Society for Immunotherapy of Cancer

Cancer Immunotherapy GUIDELINES

Immunotherapy for the Treatment of Urothelial Cancer

August 25, 2021

5:30 – 6:30 p.m. EDT

Jointly provided by Postgraduate Institute for Medicine and the Society for Immunotherapy of Cancer

This webinar is supported, in part, by independent medical education grant funding from Amgen, AstraZeneca Pharmaceuticals LP, and Merck & Co., Inc.

Webinar faculty

Ashish M. Kamat, MD, MBBS, FACS – *The University of Texas MD Anderson Cancer Center*

Peter C. Black, MD – *University of British Columbia*

Matthew D. Galsky, MD – *Tisch Cancer Institute at Mount Sinai Medical Center*

Arjun V. Balar, MD – *Perlmutter Cancer Center – NYU Langone Medical center*

Learning objectives

- Select appropriate diagnostics and biomarker testing tailored to the clinical setting for a patient being considered for immunotherapy based on the expert panel recommendations in the SITC Clinical Practice Guideline (CPG)
- Implement immunotherapy treatments effectively and appropriately for urothelial cancer according to the recommendations in the CPG
- Appraise patterns of response to immunotherapy in order to appropriately monitor and manage patients during treatment

Webinar outline

- Introduction to the Guideline
- Biomarkers in urothelial cancer
- Non-muscle invasive bladder cancer
- Advanced urothelial cancer
- Future directions for immunotherapy in urothelial cancer

Development of the guideline

- Panel included 15 members
- Developed in accordance with The Institute of Medicine's Standards for Developing Trustworthy Clinical Practice Guidelines
- Recommendations are based on literature evidence where available and expert consensus where necessary
- Consensus is defined as ≥75% agreement amongst panel members

Original guideline: 2017

Kamat *et al. Journal for ImmunoTherapy of Cancer* (2017) 5:68
DOI 10.1186/s40425-017-0271-0

Journal for ImmunoTherapy of Cancer

POSITION ARTICLE AND GUIDELINES **Open Access**

Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of bladder carcinoma

Ashish M. Kamat[1*], Joaquim Bellmunt[2], Matthew D. Galsky[3], Badrinath R. Konety[4], Donald L. Lamm[5], David Langham[6], Cheryl T. Lee[7], Matthew I. Milowsky[8], Michael A. O'Donnell[9], Peter H. O'Donnell[10], Daniel P. Petrylak[11], Padmanee Sharma[12], Eila C. Skinner[13], Guru Sonpavde[14], John A. Taylor III[15], Prasanth Abraham[16] and Jonathan E. Rosenberg[17]

Development of the guideline

Open access Position article and guidelines

Journal for ImmunoTherapy of Cancer

Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immunotherapy for the treatment of urothelial cancer

Matthew D Galsky,[1] Arjun V Balar,[2] Peter C Black,[3] Matthew T Campbell,[4] Gail S Dykstra,[5,6] Petros Grivas,[7,8] Shilpa Gupta,[9] Christoper J Hoimes,[10] Lidia P Lopez,[11] Joshua J Meeks,[12,13] Elizabeth R Plimack,[14] Jonathan E Rosenberg,[15,16] Neal Shore,[17] Gary D Steinberg,[18] Ashish M Kamat[19]

Webinar outline

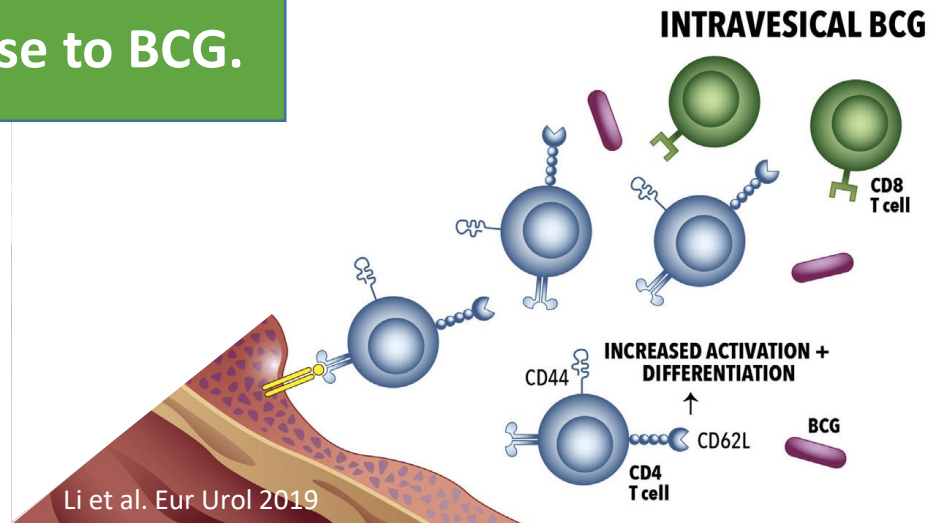
- Introduction to the Guideline
- Biomarkers in urothelial cancer
- Non-muscle invasive bladder cancer
- Advanced urothelial cancer
- Future directions for immunotherapy in urothelial cancer

Biomarkers to predict response to BCG

Exploratory markers only:

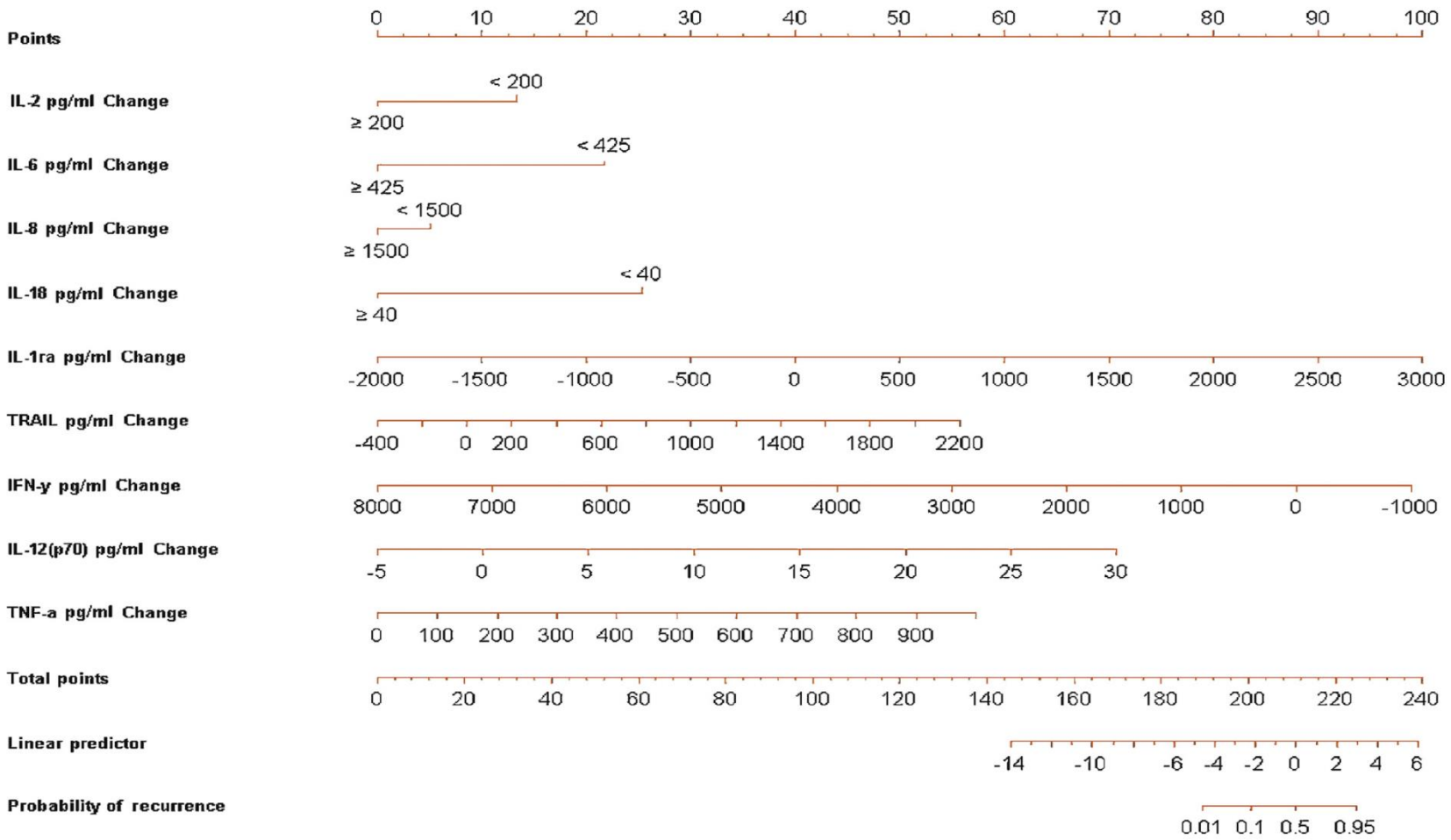
CyPRIT cytokine panel	UroVysion FISH	RNA expression signatures	ARID1A mutation
Kamat et al., Eur Urol 2016	Kamat et al., J Urol 2012	Kates et al., BCAN 2020	Pietzak et al., Eur Urol 2017

There are <u>no</u> validated biomarkers to predict response to BCG.



Li et al. Eur Urol 2019

CyPRIT predicted the probability of recurrence with 85.5% accuracy



Kamat et al. Eur Urol 2016

Biomarkers of response to anti-PD(L)1

Exploratory

- Tumor mutational burden (TMB)
- MSI/dMMR
- RNA molecular subtypes
- RNA signatures (e.g. IFNg)

Potential clinical utility

- PD-L1 IHC
  - Ventana SP142 (atezolizumab)
    - IHC-223 pharmDx (pembrolizumab)
  - IHC28-8 pharmDx (nivolumab)
    - Ventana SP263 (durva/avelumab)

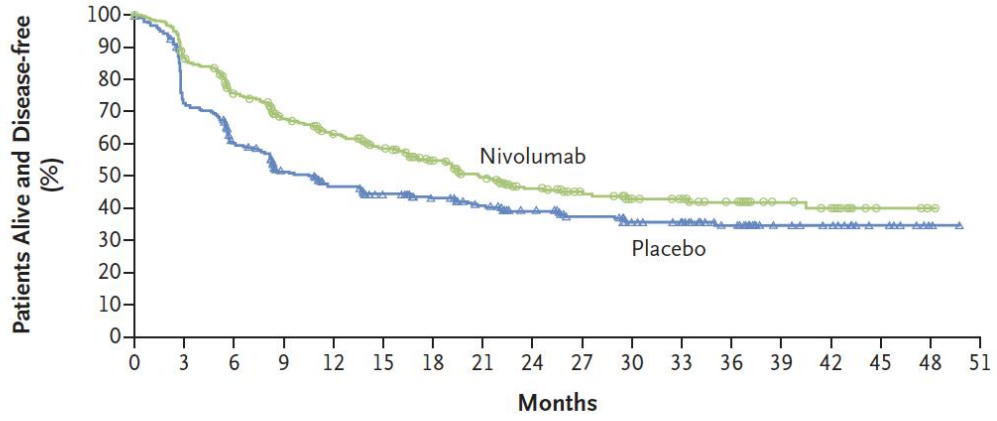
A role for PD-L1 immunohistochemistry?

BCG-unresponsive NMIBC	MIBC Adjuvant	First line mUC cisplatin ineligible	First line mUC switch maintenance	Second Line mUC
Pembrolizumab	Nivolumab	Pemrbolizumab Atezolizumab	Avelumab	Any
No value in PDL1 testing	PFS benefit in ITT, enhanced in PDL1+	Administer to carbo-eligible only if PDL1+	OS benefit in ITT, enhanced in PDL1+	No value in PDL1 testing

But carboplatin followed by switch maintenance avelumab is preferred regardless of PD-L1 status

MIBC Adjuvant: Checkmate 274

Overall

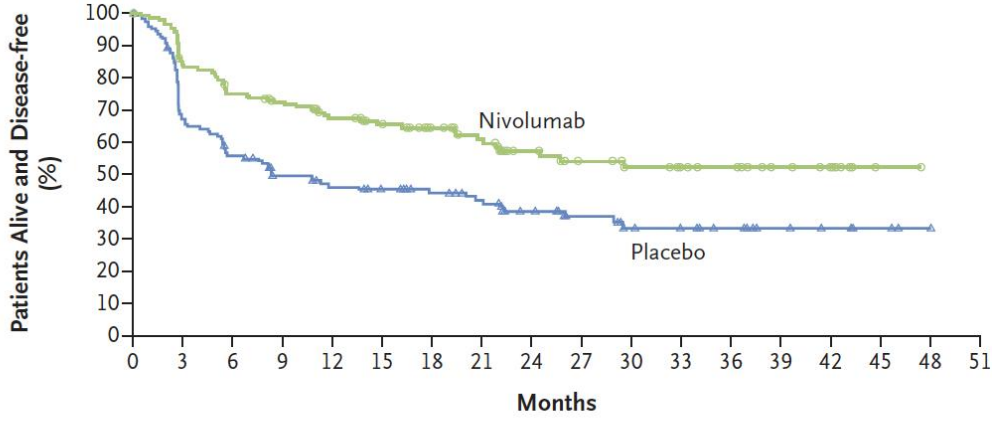


No. at Risk																		
Nivolumab	353	296	244	212	178	154	126	106	85	68	57	51	36	23	20	3	1	0
Placebo	356	248	198	157	134	121	105	94	80	65	54	50	37	22	19	10	2	0

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

Hazard ratio for disease recurrence or death:
0.70 (98.72% CI, 0.55 – 0.90) p<0.001

PD-L1+



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

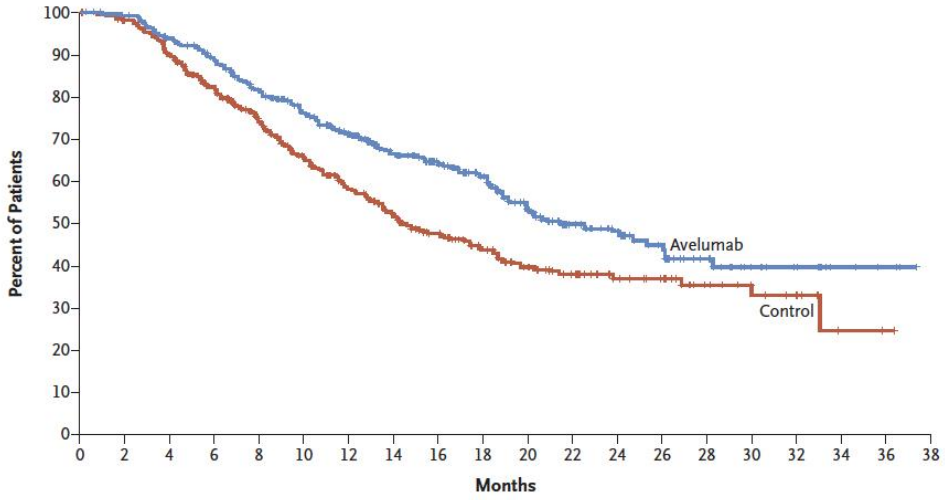
No. of Events/ No. of Patients	Disease-free Survival at 6 Mo (95% CI)	Disease-free Survival at 12 Mo (95% CI)
	%	
55/140	74.5 (66.2–81.1)	67.2 (58.4–74.5)
81/142	55.7 (46.8–63.6)	45.9 (37.1–54.2)

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

D Bajorin et al., N Engl J Med 2021;384:2102-14.

mUC Switch Maintenance: Javelin 100 Bladder

Overall



No. at Risk

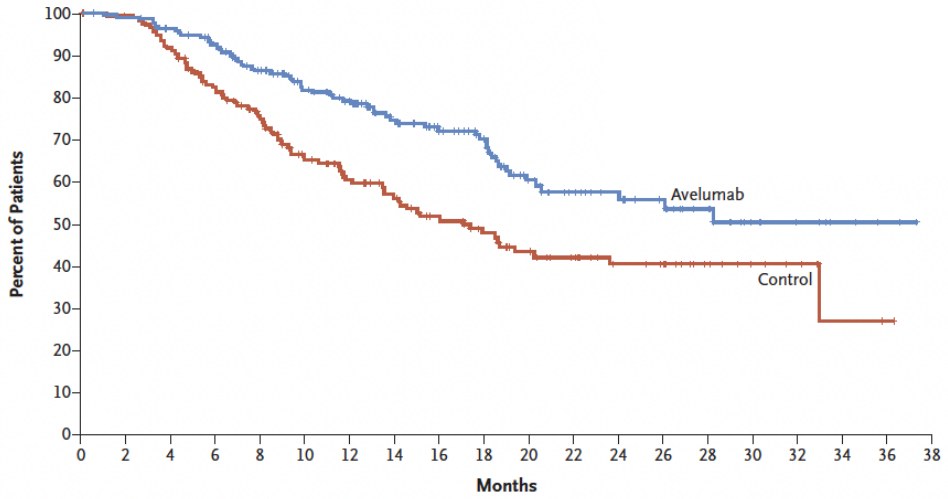
Avelumab	350	342	318	294	259	226	196	167	145	122	87	65	51	39	26	15	11	5	3	0
Control	350	335	304	270	228	186	153	125	105	83	68	55	41	33	18	12	9	2	1	0

Median Overall Survival (95% CI)

	mo
Avelumab	21.4 (18.9–26.1)
Control	14.3 (12.9–17.9)

Stratified hazard ratio for death:
0.69 (95% CI, 0.56 – 0.86) p=0.001

PD-L1+



No. at Risk

Avelumab	189	185	177	165	146	129	114	95	81	70	49	38	32	26	18	9	8	4	2	0
Control	169	165	152	132	113	89	76	67	54	45	37	30	23	21	12	8	6	2	1	0

Median Overall Survival (95% CI)

	mo
Avelumab	NE (20.3–NE)
Control	17.1 (13.5–23.7)

Stratified hazard ratio for death:
0.56 (95% CI, 0.40 – 0.79) p<0.001

T Powles et al., N Engl J Med 2020;383:1218-30.

MSI/dMMR predicts response to anti-PD(L)1

Microsatellite instability (MSI) or mismatch repair deficiency (dMMR) is found in 1% of bladder ca and 7-14% of upper tract urothelial ca (Lynch Syndrome)

Pembrolizumab is indicated in patients with metastatic or unresectable solid tumor refractory to first line therapy if MSI/dMMR

However, pembrolizumab is indicated for platinum-refractory mUC regardless of MSI/dMMR status

Similar for pembrolizumab in treatment of patients with unresectable or metastatic solid tumors with high TMB (≥10 mutations/ megabase (mut/Mb))

Biomarkers - Summary

There are currently no biomarkers to predict response to BCG therapy.

PD-L1 immunohistochemistry is only indicated to determine use of carboplatin vs. anti-PD(L)1 therapy in carboplatin-eligible, cisplatin-ineligible patients with mUC (first line).

Pembrolizumab is indicated in 2nd line mUC regardless of MSI/dMMR or TMB status, so that these markers do not currently have an established role in treatment selection.

Galsky, J Immunother Cancer 2021

Webinar outline

- Introduction to the Guideline
- Biomarkers in urothelial cancer
- Non-muscle invasive bladder cancer
- Advanced urothelial cancer
- Future directions for immunotherapy in urothelial cancer

Risk-Adapted NMIBC Therapy

Low Risk	Intermediate Risk	High Risk	Very High Risk
TURBT	TURBT	TURBT x 2	TURBT
Single dose post-op chemo Observation Office fulguration	Single dose post-op chemo Consider adjuvant chemo, or **BCG with maintenance (1 yr)**	**BCG with maintenance (3 years)** → Radical cystectomy ↓ **Pembrolizumab**	

INTRACAVITARY BACILLUS CALMETTE-GUERIN IN THE TREATMENT OF SUPERFICIAL BLADDER TUMORS

A. MORALES,* D. EIDINGER AND A. W. BRUCE

From the Departments of Urology, and Microbiology and Immunology, Queen's University, Kingston, Ontario, Canada

(Reprinted from J Urol, 116: 180–183, 1976)

0022-5347/00/1634-1124/0
THE JOURNAL OF UROLOGY®

Vol. 163, 1124–1129, April 2000
Printed in U.S.A.

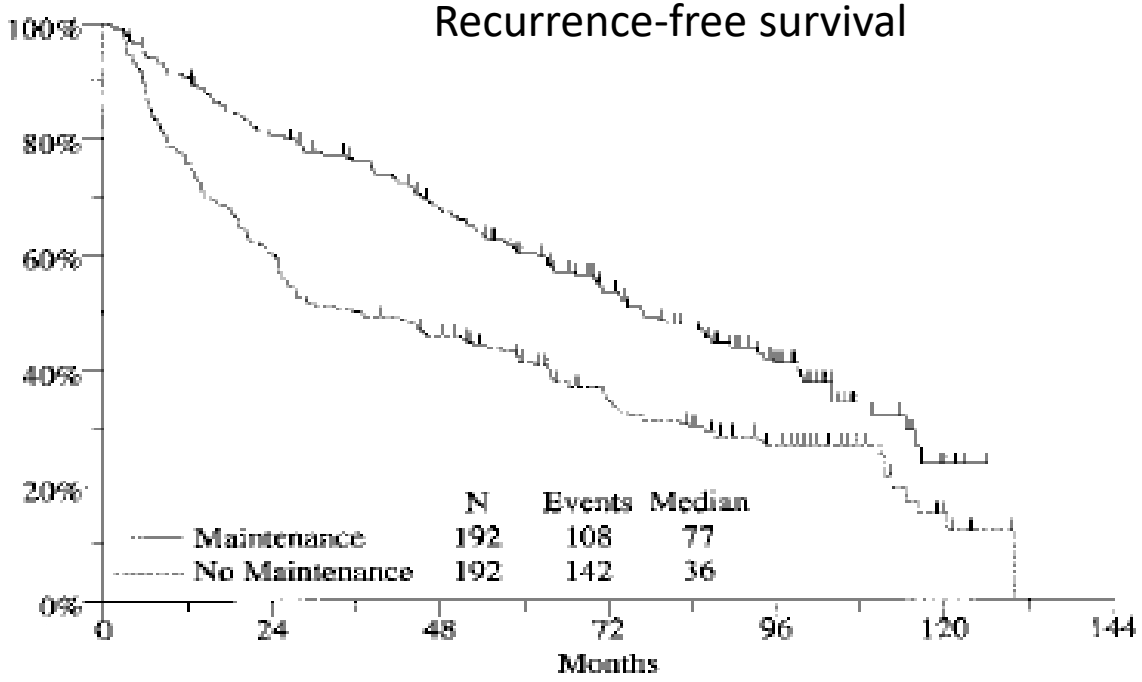
MAINTENANCE BACILLUS CALMETTE-GUERIN IMMUNOTHERAPY FOR RECURRENT TA, T1 AND CARCINOMA IN SITU TRANSITIONAL CELL CARCINOMA OF THE BLADDER: A RANDOMIZED SOUTHWEST ONCOLOGY GROUP STUDY

DONALD L. LAMM,*,† BRENT A. BLUMENSTEIN, JOHN D. CRISSMAN, JAMES E. MONTIE, JAMES E. GOTTESMAN, BRUCE A. LOWE, MICHAEL F. SAROSDY,‡ ROBERT D. BOHL, H. BARTON GROSSMAN,§ THOMAS M. BECK, JOSEPH T. LEIMERT AND E. DAVID CRAWFORD‖

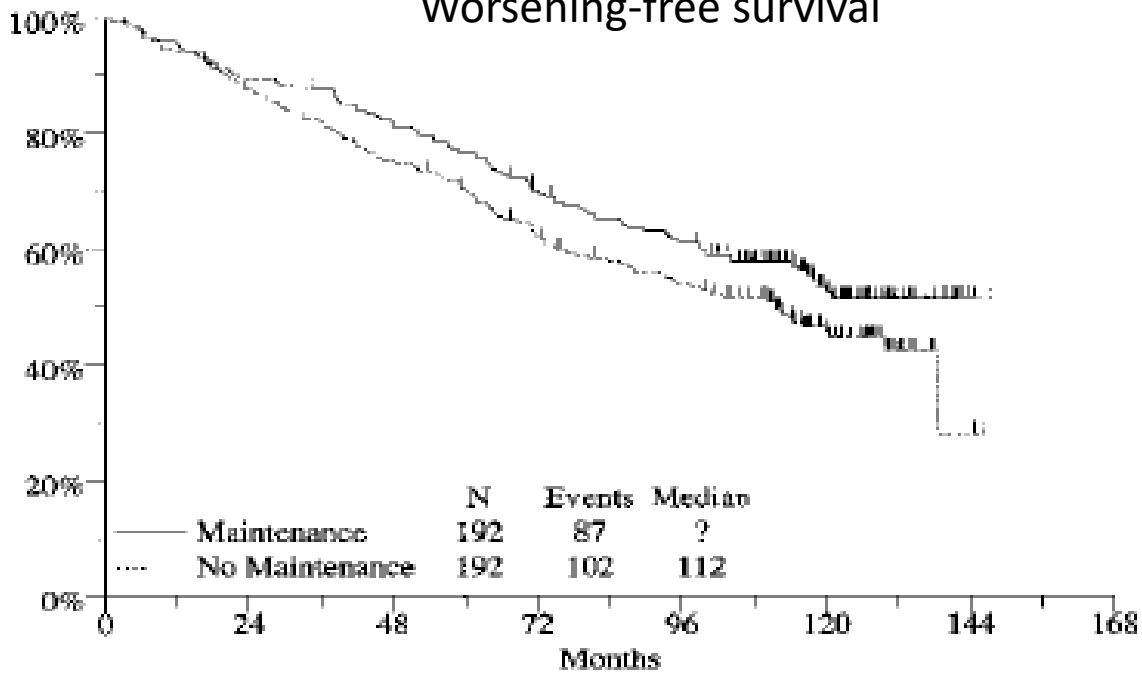
From the West Virginia University Medical Center, Morgantown, West Virginia, Southwest Oncology Group Statistical Center and Swedish Hospital Tumor Institute, Seattle, Washington, Harper Hospital, Detroit and University of Michigan Medical Center, Ann Arbor, Michigan, Oregon Health Sciences University and Northwest Clinical Oncology Program, Portland, Oregon, University of Texas Health Science Center at San Antonio, San Antonio and University of Texas M. D. Anderson Cancer Center, Houston, Texas, Columbus Clinical Oncology Program, Columbus, Ohio, St. Luke's Regional Medical Center, Boise, Idaho, and University of Colorado, Denver, Colorado

BCG: Bacillus Calmette-Guérin

Recurrence-free survival



Worsening-free survival

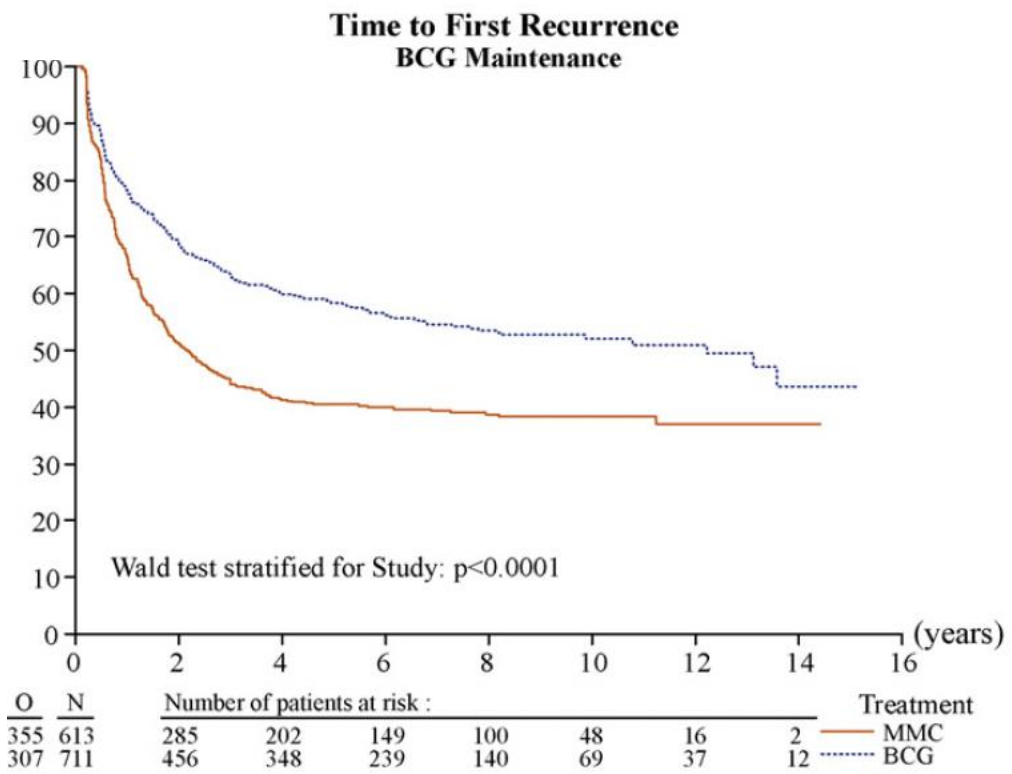


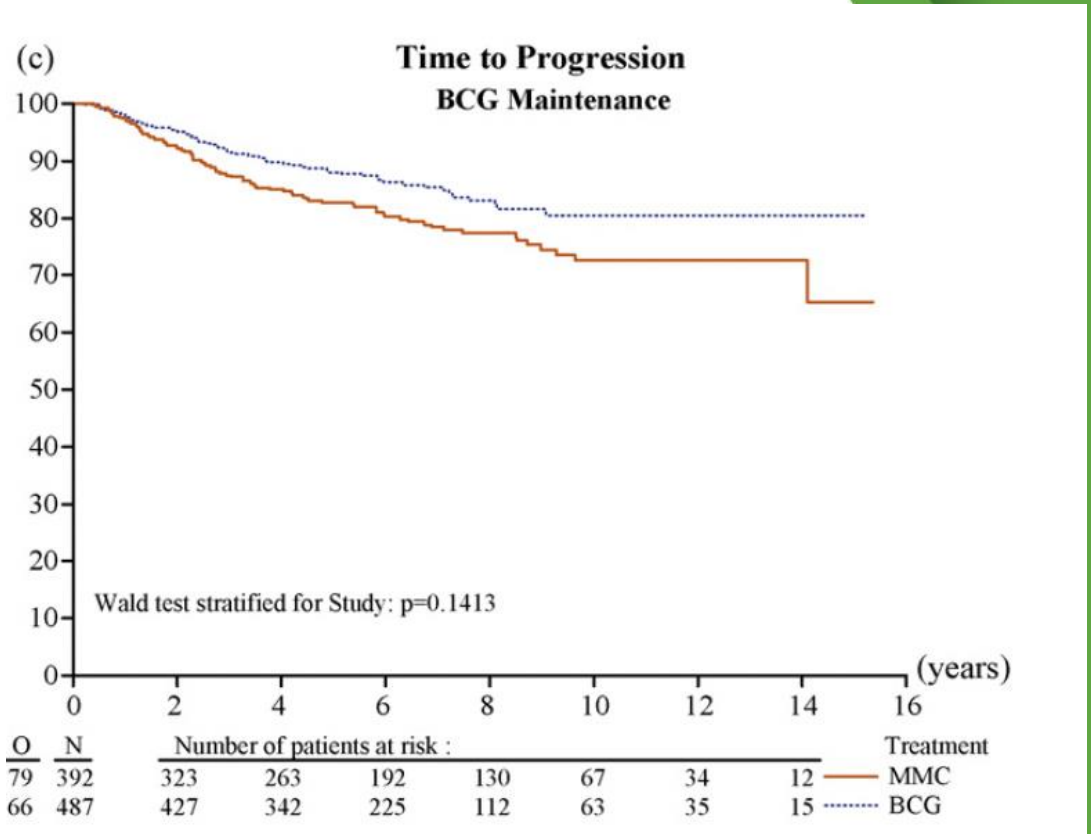
SWOG 8507

Lamm et al., J Urol 2000

BCG is Superior to Chemotherapy

Meta-analysis of 9 trials including 2820 patients





Mitomycin

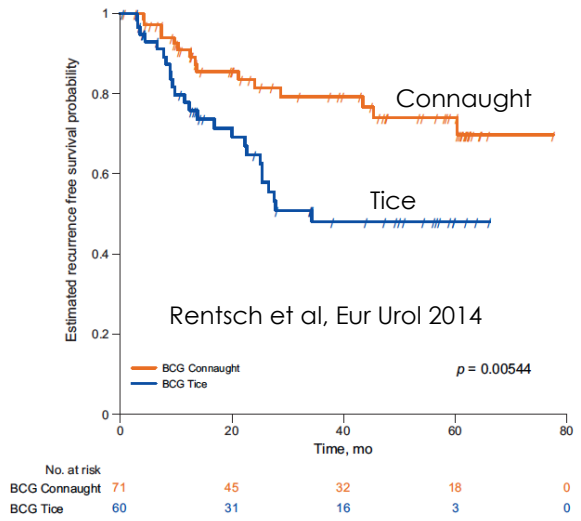
BCG

Malmström PU et al., Eur Urol. 2009

Better BCG: Building on a Solid Foundation

Completed trial: S1602 A Randomized Trial to Evaluate the Influence of BCG Strain Differences and T Cell Priming for BCG-Naïve High-Grade Non-Muscle Invasive Bladder Cancer

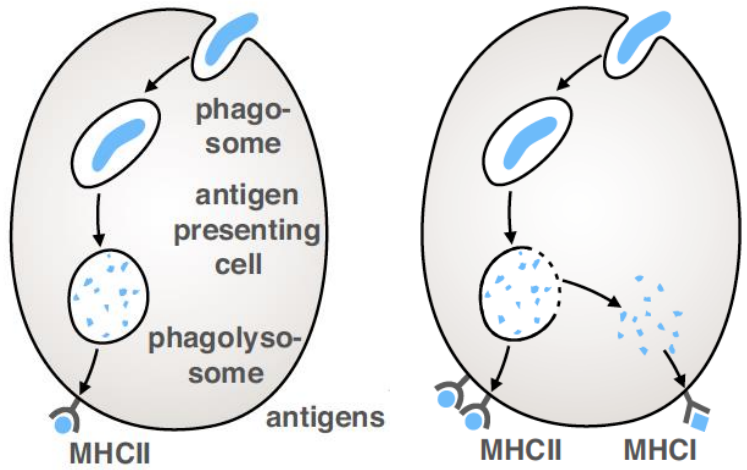
BCG Strain



Intradermal BCG

Vaccination

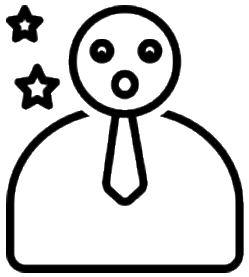
Genetically Engineered BCG



M Gengenbacher et al 2017

High risk NMIBC disease states defined by BCG

BCG Naïve



BCG ‘Exposed’

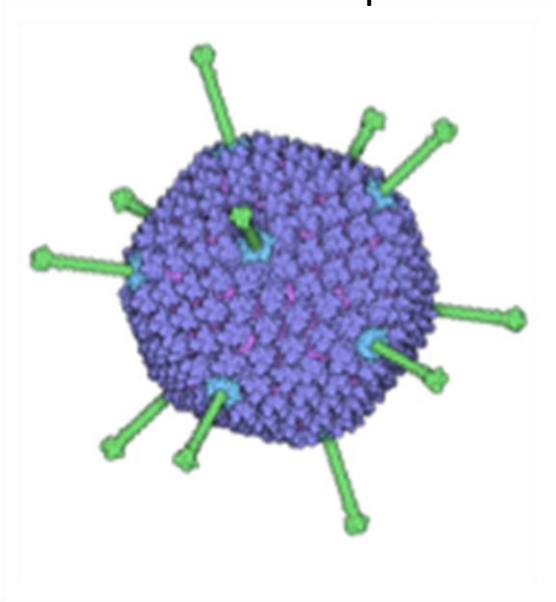
- Induction only
- Late Relapse

BCG Unresponsive

- BCG Refractory
- Early Relapse

Intravesical nadofaragene firadenovec for BCG unresponsive CIS ± Ta/T1

Gene therapy: adenovirus carrying IFN-α2b
+ SYN3 as excipient



FDA priority review ongoing

Phase III Results

CR @ 3 months: 53% (73% in Ta/T1)

CR @ 6 months: 41% (63% in Ta/T1)

CR @ 9 months: 35% (58% in Ta/T1)

CR @ 12 months: 24% (44% in Ta/T1)

(5 patients progressed to MIBC (TURBT or RC))

Boorjian et al, Lancet Oncol 2020

PD(L)1 Inhibitors for BCG unresponsive CIS ± Ta/T1

Keynote 057 Pembrolizumab

N=96

3 mo CR: 41%

6 mo CR: 31%

12 mo CR: 19%

median DOR 16 mo

Gr 3 TRAE: 13%

Balar et al, Lancet Oncol 2021

SWOG S1605 Atezolizumab

N=74

3 mo CR: 42%

6 mo CR: 27% (mandatory biopsy)

12 mo CR: 25%

median DOR 15 mo

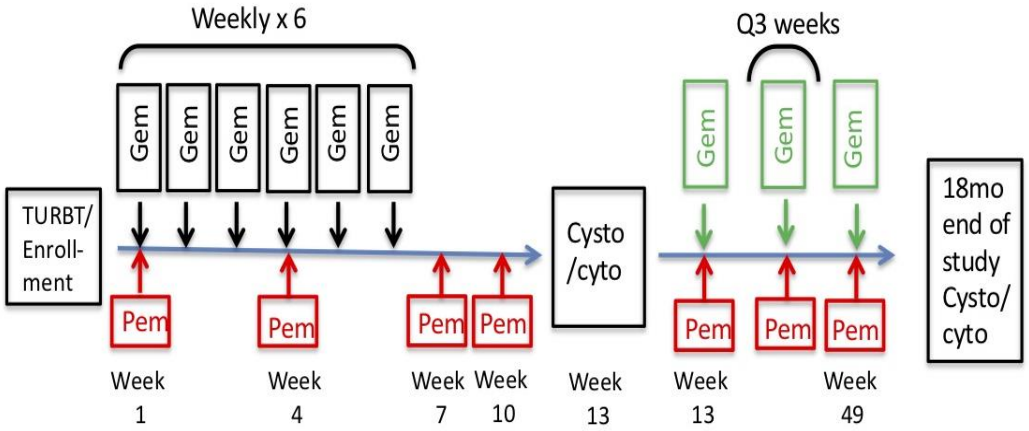
Gr 3 TRAE: 16%

Black et al, ASCO 2020 & 2021

What's next: Combination Therapy with Immune Checkpoint Inhibitors

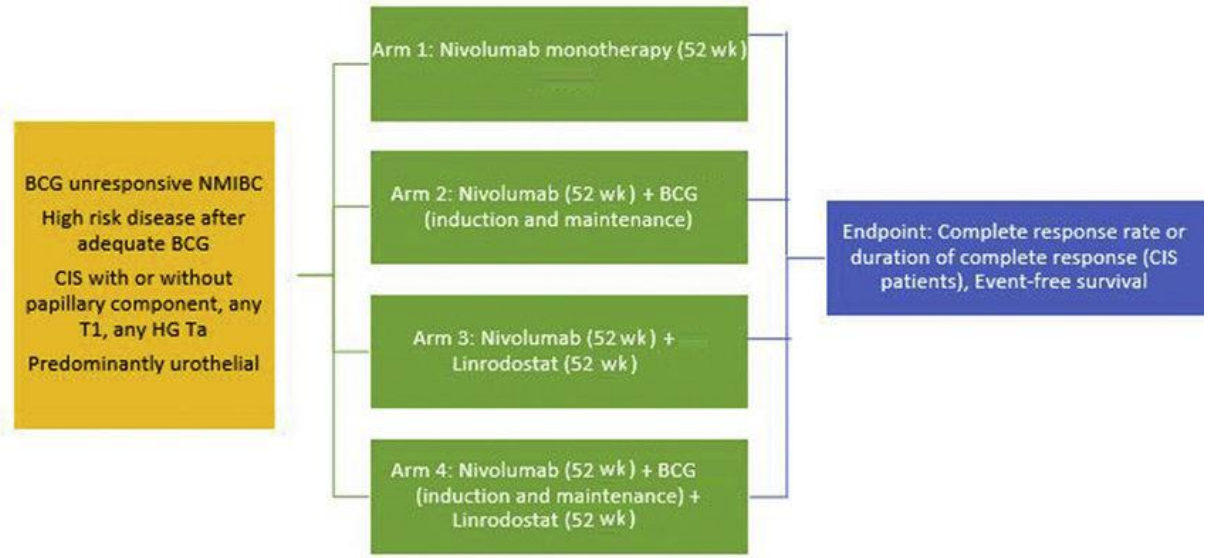
A031803 Pembrolizumab

BCG unresponsive CIS ± Ta/T1



Pembro (IV) + intravesical gemcitabine

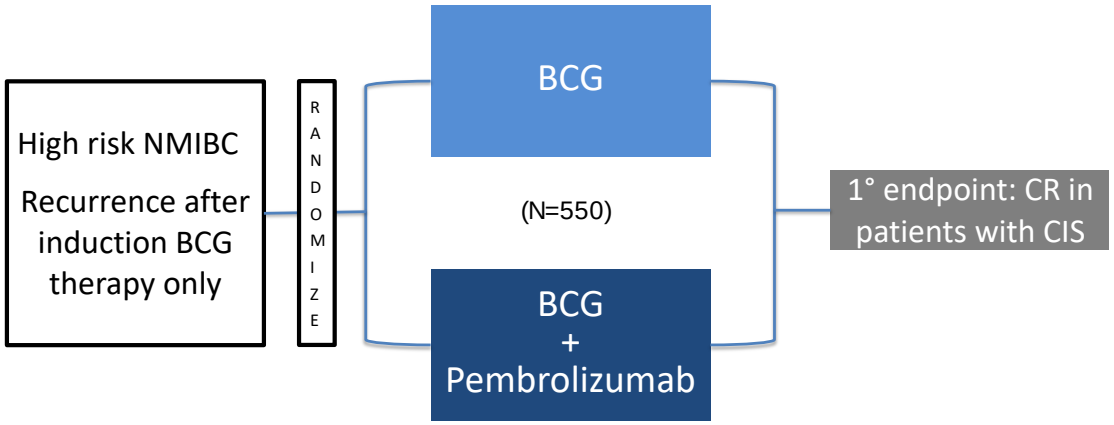
Checkmate 9UT Nivolumab



Linrodostat: once-daily PO IDO-1 inhibitor

What's next: Immune Checkpoint Inhibitors for Earlier NMIBC

BCG "Exposed"

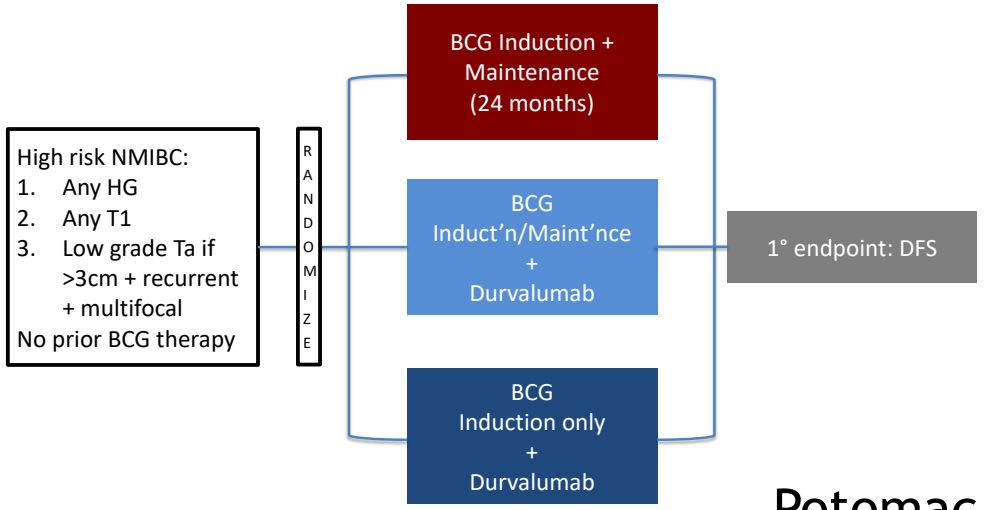


Keynote 676

Similar Trials:

- Checkmate 7G8 with nivolumab
- ADAPT-Bladder durvalumab + RT

BCG Naïve



Potomac

Similar Trials:

- ALBAN with atezolizumab
- CREST with sasanlimab (subq)

NMIBC Immunotherapy Summary

BCG induction + maintenance therapy is the standard of care for intermediate (1 year) and high risk (3 years) NMIBC

Pembrolizumab (IV) is approved for the treatment of BCG-unresponsive high risk NMIBC

Several novel immunotherapies are in clinical development as monotherapy and combination therapy in all states of NMIBC

Galsky, J Immunother Cancer 2021

Webinar outline

- Introduction to the Guideline
- Biomarkers in urothelial cancer
- Non-muscle invasive bladder cancer
- Advanced urothelial cancer
  - First-line immunotherapy
  - Second-line immunotherapy
- Future directions for immunotherapy in urothelial cancer

Immune Checkpoint Inhibitors for Locally Advanced and Metastatic UC

Agent	Ab Inhibits	Schedule	Post Platinum	Front-line Cis-Ineligible
Atezolizumab	PD-L1	Q3W	Accelerated	Accelerated
Nivolumab	PD-1	Q2W	Accelerated	--
Durvalumab	PD-L1	Q2W	Accelerated	--
Avelumab	PD-L1	Q2W	Accelerated	--
Pembrolizumab	PD-1	Q3W	Level 1	Accelerated

Approximately 50% of Patients are "Cisplatin-Ineligible"

- ECOG PS = 2
- Creatinine clearance < 60 mL/min
- Grade ≥ 2 hearing loss
- Grade ≥ 2 neuropathy
- New York Heart Association Class III CHF

Galsky MD,, et al. *Lancet Oncol*. 2011;12(3):211-214.

Immune Checkpoint Inhibitors for Locally Advanced and Metastatic UC

Agent	Ab Inhibits	Schedule	Post Platinum	Front-line Cis-Ineligible
Atezolizumab	PD-L1	Q3W	Accelerated	Accelerated
Nivolumab	PD-1	Q2W	Accelerated	--
Durvalumab	PD-L1	Q2W	Accelerated	--
Avelumab	PD-L1	Q2W	Accelerated	--
Pembrolizumab	PD-1	Q3W	Level 1	Accelerated

PD-L1/PD-1 Inhibitor Therapy: A New Standard of Care for Cisplatin-Ineligible mUC

IMvigor210[1,2]
Atezolizumab

Mature OS data for **cohort 1** of 16.3 mo

- ORR: 24%, including 8% CRs
- 1-y OS: 58%; 2-y OS: 41%
- Baseline PD-L1 expression not strongly associated with ORR
- FDA approved in February 2017

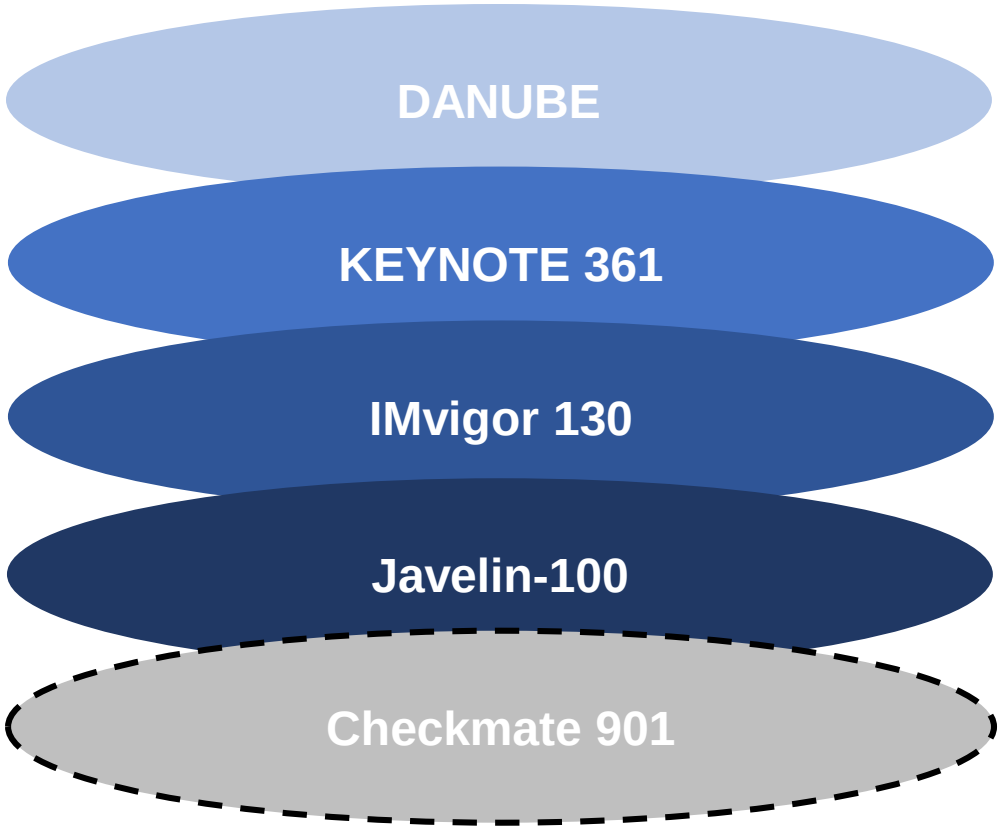
KEYNOTE-052[3]
Pembrolizumab

Updated data with OS of 11.3 mo

- ORR: 29%
- CR: 9%
- PD-L1 CPS ≥10 → 47% ORR (mOS 18.5 mo)
- FDA approved in May 2017

1. Balar AV et al. *Lancet*. 2017;389:67-76. 2. Balar AV et al. ASCO 2018. Abstract 4523. 3. O'Donnell PH et al. ASCO 2019. Abstract 4546.

A Series of Randomized Clinical Trials has Recently Refined First-line Treatment for Metastatic Urothelial CA



Is there a role for chemo + IO?

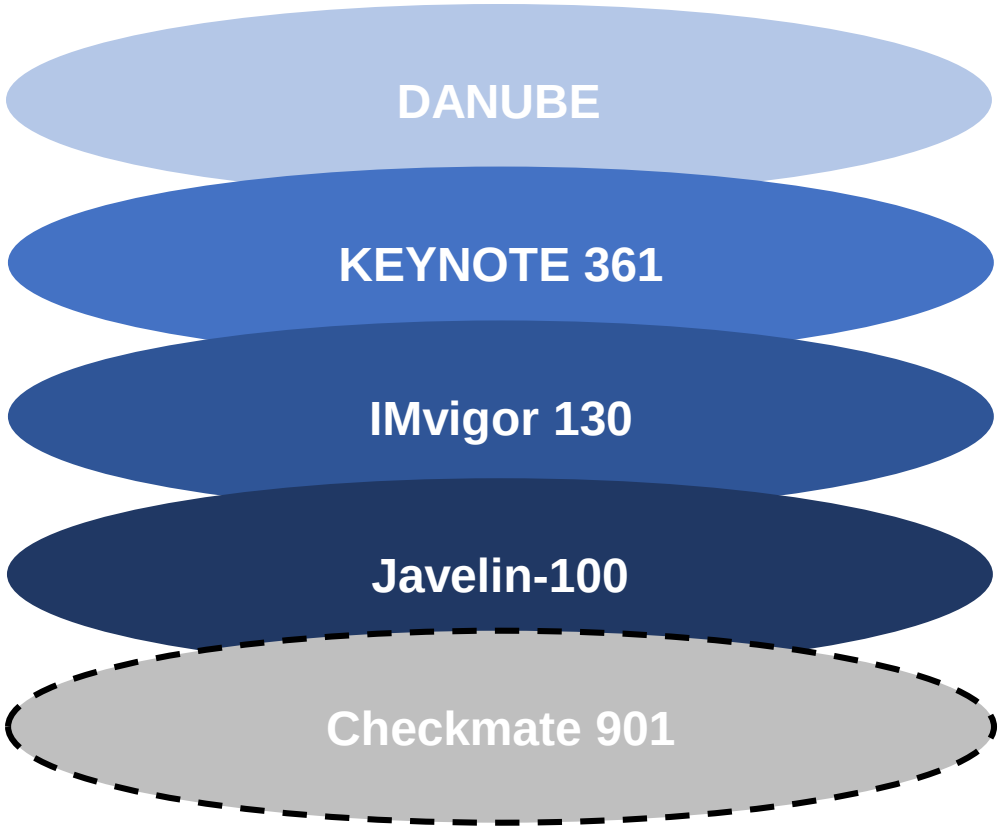
Is there a role for IO alone upfront?

Is there a role for biomarker selection for IO?

Is there a role for "switch maintenance" IO?

Is there a role for IO doublet therapy?

A Series of Randomized Clinical Trials has Recently Refined First-line Treatment for Metastatic Urothelial CA



Is there a role for chemo + IO?

Is there a role for IO alone upfront?

Is there a role for biomarker selection for IO?

Is there a role for "switch maintenance" IO?

Is there a role for IO doublet therapy?

“Switch Maintenance” PD-1/PD-L1 Blockade Improves Outcomes in Metastatic UC

HCRN 14-182 Randomized Phase 2

N=107
Patients with mUC and at least stable disease after ≤8 cycles of 1L platinum-based chemotherapy

Pembrolizumab 200 mg IV
Q3W x up to 24 mos
n=55

Placebo
Q3W x up to 24 mos
n=52

Crossover to pembrolizumab at POD

Javelin Bladder-100 Randomized Phase 3

N=700
- Unresectable locally advanced or metastatic UC
- CR, PR, or SD with standard 1L chemotherapy (4-6 cycles)
  - Cisplatin + gemcitabine OR
  - Carboplatin + gemcitabine

Treatment-free

4-10 wks

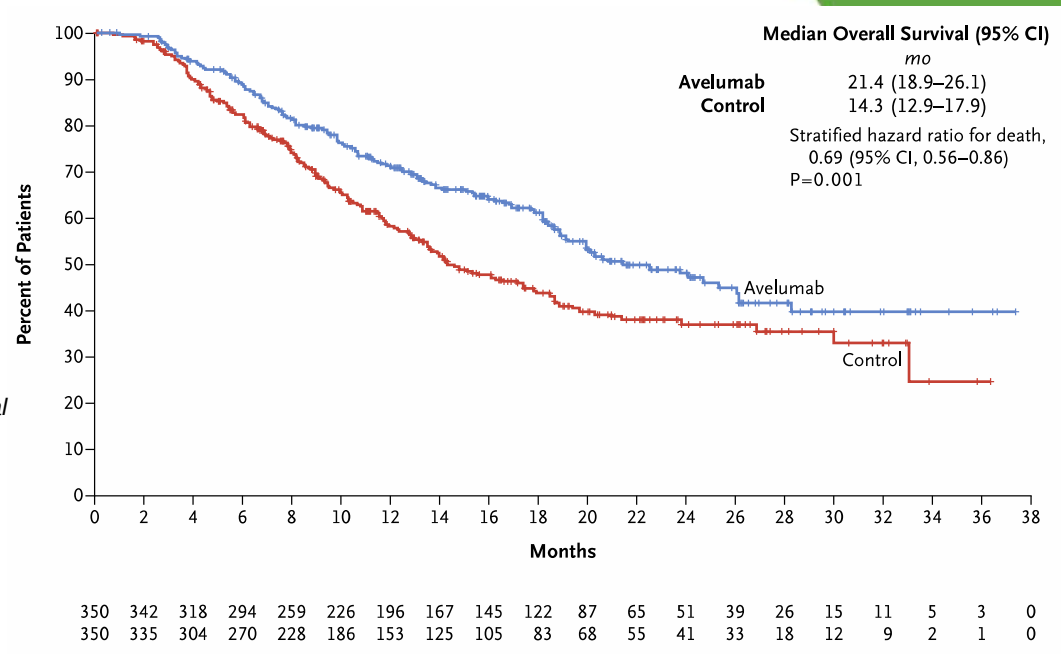
Randomize 1:1

Avelumab 10mg/kg mg IV
Q2W + **BSC**
n=350

Until PD, unacceptable toxicity or withdrawal

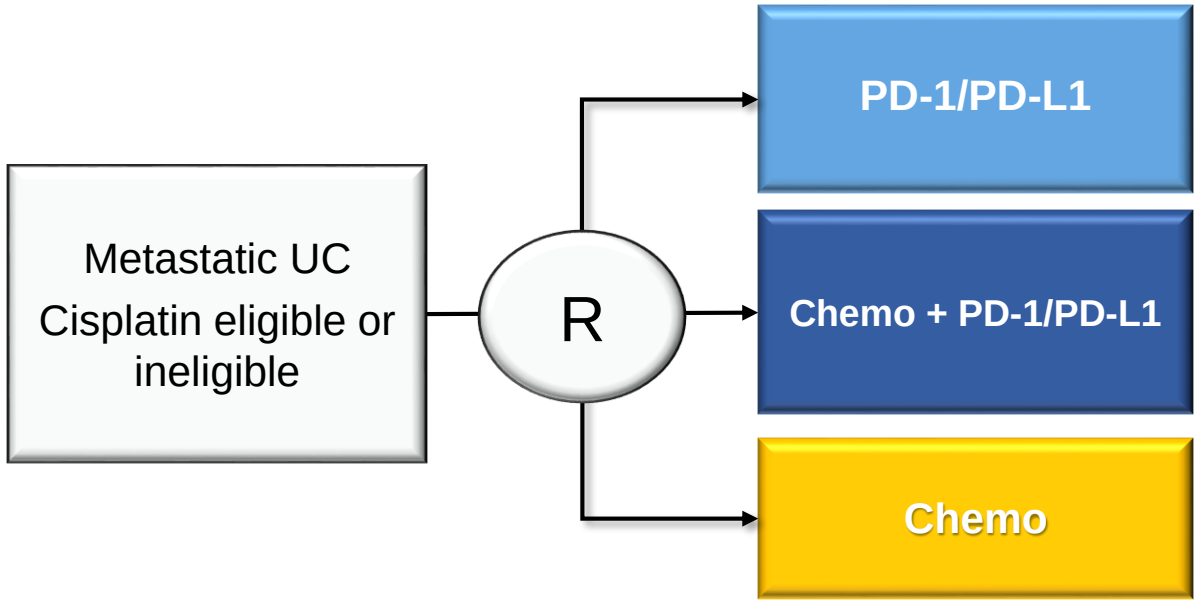
BSC alone
n=350

Javelin Bladder-100 Overall Survival

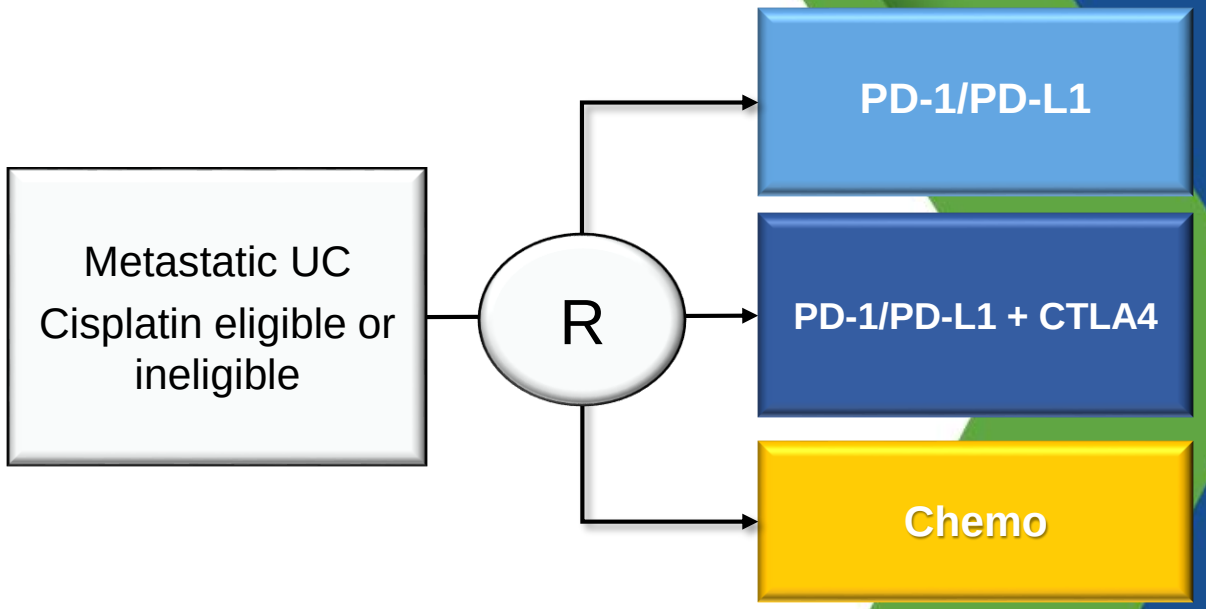


Galsky MD, et al. *J Clin Oncol*. 2020;38(16):1797-1806. Powles T, et al. *N Engl J Med.* 2020;383(13):1218-1230.

What is Optimal First-line Treatment for Metastatic UC?

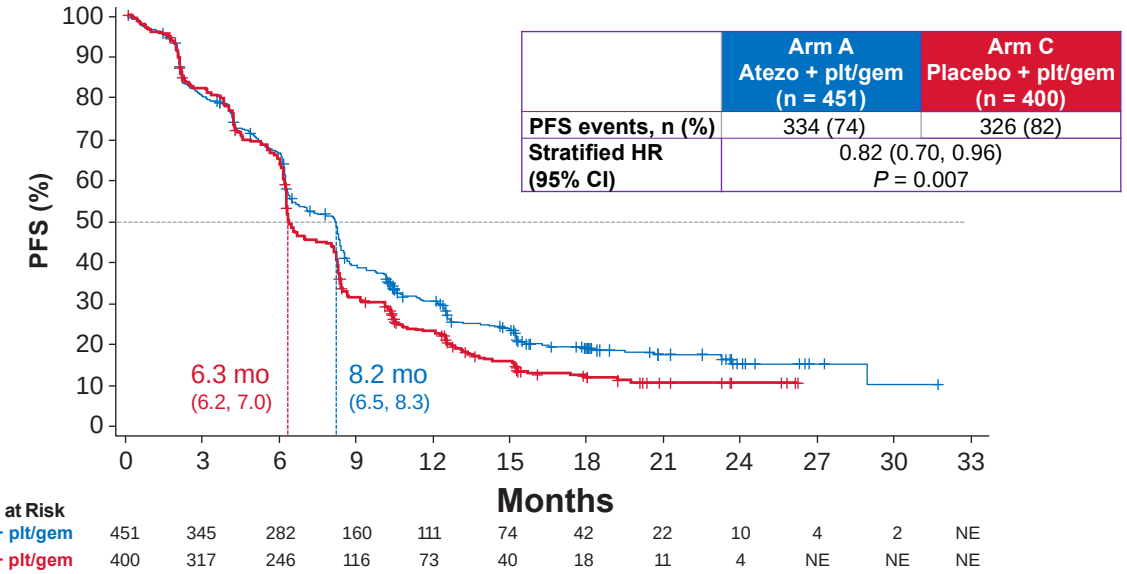


IMvigor 130✓
Keynote 361✓
Checkmate 901 (substudy)
NILE



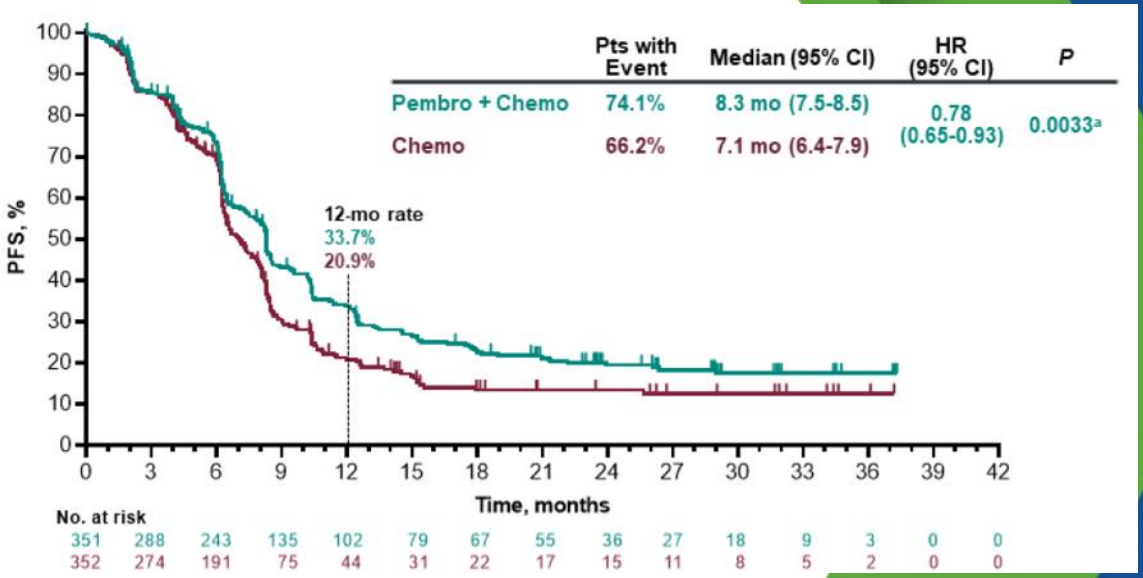
DANUBE✓
Checkmate 901 (main study)
NILE (sort of…)

Platinum-based Chemo + Anti-PD-1/PD-L1 Leads to Minor Improvements in PFS in ITT



	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	

IMvigor 130

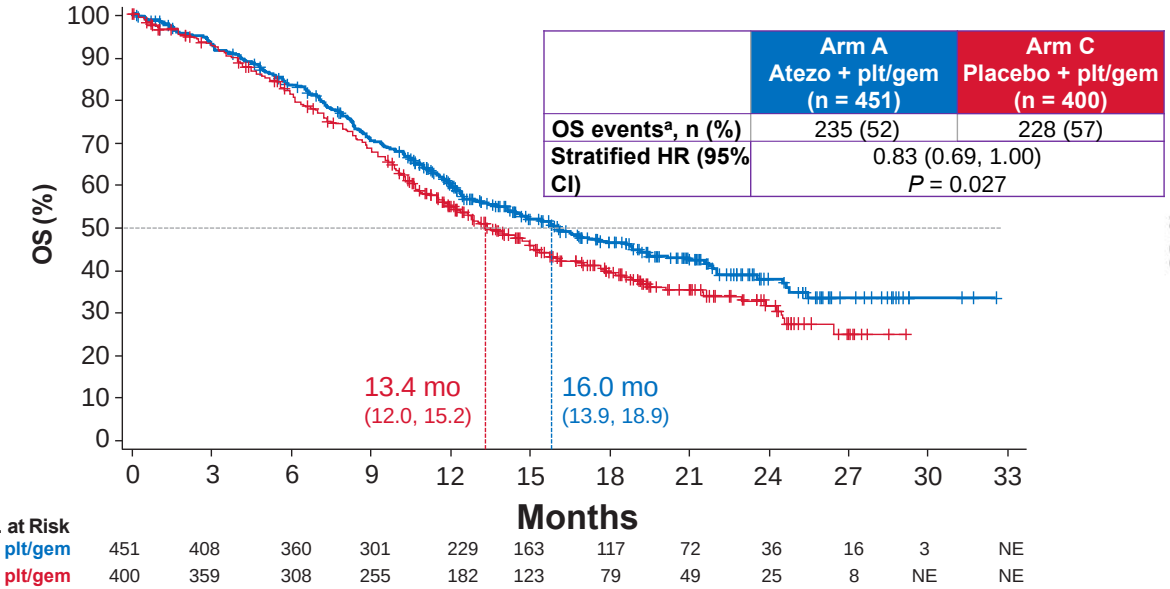


	Pts with Event	Median (95% CI)	HR (95% CI)	*P*
Pembro + Chemo	74.1%	8.3 mo (7.5-8.5)	0.78 (0.65-0.93)	0.0033[a]
Chemo	66.2%	7.1 mo (6.4-7.9)		

Keynote 361

Galsky MD, et al. *Lancet*. 2020;395(10236):1547-1557. Alva, et al. *Ann Oncol.* 2020;31 (suppl_4): S1142-S1215.

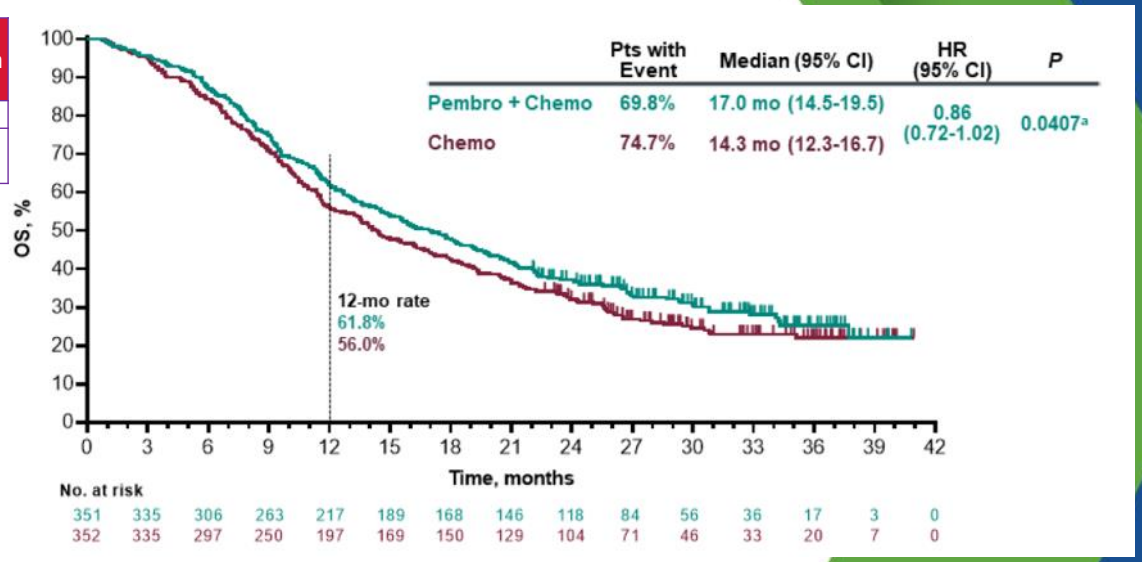
Platinum-based Chemo + Anti-PD-1/PD-L1 Leads to Non-Significant Improvements in OS in ITT



	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	

No. at Risk												
Atezo + plt/gem	451	408	360	301	229	163	117	72	36	16	3	NE
Placebo + plt/gem	400	359	308	255	182	123	79	49	25	8	NE	NE

IMvigor 130



	Pts with Event	Median (95% CI)	HR (95% CI)	*P*
Pembro + Chemo	69.8%	17.0 mo (14.5-19.5)	0.86 (0.72-1.02)	0.0407[a]
Chemo	74.7%	14.3 mo (12.3-16.7)		

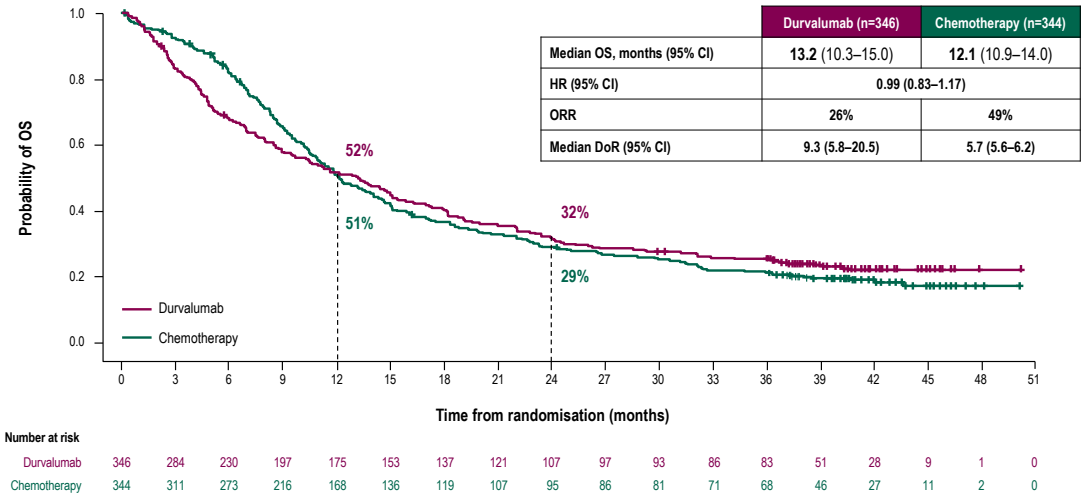
No. at risk															
	351	335	306	263	217	189	168	146	118	84	56	36	17	3	0
	352	335	297	250	197	169	150	129	104	71	46	33	20	7	0

Keynote 361

Galsky MD, et al. *Lancet*. 2020;395(10236):1547-1557. Alva, et al. *Ann Oncol.* 2020;31 (suppl_4): S1142-S1215.

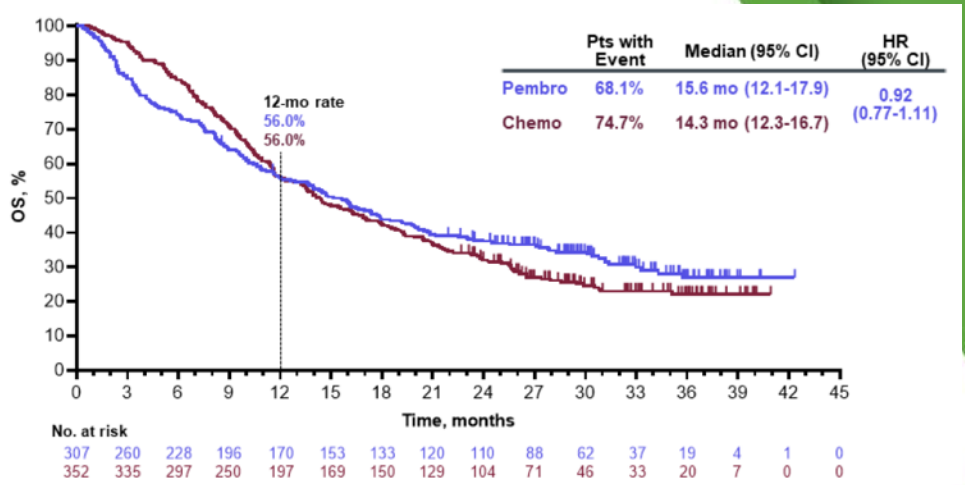
Platinum-based Chemo vs Anti-PD-1/PD-L1 in ITT Populations

DANUBE



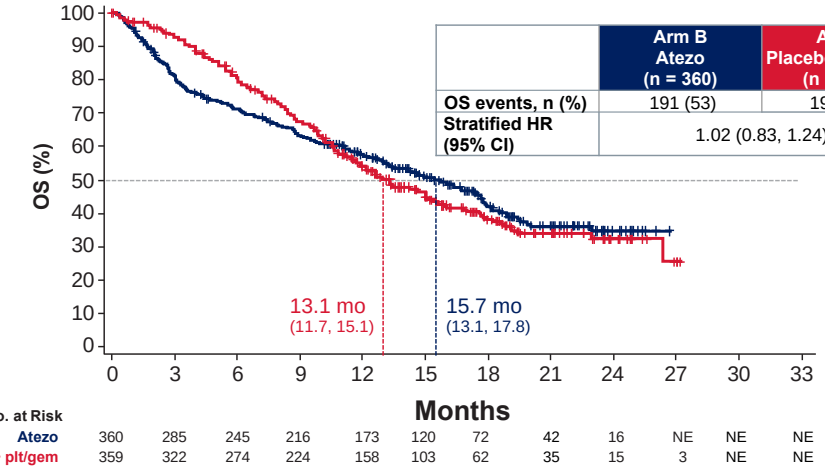
	Durvalumab (n=346)	Chemotherapy (n=344)
Median OS, months (95% CI)	**13.2** (10.3–15.0)	**12.1** (10.9–14.0)
HR (95% CI)	0.99 (0.83–1.17)	
ORR	26%	49%
Median DoR (95% CI)	9.3 (5.8–20.5)	5.7 (5.6–6.2)

Keynote 361



	Pts with Event	Median (95% CI)	HR (95% CI)
Pembro	68.1%	15.6 mo (12.1-17.9)	0.92 (0.77-1.11)
Chemo	74.7%	14.3 mo (12.3-16.7)	

IMVIGOR 130



	Arm B Atezo (n = 360)	Arm C Placebo + plt/gem (n = 359)[a]
OS events, n (%)	191 (53)	198 (55)
Stratified HR (95% CI)	1.02 (0.83, 1.24)	

Galsky MD, et al. *Lancet*. 2020;395(10236):1547-1557. Alva, et al. *Ann Oncol.* 2020;31 (suppl_4): S1142-S1215. Powles T, et al. *Lancet Oncol*. 2020;21(12):1574-1588.

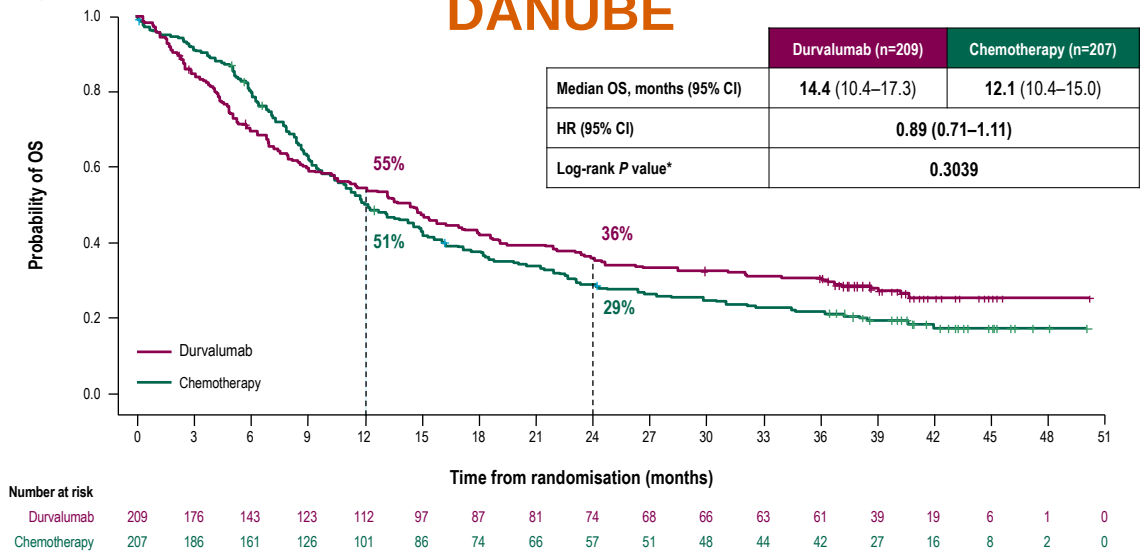
PD-L1 Testing…Clear as Mud?

Drug	Biomarker	Scoring
Pembrolizumab	22C3	TC + IC
Atezolizumab	SP142	IC
Nivolumab	28-8	TC
Durvalumab	SP263	TC + IC
Avelumab	73-10	TC + IC

TC, tumor cell; IC, immune cell

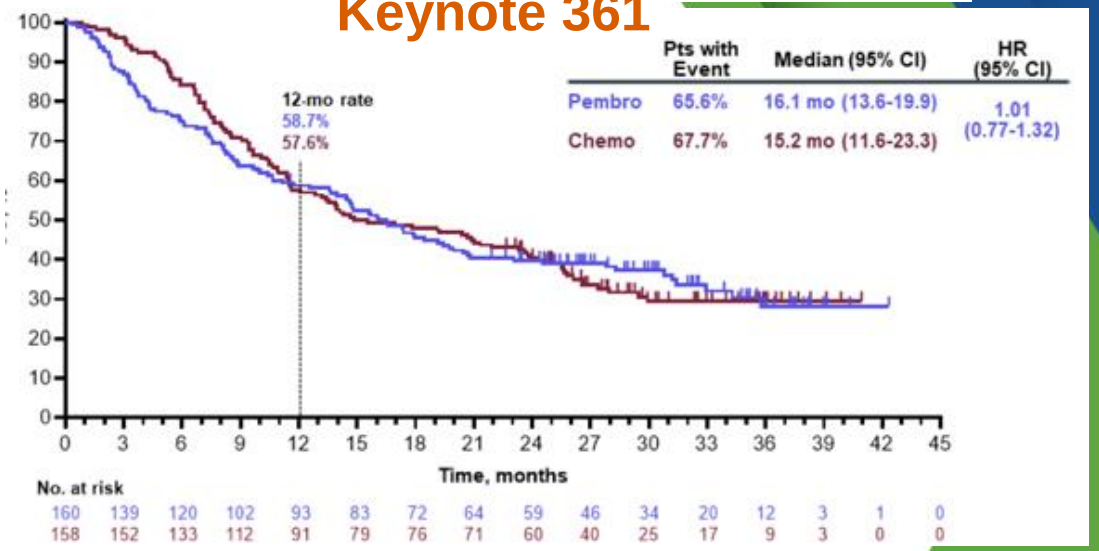
Platinum-based Chemo vs Anti-PD-1/PD-L1 in PD-L1+ Populations

DANUBE



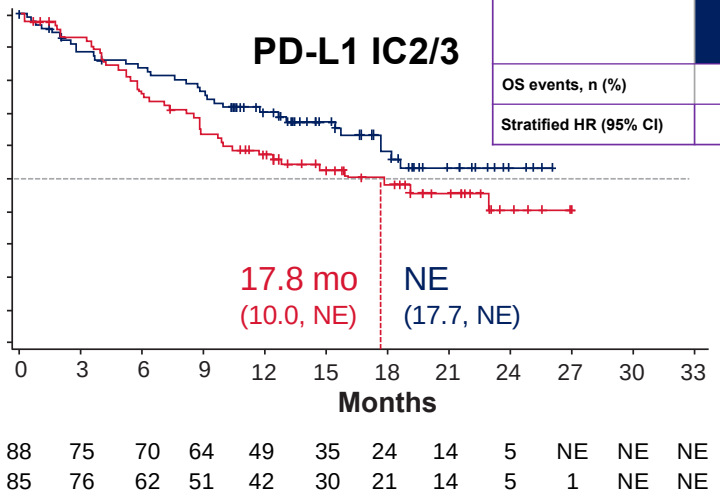
	Durvalumab (n=209)	Chemotherapy (n=207)
Median OS, months (95% CI)	**14.4** (10.4–17.3)	**12.1** (10.4–15.0)
HR (95% CI)	**0.89 (0.71–1.11)**	
Log-rank *P* value*	**0.3039**	

Keynote 361



	Pts with Event	Median (95% CI)	HR (95% CI)
Pembro	65.6%	16.1 mo (13.6-19.9)	1.01 (0.77-1.32)
Chemo	67.7%	15.2 mo (11.6-23.3)	

IMVIGOR 130

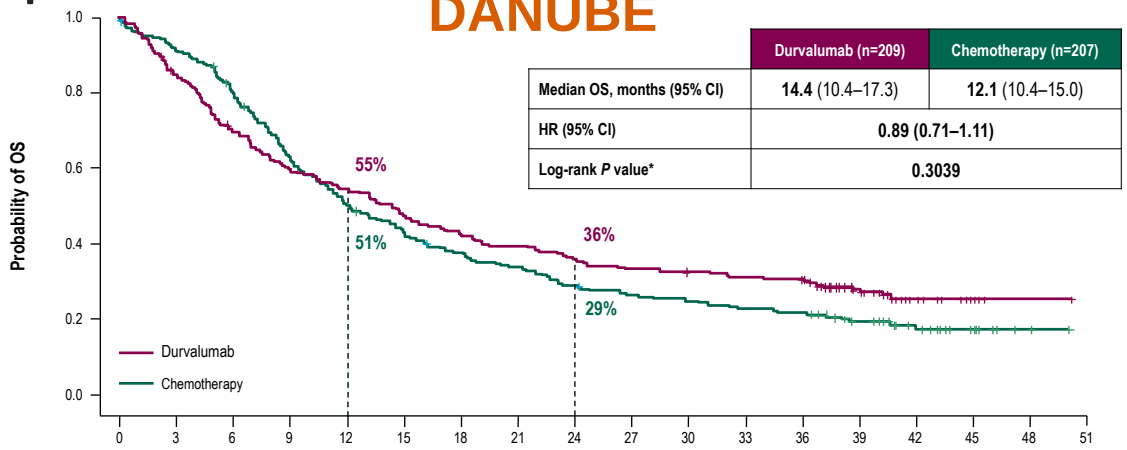


	Arm B Atezo (n = 88)	Arm C Placebo + plt/gem (n = 85)
OS events, n (%)	33 (38)	42 (49)
Stratified HR (95% CI)	0.68 (0.43, 1.08)	

Galsky MD, et al. *Lancet*. 2020;395(10236):1547-1557. Alva, et al. *Ann Oncol*. 2020;31 (suppl_4): S1142-S1215. Powles T, et al. *Lancet Oncol*. 2020;21(12):1574-1588.

Platinum-based Chemo vs Anti-PD-1/PD-L1 in PD-L1+ Populations

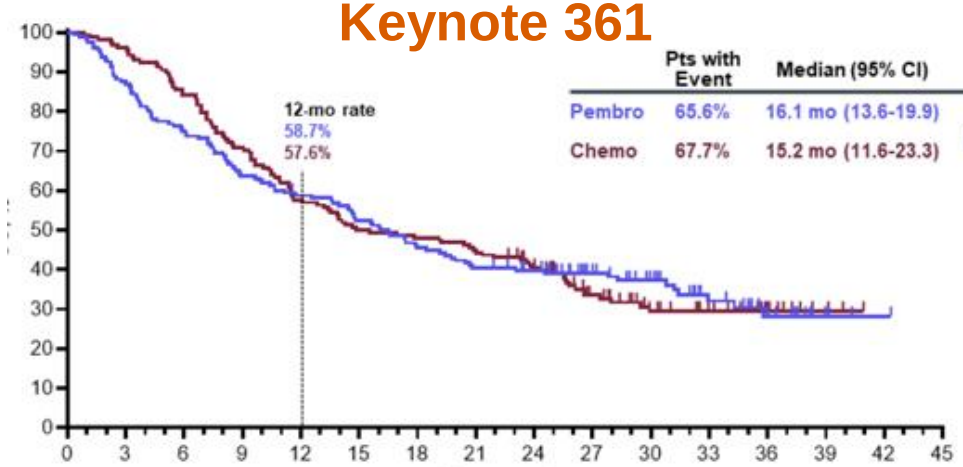
DANUBE



	Durvalumab (n=209)	Chemotherapy (n=207)
Median OS, months (95% CI)	**14.4** (10.4–17.3)	**12.1** (10.4–15.0)
HR (95% CI)	**0.89 (0.71–1.11)**	
Log-rank *P* value*	**0.3039**	

PD-L1+ (SP263) = 60%

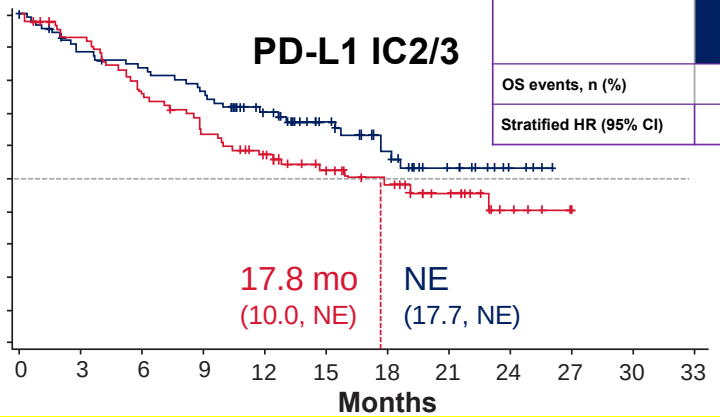
Keynote 361



	Pts with Event	Median (95% CI)	HR (95% CI)
Pembro	65.6%	16.1 mo (13.6-19.9)	1.01 (0.77-1.32)
Chemo	67.7%	15.2 mo (11.6-23.3)	

PD-L1+ (22C3) = 51%

IMVIGOR 130

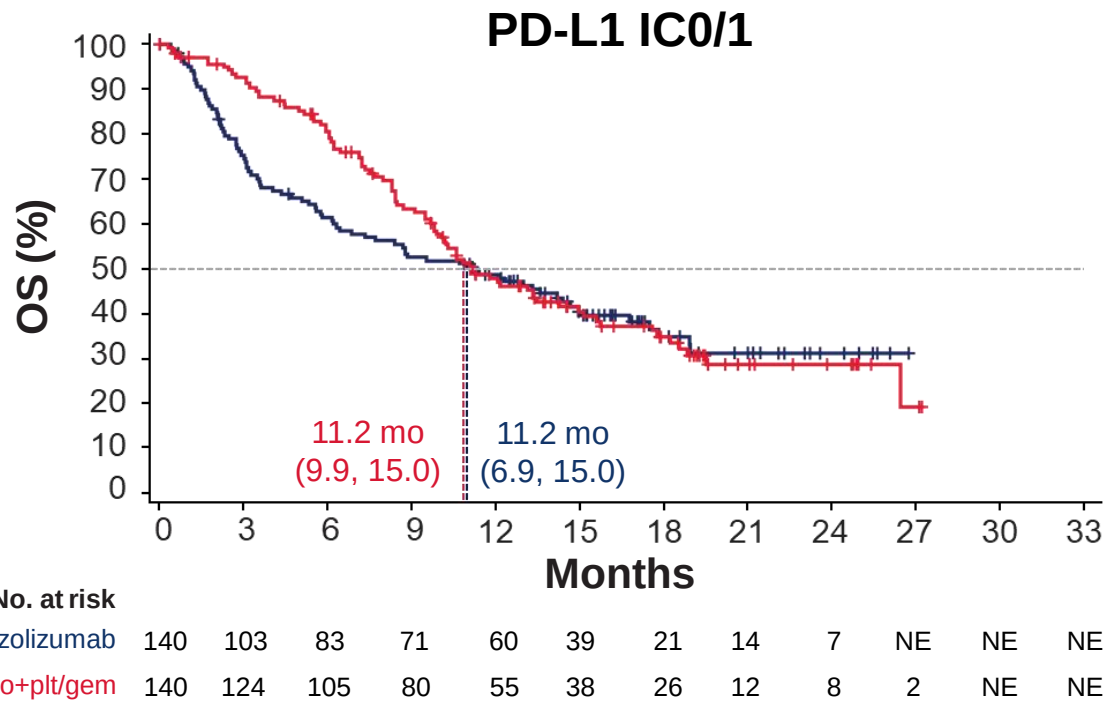


	Arm B Atezo (n = 88)	Arm C Placebo + plt/gem (n = 85)
OS events, n (%)	33 (38)	42 (49)
Stratified HR (95% CI)	0.68 (0.43, 1.08)	

PD-L1+ (SP142) = 24%

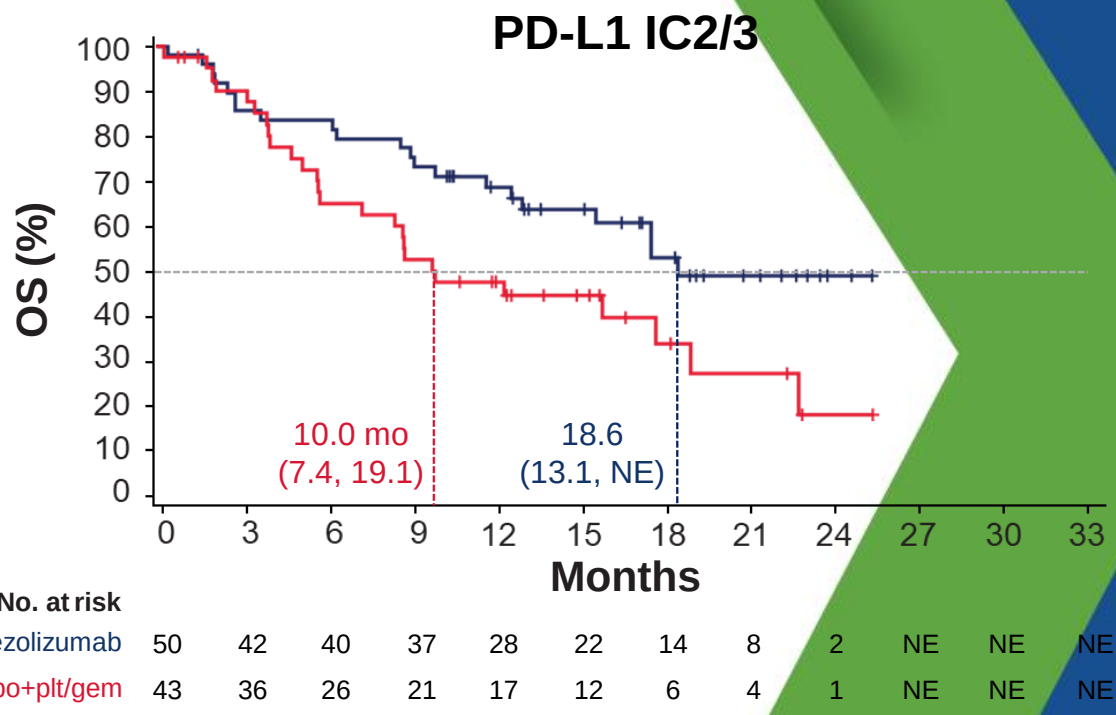
Galsky MD, et al. *Lancet*. 2020;395(10236):1547-1557. Alva, et al. *Ann Oncol.* 2020;31 (suppl_4): S1142-S1215. Powles T, et al. *Lancet Oncol*. 2020;21(12):1574-1588.

What About the Current Label (ie, Cisplatin-Ineligible + PD-L1 “high”)?



No. at risk												
Atezolizumab	140	103	83	71	60	39	21	14	7	NE	NE	NE
Placebo+plt/gem	140	124	105	80	55	38	26	12	8	2	NE	NE

	Atezolizumab (Arm B) (n=140)	Placebo + plt/gem (Arm C) (n=140)
OS events	**85**	**85**
OS HR (95% CI)	**1.11** (0.82, 1.51)	
ORR (95% CI), %[a]	**16** (10, 23)	**42** (34, 51)

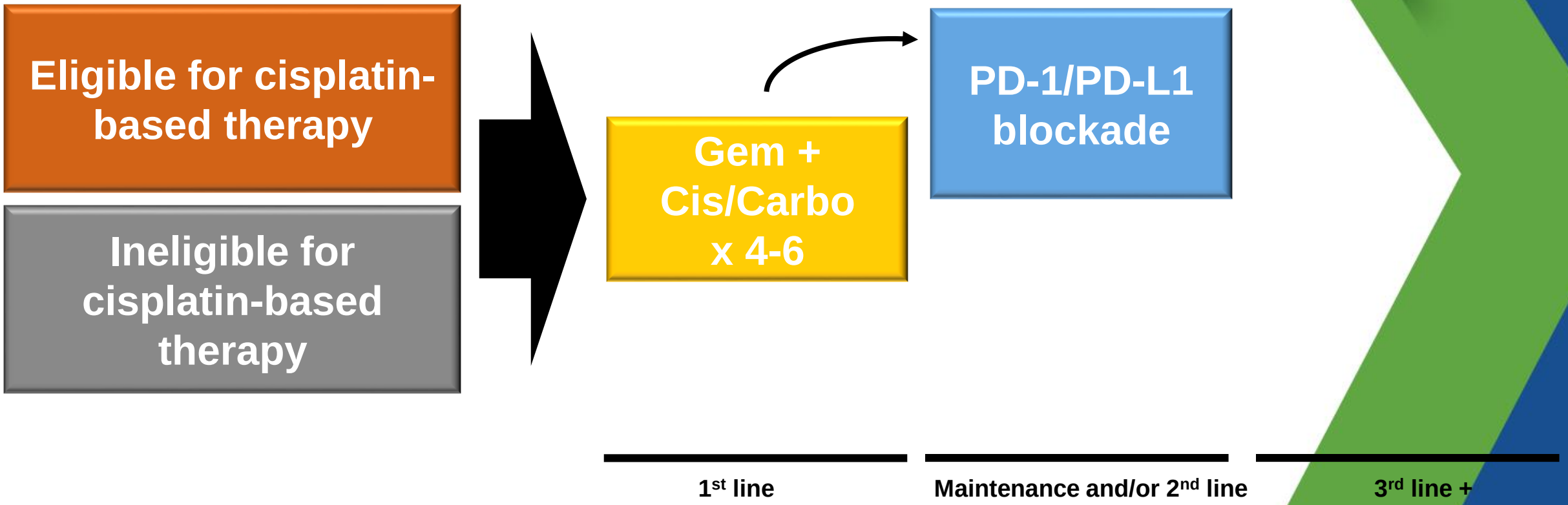


No. at risk												
Atezolizumab	50	42	40	37	28	22	14	8	2	NE	NE	NE
Placebo+plt/gem	43	36	26	21	17	12	6	4	1	NE	NE	NE

	Atezolizumab (Arm B) (n=50)	Placebo + plt/gem (Arm C) (n=43)
OS events	**21**	**26**
OS HR (95% CI)	**0.53** (0.30, 0.94)	
ORR (95% CI), %	**38** (25, 53)	**33** (19, 49)

Galsky, et al. *J Clin Oncol*. 2021;39(no. 6_suppl): 434.

Metastatic UC: 2021



Management of mUC

Patient population	Management
Cisplatin-eligible	Platinum-based chemotherapy → If no disease progression → Avelumab maintenance Platinum-based chemotherapy → If disease progression → Pembrolizumab, Avelumab, Nivolumab*
Cisplatin-ineligible	PD-L1(+) → Atezolizumab*, Pembrolizumab* PD-L1(-) → Carboplatin-based chemotherapy
Cisplatin- and carboplatin-ineligible	Atezolizumab*, Pembrolizumab*

**Accelerated approval contingent on confirmatory trials as of Guideline publication.*

Galsky, J Immunother Cancer 2021

Webinar outline

- Introduction to the Guideline
- Biomarkers in urothelial cancer
- Non-muscle invasive bladder cancer
- Advanced urothelial cancer
  - First-line immunotherapy
  - Second-line immunotherapy
- Future directions for immunotherapy in urothelial cancer

Approved checkpoint inhibitors for mUC – *post-platinum*

Drug	Indication	Dose
Avelumab	Advanced/metastatic UC	10 mg/kg Q2W
Nivolumab	Advanced/metastatic UC	240 mg Q2W or 480 mg Q4W
Pembrolizumab	Advanced/metastatic UC	200 mg Q3W or 400 mg Q6W

Trials in R/R mUC

Trial	Treatment arm(s)	Primary endpoint	Key results
JAVELIN Solid Tumor	Avelumab	ORR	ORR: 17%
JAVELIN 100	BSC +/- avelumab (maintenance post-chemo)	OS	OS HR: 0.69, p=0.001 PD-L1+ OS HR: 0.56, p<0.001

Trial	Treatment arm(s)	Primary endpoint	Key results
CheckMate 275	Nivolumab	ORR	ORR: 20.7%
KEYNOTE-045	Pembrolizumab vs. chemotherapy	OS PFS	OS HR: 0.70, p < 0.001 PFS HR: 0.96, p = 0.31

Galsky, J Immunother Cancer 2021

Management of mUC - before

Patient population	Management
Cisplatin-eligible	Platinum-based chemotherapy → If no disease progression → Avelumab maintenance Platinum-based chemotherapy → If disease progression → Pembrolizumab, Avelumab, Nivolumab*
Cisplatin-ineligible	PD-L1(+) → Atezolizumab*, Pembrolizumab* PD-L1(-) → Carboplatin-based chemotherapy
Cisplatin- and carboplatin-ineligible	Atezolizumab*, Pembrolizumab*

**Accelerated approval contingent on confirmatory trials as of Guideline publication.*

Galsky, J Immunother Cancer 2021

Management of mUC - after

Patient population	Management
Cisplatin-eligible	Cisplatin-based chemotherapy → If no disease progression → Avelumab maintenance Cisplatin-based chemotherapy → If disease progression → Pembrolizumab, Avelumab, Nivolumab*
Cisplatin-ineligible	PD-L1(+) → Carboplatin-based chemotherapy → Same options as above Atezolizumab* Pembrolizumab* PD-L1(-) → Carboplatin-based chemotherapy
Cisplatin- and carboplatin-ineligible	Atezolizumab* Pembrolizumab*

**Accelerated approval contingent on confirmatory trials as of Guideline publication.*

Galsky, J Immunother Cancer 2021

Webinar outline

- Introduction to the Guideline
- Biomarkers in urothelial cancer
- Non-muscle invasive bladder cancer
- Advanced urothelial cancer
- Future directions for immunotherapy in urothelial cancer
  - Adjuvant therapy in UC
  - Combination ICI in UC
  - Enfortumab vedotin + pembrolizumab

CheckMate 274

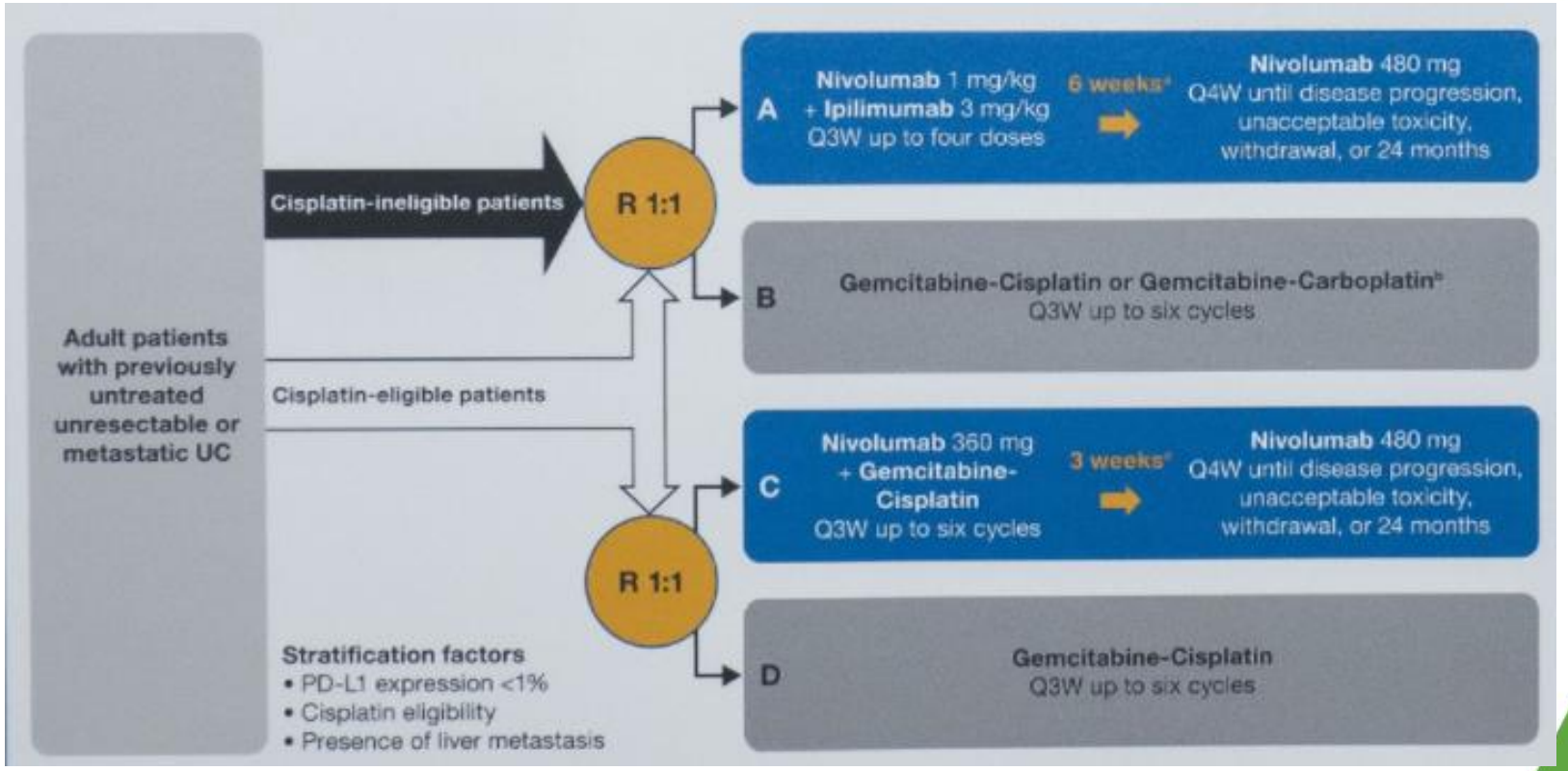
Treatment arm	mDFS	DFS @ 6 months	DFS @ 6 months (PD-L1+)	TRAEs grade 3+
Nivolumab	20.8 months	74.9%	74.5%	17.9%
Placebo	10.8 months	60.3%	55.7%	7.2%

Drug	Indication	Dose
Nivolumab	Adjuvant treatment of UC at high risk of recurrence after radical resection	240 mg Q2W or 480 mg Q4W

Nivolumab was approved for this indication 8/19/21, after publication of the Guideline.

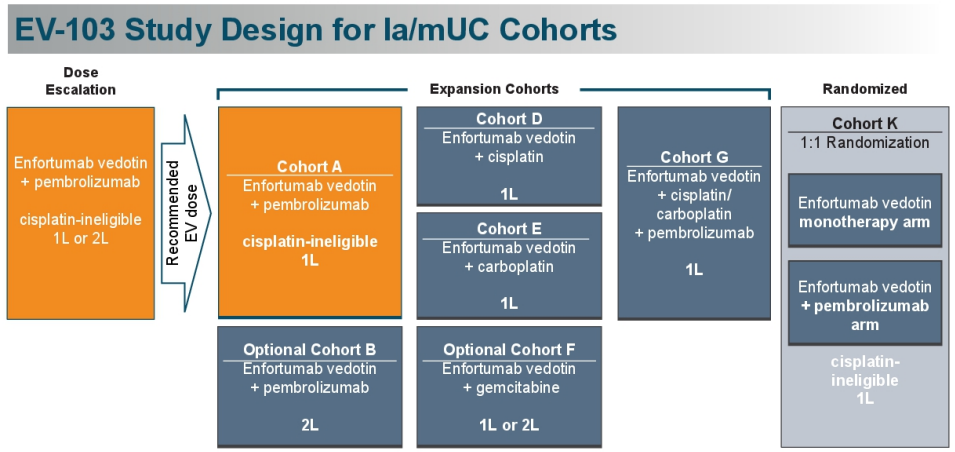
Bajorin, N Engl J Med 2021

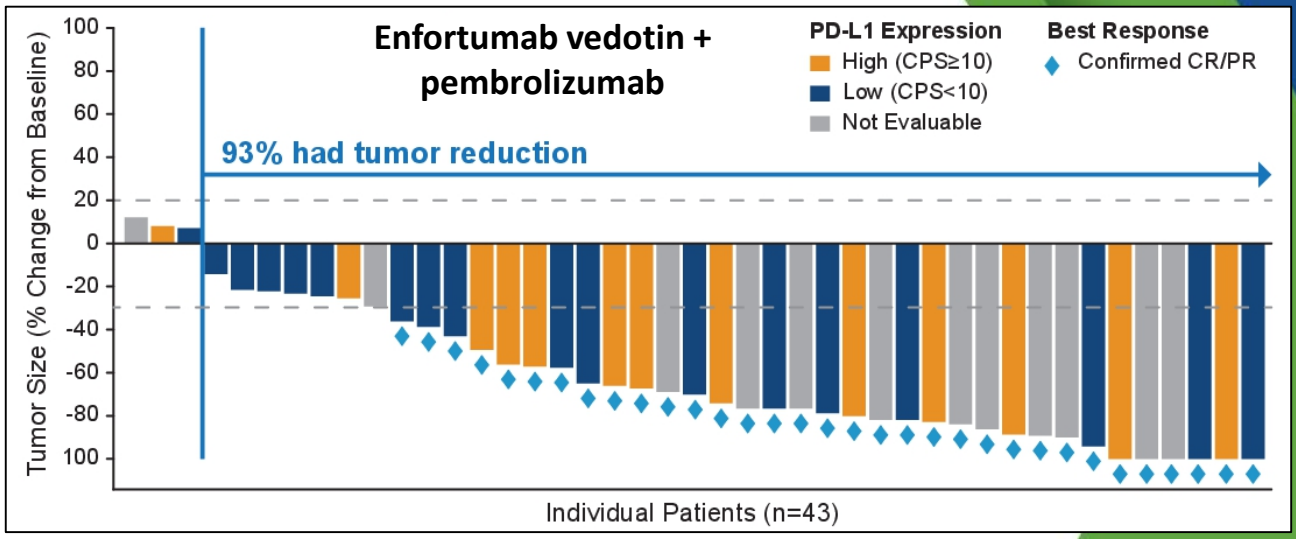
CheckMate 901

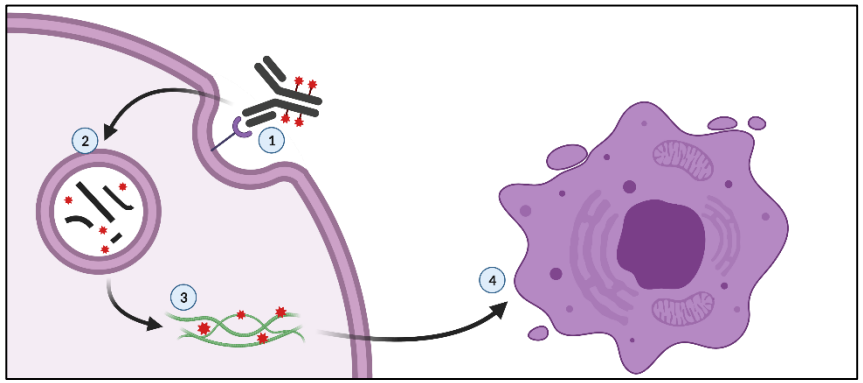


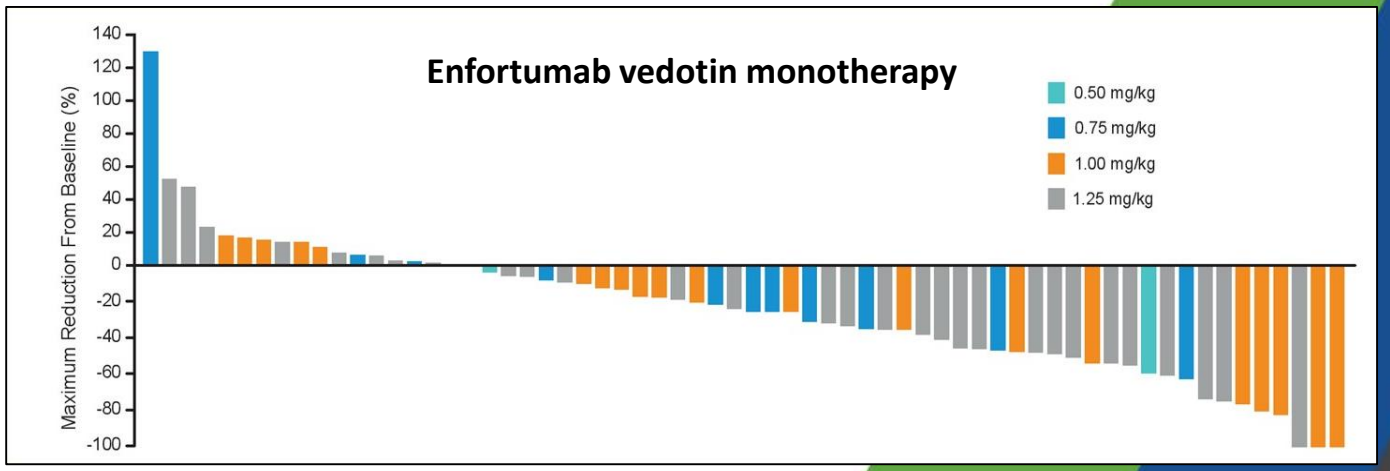
Galsky, ASCO-GU 2018

Enfortumab vedotin: EV-103







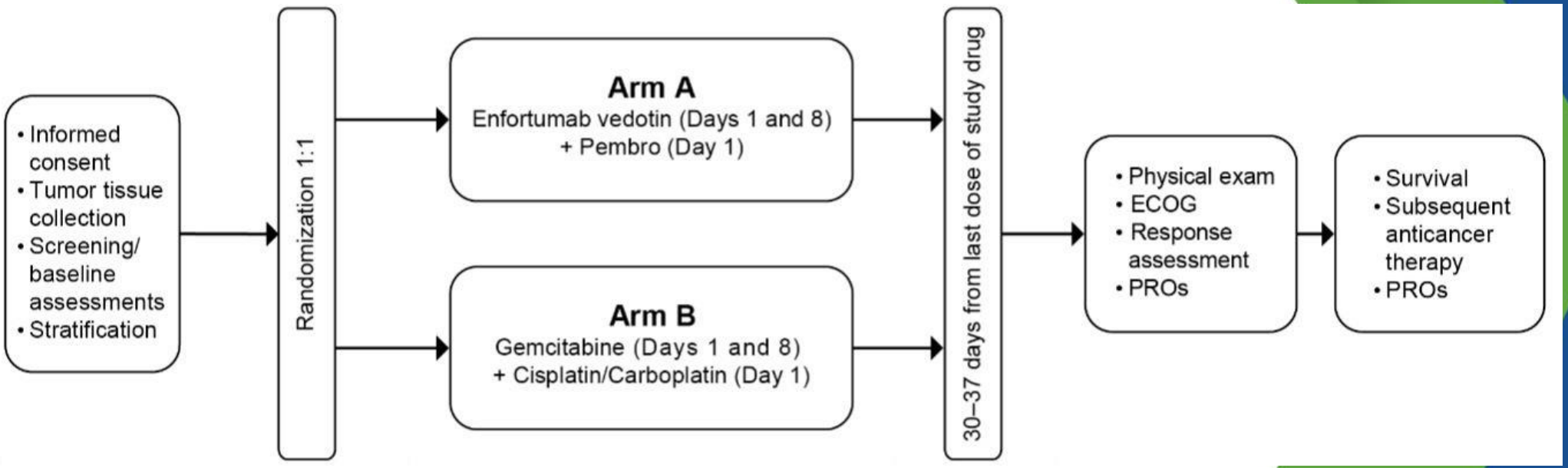


Hoimes, ASCO-GU 2018; Rosenberg, ASCO 2020

Enfortumab Vedotin plus Pembrolizumab: EV-302 Trial Schema

Eligibility

- Locally advanced or metastatic urothelial carcinoma
- 1st line systemic therapy
- Platinum-eligible



Primary Endpoint: PFS, OS
Secondary Endpoints: ORR, DOR, DCR, QOL, PRO, Safety

Society for Immunotherapy of Cancer

Cancer Immunotherapy GUIDELINES

Practical Management Pearls for Immunotherapy for the Treatment of Urothelial Cancer

October 13, 2021, 4 - 5 p.m. ET

Practical Management Pearls for Immune Checkpoint Inhibitor-related Adverse Events

September 16, 2021, 11:30 a.m. - 12:30 p.m. ET

Learn more and register at:
https://www.sitcancer.org/research/cancer-immunotherapy-guidelines/webinars

Targets for Cancer Immunotherapy: A Deep Dive Seminar Series

Eight online seminars will address key questions in the field of cancer immunotherapy **drug development**

SEMINAR 5: MACROPHAGE BIOLOGY FOR ANTI-TUMOR IMMUNITY – October 7, 2021, 10:30 a.m. - 12:30 p.m. ET

SEMINAR 6: THE 4-1BB PATHWAY – October 21, 2021, 3:30 - 5:30 p.m. ET

Learn more and register at:
https://www.sitcancer.org/education/deepdive

Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

A Focus on Gastrointestinal Cancers

September 15, 2021, 12 – 4:10 PM ET

CME-, CPE-, CNE-, MOC-certified

Learn more and register at:
https://www.sitcancer.org/education/aci

Journal for ImmunoTherapy of Cancer

Earn CME Credit as a *JITC* Reviewer

JITC also cooperates with reviewer recognition services (such as Publons) to confirm participation without compromising reviewer anonymity or journal peer review processes, giving reviewers the ability to safely share their involvement in the journal.

Learn how to become a reviewer at sitcancer.org/jitc

Acknowledgements

- Some figures created using biorender.com

Continuing Education Credits

- Continuing Education Credits are offered for Physicians, PAs, NPs, RNs and Pharmacists
- You will receive an email following the webinar with instructions on how to claim credit
- Questions and comments: connectED@sitcancer.org

Thank you for attending the webinar!

Jointly provided by Postgraduate Institute for Medicine and the Society for Immunotherapy of Cancer

PIM Postgraduate Institute for Medicine
Professional Excellence in Medical Education

sitc
Society for Immunotherapy of Cancer

This webinar is supported, in part, by independent medical education grant funding from Amgen, AstraZeneca Pharmaceuticals LP, and Merck & Co., Inc.