Society for Immunotherapy of Cancer

Advances in Cancer Immunotherapy™

Immunotherapy for Bladder Cancer

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Assistant Professor

Greenberg Bladder Cancer Institute

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October 27, 2021

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Disclosures

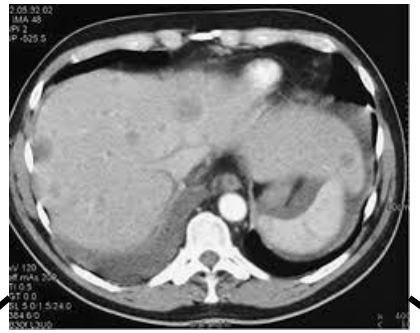
Consulting fees:

Foundation Medicine, Astra-Zeneca, Seattle Genetics

Contracted Research:

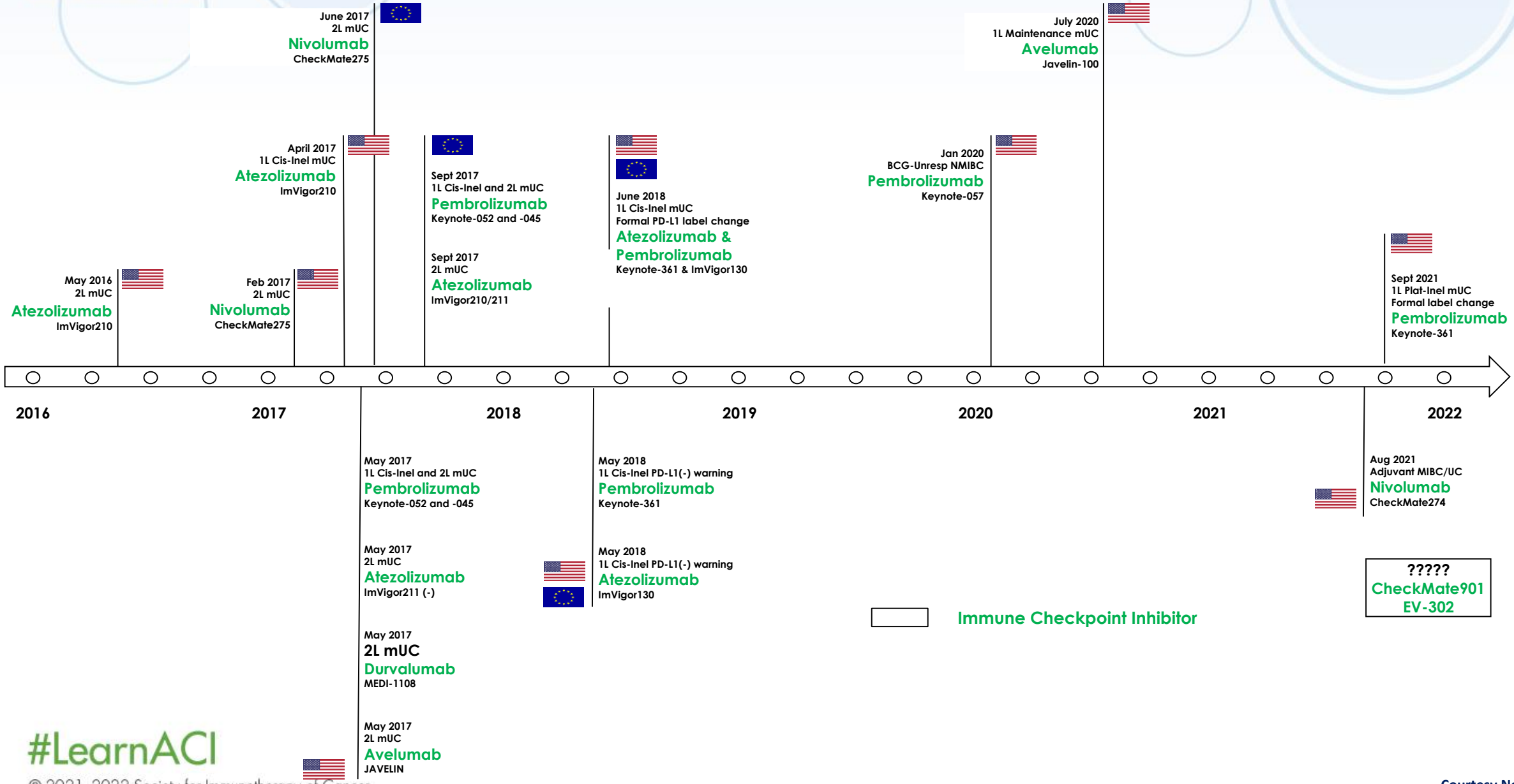
Genentech

Systemic Therapy for Advanced Urothelial Cancer Prior to Spring 2016



- Chemotherapy Ineligible
  - BSC
- Chemotherapy Eligible
  - Cisplatin Ineligible
    - Carboplatin and Gemcitabine
  - Cisplatin Eligible
    - Cisplatin and Gemcitabine
    - aMVAC

Systemic Therapy FDA Approvals



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Systemic Therapy FDA Approvals

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May 2016
2L mUC
Atezolizumab
IMvigor210

Feb 2017
2L mUC
Nivolumab
CheckMate275

April 2017
1L Cis-Inel mUC
Atezolizumab
IMvigor210

June 2017
2L mUC
Nivolumab
CheckMate275

Sept 2017
1L Cis-Inel and 2L mUC
Pembrolizumab
Keynote-052 and -045

Sept 2017
2L mUC
Atezolizumab
IMvigor210/211

June 2018
1L Cis-Inel mUC
Formal PD-L1 label change
Atezolizumab & Pembrolizumab
Keynote-361 & IMvigor130

Jan 2020
BCG-Unresp NMIBC
Pembrolizumab
Keynote-057

July 2020
1L Maintenance mUC
Avelumab
Javelin-100

Feb 2021
2L mUC
Durvalumab
DANUBE (-)

March 2021
2L mUC
Atezolizumab
IMvigor211 (-)

Sept 2021
1L Plat-Inel mUC
Formal label change
Pembrolizumab
Keynote-361

Aug 2021
Adjuvant MIBC/UC
Nivolumab
CheckMate274

?????
CheckMate901
EV-302

2016 2017 2018 2019 2020 2021 2022

May 2017
1L Cis-Inel and 2L mUC
Pembrolizumab
Keynote-052 and -045

May 2017
2L mUC
Atezolizumab
IMvigor211 (-)

May 2017
2L mUC
Durvalumab
MEDI-1108

May 2017
2L mUC
Avelumab
JAVELIN

May 2018
1L Cis-Inel PD-L1(-) warning
Pembrolizumab
Keynote-361

May 2018
1L Cis-Inel PD-L1(-) warning
Atezolizumab
IMvigor130

Immune Checkpoint Inhibitor

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Systemic Therapy FDA Approvals

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Keynote-361 & ImVigor130

April 2019
2L mUC FGFR3+
Erdafitinib
BLC2001

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EV-302

Immune Checkpoint Inhibitor

Targeted Therapy

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Systemic Therapy FDA Approvals

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Jan 2020
BCG-Unresp NMIBC
Pembrolizumab
Keynote-057

Dec 2019
3L Post-CPI mUC
Enfortumab
Vedotin
EV-201

July 2020
1L Maintenance mUC
Avelumab
Javelin-100

Feb 2021
2L mUC
Durvalumab
DANUBE (-)

March 2021
2L mUC
Atezolizumab
IMvigor211 (-)

Apr 2021
3L Post-CPI mUC
Sacituzumab
Govitecan
Trophy

Sept 2021
1L Plat-Inel mUC
Formal label change
Pembrolizumab
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2016 | 2017 | 2018 | 2019 | 2020 | 2021 | 2022

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Durvalumab
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CheckMate274

Immune Checkpoint Inhibitor

Targeted Therapy

Antibody Drug Conjugate

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CheckMate901
EV-302

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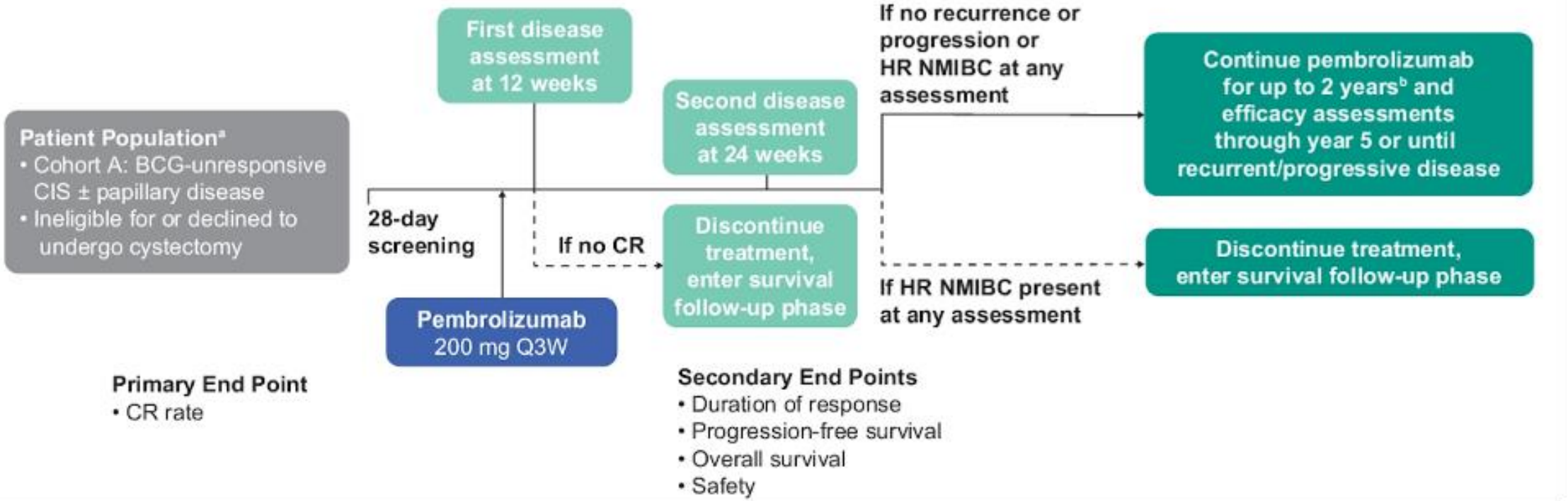
Immunotherapy for Urothelial Cancer by Disease State

Agent	NMIBC	Chemo Radio Therapy MIBC	Neo-adjuvant MIBC	Adjuvant MIBC	1L Cisplatin ineligible (PD-L1 high-Atezo) Chemo ineligible	1L Maintenance After CR/PR/SD on 1L therapy	2L and beyond
Atezolizumab PD-L1					☑		☑
Avelumab PD-L1						☑	☑
Durvalumab PD-L1							☑
Nivolumab PD-1				☑			☑
Pembrolizumab PD-1	☑				☑		☑

Pembrolizumab in high-risk non-muscle-invasive bladder cancer unresponsive to BCG: KEYNOTE-057



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	Cohort A (n=101)
Age	
Median age, years (IQR)	73 (63–79)
≥65 years	71 (70%)
Sex	
Male	85 (84%)
Female	16 (16%)
ECOG performance status	
0	74 (73%)
1	27 (27%)
Previous BCG instillations, median (IQR)	12·0 (9·0–16·5)
Tumour stage	
Carcinoma in situ with T1	12 (12%)
Carcinoma in situ with high-grade Ta	25 (25%)
Carcinoma in situ alone	64 (63%)
PD-L1 status*	
Combined positive score ≥10	38 (38%)
Combined positive score <10	58 (57%)
Not evaluable	5 (5%)
Reason for not undergoing cystectomy	
Declined	96 (95%)
Ineligible	3 (3%)
Other	2 (2%)
BCG failure category	
Persistent disease†	26 (26%)
Recurrent disease‡	70 (69%)
Not classified§	5 (5%)

	Cohort A efficacy population (n=96)*
Complete response	39 (41%, 30·7–51·1)
Non-complete response	56 (58%, 47·8–68·3)
Persistent disease†‡	40 (42%, 31·7–52·2)
Recurrent disease	6 (6%, 2·3–13·1)
Non-muscle-invasive bladder cancer stage progression§	9 (9%, 4·4–17·1)
Non-bladder malignancy¶	1 (1%, 0·0–5·7)
Progression to muscle-invasive disease (T2)	0 (NA–NA)
Non-evaluable‖	1 (1%, 0·0–5·7)

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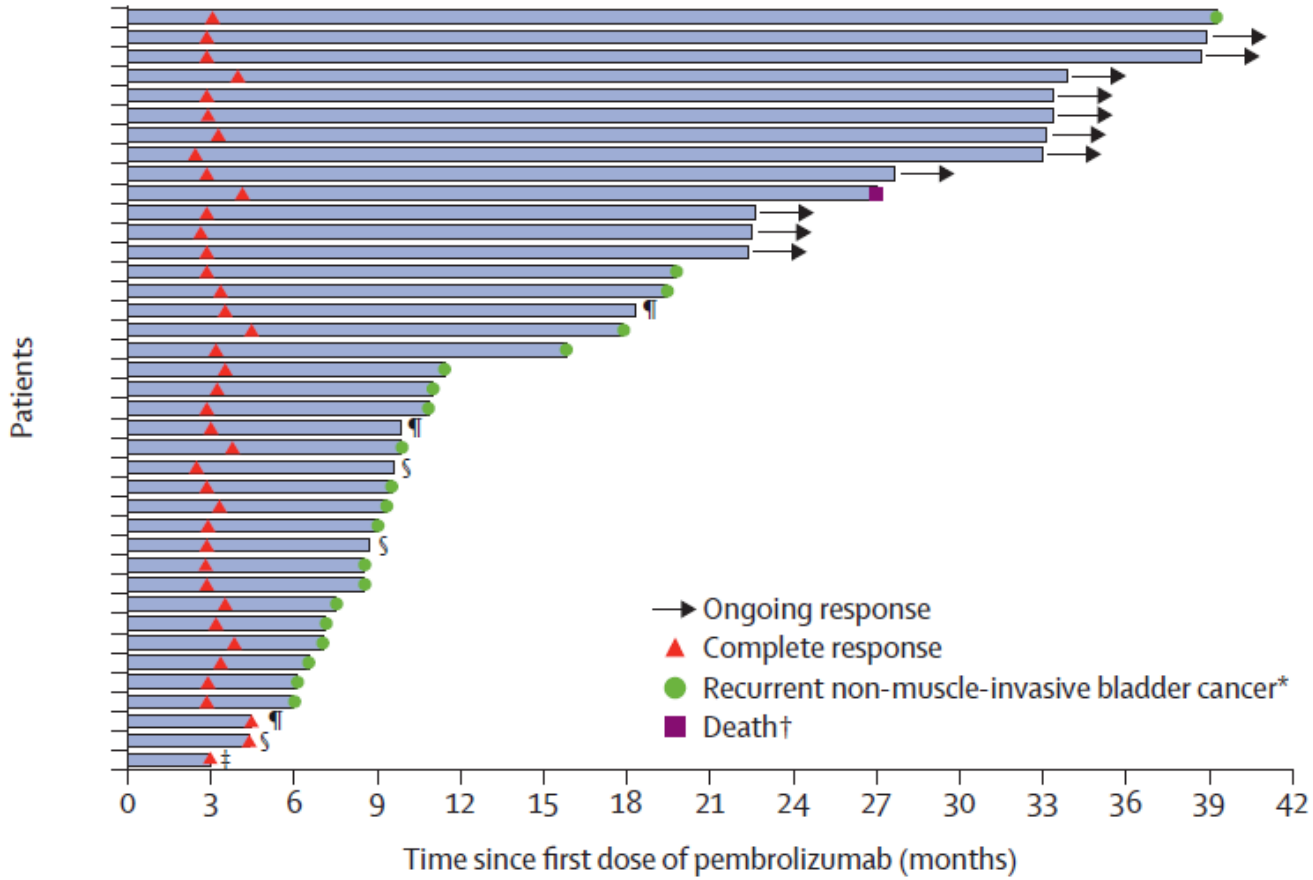

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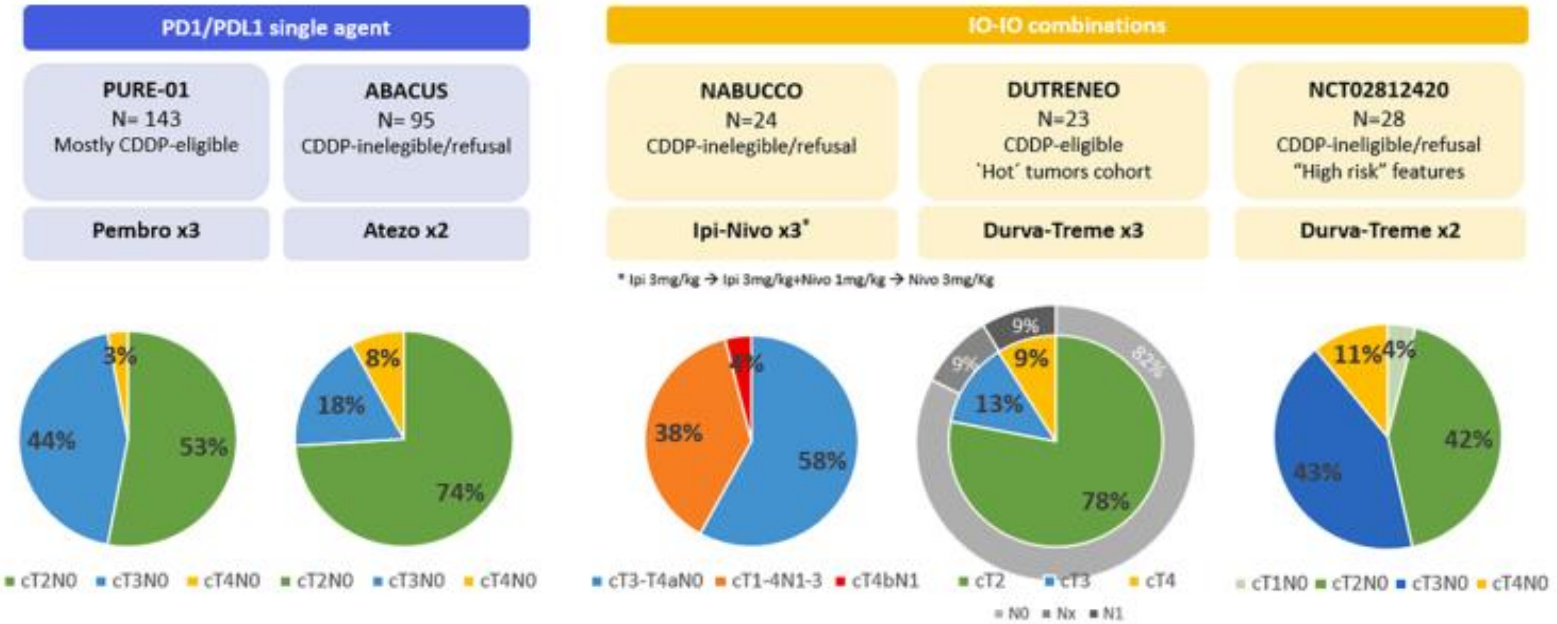
Phase II/III Active Chemoradiotherapy CPI Studies in Bladder Cancer

NCT	Agent / Title	Update
NCT03775265 N=475	Radiotherapy +/- Atezolizumab and (Cisplatin / 5FU+MMC / + Gemcitabine) in MIBC	Recruiting
NCT04241185 N=636	Radiotherapy +/- Pembrolizumab and (Cisplatin / 5FU+MMC / + Gemcitabine) in MIBC	Recruiting
NCT04216290 N=114	Durvalumab + Radiotherapy and (Cisplatin / 5FU+MMC / + Gemcitabine) in LN+ MIBC	Recruiting
NCT04658862 N=550	TAR200 + Cetrelimab (anti- PD-1) vs Radiotherapy + (Cisplatin or Gemcitabine)	Recruiting
NCT04186013 N=39	Atezolizumab + Radiotherapy in MIBC	Recruiting
NCT04543110 N=25	Durvalumab + Radiotherapy as neoadjuvant therapy for MIBC	Recruiting
NCT03993249 N=78	Radiotherapy +/- Nivolumab and (Cisplatin / 5FU+MMC / + Gemcitabine) in MIBC	Recruiting

Neoadjuvant Immunotherapy



	PURE-01	ABACUS	NABUCCO	DUTRENEO	NCT02812420	BLASST-1	SAKK 06/17	GU14-188 C1	GU14-188 C2	NEODURVARIB
ypT0	38%	31% (pT0+pTis)	46%	35%	37% (pT0+pTis)	34%	33%	44%	45%	50%
<ypT2N0	56%	39%	58%	NR	58%	66%	60%	61%	52%	NR
ypT2-4 N0	20%	NR	NR	NR	21%	NR	NR	39%	48%	NR
ypN+	13%	24%	NR	NR	21%	NR	NR	14%	15%	NR
RC rate	94%	92%	100%	87%	86%	98%	88%	84%	92%	90%

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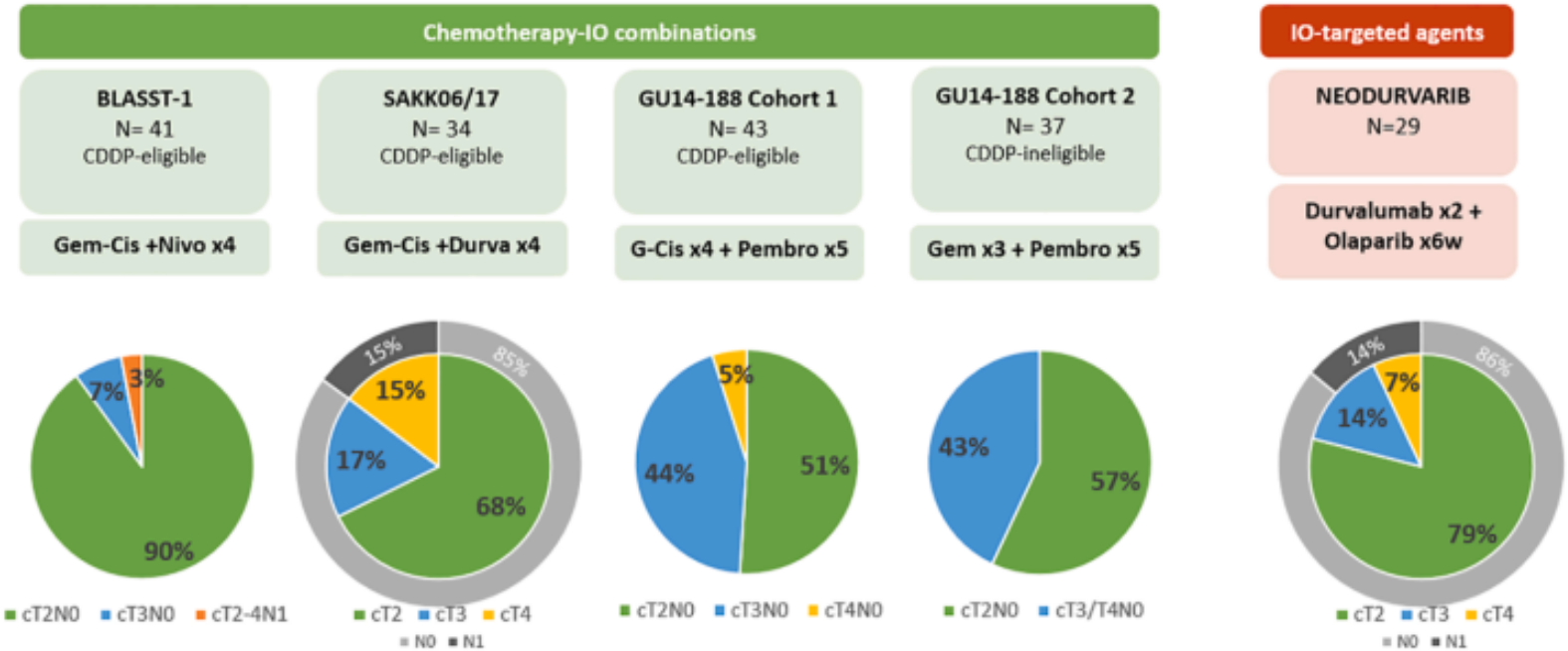

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<ypT2N0	56%	39%	58%	NR	58%	66%	60%	61%	52%	NR
ypT2-4 N0	20%	NR	NR	NR	21%	NR	NR	39%	48%	NR
ypN+	13%	24%	NR	NR	21%	NR	NR	14%	15%	NR
RC rate	94%	92%	100%	87%	86%	98%	88%	84%	92%	90%

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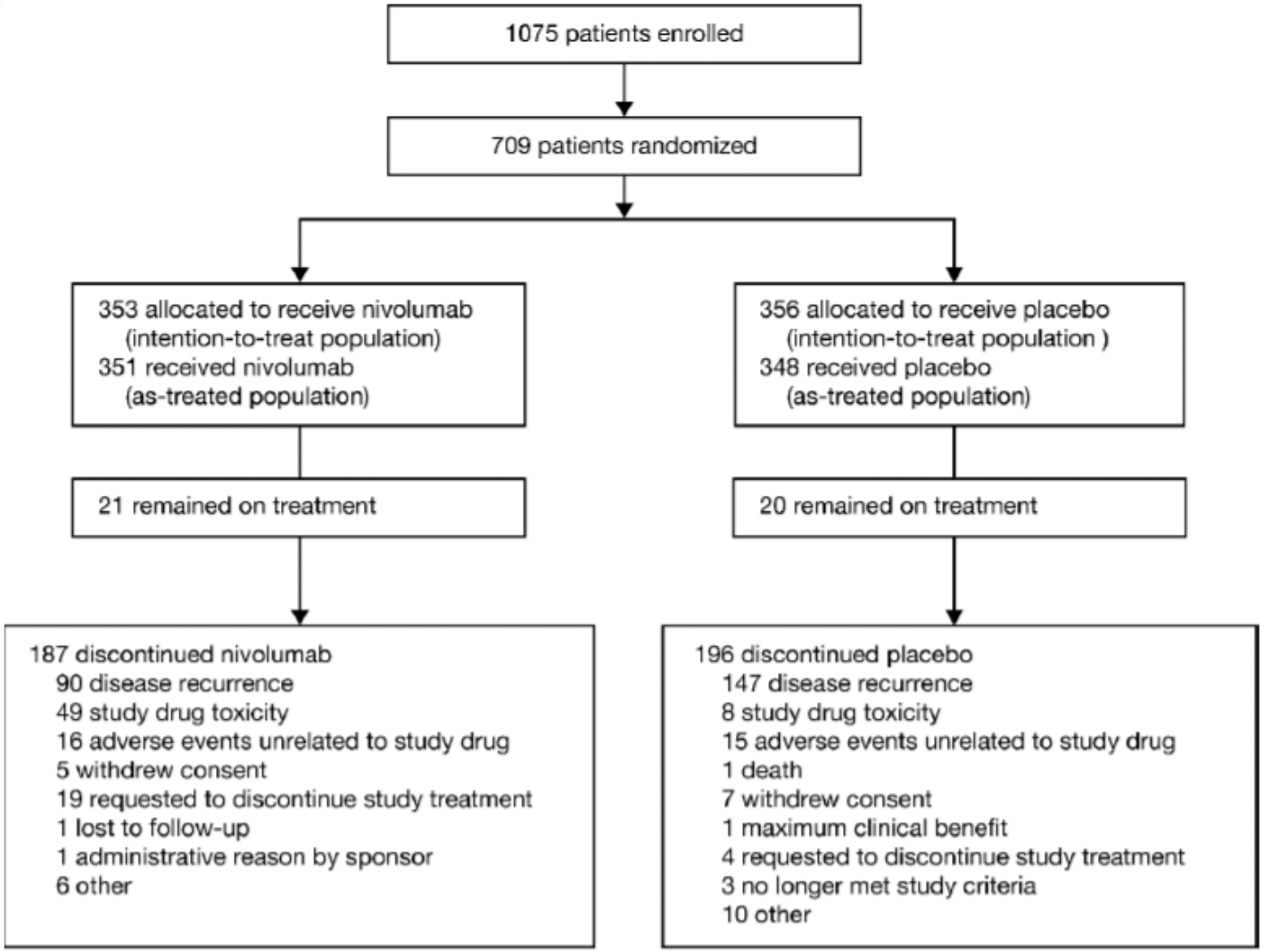
Phase III Neodjuvant CPI Studies in Bladder Cancer

NCT	Agent / Title	Update
NCT03732677 N=988	Gemcitabine/Cisplatin +/- Durvalumab NIAGARA	Maturing
NCT04700124 N=784	Perioperative Enfortumab Vedotin +Pembrolizumab Vs Chemotherapy for Cisplatin-eligible MIBC KEYNOTE-B15	Recruiting
NCT03924895 N=836	Perioperative Pembrolizumab +/- Enfortumab + Surgery Vs Surgery for Cisplatin-Ineligible MIBC KEYNOTE-905	Recruiting
NCT03924856 N=870	Perioperative Pembrolizumab + NAC Vs NAC for Cisplatin-eligible MIBC KEYNOTE-866	Recruiting
NCT04209114 N=540	Nivolumab Plus Bempegaldesleukin (Bempeg/NKTR-214) vs Nivolumab + Surgery in Cisplatin Ineligible pts	Recruiting
NCT03661320 N=1200	Gemcitabine/Cisplatin Vs Gemcitabine/Cisplatin + Nivo + / - BMS-986205	Recruiting

Adjuvant Nivolumab versus Placebo in Muscle-Invasive Urothelial Carcinoma

Eligible patients must:

- **have had radical R0 surgery within 120 days before randomization**
- **with or without neoadjuvant cisplatin-based chemotherapy**
- **pT3, pT4a, or pN+ and patient not eligible for or declined adjuvant cisplatin-based combination chemotherapy**
- **ypT2 to ypT4a or ypN+ for patients who received neoadjuvant cisplatin**



Barjorin D et al NEJM June 2021

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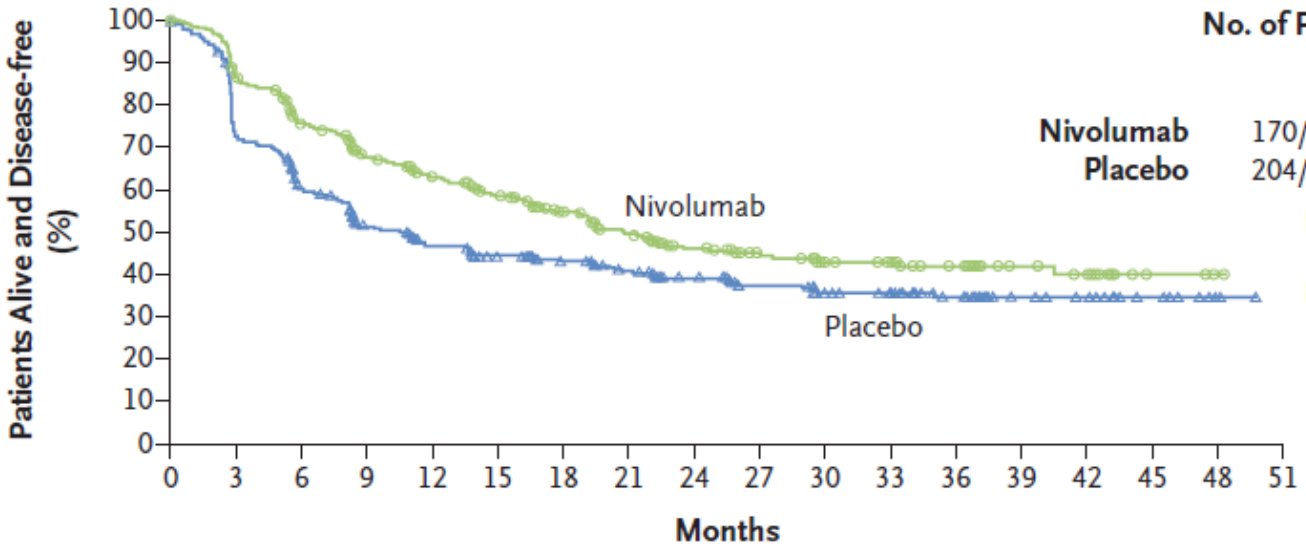
Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Nivolumab (N=353)	Placebo (N=356)
Age		
Mean (range) — yr	65.3 (30–92)	65.9 (42–88)
<65 yr — no. (%)	155 (43.9)	136 (38.2)
≥65 yr — no. (%)	198 (56.1)	220 (61.8)
Sex — no. (%)		
Male	265 (75.1)	275 (77.2)
Female	88 (24.9)	81 (22.8)
Race or ethnic group — no. (%)†		
White	264 (74.8)	272 (76.4)
Asian	80 (22.7)	75 (21.1)
Black	2 (0.6)	3 (0.8)
American Indian or Alaska Native	1 (0.3)	0
Other	6 (1.7)	5 (1.4)
Not reported	0	1 (0.3)
ECOG performance-status score — no. (%)‡		
0	224 (63.5)	221 (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 — no. (%)		
Urinary bladder	279 (79.0)	281 (78.9)
Renal pelvis	44 (12.5)	52 (14.6)
Ureter	30 (8.5)	23 (6.5)

A Intention-to-Treat Population



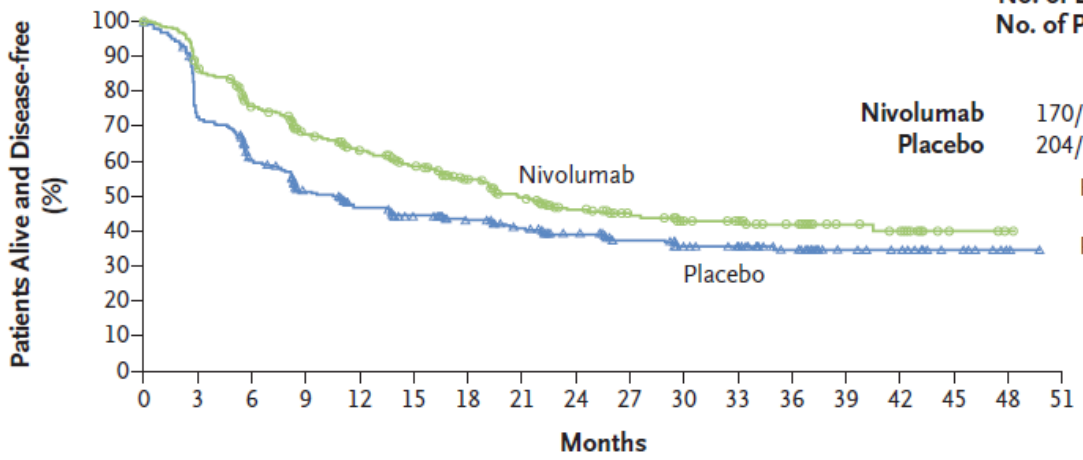
	No. of Events/ No. of Patients	Disease-free Survival at 6 Mo (95% CI)	Disease-free Survival at 12 Mo (95% CI)
		%	
Nivolumab	170/353	74.9 (69.9–79.2)	62.8 (57.3–67.8)
Placebo	204/356	60.3 (54.9–65.3)	46.6 (41.1–51.9)

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

A Intention-to-Treat Population



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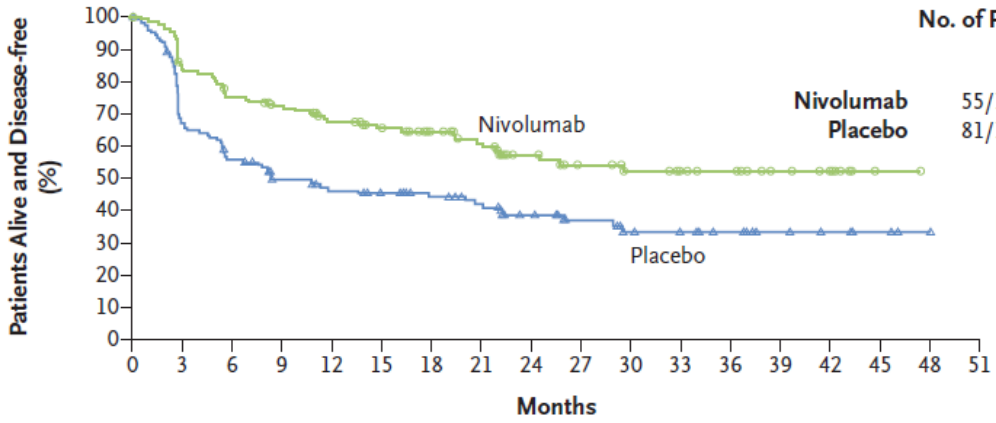
B Patients with a PD-L1 Expression Level of ≥1%



	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

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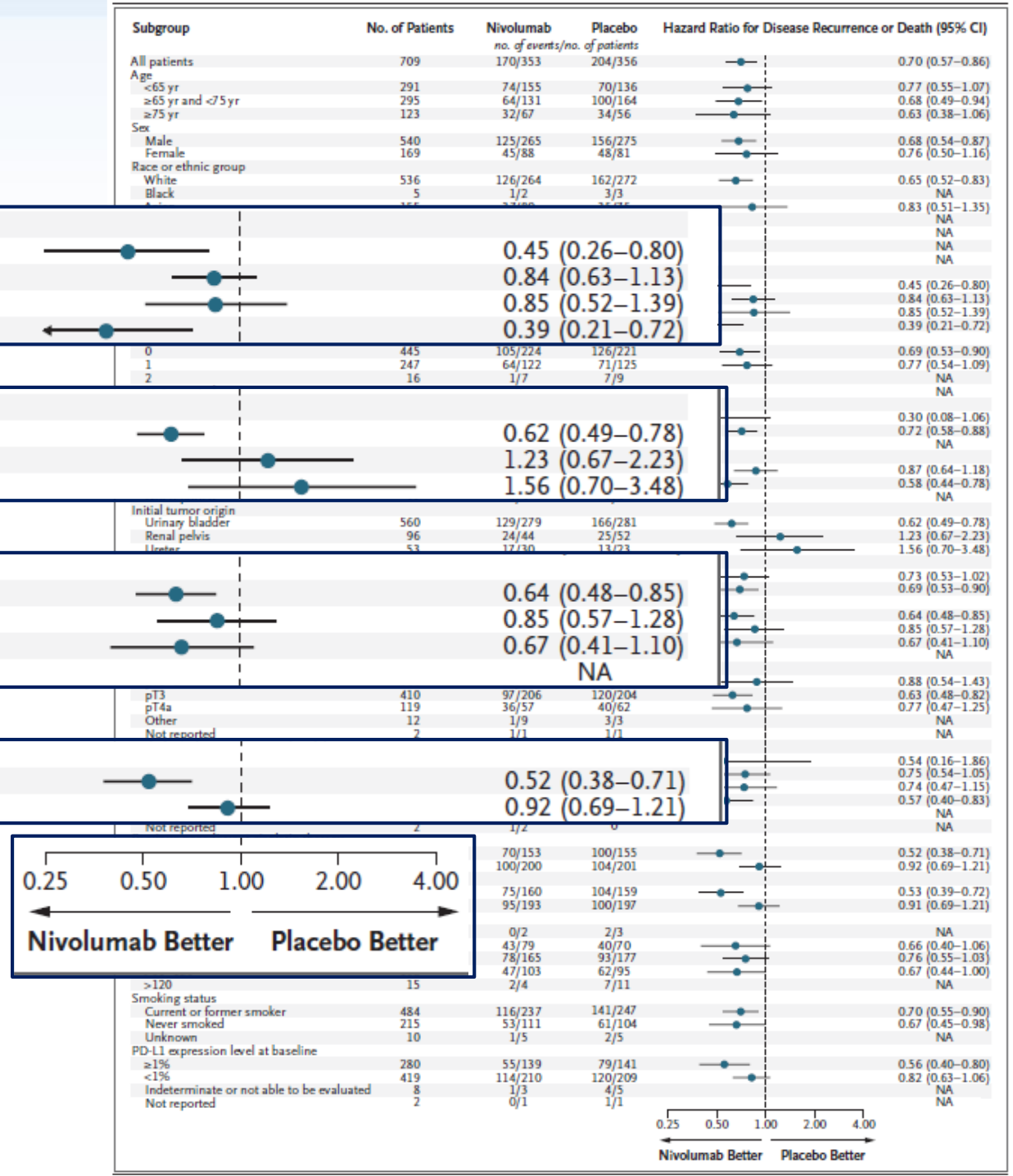
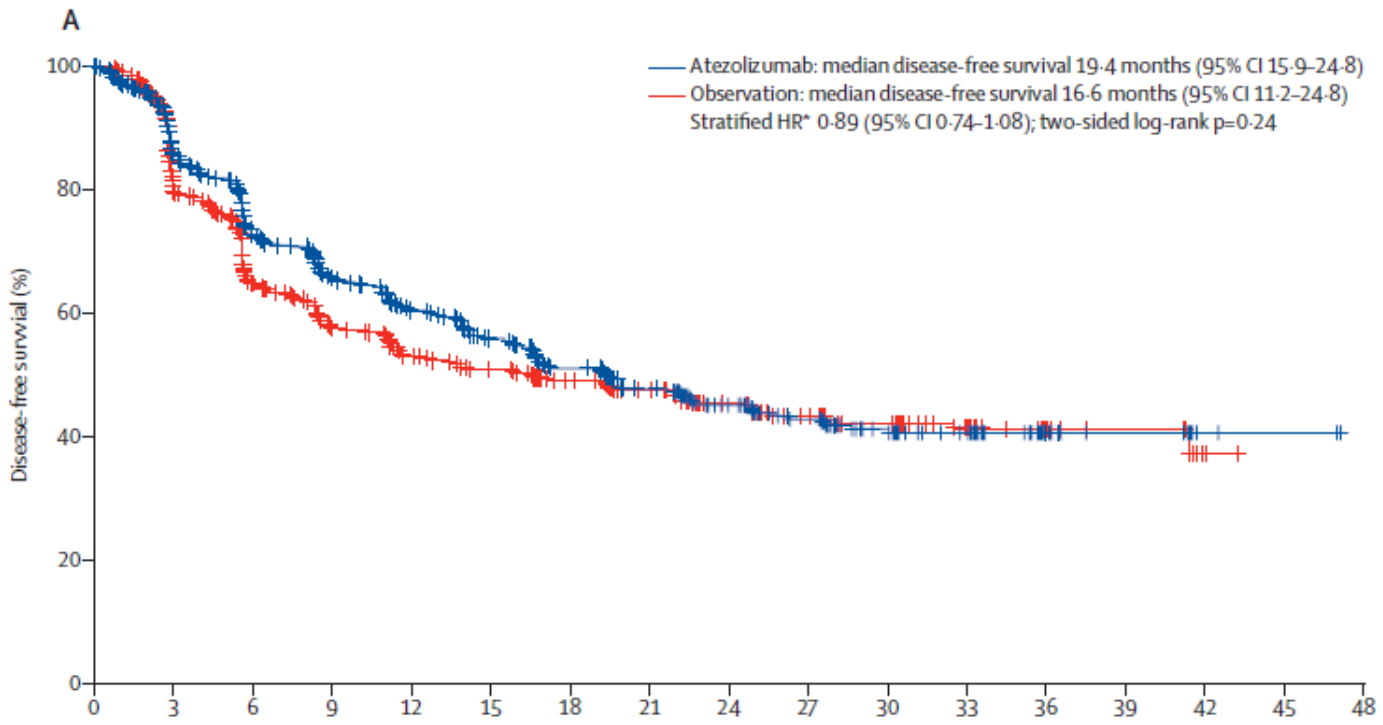
Subgroup	No. of Patients	Nivolumab	Placebo	Hazard Ratio for Disease Recurrence or Death (95% CI)
		no. of events/no. of patients		
All patients	709	170/353	204/356	0.70 (0.57–0.86)
Age				
<65 yr	291	74/155	70/136	0.77 (0.55–1.07)
≥65 yr and <75 yr	295	64/131	100/164	0.68 (0.49–0.94)
≥75 yr	123	32/67	34/56	0.63 (0.38–1.06)
Sex				
Male	540	125/265	156/275	0.68 (0.54–0.87)
Female	169	45/88	48/81	0.76 (0.50–1.16)
Race or ethnic group				
White	536	126/264	162/272	0.65 (0.52–0.83)
Black	5	1/2	3/3	NA
				0.83 (0.51–1.35)
				NA
				NA
				NA
				NA
				0.45 (0.26–0.80)
				0.84 (0.63–1.13)
				0.85 (0.52–1.39)
				0.39 (0.21–0.72)
0	445	105/224	126/221	0.69 (0.53–0.90)
1	247	64/122	71/125	0.77 (0.54–1.09)
2	16	1/7	7/9	NA
				NA
				0.30 (0.08–1.06)
				0.72 (0.58–0.88)
				NA
				0.87 (0.64–1.18)
				0.58 (0.44–0.78)
				NA
Initial tumor origin				
Urinary bladder	560	129/279	166/281	0.62 (0.49–0.78)
Renal pelvis	96	24/44	25/52	1.23 (0.67–2.23)
Ureter	53	17/30	13/23	1.56 (0.70–3.48)
				0.73 (0.53–1.02)
				0.69 (0.53–0.90)
				0.64 (0.48–0.85)
				0.85 (0.57–1.28)
				0.67 (0.41–1.10)
				NA
				0.88 (0.54–1.43)
pT3	410	97/206	120/204	0.63 (0.48–0.82)
pT4a	119	36/57	40/62	0.77 (0.47–1.25)
Other	12	1/9	3/3	NA
Not reported	2	1/1	1/1	NA
				0.54 (0.16–1.86)
				0.75 (0.54–1.05)
				0.74 (0.47–1.15)
				0.57 (0.40–0.83)
				NA
Not reported	2	1/2	0	NA
		70/153	100/155	0.52 (0.38–0.71)
		100/200	104/201	0.92 (0.69–1.21)
		75/160	104/159	0.53 (0.39–0.72)
		95/193	100/197	0.91 (0.69–1.21)
		0/2	2/3	NA
		43/79	40/70	0.66 (0.40–1.06)
		78/165	93/177	0.76 (0.55–1.03)
		47/103	62/95	0.67 (0.44–1.00)
>120	15	2/4	7/11	NA
Smoking status				
Current or former smoker	484	116/237	141/247	0.70 (0.55–0.90)
Never smoked	215	53/111	61/104	0.67 (0.45–0.98)
Unknown	10	1/5	2/5	NA
PD-L1 expression level at baseline				
≥1%	280	55/139	79/141	0.56 (0.40–0.80)
<1%	419	114/210	120/209	0.82 (0.63–1.06)
Indeterminate or not able to be evaluated	8	1/3	4/5	NA
Not reported	2	0/1	1/1	NA



Adjuvant Atezolizumab versus observation in muscle-invasive urothelial carcinoma (IMvigor010)



	Atezolizumab group (n=406)	Observation group (n=403)
Age, years	67 (60–72)	66 (60–73)
Race		
White	320 (79%)	307 (76%)
Asian	64 (16%)	68 (17%)
Black or African American	3 (1%)	3 (1%)
American Indian or Alaska Native	1 (<1%)	0
Other or unknown	18 (4%)	25 (6%)
Sex		
Male	322 (79%)	316 (78%)
Female	84 (21%)	87 (22%)
Region		
North America	115 (28%)	126 (31%)
Europe	227 (56%)	210 (52%)
Asia	61 (15%)	64 (16%)
Australia	3 (1%)	3 (1%)
Primary tumour site		
Bladder	377 (93%)	378 (94%)
Upper tract (ureter, renal pelvis)	29 (7%)	25 (6%)
Pathological tumour stage*		
≤pT2	104 (26%)	101 (25%)
pT3 or pT4	302 (74%)	302 (75%)

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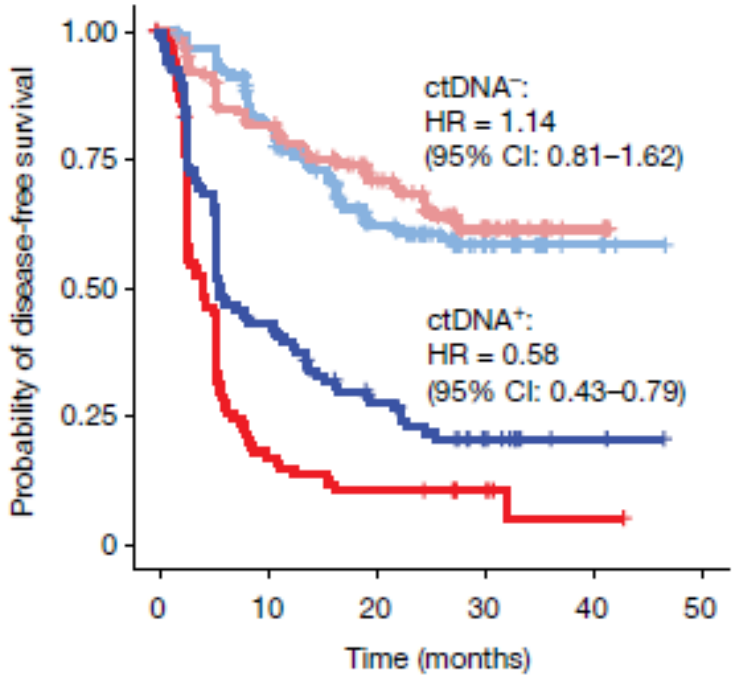
Bellmunt J et al Lancet 2021

ctDNA Guiding Adjuvant Immunotherapy in Urothelial Cancer

ctDNA– patients
medians not reached

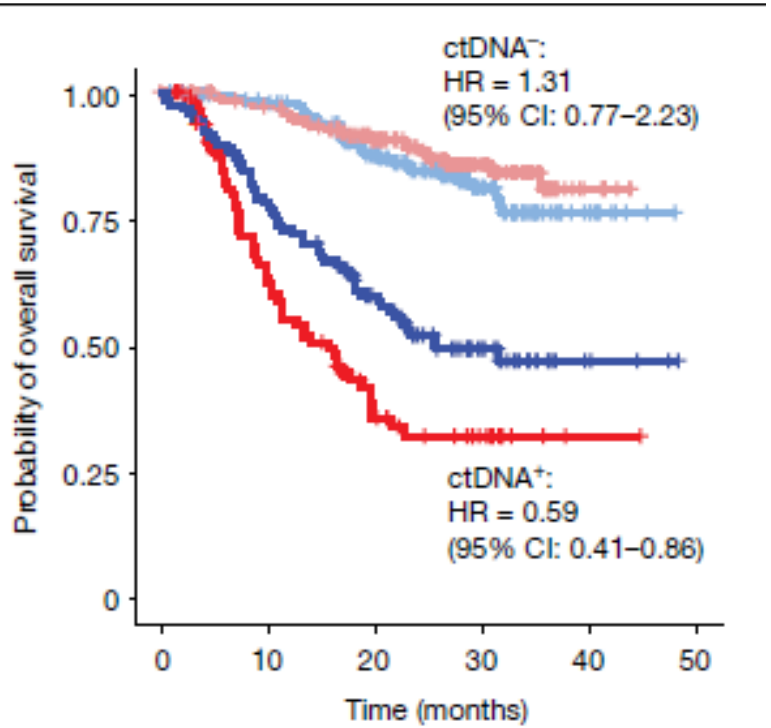
ctDNA+ patients treated with atezo (navy)
observation (red)
Median DFS 5.9 vs 4.4 mos



No. at risk						
Atezolizumab (ctDNA⁻)	184	144	85	44	5	0
Observation (ctDNA⁻)	183	140	90	46	6	0
Atezolizumab (ctDNA⁺)	116	48	25	13	2	0
Observation (ctDNA⁺)	98	17	10	5	1	0

ctDNA– patients
medians not reached

ctDNA+ patients treated with atezo (navy)
observation (red)
Median OS 25.8 vs 15.8 mos



Atezolizumab (ctDNA⁻)	184	174	129	57	10	0
Observation (ctDNA⁻)	183	170	130	65	7	0
Atezolizumab (ctDNA⁺)	116	88	55	25	4	0
Observation (ctDNA⁺)	98	54	24	11	1	0

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Powles T et al Nature 2021

Phase III Adjuvant CPI Studies in UC

NCT	Agent / Title	Eligibility NAC	Eligibility no NAC	Update
NCT03244384 N=739	Pembrolizumab Versus Observation AMBASSADOR	≥ypT2 and/or N+	≥pT3 or pN+	Maturing
NCT02450331 N=809	Atezolizumab Versus Observation IMvigor010	≥ypT2-4 or ypN+	≥pT3-4 or pN+	Negative
NCT04660344 N=495	Atezolizumab Versus Placebo for High-Risk Muscle-Invasive Bladder Cancer ctDNA Positive Following Cystectomy IMvigor011	≥ypT2-4 or ypN+	≥pT3-4 or pN+	Recruiting
NCT02632409 N=700	Nivolumab Versus Placebo CheckMate 274			Positive

Phase III Adjuvant Studies in UC

NCT	Agent / Title	Eligibility NAC	Eligibility no NAC	Update
NCT03244384 N=739	Pembrolizumab Versus Observation AMBASSADOR	≥ypT2-4 and/or N+	≥pT3 or pN+	Maturing
NCT02450331 N=809	Atezolizumab Versus Observation IMvigor010	≥ypT2-4 or ypN+	≥pT3-4 or pN+	Negative
NCT04660344 N=495	Atezolizumab Versus Placebo for High-Risk Muscle-Invasive Bladder Cancer ctDNA Positive Following Cystectomy IMvigor011	≥ypT2-4 or ypN+	≥pT3-4 or pN+	Recruiting
NCT02632409 N=700	Nivolumab Versus Placebo CheckMate 274			Positive
NCT04197986 N=218	Oral Infigratinib for Invasive Urothelial Carcinoma With Susceptible FGFR3 Genetic Alterations	≥ypT2-4 or ypN+	≥pT3-4 or pN+	Recruiting

1L Treatment of Chemotherapy Ineligible Pts

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

	Group A (n=451)	Group B (n=362)	Group C (n=400)
(Continued from previous page)			
Cisplatin ineligibility per Galsky criteria¶	263 (58%)	192 (53%)	222 (56%)
Renal impairment‖	222 (49%)	172 (48%)	202 (51%)
Hearing loss of ≥25 dB	16 (4%)	11 (3%)	8 (2%)
Peripheral neuropathy grade ≥2	6 (1%)	2 (1%)	3 (1%)
ECOG performance status 2	60 (13%)	31 (9%)	40 (10%)
Investigator choice of chemotherapy**			
Carboplatin	314 (70%)	227 (63%)	264 (66%)
Cisplatin	137 (30%)	135 (37%)	136 (34%)

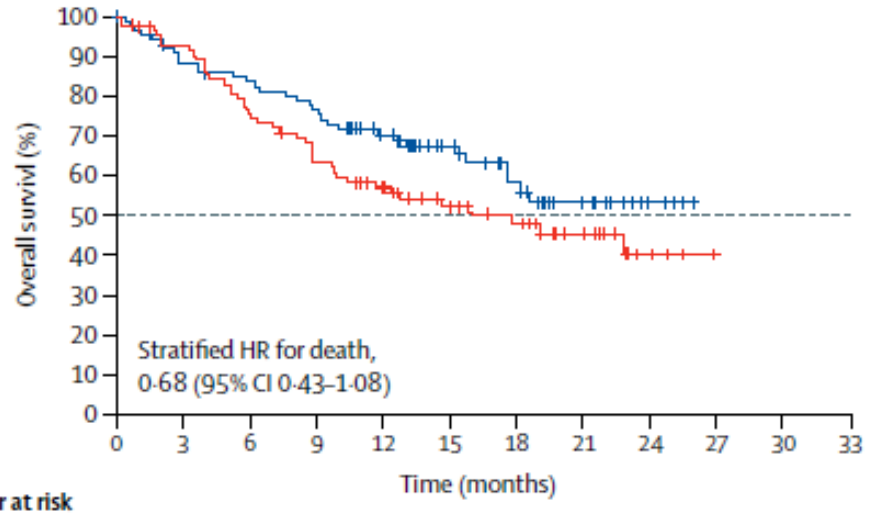
Data are median (IQR) or n (%). ECOG=Eastern Cooperative Oncology Group. *One patient in group A reported both locally advanced and metastatic disease. †Defined as lung, liver, and bone metastases. ‡n=444 for group A; n=359 for group B; n=394 for group C. §Bajorin risk factor 0=score 0 and no liver metastases, 1=score 1 and no liver metastases, 2=score 2 or liver metastases. ¶Per protocol, excluding New York Heart Association functional classification. ‖Creatinine clearance could not be evaluated for one patient without a bodyweight measurement in group B. **Investigator's choice of platinum therapy refers to the choice before randomisation; patients randomly assigned to group B did not receive platinum as part of the initial study design.

Table 1: Baseline characteristics

Galsky M et al Lancet 2020

E

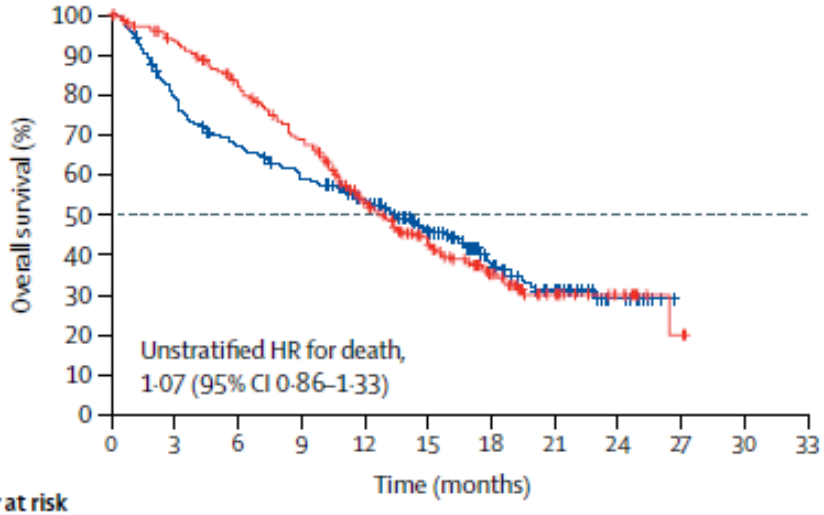
	Number of events/ number of patients	Median overall survival (95% CI), months
Atezolizumab monotherapy (group B)	33/88	NE (17·7–NE)
Placebo + platinum-based chemotherapy (group C)	42/85	17·8 (10·0–NE)



Number at risk (number censored)												
Atezolizumab monotherapy (group B)	88 (0)	75 (3)	70 (4)	64 (4)	49 (14)	35 (26)	24 (33)	14 (41)	5 (50)	NE	NE	NE
Placebo + platinum-based chemotherapy (group C)	85 (0)	76 (3)	62 (3)	51 (4)	42 (8)	30 (17)	21 (24)	14 (30)	5 (38)	1 (42)	NE	NE

F

	Number of events/ number of patients	Median overall survival (95% CI), months
Atezolizumab monotherapy (group B)	158/272	13·5 (11·1–16·4)
Placebo + platinum-based chemotherapy (group C)	156/274	12·9 (11·3–15·0)



Number at risk (number censored)												
Atezolizumab monotherapy (group B)	272 (0)	210 (7)	175 (10)	152 (12)	124 (27)	85 (49)	48 (74)	28 (87)	11 (103)	NE	NE	NE
Placebo + platinum-based chemotherapy (group C)	274 (0)	246 (10)	212 (16)	173 (20)	116 (40)	73 (62)	41 (83)	21 (98)	10 (109)	2 (116)	NE	NE

PD-L1 IC2/3 tumors

PD-L1 IC 0/1 tumors

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August 31, 2021 - PD-L1 No Longer SOC Biomarker for Pembrolizumab in 1L mUC

1L mUC label for Pembrolizumab changed from accelerated to full FDA approval

- Now requires:
  - **Ineligible for any platinum regardless of PD-L1 status**

- No changes YET to Atezolizumab 1L mUC label:
  - **Are not eligible for cisplatin-containing therapy, and whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥5% of the tumor area), as determined by an FDA-approved test, or**

  - **Are not eligible for any platinum-containing therapy regardless of PD-L1 status.**

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-limits-use-tecentriq-and-keytruda-some-urothelial-cancer-patients

Atezolizumab and Pembrolizumab Remain Options for Select pts in 1L Setting

Platinum Ineligible Consensus

≥1 of the following[1]:

- ECOG PS ≥3
- Cr Cl <30 ml/min
- Peripheral neuropathy ≥ G3
- NYHA HF class ≥3
- ECOG PS 2 + Cr Cl <30 ml/min

Atezolizumab Phase II[2]

- **ORR 23%, CR 9%**
- **Median OS 15.9 mos**

5 year FU[4]

- **ORR 24%, CR 10%**
- **Median OS 16.3 mos**

Pembrolizumab Phase II[3]

- **ORR 24%, CR 5%**
- **6 month OS 67%mos**

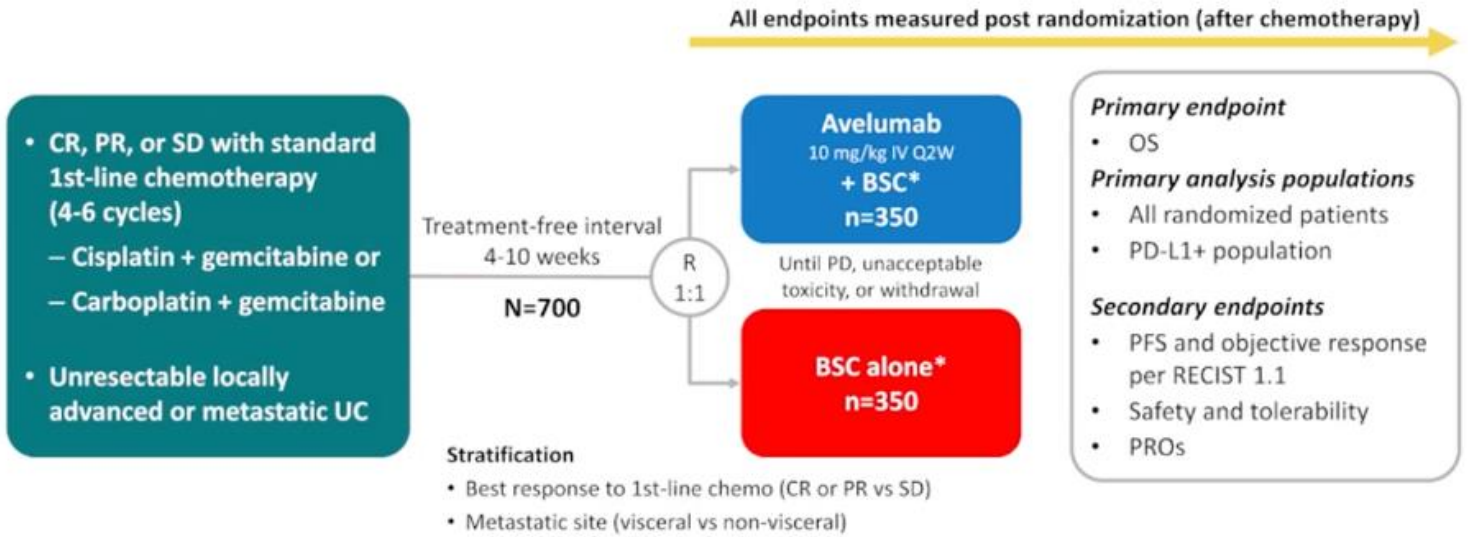
2 year FU[5]

- **ORR 29%, CR 9%**
- **Med DOR 30.1 mos**
- **Med OS 11.3 mos, CPS>10 18.5 mos**
- **LN OS 27 mos**

1. Gupta S et al GU ASCO 2019
2. Balar A et al Lancet 2017
3. Balar A et al Lancet Onc 2017
4. Rosenberg et al ESMO 2021
5. Vuky J et al JCO 2020

Avelumab Maintenance Following Clinical Benefit of 1L Platinum 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

BSC, best supportive care; **CR**, complete response; **IV**, intravenous; **PR**, partial response; **PRO**, patient reported outcome; **Q2W**, every 2 weeks; **R**, randomization; **RECIST 1.1**, Response Evaluation Criteria in Solid Tumors version 1.1; **SD**, stable disease

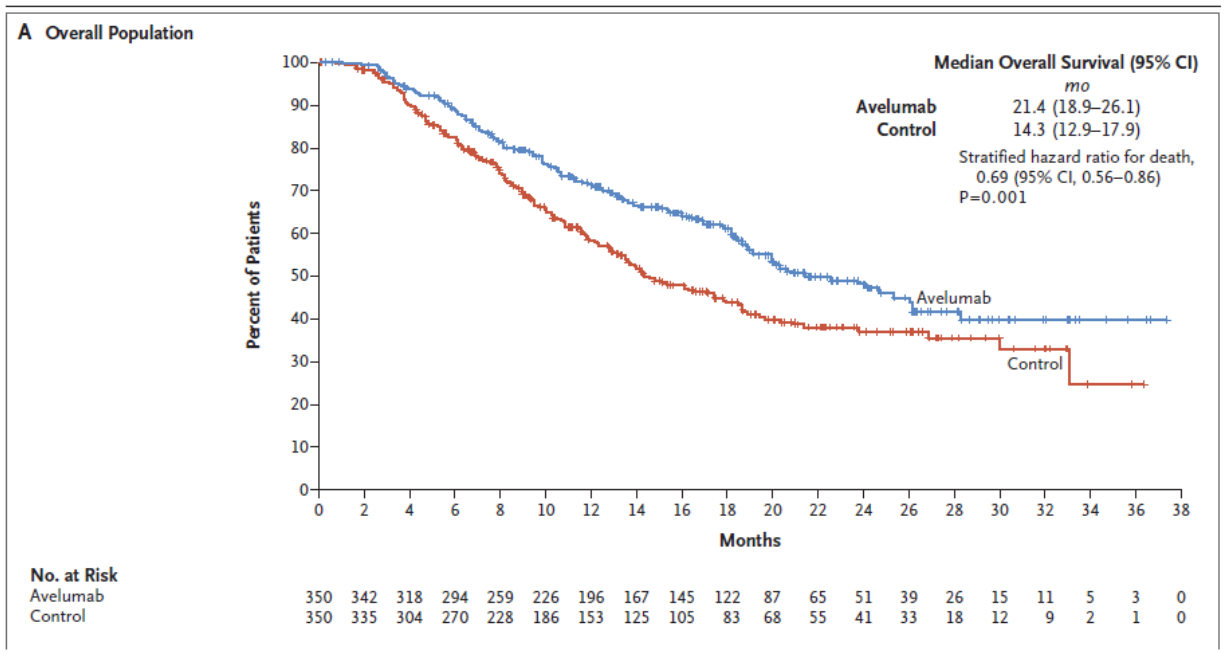
*BSC (eg, antibiotics, nutritional support, hydration, or pain management) was administered per local practice based on patient needs and clinical judgment; other systemic antitumor therapy was not permitted, but palliative local radiotherapy for isolated lesions was acceptable

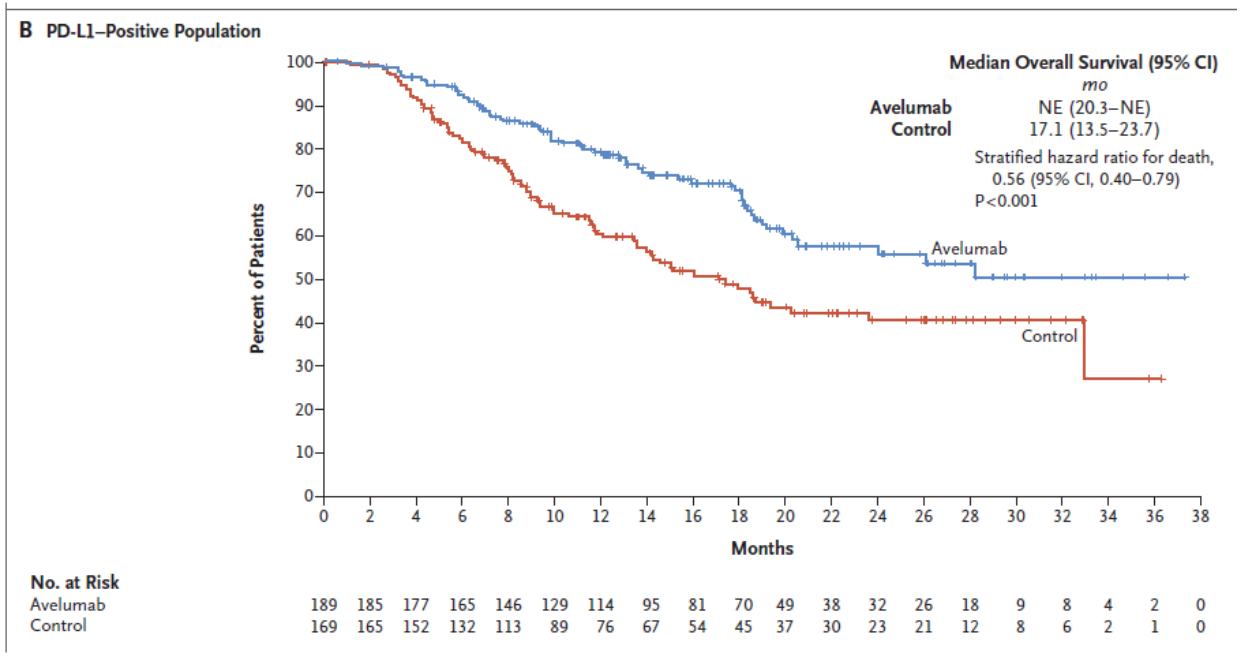
Powles T et al Sept 2020 NEJM

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Overall Population		PD-L1–Positive Population	
	Avelumab Group (N=350)	Control Group (N=350)	Avelumab Group (N=189)	Control Group (N=169)
Age — yr				
Median	68	69	70	70
Range	37–90	32–89	37–90	32–84
Site of primary tumor — no. (%)†				
Upper tract	106 (30.3)	81 (23.1)	44 (23.3)	35 (20.7)
Lower tract	244 (69.7)	269 (76.9)	145 (76.7)	134 (79.3)
Site of baseline metastasis before chemotherapy — no. (%)				
Visceral site	191 (54.6)	191 (54.6)	88 (46.6)	79 (46.7)
Nonvisceral site‡	159 (45.4)	159 (45.4)	101 (53.4)	90 (53.3)
PD-L1 status — no. (%)				
Positive	189 (54.0)	169 (48.3)	189 (100)	169 (100)
Negative	139 (39.7)	131 (37.4)	0	0
Unknown	22 (6.3)	50 (14.3)	0	0
First-line chemotherapy regimen — no. (%)				
Gemcitabine plus cisplatin	183 (52.3)	206 (58.9)	101 (53.4)	98 (58.0)
Gemcitabine plus carboplatin	147 (42.0)	122 (34.9)	74 (39.2)	54 (32.0)
Gemcitabine plus cisplatin or carboplatin§	20 (5.7)	20 (5.7)	14 (7.4)	15 (8.9)
Not reported	0	2 (0.6)	0	2 (1.2)
Best response to first-line chemotherapy — no. (%)				
Complete response or partial response	253 (72.3)	252 (72.0)	139 (73.5)	128 (75.7)
Stable disease	97 (27.7)	98 (28.0)	50 (26.5)	41 (24.3)

OS was Improved by Maintenance Avelumab in IIT and More Pronounced in PD-L1+ CA





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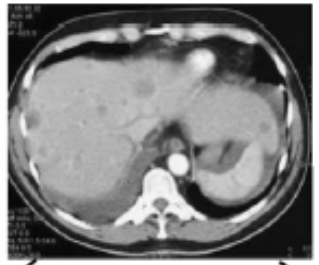
Phase III Frontline CPI Studies in Bladder Cancer

NCT	Agent / Title	Update
NCT03732677 N=1292	Gemcitabine/Cis(carbo)platin +/- Durvalumab +/- Tremelimumab NILE	Recruiting
NCT04223856 N=760	Enfortumab Vedotin + Pembrolizumab vs Gemcitabine/Cis(carbo)platin EV 302	Recruiting
NCT03036098 N=897	Gemcitabine/Cis(carbo)platin +/- Nivolumab vs Ipilimumab+ Nivolumab Checkmate 901	Recruiting
NCT03967977 N=420	Gemcitabine/Cis(carbo)platin +/- Tislelizumab (anti PD-1)	Recruiting
NCT04568304 N=364	Gemcitabine/Cis(carbo)platin +/- Toripalimab (anti PD-1)	Pending

Metastatic Therapy Spring 2021



Chemotherapy Ineligible

CPI
Pembrolizumab or Atezolizumab

Chemotherapy Eligible

Cisplatin Ineligible

Carboplatin and Gemcitabine

Pembrolizumab, Atezolizumab, nivolumab, durvalumab, avelumab

Cisplatin Eligible

Cisplatin and Gemcitabine
aMVAC

Pembrolizumab, Atezolizumab, nivolumab, durvalumab, avelumab

CR/PR/SD on
1L Platinum

Avelumab
Maintenance

PD on
1L Platinum

Pembrolizumab, ~~Atezolizumab,~~ nivolumab, ~~durvalumab~~, avelumab

FGFR3 mut/fusion +

Enfortumab Vedotin

Erdafitinib

Sacituzumab

FGFR3 mut/fusion -

Enfortumab Vedotin

Sacituzumab

Summary Checkpoint Immunotherapy in Urothelial Cancer

- CPI therapy alone is approved in several UC disease states, with more pending
- Toxicity is consistent across disease states
- Sequencing after, rather than combining with 1L platinum, is proven SOC
- Optimal sequence of CPI given all approved agents, yet to be determined
- Future combination strategies may prove more successful than chemo/CPI combinations
- Improvement in biomarkers may help with optimization
- Approval in dMMR / MSI-H may have implications for pts with Lynch associated UC

Thank you!