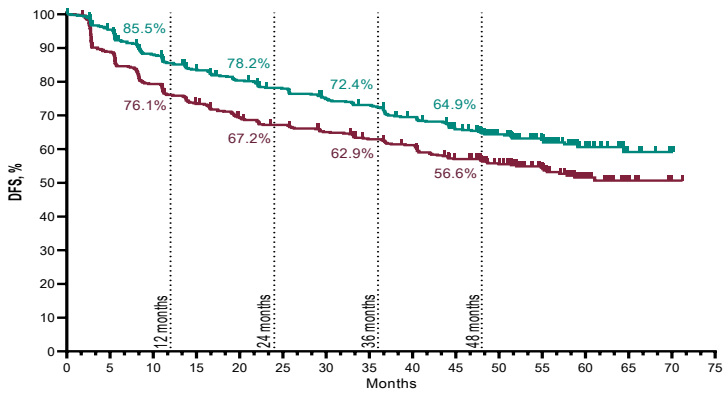
Choueiri TK, et al. *N Engl J Med*. 2021; 385(8):683-694.
Powles T, et al. *Lancet Oncol*. 2022;23(9):1133-1144.

KEYNOTE-564 DFS & OS benefit Not By Chance!

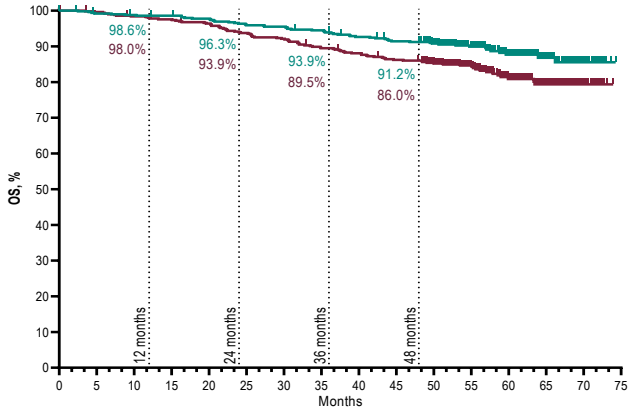
	June 2021	Sep 2022	Jan 2024
Analysis	1st	2nd	3rd
Median follow up, months	24.1	30	57.2
Disease free survival (HR, CI 95%), p-value	0.68 *P=0.0010*	0.63 *P<0.0001*	0.72 NE
DFS events	109 vs 151	114 vs 169	174 vs 224
Overall survival (HR, CI 95%)	0.54 *P=0.0164 (int)*	0.52 *P=0.0048 (int)*	0.62 ***P=0.002****
OS events	18 vs 33	23 vs 43	55 vs 86

- 1st ICI to improve DFS in RCC 1st ICI to improve OS in any GU tumor

Disease-free survival



Overall survival



Up to 0.2% chance of **Being Struck by Lightning in a Lifetime in certain regions**

Source: ChatGPT

Adjuvant RCC ICI Phase 3 Trials

Small numbers, subgroup analysis

	PROSPER (Perioperative Nivo)	IMmotion010 (Atezo)	CheckMate 914 Part A (Ipi/Nivo)	CheckMate 914 Part B (Nivo)	KEYNOTE-564 (Pembro)
Median follow-up	16 months	45 months	37 months	27 months	57.2 months
ICI Sample Size	404	390	405	411	496
Histology Clear cell Non-Clear Cell	 78% 22%	 93% 7%+	 100% pred. clear cell 0%	 100% pred. clear cell 0%	 100% 0%
Stage - M1 NED	~3% (HR 0.85)	14% (HR 0.93)	0%	0%	6% (HR 0.40)
Sarcomatoid	8% (HR 0.85)	9% (HR 0.77)	5% (HR 0.29)	7% (HR 0.42)	11% (HR 0.63)
PDL1+[ϵ]	NA	59% (HR 0.83)	14% (HR 0.40)	11% (HR 0.53)	74% (HR 0.68)
DFS^	HR 0.97	HR 0.93	HR 0.92	HR 0.87	HR 0.72
OS	NR	HR 0.97	NM	NR	HR 0.62

*includes *pT2 (grade 4 tumor or sarcomatoid) or pT3 (any grade), N0, M0;* **includes *pT4 or N+;* ^From randomization to local, distant recurrence or death; + RCC with sarcomatoid features; Recurrence Free Survival: Patients who did not get surgery or were not disease-free post surgery were considered as an event at Day 1; [ϵ]different assays; NM: not mature; NR: not reported

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Allaf et al, ESMO 2022; Pal et al, Lancet 2022; Motzer et al, Lancet 2023; Motzer et al, ASCO GU 2024; 2022 Choueiri et al, NEJM 2021

My Approach For ICI-Eligible Patients

Free *online* calculators:

https://www.mdcalc.com/calc/3009/ucla-integrated-staging-system-uiss-renal-cell-carcinoma-rcc

https://www.mskcc.org/cancer-care/types/kidney/prediction-tools

https://cancernomograms.com/nomograms/492

Pick your own risk calculator!

Nephrectomy

pathology

Clear cell

Non-Clear cell

M0 disease

M0 disease

M1 disease – amenable to resection/ local therapy

Risk Score Calculator

Treat M1

Observation

High risk

Intermediate risk

Low risk

Stage II G4

≤ Stage II G3

?

- Sarcomatoid
- PD-L1?*

No

Yes

consider

Pembrolizumab

Recurrence

*commonly PD-L1 staining not ordered in this setting

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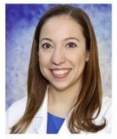
ASCO Daily News

Clinical News From the American Society of Clinical Oncology

Using Clinical Characteristics to Guide Treatment of Recurrent RCC After Adjuvant Pembrolizumab



Bourlon et al, 2024

The Latest Evidence-based Guidance for the Management of First-line Metastatic RCC

University Hospitals
Seidman Cancer Center

SCHOOL OF MEDICINE
CASE WESTERN RESERVE UNIVERSITY

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Front Line Treatment Options in Metastatic RCC

IO-IO

- Nivolumab + Ipilimumab

IO-VEGF

- Pembrolizumab + Axitinib
- Avelumab + Axitinib
- Nivolumab + Cabozantinib
- Pembrolizumab + Lenvatinib

VEGF

- Cabozantinib
- Sunitinib
- Pazopanib

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Recent Clinical Trials In Frist Line RCC

Inclusion criteria:
- ccRCC
- Measurable metastatic disease by RECIST criteria
- No prior systematic treatments
- Good performance status
- Archival tissue available

Stratification factors:
- IMDC criteria (favorable, intermediate, poor)
- Region (US vs outside US)
- Performance status

R

Sunitinib
Sunitinib, 50 mg orally once daily
4 weeks on, 2 weeks off

Treatment Population

CheckMate 214
Ipilimumab IV + nivolumab IV

KEYNOTE-426
Axitinib oral + pembrolizumab IV

JAVELIN Renal 101
Axitinib oral + avelumab IV

IMmotion 151
Atezolizumab IV + bevacizumab IV

CheckMate 9ER
Nivolumab IV + cabozantinib oral

KEYNOTE-581/CLEAR
Lenvatinib oral + everolimus oral
Lenvatinib oral + pembrolizumab IV

Primary endpoints:
- OS
- PFS

Secondary endpoints:
- ORR
- Duration of response (DoR)
- PROs
- Safety

Treat until disease progression or unacceptable toxicity

Frontline Immunotherapy Combination Studies

Baseline Characteristics

Variable		Nivolumab + Ipilimumab CheckMate-214 n=1096	Pembrolizumab + Axitinib Keynote 426 n=861	Avelumab + Axitinib Javelin 101 n=886	Nivolumab + Cabozantinib CheckMate-9ER n=651	Pembrolizumab + Lenvatinib n=1096
IMDC Risk Group	Favorable	23%	33%	21%	23%	32%
	Intermediate	61%	56%	62%	58%	54%
	Poor	17%	13%	16%	19%	10%
Previous Nephrectomy		81%	83%	80%	69%	73%
PD-L1 Expression ≥1%		24% (Dako PD-L1 28-8; Tumor)	60% (Agilent Tech PD-L1 22C3; CPS)	63% (Ventana PD-L1 SP263; Immune)	25% (Dako PD-L1 28-8; Tumor)	31% (Agilent Tech PD-L1 22C3; CPS)
Primary Endpoint		ORR, PFS, OS in Int/Poor (IRC)	OS, PFS (IRC)	OS, PFS in PD-L1+ (IRC)	PFS (IRC)	PFS (IRC)

Motzer RJ, et al. *N Engl J Med*. 2018;378(14):1277-1290.
Rini BI, et al. *N Engl J Med*. 2019;380(12):1116-1127.
Motzer RJ, et al. *N Engl J Med*. 2019;380(12):1103-1115.
MotzerRJ, et al. *N Engl J Med*. 2021;384(14):1289-1300.

IMDC=International Metastatic RCC Database Consortium; PD-L1=Programmed Death Ligand 1; CPS=Combined positive score (TC+IC positive/TC all); ORR=Objective response rate; PFS=Progression-free survival; OS=Overall survival; Int=Intermediate; IRC=Independent review committee.

Summary of Select Immunotherapy Combination Trials

	Nivolumab + Ipilimumab CheckMate-214 n=1096	Pembrolizumab + Axitinib Keynote 426 n=861	Nivolumab + Cabozantinib CheckMate-9ER n=651	Pembrolizumab + Lenvatinib Clear n=1096
Follow-up, mo	67.7 (median)	42.8 (median)	32.9 (median)	33.7 (median)
Median PFS, mo	12.3	15.7	16.6	23.9
PFS HR	0.86	0.68	0.56	0.39
Median OS, mo	55.7	45.7	37.7	NR
12-month OS, %	83	90	86	90
24-month OS, %	71	74	70	79
OS HR	0.72	0.73	0.70	0.72
ORR, %	39	60	56	71
CR, %	12	10	12	16
PD, %	18	11	6	3

Motzer RJ, et al. *N Engl J Med*. 2018;378(14):1277-1290.
Rini BI, et al. *N Engl J Med*. 2019;380(12):1116-1127.
Motzer RJ, et al. *N Engl J Med*. 2019;380(12):1103-1115.
MotzerRJ, et al. *N Engl J Med*. 2021;384(14):1289-1300.

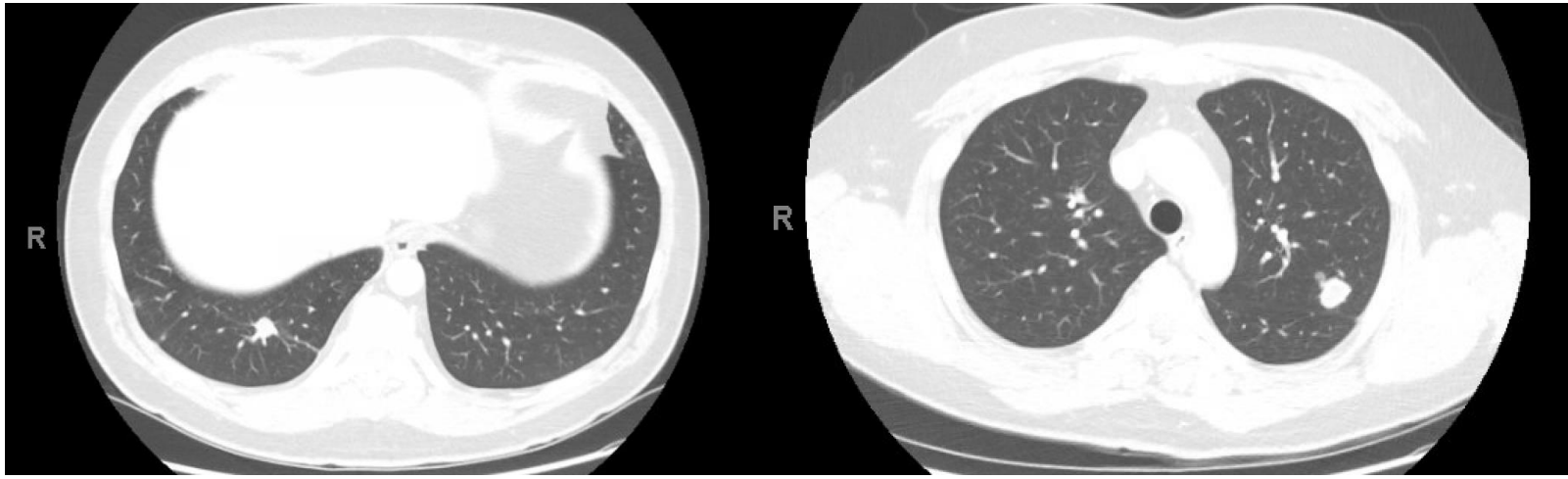
Not Intended for Direct Comparison

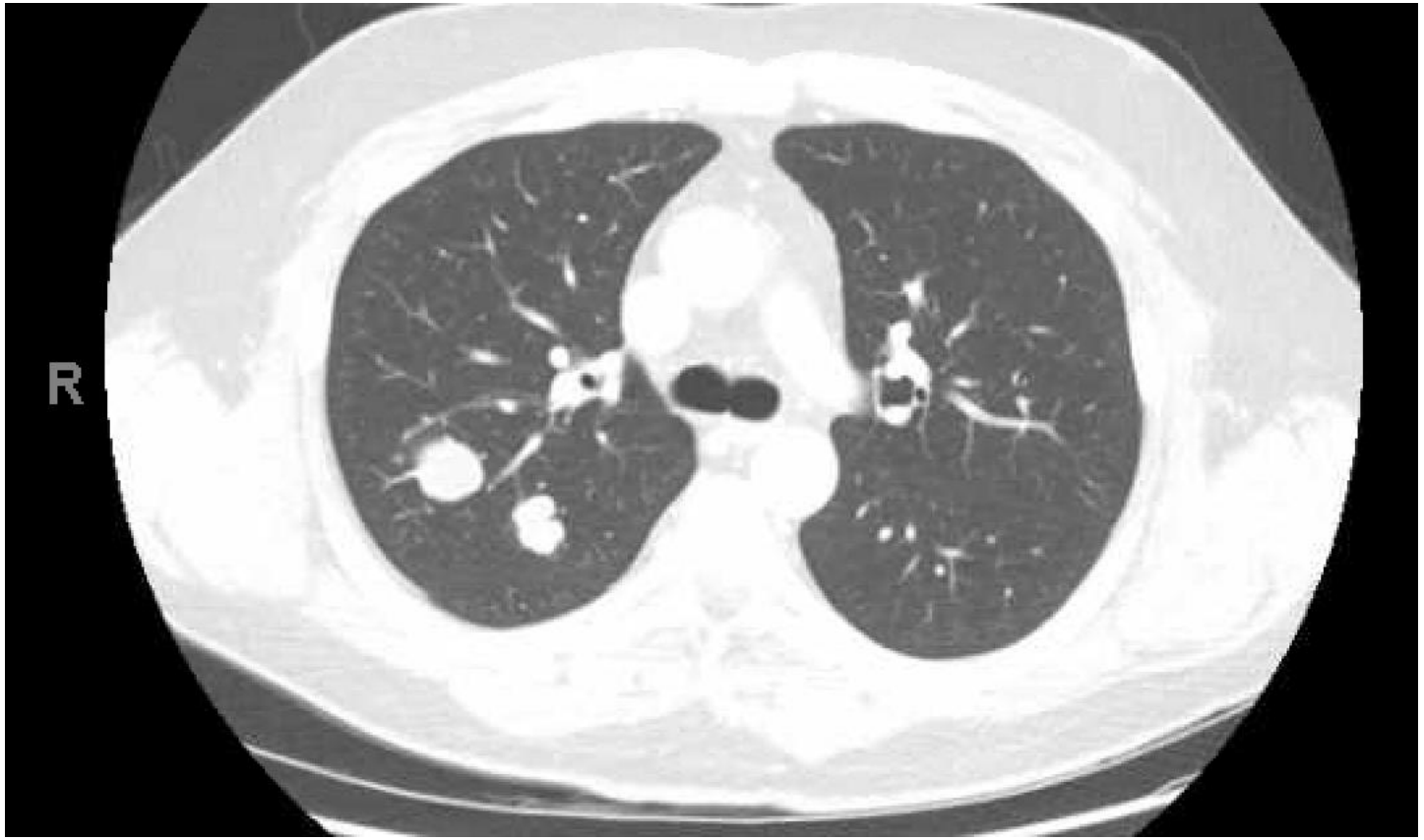
Mo=months; PFS=Progression-free survival; HR=Hazard ratio; ORR=Objective response rate; CR=Complete response rate; PD=Progressive disease rate; TTR=Time to response; DOR=Duration of response.

Back to our Case…

70-year-old man presented with gross hematuria

- CT shows 13cm R renal mass with hemorrhage into ureter and bladder
- R nephrectomy: pathology showing clear cell RCC, 11cm, extensive involvement of renal vein, renal sinus fat, rhabdoid and focal sarcomatoid differentiation, multifocal tumor necrosis; margins negative pT3aNxMx
- Opted for surveillance
- 9 months later, on surveillance scans developed multifocal bilateral pulmonary nodules
- Hgb 9.1, Ca, neutrophils, platelets normal, ECOG PS 1
- Started ipilimumab/nivolumab





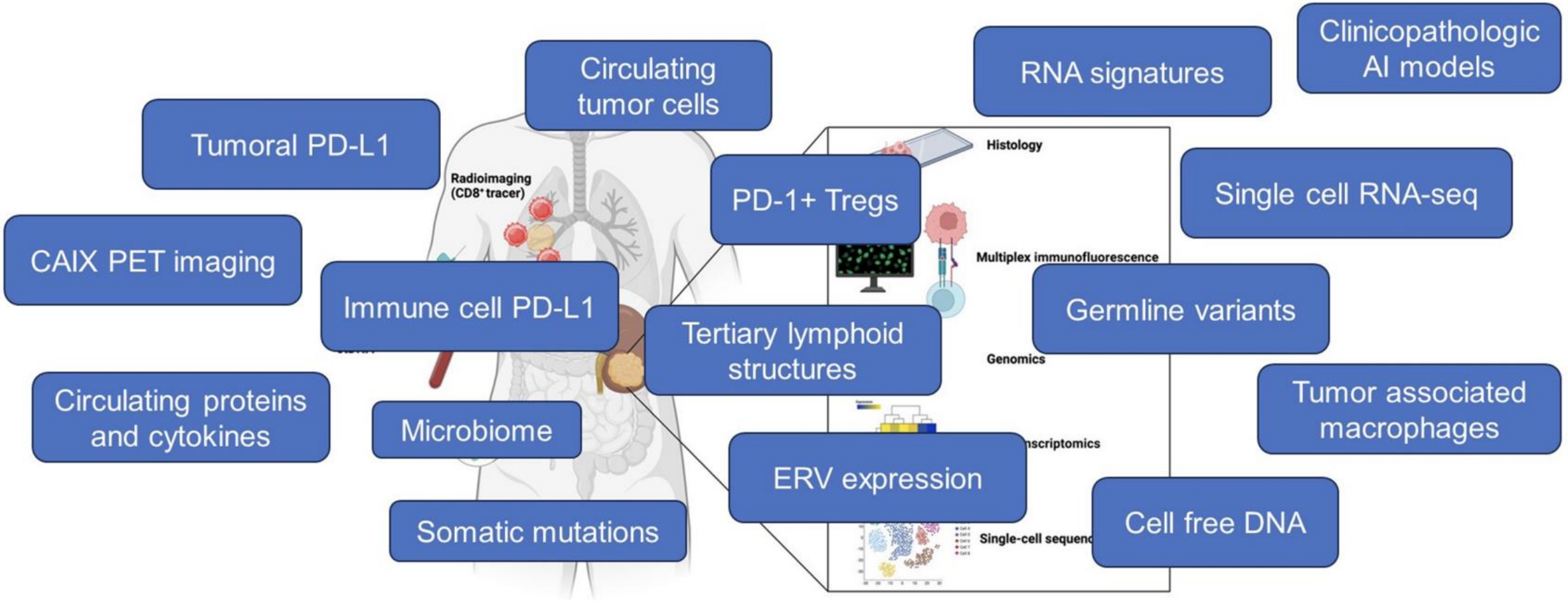
What about Toxicity?

	Nivolumab + Ipilimumab CheckMate-214 n=1096 Minimum Follow-Up 48 mo	Pembrolizumab + Axitinib Keynote 426 n=861 Minimum Follow-Up 23 mo	Nivolumab + Cabozantinib CheckMate-9ER n=651 Median Follow-Up 23.5 mo	Pembrolizumab + Lenvatinib Clear n=1096 Median Follow-Up 26.6 mo
TRAE Grade 3-5	48%	67%	62%	82%
TRAE leading to D/C (either/both drugs)	22.1%*	27.7%/6.5%#	23.4%/6.6%	29% pembrolizumab 26% lenvatinib 13% both
HD Corticosteroid	29%	27%	21%	Not reported
TR deaths, n (%)	8 (1.5%)	4 (0.9%)	1 (0.3%)	15 (4.2%)

Motzer RJ, et al. *N Engl J Med*. 2018;378(14):1277-1290.
Rini BI, et al. *N Engl J Med*. 2019;380(12):1116-1127.
Motzer RJ, et al. *N Engl J Med*. 2019;380(12):1103-1115.
MotzerRJ, et al. *N Engl J Med*. 2021;384(14):1289-1300.

*From minimum 42 month follow-up. #From median 16.6 month follow-up.
Mo=Months; TRAE=Treatment-related adverse events; D/C=Discontinue; HD=high dose; TR=Treatment-related.

Individualized Biomarker Therapy Remains Elusive In Clinical Practice



Saliby et al., *ASCO Educational Book* 2024; Meylan et al., *Immunity* 2022; Motzer et al., *Cancer Cell* 2020; Xu et al., *Clin Cancer Res* 2020; Smith et al., *J Clin Invest* 2018; Panda et al., *JCI Insight* 2018; Ficial et al., *Clin Cancer Res* 2021; Denize et al., *Clin Cancer Res* 2023; Rasmussen et al., *ASCO Educational Book* 2022; Nuzzo et al., *Nat Med* 2020; Shuch et al., *GU ASCO* (LBA 602) 2023; Rini et al., *Lancet Oncol* 2015; Brooks et al., *Eur Urol* 2014; Xu et al., *J Immunother Cancer* 2023; Morrissey et al., *JAMA Onc* 2015.

Second Line and Beyond

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National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2024
Kidney Cancer

NCCN Guidelines Inde
Table of Content
Discussio

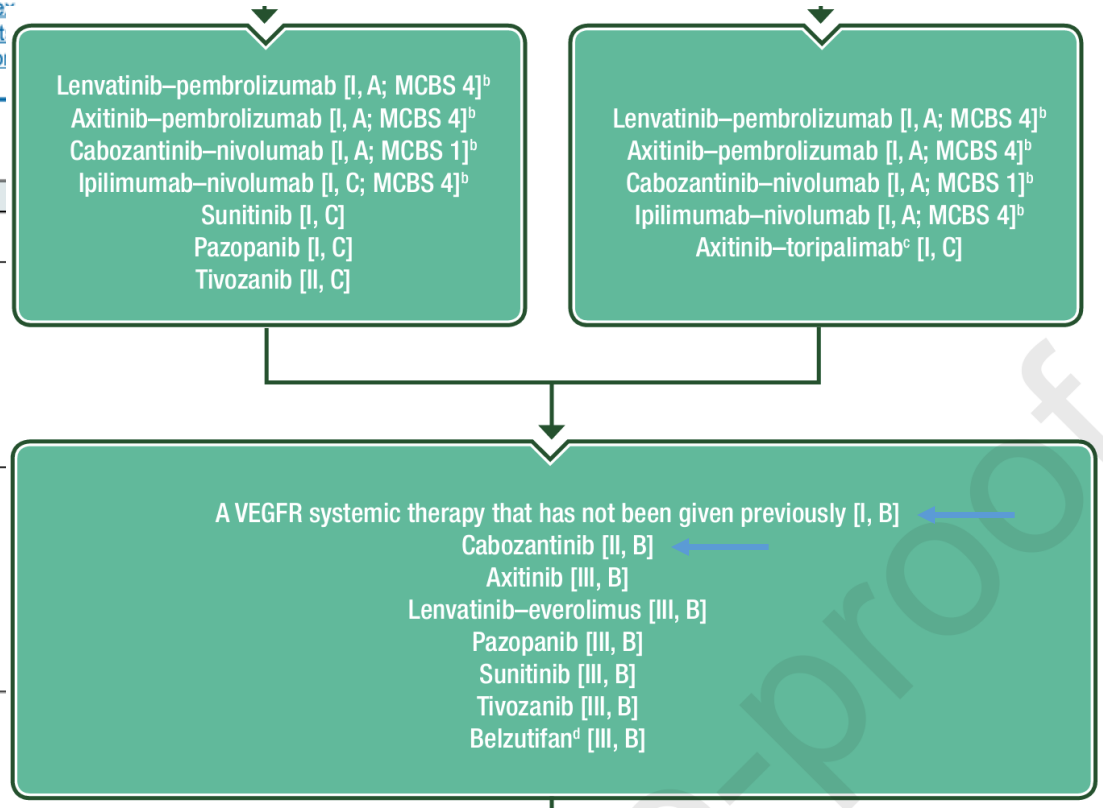
PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

SUBSEQUENT THERAPY FOR CLEAR CELL HISTOLOGY (IN ALPHABETICAL ORDER BY CATEGORY)

Immuno-oncology (IO) Therapy History Status	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
IO Therapy Naïve	• None	• Axitinib + pembrolizumab[b] • Cabozantinib • Cabozantinib + nivolumab[b] • Ipilimumab + nivolumab[b] • Lenvatinib + everolimus • Lenvatinib + pembrolizumab[b] • Nivolumab[b]	• Axitinib • Everolimus • Pazopanib • Sunitinib • Tivozanib[g] • Belzutifan (category 2B) • Bevacizumab[h] (category 2B) • High-dose IL-2 for selected patients[d] (category 2B) • Temsirolimus[e] (category 2B) • Axitinib + avelumab[b] (category 3)
Prior IO Therapy	• None	• Axitinib • Belzutifan[f] • Cabozantinib • Lenvatinib + everolimus • Tivozanib[g]	• Axitinib + pembrolizumab[b] • Cabozantinib + nivolumab[b] • Everolimus • Ipilimumab + nivolumab[b] • Lenvatinib + pembrolizumab[b] • Pazopanib • Sunitinib • Bevacizumab[h] (category 2B) • High-dose IL-2 for selected patients[d] (category 2B) • Temsirolimus[e] (category 2B) • Axitinib + avelumab[b] (category 3)

No salvage IO

[b] NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[d] Patients with excellent performance status and normal organ function.
[e] The poor risk model used in the global ARCC trial to direct treatment with temsirolimus included at least 3 of the following 6 predictors of short survival: <1 year from the time of diagnosis to start of systemic therapy, Karnofsky performance status score 60–70, hemoglobin <LLN, corrected calcium >10 mg/dL, LDH >1.5 times the ULN, and metastasis in multiple organs. Hudes G, et al. N Engl J Med 2007;356:2271-2281.
[f] This regimen is for patients that have received a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor and a vascular endothelial growth factor tyrosine kinase inhibitor (VEGF TKI).
[g] For patients who received ≥2 prior systemic therapies.
[h] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.



ESMO RCC Guidelines, 2024

* Belzutifan is only FDA-approved only for the treatment of VHL-associated RCC, CNS hemangioblastomas, or pNET not requiring immediate surgery.

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Is IO active after prior IO?

The role of NIVO + IPI (salvage/rescue)

	HCRN GU16-260 ASCO 2020	OMNIVORE ASCO 2020	FRACTION ASCO 2020	TITAN RCC ESMO 2019	Salvage Ipi/Nivo (JCO 2020)
N	123	83	46	207	45
Prior TKI	No	Yes	Yes	Yes	Yes
Timing	Nivo→Ipi	Nivo→Ipi	Nivo+Ipi	Nivo→Ipi	I/N after prior IO
Ipi doses	4	2	4	4	4
ORR	13%	4%	15%	12%	20%
CR	0%	0%	0%	3%	0%

Nivo+ipi combo untreated ccRCC ORR 42%, CR 11% (Checkmate 214)

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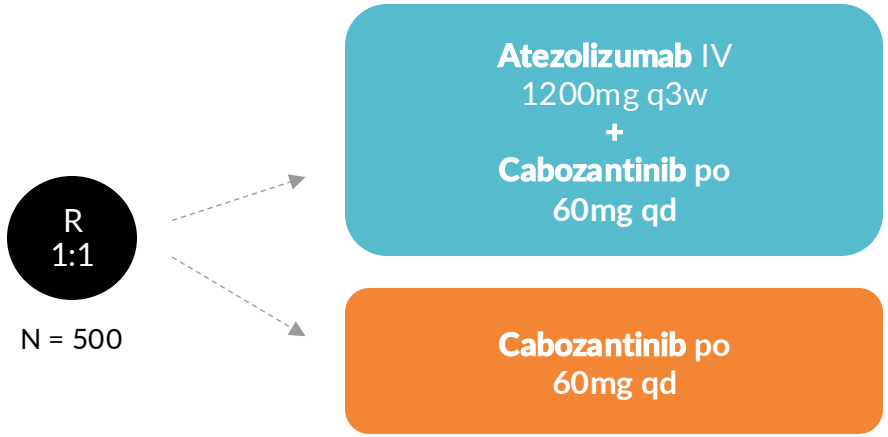
Salvage PD-L1 Inhibitor is not superior to TKI alone

CONTACT-03

- Histologically confirmed advanced, metastatic ccRCC or nccRCC
- Radiographic progression during or following ICI treatment



No crossover allowed

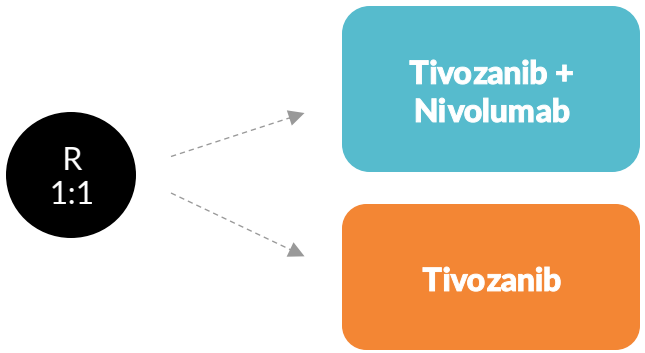
Negative Trial

Treatment until progression

- Primary endpoint: PFS, OS
- Secondary endpoint: PFS, ORR, DoR, Safety and Tolerability

TINIVO-2

- Histologically/cytologically confirmed recurrent/ metastatic RCC
- ECOG PS 0 or 1
- Progressed following immediate prior immunotherapy treatment in first or second line
- Stratified by IMDC and prior TKI



Negative Trial: ESMO 2024

Treatment until progression

- Primary endpoint: PFS
- Secondary endpoint: OS, ORR, DoR, Safety and Tolerability

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Summary Points

- The gold-standard for mRCC is an IO-based combination (TKI monotherapy is the exception, not the rule!)
- Primary renal tumors respond to systemic therapy with IO-based therapy (but less than metastatic sites)
- TKI is the current SOC (includes novel agents, ie tivozanib). IO rechallenge should NOT be offered to most patients (CONTACT-03 / TINIVO-2)
- The benefit of adjuvant IO seems associated with the higher risk of recurrence/progression

- Urothelial Carcinoma

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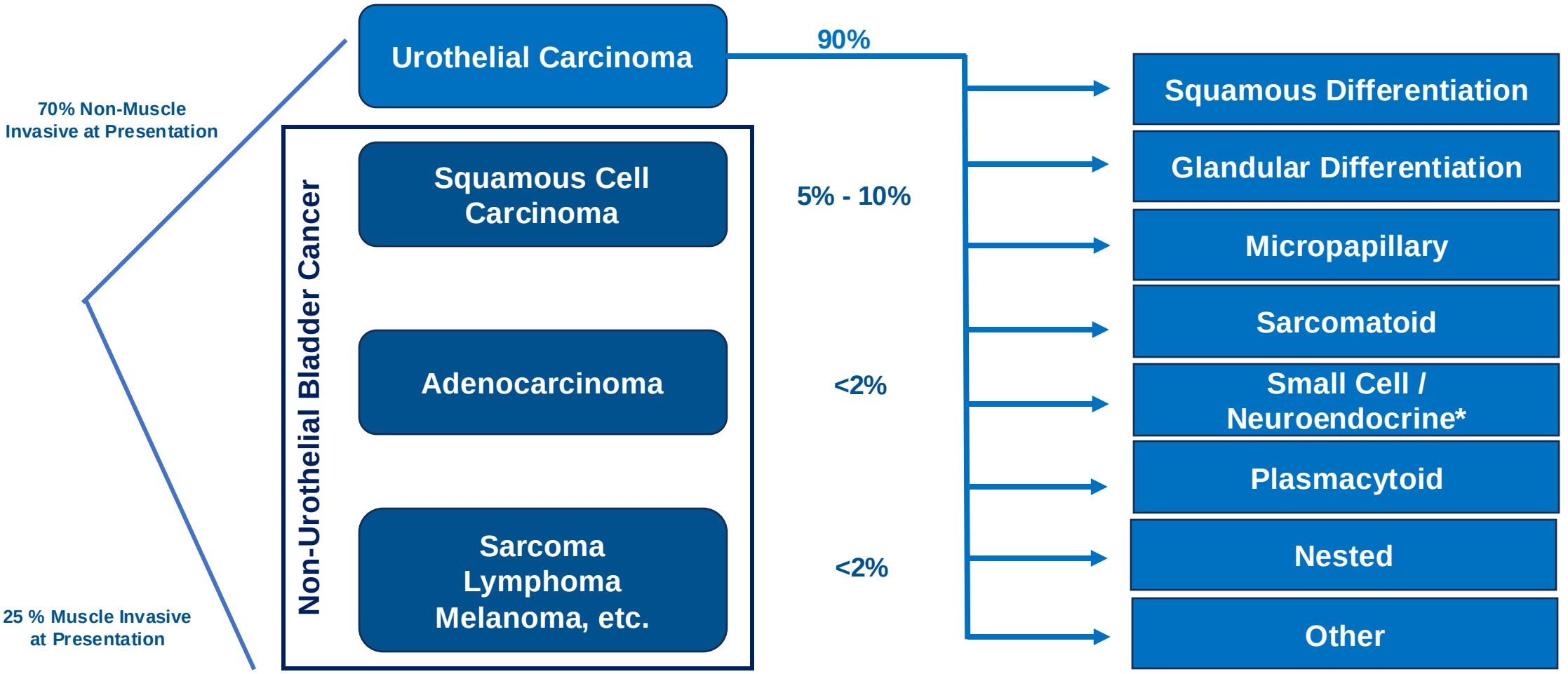
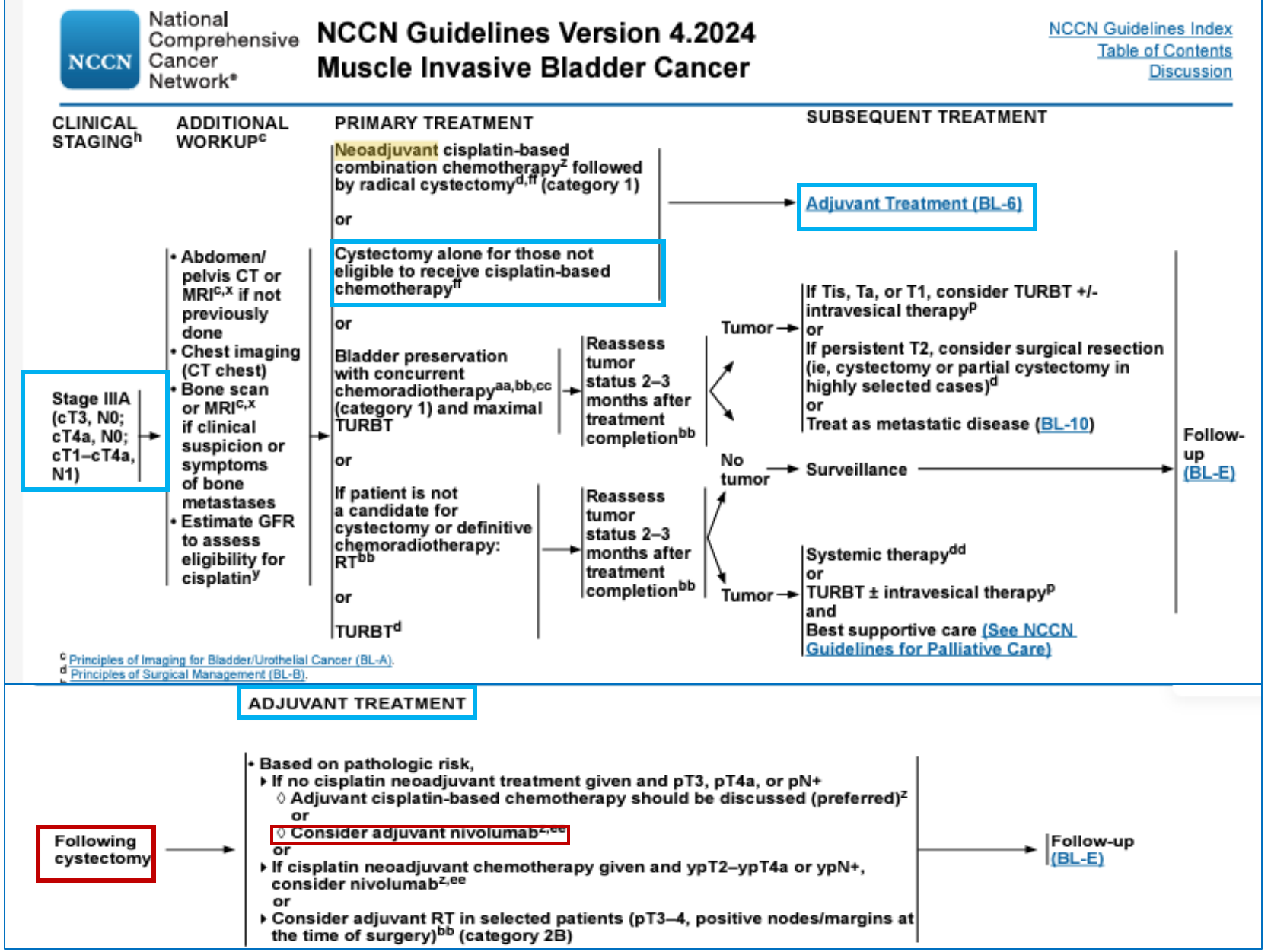
Subtype Histologies of Bladder Cancer



Black A, Black P. *Transl Cancer Res* 2020;9(10):6565-6575.



National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines. Bladder Cancer. (Version 4. 2024). https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1417

Phase III CheckMate 274 Clinical Trial: Study Design

Inclusion Criteria

- *Patients with urothelial carcinoma at high risk of recurrence after radical resection*:
- ypT2-ypT4a† or ypN+ † with prior neoadjuvant cisplatin-based chemotherapy
- pT3-pT4a† or pN+ † without prior neoadjuvant cisplatin-based chemotherapy and not eligible for or refused adjuvant cisplatin-based chemotherapy
- Radical resection within the last 120 days
- Disease-free status within 4 weeks prior to randomization
- ECOG PS 0-1
  - ECOG PS 2 if no neoadjuvant cisplatin-based chemotherapy and ineligible for adjuvant cisplatin-based chemotherapy
- No condition, which requires systemic immunosuppressant therapy, i.e., glucocorticoids, within two (2) weeks of treatment

Stratification Factors

- **PD-L1 status‡ [≥1% vs <1% or Indeterminate]**
- **Prior neoadjuvant cisplatin-based chemotherapy [Yes or No]**
- **Nodal status**
  - **N+ vs N0 or Nx with <10 nodes removed vs**
  - **N0 with ≥10 nodes removed**

N=709

R 1:1

Placebo IV Q2W

Nivolumab 240 mg IV Q2W

Treat Until Recurrence or Unacceptable Toxicity for a Maximum of One Year

Primary Endpoints

- **Investigator Assessed Disease-Free Survival**
  - **In all randomized patients**
  - **In patients with PD-L1 ≥1%**

Key Secondary Endpoints

- **Overall Survival**
- **Disease Specific Survival**
- **Non-Urothelial Disease-Free Survival**

Disease free-survival (DFS) was defined as the time to first recurrence, i.e., local urothelial tract, local non-urothelial tract, or distant metastasis, or death.

- Minimum follow-up time in all randomized patients was 5.9 months.
- Median follow-up time in all randomized patients was 20.9 months for nivolumab and 19.5 months for placebo.

Bajorin DF, et al. *N Engl J Med*. 2021;384(22):2102-2114.

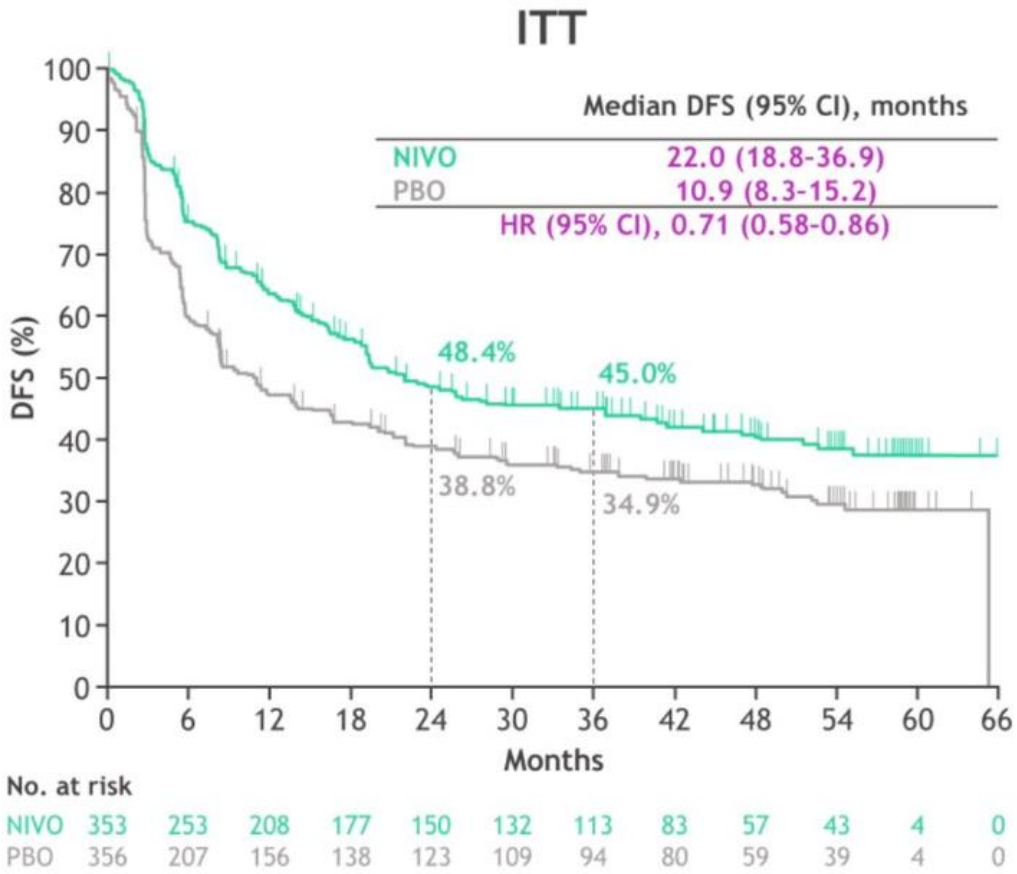
CheckMate 274 Clinical Trial: Baseline Characteristics of Interest

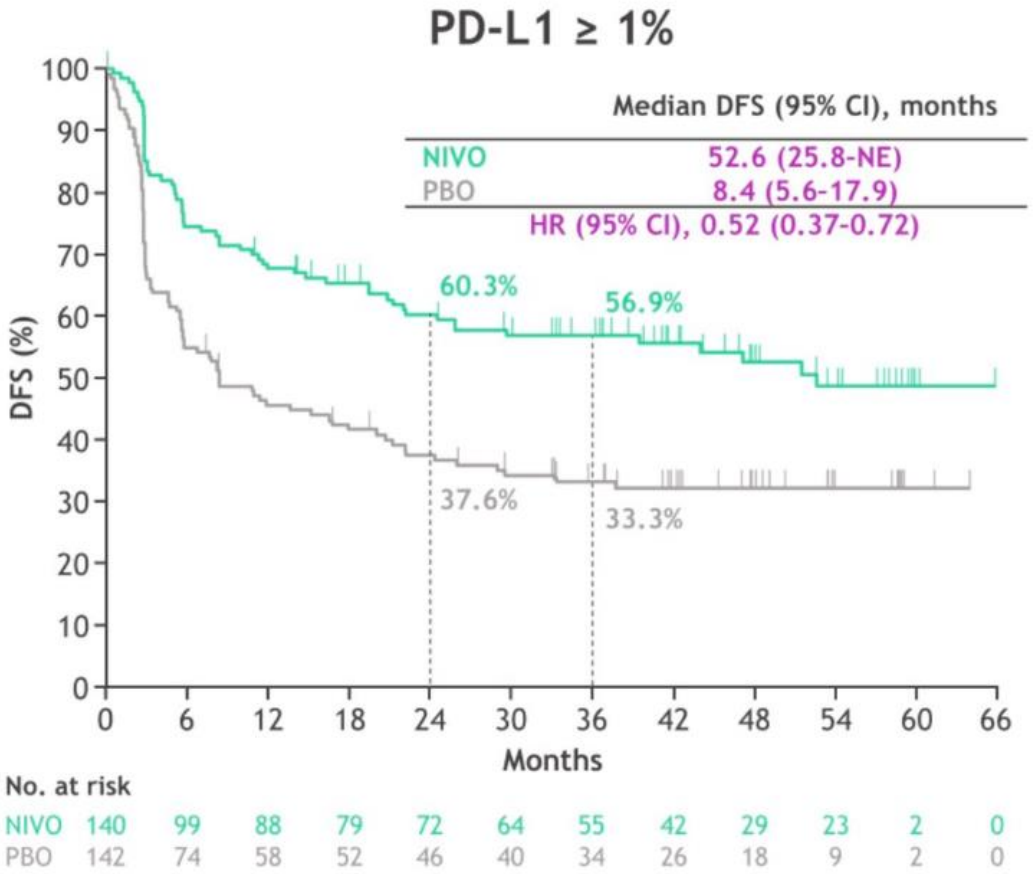
Characteristic	Nivolumab (n=355)	Placebo (n=356)
Mean Age, Years (range), n (%)	65.3 (30-92)	65.9 (42-88)
• <65 Years	155 (43.9)	136 (38.2)
• ≥65 Years	198 (56.1)	220 (61.8)
Sex, n (%)		
• Male	265 (75.1)	225 (77.2)
• Female	88 (24.9)	81 (22.8)
ECOG PS Score, n (%)‡		
• 0	224 (63.5)	121 (62.1)
• 1	122 (34.6)	125 (35.1)
• 2	7 (2.0)	9 (2.5)
• Not Reported	0	1 (0.3)
Tumor Origin at Initial Diagnosis, n (%)		
• Urinary Bladder	279 (79.0)	281 (78.9)
• Renal Pelvis	44 (12.5)	52 (14.6)
• Ureter	30 (8.5)	23 (6.5)
Time From Initial Diagnosis to Randomization, n (%)		
• <1 Year	325 (92.1)	324 (91.0)
• ≥1 Year	28 (7.9)	32 (9.0)
PD-L1 Expression Level >1% by IVRS, n (%)	140 (39.7)	142 (39.9)
Previous Neoadjuvant Cisplatin Therapy, n (%)	153 (43.3)	155 (43.5)

Characteristic	Nivolumab (n=355)	Placebo (n=356)
Pathological Tumor Stage and Nodal Status at Resection, n (%)		
• pT2N-	25 (7.1)	29 (8.1)
• pT3, 4N-	158 (44.8)	159 (44.7)
• pT0-4N1	71 (20.1)	72 (20.2)
• pT0-4N2,3	96 (27.2)	96 (27.0)
• pTisN-	1 (0.3)	0
• Not Reported	2 (0.6)	0
Pathological Tumor Stage at Resection , n (%)¶		
• pTx	5 (1.4)	0
• pT0	5 (1.4)	7 (2.0)
• pTis	4 (1.1)	3 (0.8)
• pT1	13 (3.7)	14 (3.9)
• pT2	62 (17.6)	65 (18.3)
• pT3	206 (58.4)	204 (57.3)
• pT4a	57 (16.1)	62 (17.4)
• Not Reported	1 (0.3)	1 (0.3)
Nodal Status at Resection, n (%)		
• N0 or NX with <10 Nodes Removed	94 (26.6)	99 (27.8)
• N0 with ≥10 Nodes Removed	91 (25.8)	88 (24.7)
• N1	71 (20.1)	72 (20.2)
• N2	84 (23.8)	76 (21.3)
• N3	12 (3.4)	20 (5.6)
• Not Reported	1 (0.3)	1 (0.3)

Bajorin DF, et al. *N Engl J Med*. 2021;384(22):2102-2114.

CheckMate 274: Updated DFS
Median follow-up: 36.1 Months

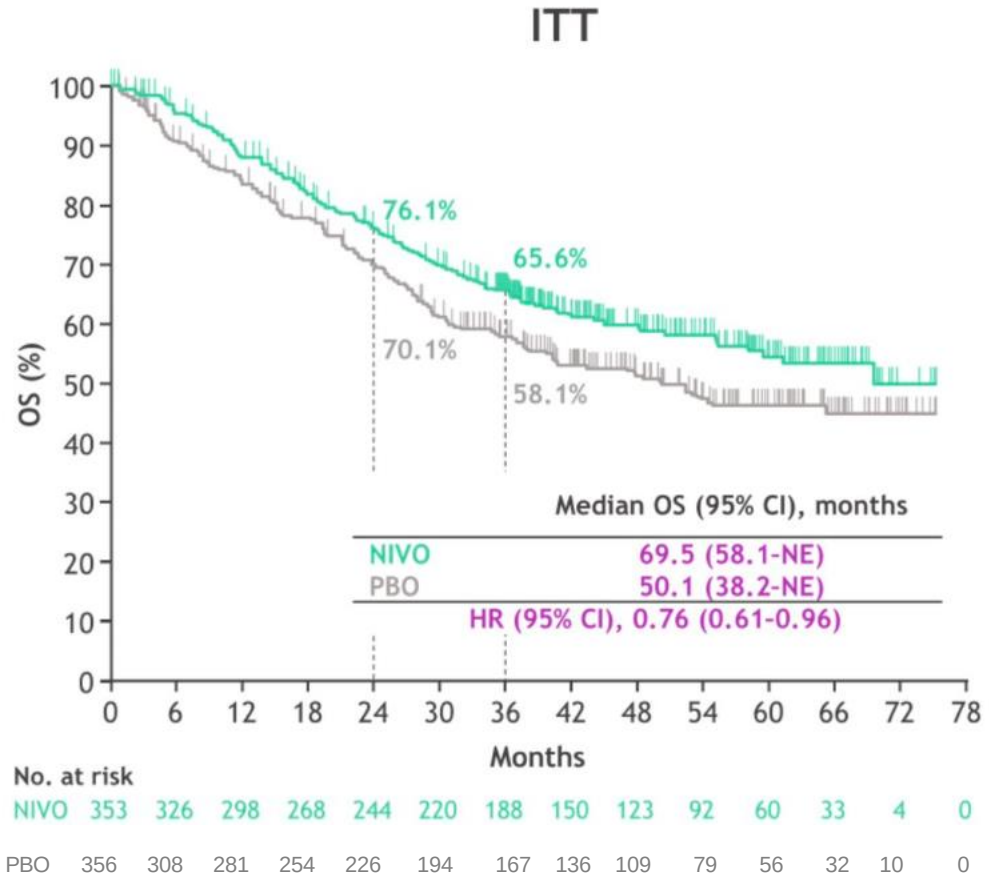


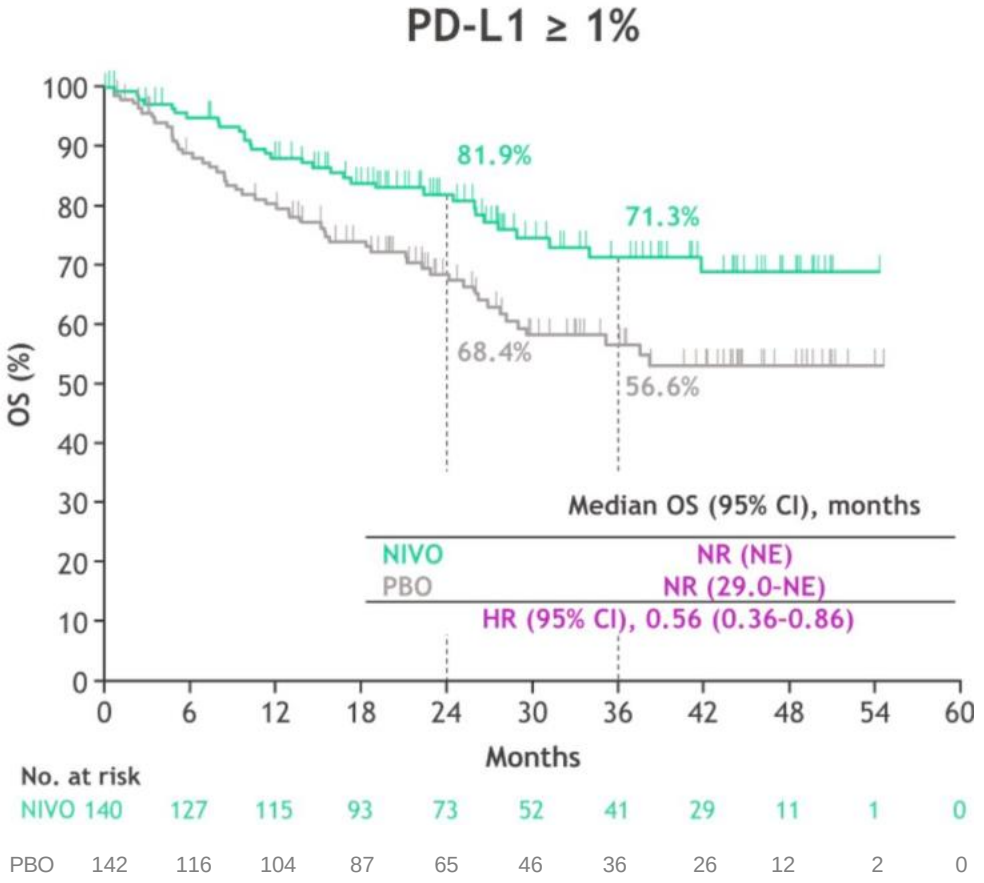


Galsky MD, et al. *J Clin Oncol*.
2024 Oct 11:JCO2400340. doi: 10.1200/JCO.24.00340.

DFS, disease-free survival

CheckMate 274: Interim OS
Median follow-up: 36.1 Months





Galsky MD, et al. *J Clin Oncol*.
2024 Oct 11:JCO2400340. doi: 10.1200/JCO.24.00340.

Phase III AMBASSADOR (A031501) Clinical Trial: Study Design

Key Eligibility Criteria

- *Muscle-invasive* urothelial carcinoma bladder, urethra, renal pelvis, ureter
- *Post-radical surgery*: cystectomy, nephrectomy, nephroureterectomy, or ureterectomy, ≥4 but ≤16 weeks
- *Post-neoadjuvant* chemotherapy and >pT2 and/or N+/or + margins OR
- *Cisplatin-ineligible or refusing* and >pT3 or pN+/or + margins

N = 702

R 1:1

- Pembrolizumab 200 mg IV Q3W x 1 Year (18 Cycles)
- Observation

Stratification Factors

- PD-L1 status*
- Neoadjuvant chemotherapy [Yes or No]
- Pathologic stage:
- pT2/3/4aN0
- pT4a N0
- pT4bNx or pT4b N1 - 3
- Positive surgical margins

Planned Enrollment: N = 734
Trial Closed Early Due to FDA Approval of Adjuvant Nivolumab for Muscle Invasive Urothelial Carcinoma (MIUC)

Dual Primary Endpoints

- Disease-Free Survival
- Overall Survival

Key Secondary Endpoints

- DFS/OS PD-L1 + or PD-L1-
- Safety

Correlative Endpoints

- DFS/OS ctDNA +/-
- DFS/OS Immune Gene Signatures
- DFS/OS Tumor Molecular Subtype
- DFS/OS TCR Clonality
- Quality of Life

*PD-L1 status was tested centrally and defined using the combined positive score: percentage of PD-L1-positive tumor cells and infiltrating immune cells relative to the total number of tumor cells. PD-L1 positive = CPS ≥10%, Dako Pd-L1 immunohistochemistry 22C3 pharmDx assay.
DFS, disease-free survival, defined as new muscular-invasive urothelial carcinoma (MIUC), metastatic disease, or death without recurrence; OS, overall survival

NCT05092958

Apolo AB, et al. *J Clin Oncol.* 2024;42(4 Suppl):LBA531.

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AMBASSADOR (A031501) Clinical Trial: Baseline Characteristics of Interest

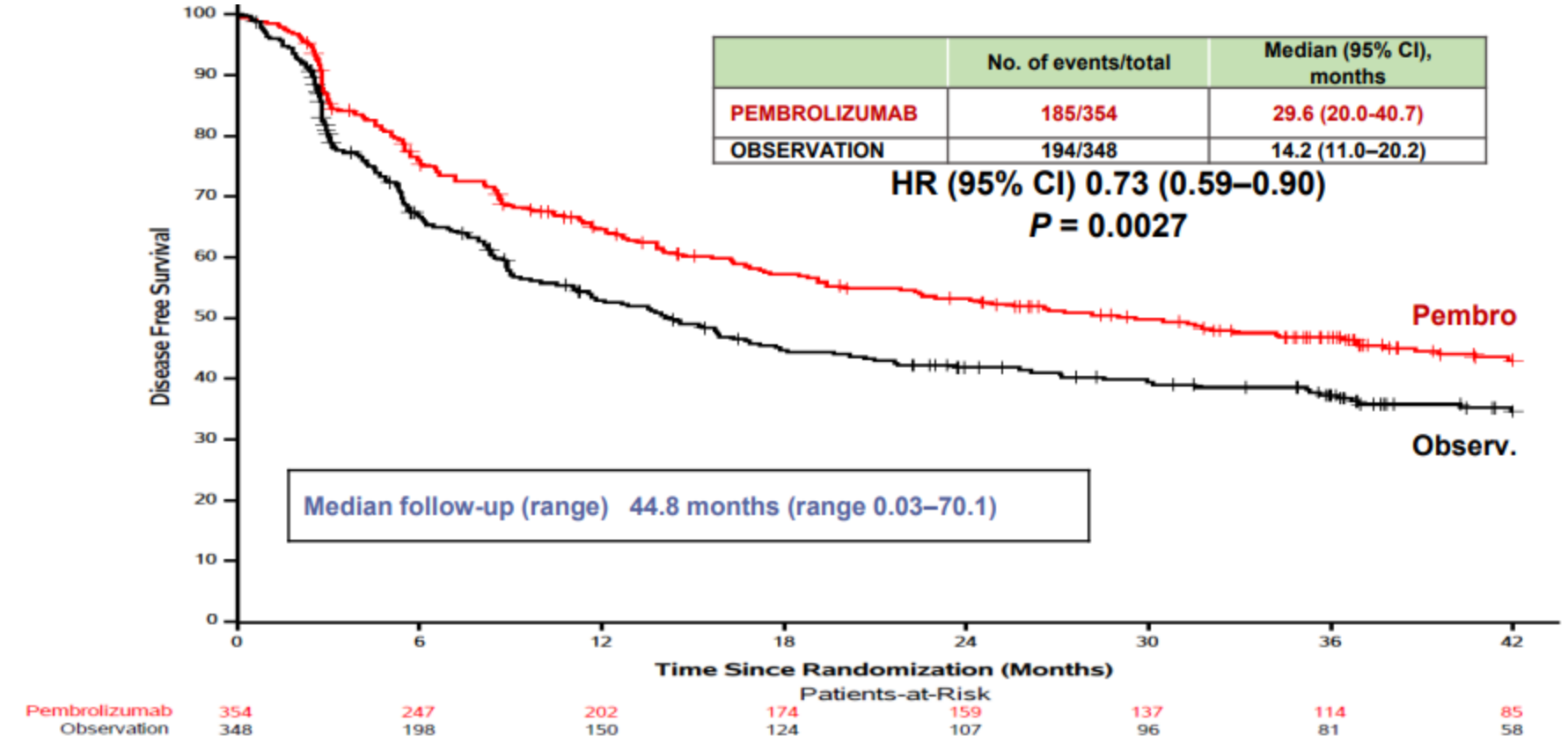
Characteristic	Pembrolizumab (n=354)	Observation (n=348)
Median Age, Years (range)	69.0 (22.0 - 92.0)	68.0 (34.0 - 90.0)
Gender • Female • Male	 83 (23.4%) 271 (76.6%)	 95 (27.3%) 253 (72.7%)
Neoadjuvant Therapy • Yes	 231 (65.3%)	 218 (62.6%)
Pathologic Stage + Surgical Margins • pT-any, N+ (any) • pT2/3, N0 or NX • pT4, N0 or NX	 9 (2.5%) 180 (50.9%) 146 (41.2%) 19 (5.4%)	 8 (2.3%) 170 (48.8%) 150 (43.1%) 20 (5.8%)
PD-L1 Status Positive (Central Testing, Dako22C3) • CPS≥10%	 207 (57.1%)	 201 (57.8%)
Primary Tumor Site • Bladder • Urethra • Upper Trace: Renal Pelvis and Ureter	 267 (75.4%) 6 (1.7%) 8 (22.9%)	 264 (75.9%) 12 (3.4%) 72 (20.7%)
Histology • **Variant:** Mixed Urothelial Histology Excluding Any Neuroendocrine Carcinoma	60 (16.9%)	51 (14.7%)

CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; NE, not estimable; NR, not reached.

Apolo AB, et al. *J Clin Oncol.* 2024;42(4 Suppl):LBA531.

AMBASSADOR (A031501) Clinical Trial: DFS (ITT)
Median follow up: 45 Months

ESMO 2024



	No. of events/total	Median (95% CI), months
PEMBROLIZUMAB	185/354	29.6 (20.0-40.7)
OBSERVATION	194/348	14.2 (11.0–20.2)

HR (95% CI) 0.73 (0.59–0.90)
***P* = 0.0027**

Apolo AB, et al. ESMO 2024. Abstract. 1964MO.

Adjuvant therapy for MIUC is not an FDA-approved indication for pembrolizumab

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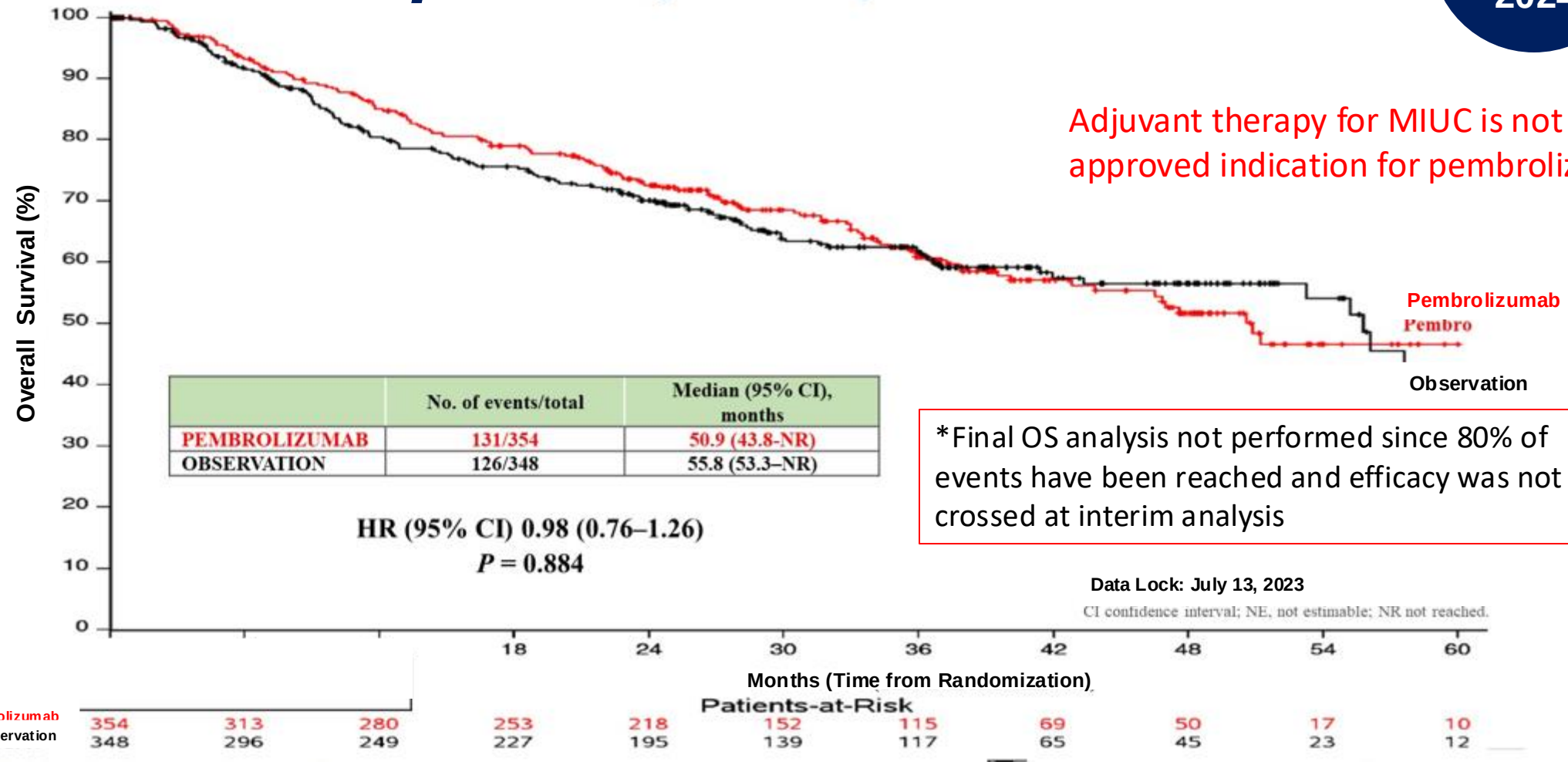
AMBASSADOR: Interim OS*
Median Follow-Up: 39.4 Months

ASCO GU 2024

Adjuvant therapy for MIUC is not an FDA-approved indication for pembrolizumab



	No. of events/total	Median (95% CI), months
PEMBROLIZUMAB	131/354	50.9 (43.8-NR)
OBSERVATION	126/348	55.8 (53.3–NR)

*Final OS analysis not performed since 80% of events have been reached and efficacy was not crossed at interim analysis

NCT05092958
Apolo AB, et al. ASCO GU 2024. Abstract LBA531.

NIAGARA Phase III Clinical Trial: Study Design

Eligibility Criteria

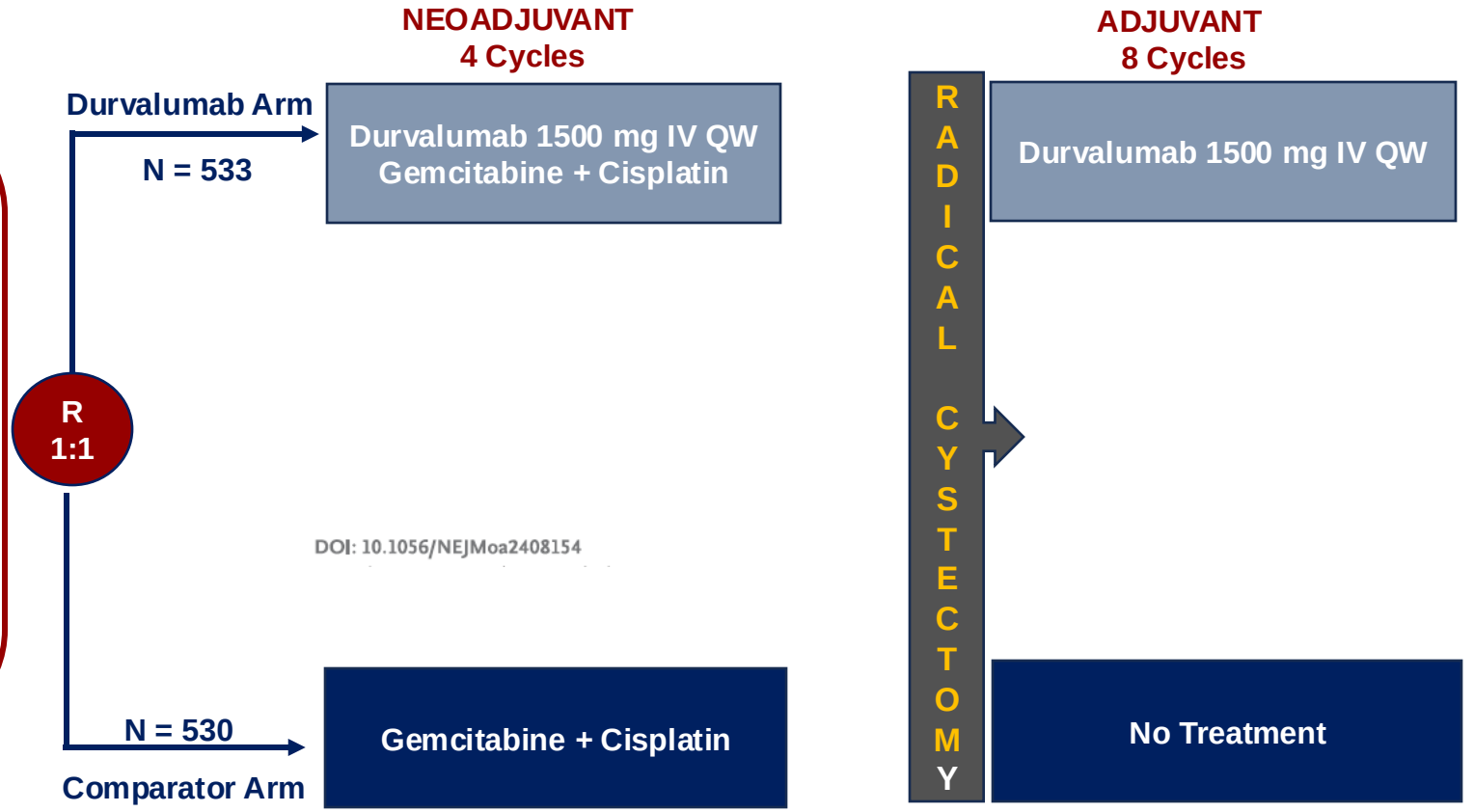
- ≤18 years of age
- Cisplatin-eligible muscle-invasive bladder cancer
- Clinical stage T2-T4aN0/N1/M0
- Urothelial cancer (UC) or UC with divergent differentiation or histologic subtypes
- Evaluated and confirmed for radical cystectomy
- Creatinine clearance of ≥40 mL/min per 1.73 m^2 per BSA
- Tumor biopsy specimen obtained at screening to assess tumor PD-L1 expression

Stratification Factors:

- Clinical Tumor Stage (T2N0 vs ≥T2N0)
- Renal Function

(CrCl ≥60 mL/min vs ≥40-<60 mL/min)

- PD-L1 Status (High vs Low or Negative)



DOI: 10.1056/NEJMoa2408154

Gemcitabine and Cisplatin Dosing

CrCl ≥60 mL/min: Cisplatin 70 mg/m^2 + gemcitabine 1000 mg/m^2 Day 1, then gemcitabine 1000 mg /m^2 Day 8, Q3W x 4 Cycles

CrCl ≥40-<60 mL/min: Split-dose cisplatin 35 mg/m^2 + gemcitabine 1000 mg/m^2 Days 1 and 8, Q3W X 4 Cycles

EFS Was Defined As:

- Progressive disease that precluded RC
- Recurrence after RC
- Date of expected surgery in patients who did not undergo RC
- Death from any cause
- Other: DFS, DSS, MFS, HRQoL, 5-Year OS

Powles TB, et al. *N Engl J Med*. 2024. e-published on September 15, 2024. DOI: 10.1056/NEJMoa2408154.

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NIAGARA Clinical Trial: Baseline Characteristics of Interest

Characteristic	Durvalumab (n=533)	Comparison (n=530)
Median Age in Years (range)	65 (34 - 84)	66 (32 - 83)
• >75 Year, n (%)	58 (10.9%)	63 (11.9%)
Sex, n (%)		
• Male	437 (82.0%)	433 (81.7%)
• Female	96 (18.0%)	97 (18.3%)
ECOG PS, n (%)		
• 0	418 (78.4%)	415 (78.3%)
• 1	115 (21.6%)	115 (21.7%)
Smoking Status, n (%)		
• Current	122 (22.9%)	130 (24.5%)
• Former	255 (47.8%)	269 (50.8%)
• Never	144 (27.0%)	120 (22.6%)
• Missing Data	12 (2.3%)	11 (2.1%)

Characteristic	Durvalumab (n=533)	Comparison (n=530)
Histologic Type, n (%)		
• Invasive Urothelial Carcinoma, NOS	457 (85.7%)	441 (83.2%)
• Urothelial Carcinoma with Glandular Differentiation	38 (7.1%)	49 (9.2%)
• Urothelial Carcinoma with Other Histologic Subtype	10 (1.9%)	15 (2.8%)
	28 (5.3%)	25 (4.7%)
Tumor Stage, n (%)		
• T2N0	215 (40.3%)	213 (40.2%)
• Higher than T2N0	318 (59.7%)	317 (59.8%)
Regional Lymph-Node Stage, n (%)		
• N0	505 (94.7%)	500 (94.3%)
• N1	28 (5.3%)	30 (5.7%)
Tumor PD-L1 Expression Level, n (%)		
• High	389 (73.0%)	388 (73.2%)
• Low or None	144 (27.0%)	142 (26.8%)

Shown are data for the intention-to-treat population, which included all the patients who were randomly assigned to receive neoadjuvant chemotherapy plus durvalumab, followed by adjuvant durvalumab after cystectomy (durvalumab group), or neoadjuvant chemotherapy followed by cystectomy alone (comparison group). Percentages may not sum to 100 because of rounding.
Eastern Cooperative Oncology Group (ECOG) performance-status scores range from O to 5, with higher scores indicating greater disability.
Histologic type, tumor stage, and regional lymph-node stage were assessed by the investigator on the basis of a pathological tumor assessment of a sample obtained during transurethral resection of the bladder tumor, an examination of the patient under anesthesia after the transurethral resection of the bladder tumor, and findings on computed tomography or magnetic resonance imaging.
Tumor staging was performed according to the eighth edition of the American Joint Committee on Cancer *AJCC Cancer Staging Manual.*
Baseline samples were assessed with the Ventana PD-LI (SP263) assay (Ventana Medical Systems) according to the TC/IC25% algorithm, in which a high expression level was defined as PD-LI expression on ≥25% of tumor cells, ≥25% of immune cells if immune cells were present in >1% of the tumor area, or 100% of immune cells if immune cells were present in 1% of the tumor area.

Powles TB, et al. *N Engl J Med*. 2024. e-published on September 15, 2024. DOI: 10.1056/NEJMoa2408154.

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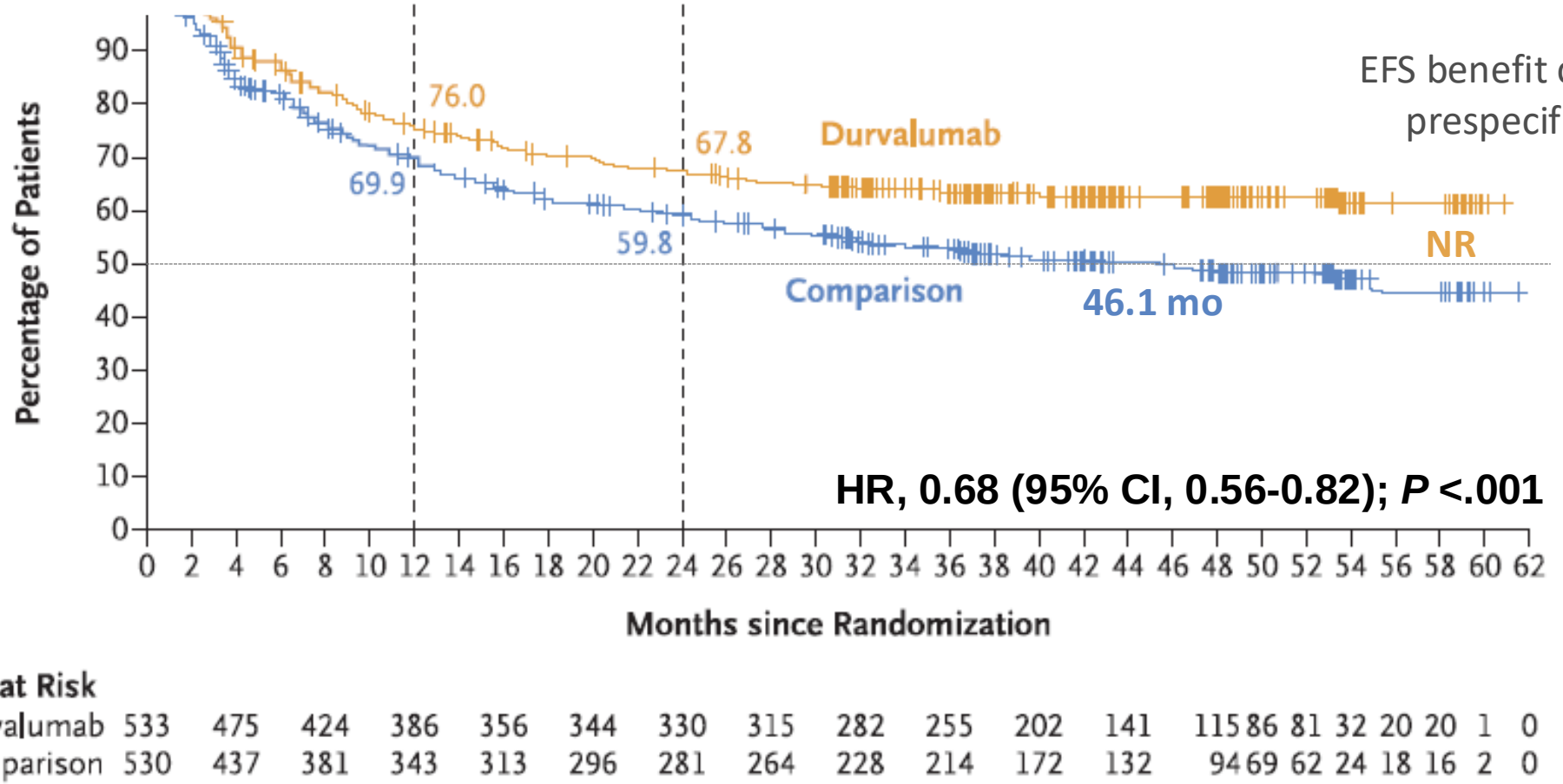
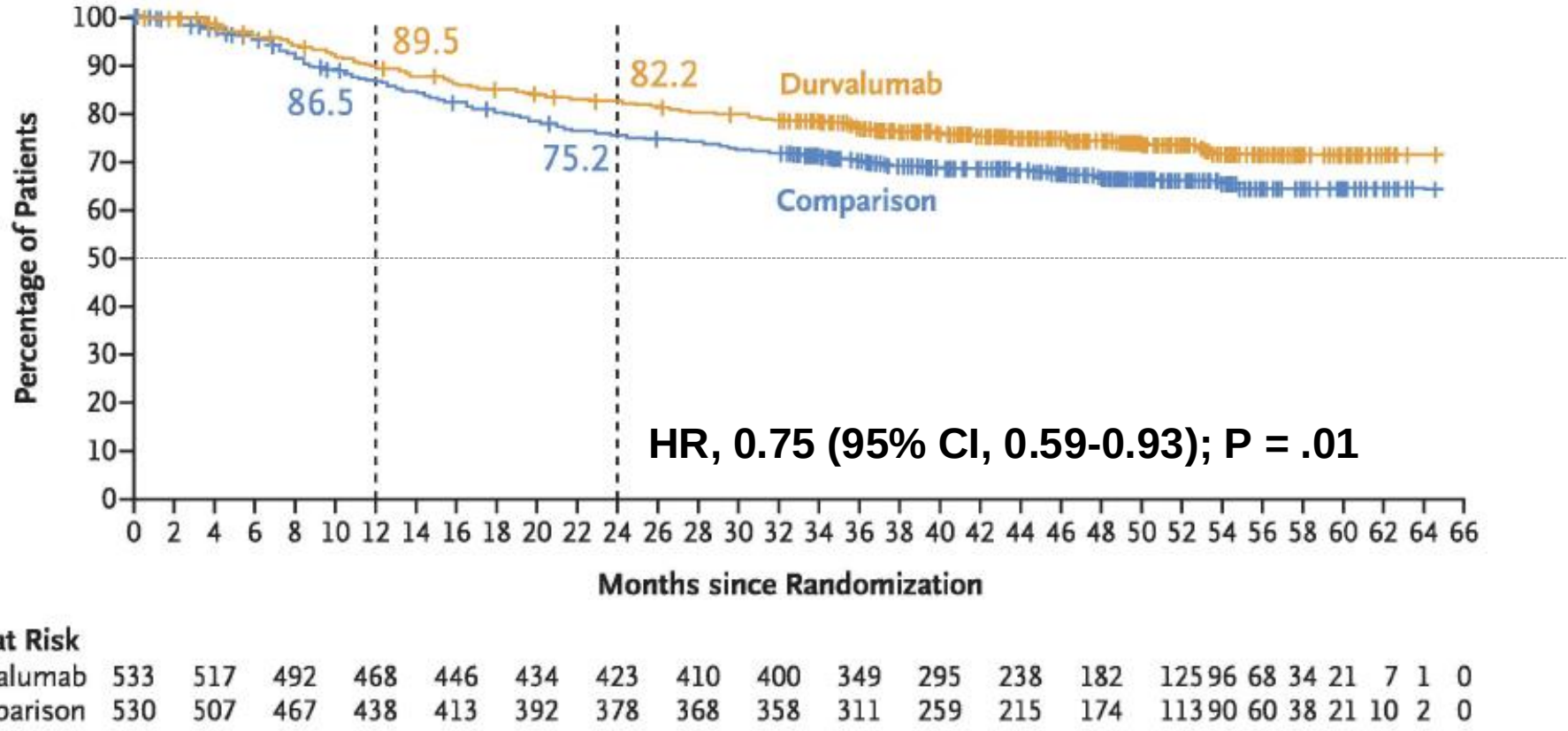
NIAGARA Clinical Trial: Event-Free Survival
Median Follow Up: **42.3 Months**



EFS benefit consistent across prespecified subgroups

Powles TB, et al. *N Engl J Med*. 2024. Sep 15, 2024.
DOI: 10.1056/NEJMoa2408154.

NIAGARA Clinical Trial: Overall Survival (ITT)



Powles TB, et al. *N Engl J Med*. 2024. Sep 15, 2024.
DOI: 10.1056/NEJMoa2408154.

NIAGARA Clinical Trial: Safety Profile

Adverse Event , n (%)	Durvalumab (n=530)	Comparison (n=526)
Adverse Event of Any Grade	527 (99.4%)	525 (99.8%)
Adverse Event of Grade 3 or 4	368 (69.4%)	355 (67.5%)
Serious Adverse Event	326 (61.5%)	287 (54.6%)
Adverse Event Leading to Death	27 (5.1%)	29 (5.5%)
Adverse Event Leading to Discontinuation of Trial Treatment	112 (21.1%)	80 (15.2%)
Adverse Event Leading to Discontinuation of Durvalumab	86 (16.2%)	----------
Adverse Event Leading to Discontinuation of Chemotherapy	72 (13.6%)	80 (15.2%)
Adverse Event Leading to Cancellation of Surgery	6 (1.1%)	7 (1.3%)

Adverse Event , n (%)	Durvalumab (n=530)	Comparison (n=526)
Adverse Event Leading to Delay in Surgery	9 (1.7%)	6 (1.1%)
Treatment-Related Adverse Event of Any Grade	502 (94.7%)	487 (92.6%)
Treatment-Related Adverse Event of Grade 3 or 4	215 (40.6%)	215 (40.9%)
Serious Treatment-Related Adverse Event	86 (16.2%)	63 (12.0%)
Treatment-Related Adverse Event Leading to Death	3 (0.6%)	3 (0.6%)
Durvalumab-Related Adverse Event Leading to Discontinuation	42 (7.9%)	----------
Chemotherapy-Related Adverse Event Leading to Discontinuation	55 (10.4%)	64 (12.2%)

Powles TB, et al. *N Engl J Med*. 2024. e-published on September 15, 2024. DOI: 10.1056/NEJMoa2408154.

PRINCIPLES OF SYSTEMIC THERAPY

First-Line Systemic Therapy for Locally Advanced or Metastatic Disease (Stage IV)	
Cisplatin eligible	**Preferred regimens** • Pembrolizumab and enfortumab vedotin-ejfv[15] (category 1) **Other recommended regimens** • Gemcitabine and cisplatin[4] (category 1) followed by avelumab maintenance therapy (category 1)[a,13] • Nivolumab, gemcitabine, and cisplatin (category 1) followed by nivolumab maintenance therapy[14] (category 1) **Useful under certain circumstances** • DDMVAC with growth factor support (category 1)[2,8] followed by avelumab maintenance therapy (category 1)[a,13]
Cisplatin ineligible	**Preferred regimens** • Pembrolizumab and enfortumab vedotin-ejfv[15,17] (category 1) **Other recommended regimens** • Gemcitabine and carboplatin[16] followed by avelumab maintenance therapy (category 1)[a,13] **Useful under certain circumstances** • Gemcitabine[18] • Gemcitabine and paclitaxel[19] • Ifosfamide, doxorubicin, and gemcitabine[21] (for patients with good kidney function and good performance status) • Pembrolizumab[22] (for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for any platinum-containing chemotherapy) • Atezolizumab[20] (only for patients whose tumors express PD-L1[b] or who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression) (category 2B)

- The presence of both non-nodal metastases and ECOG performance score ≥2 strongly predict poor outcome with chemotherapy. Patients without these adverse prognostic factors have the greatest benefit from chemotherapy. The impact of these factors in relation to immune checkpoint inhibition is not fully defined, but they remain poor prognostic indicators in general.
- For most patients, the risks of adding paclitaxel to gemcitabine and cisplatin outweigh the limited benefit seen in the randomized trial.[23]
- A substantial proportion of patients cannot receive cisplatin-based chemotherapy due to renal impairment or other comorbidities.
  - Participation in clinical trials of new or more tolerable therapy is recommended.

[a] Maintenance therapy with avelumab only if there is no progression on first-line platinum-containing chemotherapy.
[b] Atezolizumab: SP142 assay, PD-L1–stained tumor-infiltrating immune cells covering ≥5% of the tumor area.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Continued
References

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines. Bladder Cancer. (Version 4. 2024). https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1417

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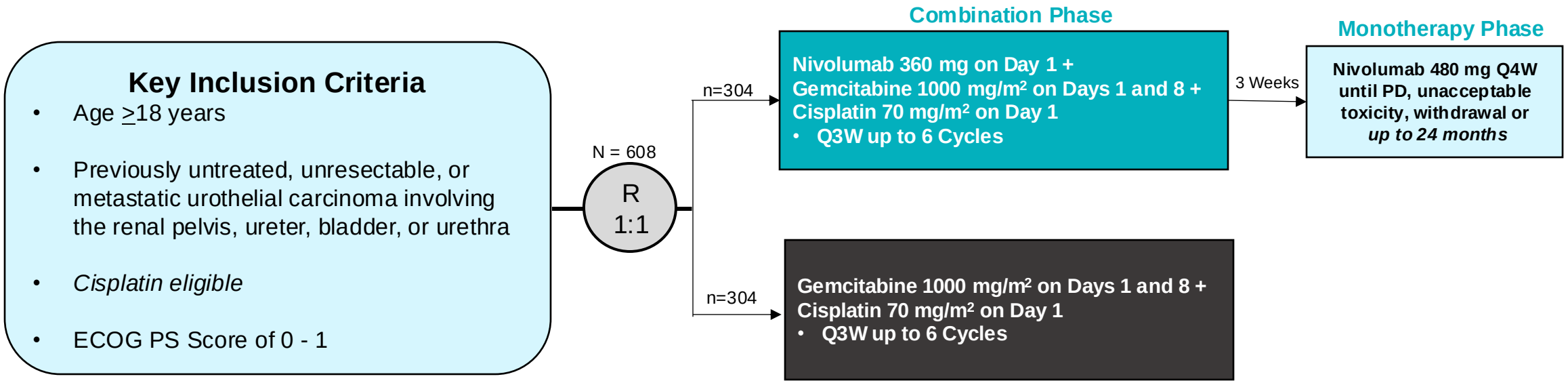
Phase III CheckMate 901: Study Design



Stratified by

- Tumor PD-L1 expression (≥1% vs <1%)
- Liver metastases (Yes vs No)

Baseline Disease State Characteristics, n (%)	Nivolumab + Gemcitabine + Cisplatin Arm (n = 304)	Gemcitabine + Cisplatin Arm (n=304)
• Metastatic	261 (85.9%)	269 (88.5%)
• Locally Unresectable	41 (13.5%)	33 (10.9%)

Median Study Follow-Up: 33.6 Months (7.4 - 62.4)

Primary Endpoints:
- Overall Survival per BICR
- Progression-Free Survival per BICR

Key Secondary Endpoints:
- Overall Survival and Progression by PD-L1 ≥1%
- Health-Related Quality of Life

Key Exploratory Endpoints:
- Objective Response Rate per BICR
- Safety

van der Heijden MS, et al. *N Engl J Med*. 2023;389(19):1778-1789.

CheckMate 901 Clinical Trial: Improvements in PFS and OS

	Nivolumab + Gemcitabine-Cisplatin (n=304)	Gemcitabine + Cisplatin Alone (n=304)	Hazard Ratio (95% CI)
Median OS, months (95% CI)	21.7 (18.6 - 26.4)	18.9 (14.7 - 22.4)	0.78 (0.63 - 0.96) **P = 0.0171**
12-Month OS Probability, (%)	70.2%	62.7%	----------
24-Months OS Probability, (%)	46.9%	40.7%	----------
Median PFS, months (95% CI)	7.9 (7.6 - 9.5)	7.6 (6.1 - 7.8)	0.72 (0.59 - 0.88) **P = 0.0012**
12-Month PFS Probability, (%)	34.2%	21.8%	----------
24-Month PFS Probability, (%)	23.5%	9.6%	----------

van der Heijden M. *Ann Oncol*. 2023;34(suppl_2):S1254-S1335

Phase III EV-302 Clinical Trial: Study Design

Patient Population

- Previously untreated locally advanced or metastatic urothelial carcinoma
- Eligible for platinum, enfortumab vedotin, and pembrolizumab
- PD-(L)1 inhibitor naïve
- GFR ≥30 mL/min[a]
- ECOG PS ≤2[b]

N=886

R
1:1

Enfortumab Vedotin + Pembrolizumab
No Maximum Treatment Cycles for Enfortumab Vedotin
Maximum 35 Cycles for Pembrolizumab

Treat Until Disease Progression per BICR, Clinical Progression, Unacceptable Toxicity, or Completion of Maximum Cycles

Chemotherapy[c]

Cisplatin or Carboplatin + Gemcitabine
Maximum 6 Cycles

Dual Primary Endpoints:

- **PFS by BICR**
- **OS**

Select Secondary Endpoints:

- **ORR per RECIST v1.1 by BICR and Investigator Assessment**
- **Safety**

Stratification Factors

- Cisplatin eligibility (eligible or ineligible)
- PD-L1 expression (high or low)
- Liver metastases (present or absent)

Cisplatin eligibility and assignment or dosing of cisplatin vs carboplatin were protocol-defined

- Patients received 3-week cycles of enfortumab vedotin at 1.25 mg/kg IV on Days 1 and 8 and pembrolizumab, 200 mg IV on Day 1

Statistical Plan

The first planned analysis was performed atter approximately 526 PFS (final) and 356 OS (interim) events.

- If OS was positive at interim, the OS interim analysis was considered final

Stage of Disease	EV + Pembrolizumab (n=442)	Platinum-Based + Gemcitabine (n=444)
Metastatic	421 (95.2%)	420 (94.6%)

BICR, blinded independent central review
ECOG PS, Eastern Cooperative Oncology Group Performance Status
GFR, glomerular filtration rate
ORR, objective response rate
OS, overall survival
PD-L1, programmed cell death ligand-1
PFS, progression-free survival
RECIST, Response Evaluation Criteria in Solid Tumors

Powles T, et al. *N Engl J Med*. 2024;390(10):875-888.

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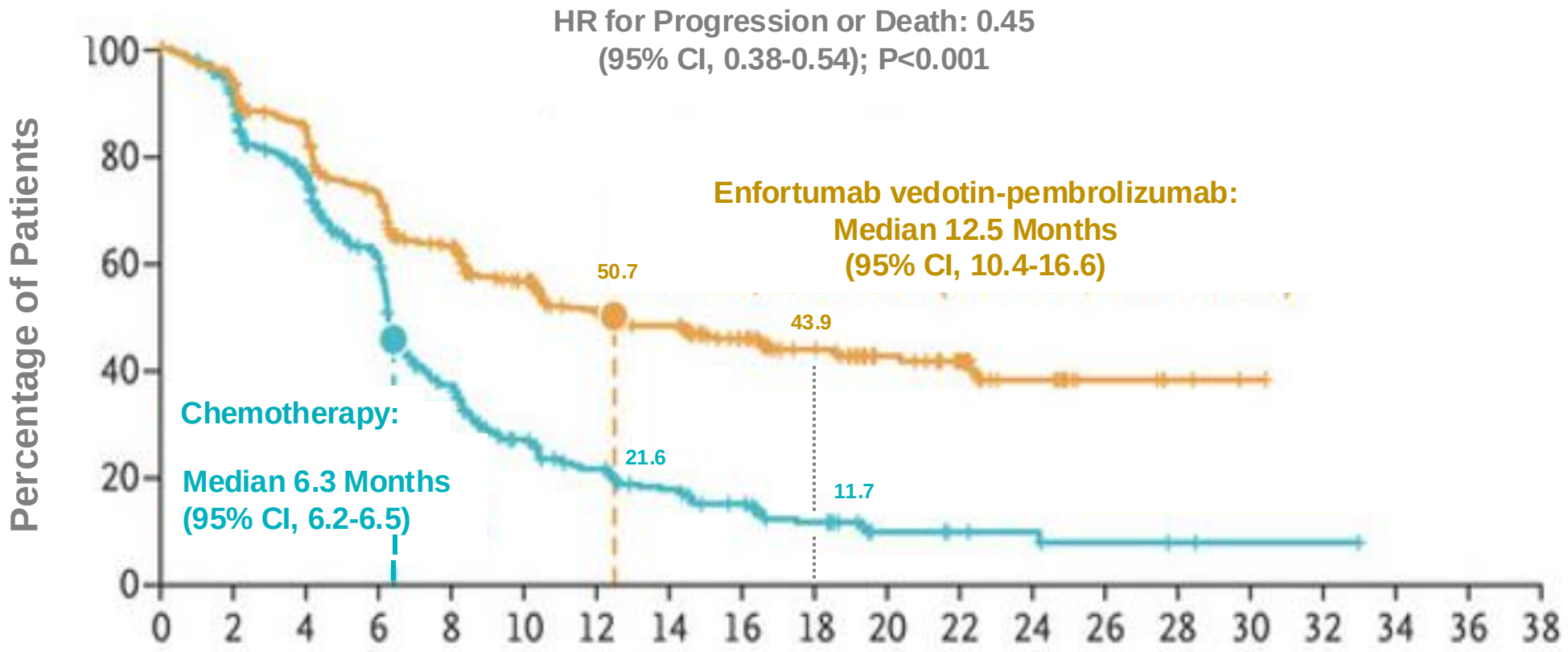
Phase III EV-302 Clinical Trial: PFS



Powles T, et al. *N Engl J Med*. 2024; **390(10):875-888.**

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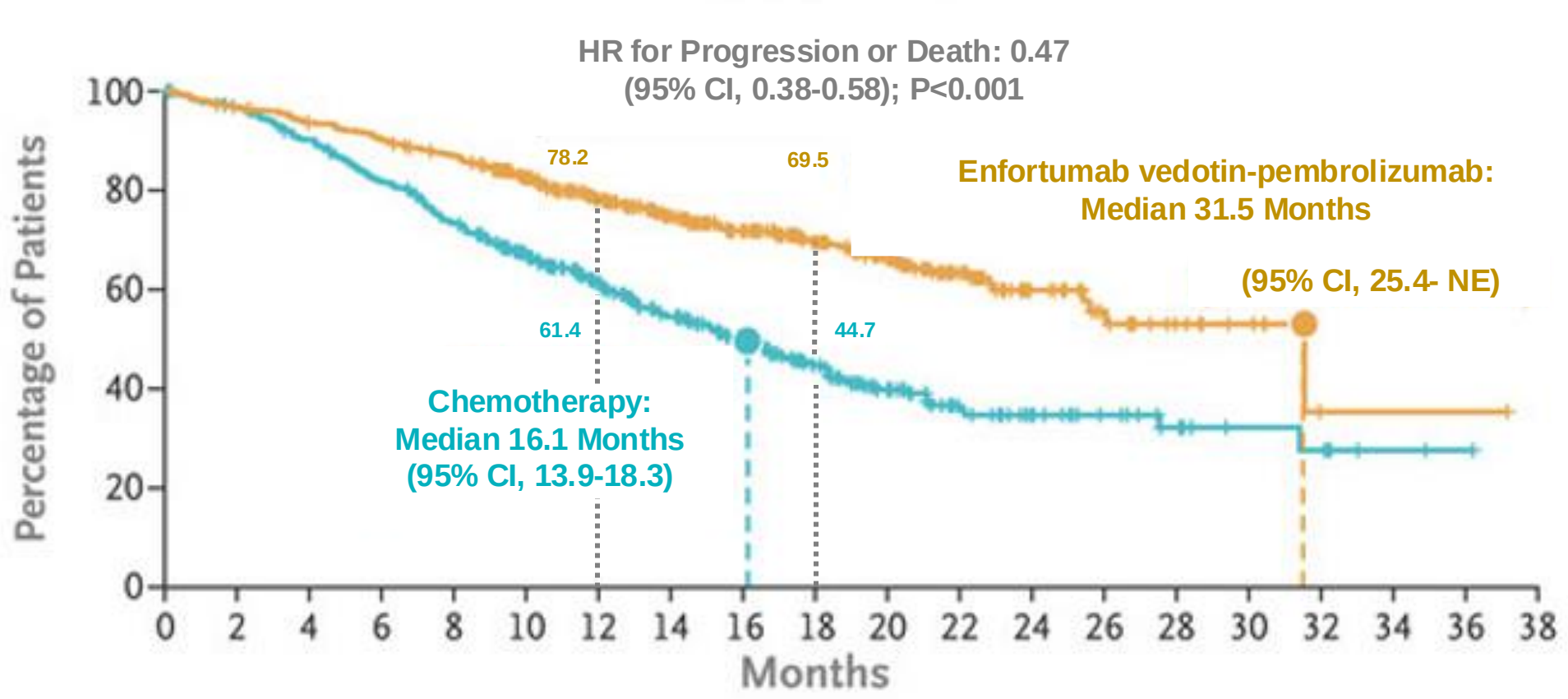
Phase III EV-302 Clinical Trial: OS



Powles T, et al. *N Engl J Med*. 2024; **390(10):875-888.**

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Summary Points

- The gold-standard for localized MIBC is peri-operative IO + chemo. Unclear if superior to chemo → surgery → IO (adj)
- Adjuvant IO is SOC; efforts to optimize to needs it are ongoing
- EV+Pembro changed front line la/mUC.. Maybe it will change peri-operative setting also
- What to do for patients who progress is unclear but likely does NOT involve IO

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Thank You!

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