Practical Management Pearls for Immunotherapy for the Treatment of Urothelial Cancer

October 13, 2021

4 – 5 p.m. ET

sitc Society for Immunotherapy of Cancer

Cancer Immunotherapy GUIDELINES

AMGEN MERCK

The Practical Management Pearls and Case Studies Webinars are part of the Cancer Immunotherapy Clinical Practice Guidelines Advanced Webinar Series supported, in part, by grants from Amgen and Merck & Co., Inc. (as of 9/15/2021)

Webinar faculty

Shilpa Gupta, MD – *Cleveland Clinic Taussig Cancer Institute*

Neal D. Shore, MD – *Carolina Urologic Research Center*

Petros Grivas, MD – *University of Washington*

Learning objectives

- Consider the integration of immunotherapies into treatment plans for early-stage urothelial cancers
- Determine the optimal sequencing of immunotherapies in relapsed and/or refractory disease
- Appropriately manage toxicities/irAEs associated with immunotherapy in urothelial cancer

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]

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

Webinar outline

- Intravesical therapies in NMIBC
  - BCG is the SOC NMIBC – what we know and don't know - BCG shortage
  - MOA
  - NMIBC – BCG naïve versus BCG unresponsive
  - Trials or Radical Cystectomy
- Systemic therapies in UC
  - Pembro in NMIBC
  - Adjuvant treatment of MIBC
  - First-line & maintenance treatment
  - Pt-refractory
- Immunotherapy toxicities and management

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Stratified Approach to NMIBC

Low-grade NMIBC

- Standard of care – TURBT + adjuvant therapy
- Reducing the burden of recurrence and the need for new treatment options
- Intravesical chemotherapy (MitomycinC, Gemcitabine, Docetaxel, or Combinations)
- Eligibility for recruiting trials

High-grade NMIBC

- Point of care decision: BCG vs trials
- Intravesical chemotherapy if BCG unavailable
- Emerging agents and ongoing clinical trials

What to Do During the BCG Shortage?

- Focus on those who derive most benefit (CIS or other high-risk patients) **AND**
- Reduce dose concentration (up to 1/3) and # of each cycle (i.e., 5 instead of 6 for induction or 2 instead of 3 for maintenance)
- **Forego maintenance and do NOT use for low-risk patients**

Address modifiable risk factors for recurrence (e.g., smoking cessation)	Perform a high-quality TURBT
Ration BCG (www.auanet.org/practice-resources/bcg-info/bcg-shortage-notice)	Proceed to radical cystectomy (especially for group at higher risk for advanced disease, HGT1 +/- CIS, variant histology)
Use intravesical chemotherapy (e.g., gemcitabine, MMC, combination chemotherapy)	**Clinical Trial!**

Low Risk

- Risk of Recurrence: **~50% at 3 years**
- Risk of progression: **NEGLIGIBLE**

Goals: **Reduce recurrences, minimize burden of treatment**

- Consider post-TUR intravesical therapy
- Less frequent cystoscopy
  - *EAU AUA guidelines: if 3-month cystoscopy is negative, go 9 months and then yearly*
- **Don't use BCG**
- Delayed treatment, **office-based fulguration (diathermy)** for small recurrent tumors

Urologists administer ~1.2 million doses of BCG for bladder cancer.

BCG refractory	Persistent HG disease at 6 months despite adequate BCG; also includes any stage/grade progression by 3 months after iBCG cycle (i.e., T1HG at 3 months after initial Ta, or CIS)
BCG relapsing	Recurrence of HG disease after achieving a disease-free state at 6 months following adequate BCG; previously been subdivided based on time to recurrence after stopping BCG (i.e., early [< 12 months], intermediate [1–2 years] or late [> 24 months])
BCG intolerant	Disease persistence due to inability to receive adequate BCG* due to toxicity
BCG unresponsive	BCG refractory + BCG relapsing disease (within 6–12 months of last BCG exposure); meant to denote a subgroup of patients at highest risk of recurrence and progression for whom additional BCG therapy is not a feasible option; these patients can be considered for single-arm studies.

Kamat AM, et al. *J Clin Oncol.* 2016.

Definition of BCG Unresponsive Disease

- Persistent or new **T1 HG** disease
  - At first evaluation (3 months) following induction BCG
- Persistent or recurrent **CIS**
  - Within 12 months of completion of adequate BCG therapy
- Recurrent **HG Ta/T1** disease
  - Within 6 months of completion of adequate BCG therapy

Adequate BCG therapy defined as:

at least 5 of 6 doses of iBCG + at least 2 additional doses of mBCG

Kamat AM, et al. *J Clin Oncol*. 2016; Lerner SP, et al. *Bladder Cancer*. 2015; FDA Guidance Document. BCG-unresponsive NMIBC. 2018.

Role of bladder cancer cells in the efficacy of BCG therapy for bladder cancer

Process	Evidence for role in response to BCG
Attachment of BCG to the urothelium	BCG attaches to urothelial cells through bridging of FAP and integrin α5β1 by fibronectin Blocking fibronectin can reduce BCG efficacy in the mouse model
Internalization of BCG by bladder cancer cells	Internalized BCG can be identified in urothelial cells of patients treated with BCG *In vitro*, bladder cancer cells internalize BCG, while benign urothelial cells do not Uptake of BCG by bladder cancer cells is dependent on activation of macropinocytosis by oncogenic aberrations in *PTEN* and *RAS*
Immune system recruitment by bladder cancer cells	Bladder cancer cells secrete IL-6, IL-8, GM-CSF and TNF in response to BCG *In vitro*, bladder cancer cells can act as antigen-presenting cells after exposure to and internalization of BCG
Direct cytotoxicity of BCG against bladder cancer cells	Reduced proliferation of BCG-exposed bladder cancer cells BCG internalization by bladder cancer cells can result in cell death No evidence currently supports direct cytotoxicity on bladder *in vivo*

Abbreviations: FAP, fibronectin attachment protein; GM-CSF, granulocyte–macrophage colony-stimulating factor; TNF, tumour necrosis factor.

Redelman-Sidi, G. et al. *Nat. Rev. Urol.* 2014

Role of the immune system in the efficacy of BCG therapy for bladder cancer

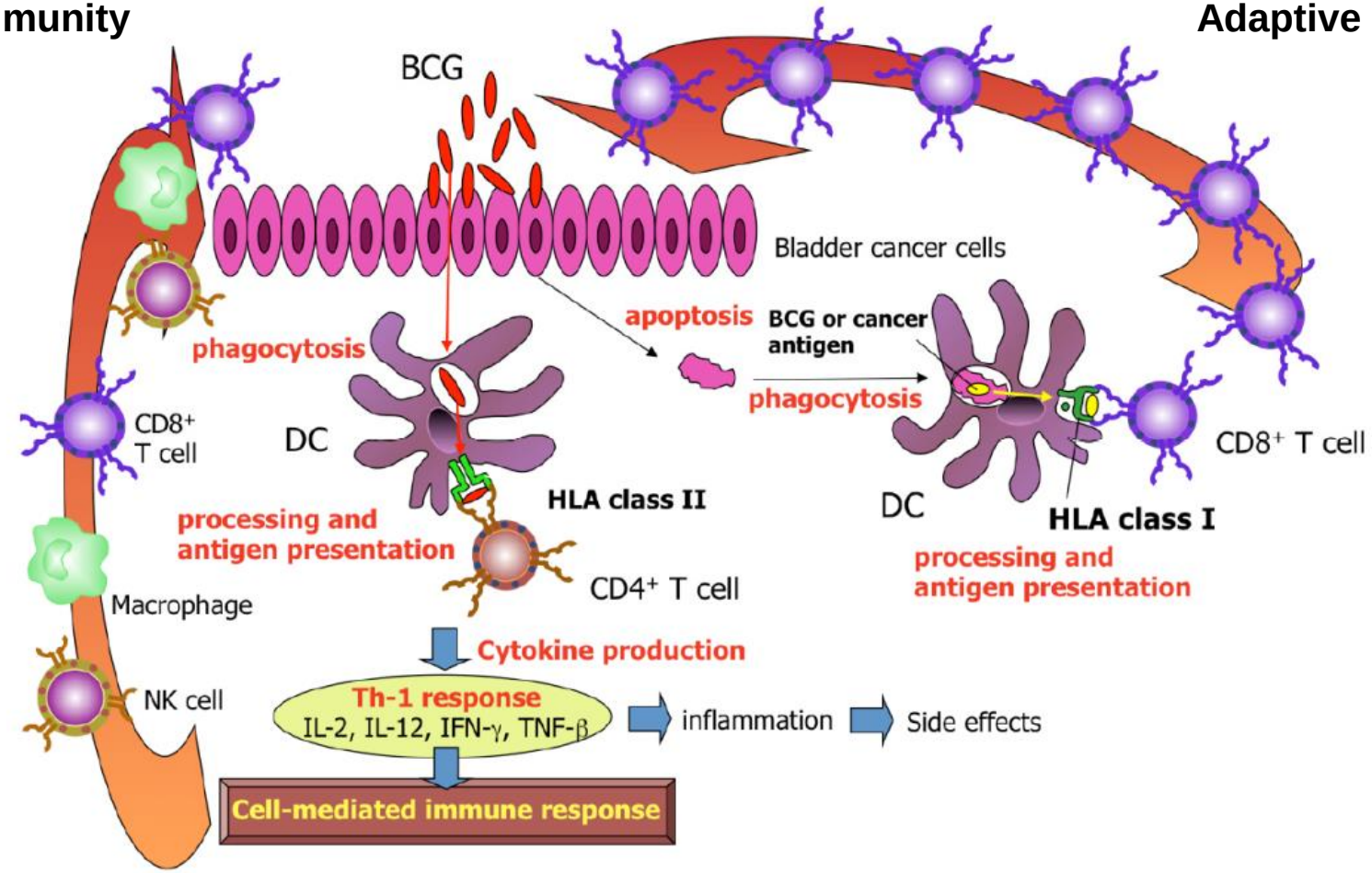
Immune system component	Evidence for role in response to BCG
Lymphocytes	Lymphocytes are a component of the inflammatory infiltrate in the bladders of patients treated with BCG $CD4^+$ and $CD8^+$ T cells are required for response to BCG in the mouse model
NK cells	Infiltration of NK cells in bladder wall of BCG-treated mice NK cells are cytotoxic against BCG-infected bladder cancer cells *in vitro* NK cells are required for response to BCG in the mouse model
Granulocytes	Granulocytes are the major component of the inflammatory infiltrate in the bladders of patients treated with BCG PMN are required for efficacy of BCG in the mouse model
Macrophages	Macrophages are a component of the inflammatory infiltrate in the bladders of patients treated with BCG BCG-stimulated macrophages are cytotoxic against bladder cancer cells *in vitro*
Dendritic cells	Immature dendritic cells can be found in the urine of patients treated with BCG *In vitro*, BCG-exposed dendritic cells can induce T cells to exhibit cytotoxicity against BCG-infected bladder cancer cells
Cytokines and chemokines	Massive release of cytokines and chemokines occurs in urine of patients treated with BCG BCG therapy shifts the urinary cytokine milieu from T_H2-like to T_H1-like Augmentation of a T_H1-like response can improve the efficacy of BCG in the mouse model TRAIL, an apoptosis-promoting protein, is released into the urine of patients treated with BCG, and can kill bladder cancer cells *in vitro*
Toll-like receptors	TLR 2, 4 and 9 can recognize mycobacterial components and lead to the production of various proinflammatory cytokines TLR 2 and 4 are responsible for release of TRAIL by neutrophils in response to BCG

Abbreviations: NK, natural killer; PMN, polymorphonuclear cells; TRAIL, tumour necrosis factor-related apoptosis-inducing ligand; TLR, Toll-like receptor.

Redelman-Sidi, G. et al. *Nat. Rev. Urol.* 2014

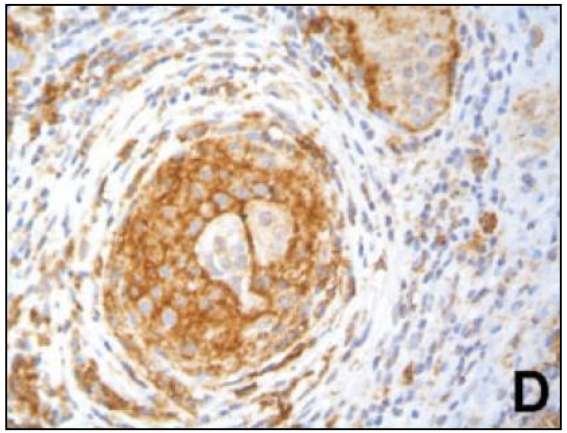
BCG Immunology Targets

Innate Immunity **Adaptive Immunity**

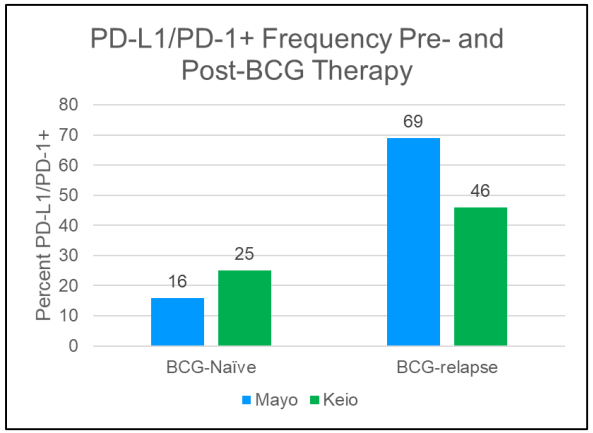


Kitamura H et al, Cancers 2011;3:3055-72, Shelley MD et al, Cochrane Database of Systemic Reviews 2006;2:1-29

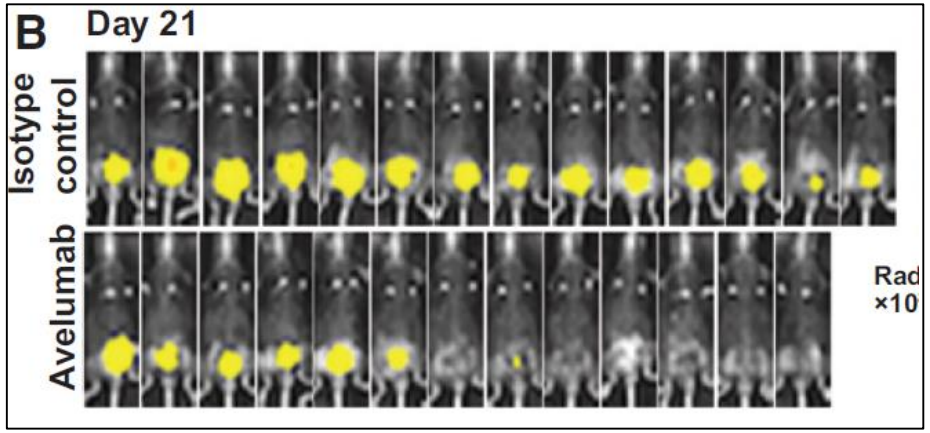
Basis of PD-L1/PD-1 Therapy in NMIBC



PD-L1(+) IHC BCG-relapse



PD-L1(+) IHC Frequency BCG-relapse



Avelumab (anti-PD-L1 Ab) NMIBC Activity

Inman BA et al, Cancer 2007;109:1499-505, Fukumoto K et al, Ann Surg Oncol 2018;25:2484-91, Vandeveer AJ et al, Cancer Immunol Res 2016;4(5):452-62

BCG Immunology Targets

Innate Immunity

Adaptive Immunity

PD-1/PD-L1

STING

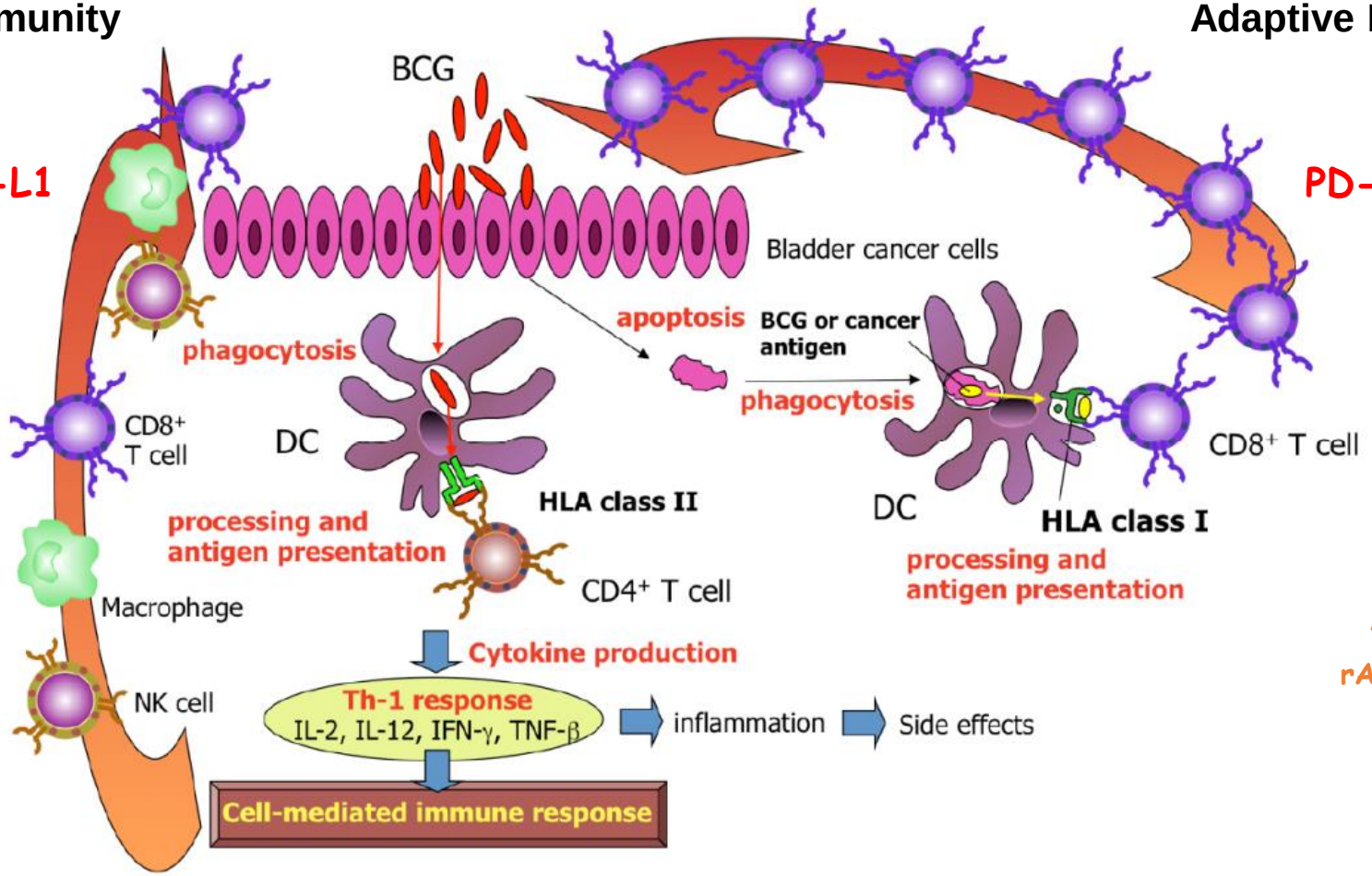
CD40

CSF-1R

IDO1

KIR2DL

4-1BB



PD-1/PD-L1

4-1BB

CTLA-4

OX40

GITR

TIM3

ADA2R

Ag Vaccines

rAdIfN/Syn3

Kitamura H et al, Cancers 2011;3:3055-72, Shelley MD et al, Cochrane Database of Systemic Reviews 2006;2:1-29

Key Points

- Despite ~ four decades of BCG experience with bladder cancer, the MOA is still under investigation as well as biomarkers of response
- The requirements for effective BCG therapy include an intact immune system, live BCG, and close contact of BCG with bladder cancer cells
- Important constituents of the cellular inflammatory response to BCG include $CD4^+$ and $CD8^+$ lymphocytes, natural killer cells, and granulocytes
- Important elements of the humoral immune response to BCG include TRAIL (tumor necrosis factor-related apoptosis-inducing ligand), IL-2, IL-8, IL-18, IL-12, interferon (IFN)-γ, and tumor necrosis factor (TNF)
- Bladder cancer cells and benign urothelial cells might have a role in the initial recognition and processing of BCG, leading to immune system recruitment
- Future investigation will hopefully lead to the discovery of clinically useful predictors of response to BCG and development of recombinant BCG strains with improved efficacy, accessibility and perhaps decreased toxicity

Redelman-Sidi, G. et al. *Nat. Rev. Urol.* 2014

Urologists: How Novel Immunotherapy and Molecular Markers Imaging May Change the Management of NIMBC

Table 1 – Phase 2 and 3 trials testing immune checkpoint inhibitors as single agents or in combinations for the treatment of high-risk NMIBC (searched at ClinicalTrials.gov)

Trial	Phase	Design	Enrolled population	Target number of participants	Experimental arm vs control arm	Route of ICI administration	Primary endpoint (s)
Single-agent							
NCT02625961 KEYNOTE-057	2	Single-arm assignment	BCG-unresponsive	260	Pembrolizumab	Intravenous	CRR, DFS rate
NCT02844816 SWOG 1605	2	Single-arm assignment	BCG unresponsive	202	Atezolizumab	Intravenous	CRR at 25 wk for Cis, EFS at 18 mo
NCT02901548	2	Single-arm assignment	BCG-refractory Cis	17	Durvalumab	Intravenous	CRR at 6 mo
NCT03504163	2	Single-arm assignment	BCG-naïve	37	Pembrolizumab	Intravenous	Disease free rate at 6 mo
NCT03759496	2	Single-arm assignment	BCG-refractory	39	Durvalumab	Intravenous	Maximum tolerated dose, high-grade relapse-free rate
NCT04738630	2	Single-arm assignment	BCG-unresponsive	110	HX008 (anti-PD-1 antibody)	Intravenous	CRR at 24 mo, EFS at 36 mo
Combined with BCG							
NCT03519256 CheckMate 9UT	2	Randomised, parallel assignment	BCG-unresponsive	358	Nivolumab vs Nivolumab + BCG vs Nivolumab + BMS-986205 vs Nivolumab + BMS 986205 + BCG	Intravenous	CRR in Cis, CR duration in Cis
NCT03528694 POTOMAC	3	Randomised, parallel assignment	BCG-naïve	1018	Durvalumab + BCG (I + M) vs Durvalumab + BCG (induction only) vs BCG (I + M)	Intravenous	DFS
NCT03711032 KEYNOTE-676	3	Randomised, parallel assignment	Recurrence/persistence after BCG induction (cohort A), BCG-naïve (cohort B)	1525	Cohort A Pembrolizumab + BCG (I + M) vs BCG (I + M) vs Cohort B Pembrolizumab + BCG (I + reduced M) vs Pembrolizumab + BCG (I + full M) vs BCG (I + M)	Intravenous	CCR (cohort A), EFS (cohort B)
NCT03799835 ALBAN	3	Randomised, parallel assignment	BCG naïve	516	Atezolizumab + BCG (I + M) vs BCG (I + M)	Intravenous	RFS
NCT04149574 CheckMate 7G8	3	Randomised, parallel assignment	Recurrence/persistence after BCG	700	Nivolumab + BCG vs Placebo + BCG	Intravenous	EFS
NCT04165317 CREST	3	Randomised, parallel assignment	BCG-naïve	999	Sasanlimab + BCG (I + M) vs Sasanlimab + BCG (induction only) vs BCG (I + M)	Subcutaneous	EFS
Combined with other agents							
NCT04164082	2	Single-arm assignment	BCG-unresponsive	161	Pembrolizumab + intravesical gemcitabine	Intravenous	CRR at 6 mo (Cis), EFS at 18 mo
NCT04387461 CORE-001	2	Single-arm assignment	BCG-unresponsive	37	Pembrolizumab + intravesical CG0070 (oncolytic adenovirus)	Intravenous	CRR at 12 mo
NCT04640623	2	Randomised, parallel assignment	BCG-unresponsive	200	Cetrelimab + TAR-200 vs TAR-200 vs Cetrelimab	Intravenous	Overall CRR
NCT04730232	2	Single-arm assignment	BCG-naïve, not completely resectable	63	Tislelizumab + intravenous nab-paclitaxel	Intravenous	CRR at the time of TURBT
Combined with EBRT							
NCT03317158 ADAPT-BLADDER	1/2	Randomised, crossover assignment	Recurrence/persistence of intermediate-/high-risk NMIBC after BCG	186	Durvalumab + BCG vs Durvalumab + EBRT vs Retreatment with BCG	Intravenous	RFS at 6 mo
NCT03950362 PREVERT	2	Single-arm assignment	BCG-unresponsive	67	Avelumab + EBRT + avelumab	Intravenous	High-risk RFS at 1 yr

BCG = bacillus Calmette-Guérin; BMS-986205 = inhibitor of indoleamine 2,3-dioxygenase 1; Cis = carcinoma in situ; CR = complete response; CRR = complete response rate; DFS = disease-free survival; EBRT = external beam radiation therapy; EFS = event-free survival; I + M = induction plus maintenance; ICI = immune checkpoint inhibitor; NMIBC = non-muscle-invasive bladder cancer; RFS = recurrence-free survival; TAR-200 = intravesical gemcitabine delivery system; TURBT = transurethral resection of bladder tumour.

Trial number	Phase	Design	Enrolled population	Target number of participants	Experimental arm vs control arm	Route of administration	Primary endpoint(s)
NCT00704950	2	Single-arm assignment	BCG-naïve	43	BCG (induction) + sunitinib	Oral	CRR at 3 mo
NCT01372294	2	Nonrandomised, parallel assignment	BCG-naïve	17	Lenalidomide + BCG vs BCG	Oral	PFS
NCT02015104	2	Randomised, parallel assignment	BCG-failure after ≥1 induction course	32	BCG (induction) + PANVAC vs BCG (induction)	Subcutaneous	RFS
NCT02138734	3	Randomised, parallel assignment	BCG-naïve Cis (cohort A), high-grade Ta/T1 (cohort B)	506	N-803 (IL-15 superagonist complex) + BCG vs BCG	Intravesical	CRR at 12 mo (cohort A), DFS at 24 mo (cohort B)
NCT02365818	2	Single-arm assignment	BCG-unresponsive	66	CG0070 (engineered oncolytic adenovirus)	Intravesical	Durable CRR
NCT02449239	3	Single-arm assignment	BCG-unresponsive	134	Vicinium (antibody-drug conjugate)	Intravesical	CRR (Cis)
NCT02773849	3	Single-arm assignment	BCG-unresponsive	157	Nadofaragene firadenovec	Intravesical	CRR at 12 mo (Cis)
NCT02982395	3	Randomised, parallel assignment	BCG-refractory	56	Docetaxel vs intravesical MMC	Intravesical	RFR at 12 mo
NCT03022825 QUILT-3.032	2/3	Single-arm assignment	BCG-unresponsive	180	N-803 (IL-15 superagonist complex) + BCG	Intravesical	CR (cohorts A and C), DFR at 12 mo (cohort B)
NCT03664869	3	Randomised, parallel assignment	BCG-naïve	300	Sequential BCG + MMC (I + M) vs BCG (I + M)	Intravesical electromotive	Bladder cancer recurrence
NCT03719300	2	Single-arm assignment	BCG-unresponsive	32	BC-819 (inodiftagene victeplasmid)	Intravesical	CRR at 12 wk (Cis)
NCT03945162	2	Single-arm assignment	BCG-unresponsive	125	TLD1433 (ruthenium-based photosensitiser)	Intravesical	CRR at 12 mo
NCT04172675	2	Randomised, parallel assignment	BCG-unresponsive with FGFR mutations or fusions (cohort 1)	280	Erdafitinib vs Intravesical gemcitabine or MMC/ hyperthermic MMC	Oral	RFS
NCT04315480	2	Single-arm assignment	BCG failure	52	MMC	Intravesical electromotive	Time to first recurrence
NCT04386746	2	Single-arm assignment	BCG-naïve	26	Gemcitabine + docetaxel	Intravesical	CRR at 3 mo
NCT04452591	3	Single arm assignment	BCG unresponsive	110	CG0070 (engineered oncolytic adenovirus)	Intravesical	CRR (Cis)
NCT04490993	3	Randomised, parallel assignment	Intermediate/high-risk chemorefractory NMIBC	359	APL-1202 + intravesical epirubicin vs Placebo + intravesical epirubicin	Oral	EFS
NCT04498702	2	Single-arm assignment	Relapse after intravesical chemotherapy or BCG	41	APL-1202	Oral	RFR at 12 mo
NCT04859751	3	Single arm assignment	BCG unresponsive	53	VB4 845 (antibody drug conjugate)	Intravesical	CRR at 6 mo

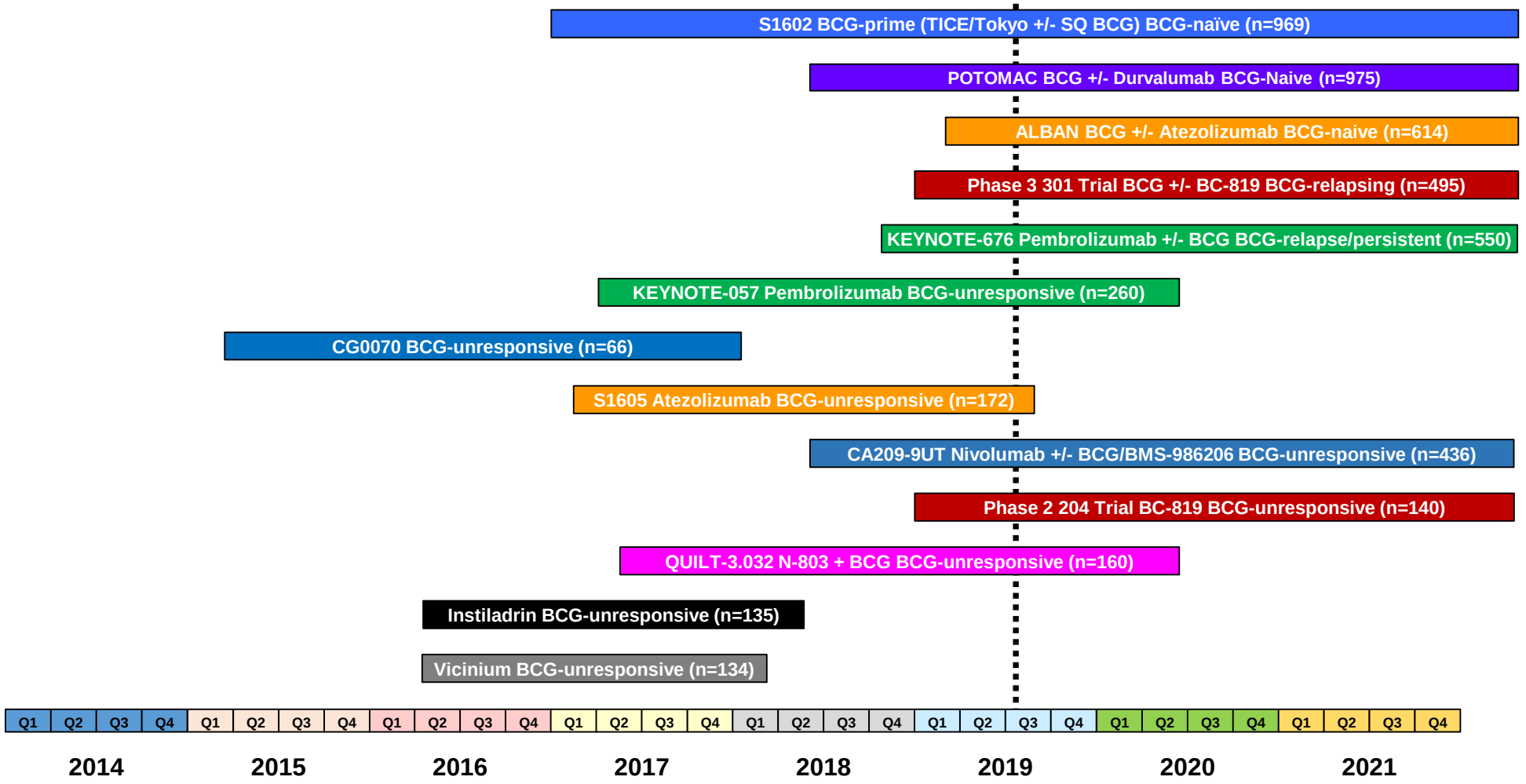
APL-1202 = methionine aminopeptidase II inhibitor; BCG = Bacillus Calmette-Guérin; Cis = carcinoma in situ; CR = complete response; CRR = complete response rate; DFR = disease-free rate; EFS = event-free survival; I + M = induction plus maintenance; MMC = mitomycin C; NMIBC = non-muscle-invasive bladder cancer; PANVAC = recombinant virus vector vaccine containing genes for human carcinoembryonic antigen and mucin-1, and three co-stimulatory molecules; PFS = progression-free survival; RFR = recurrence-free rate; RFS = recurrence-free survival.

Note: this slide is purposefully hard to read

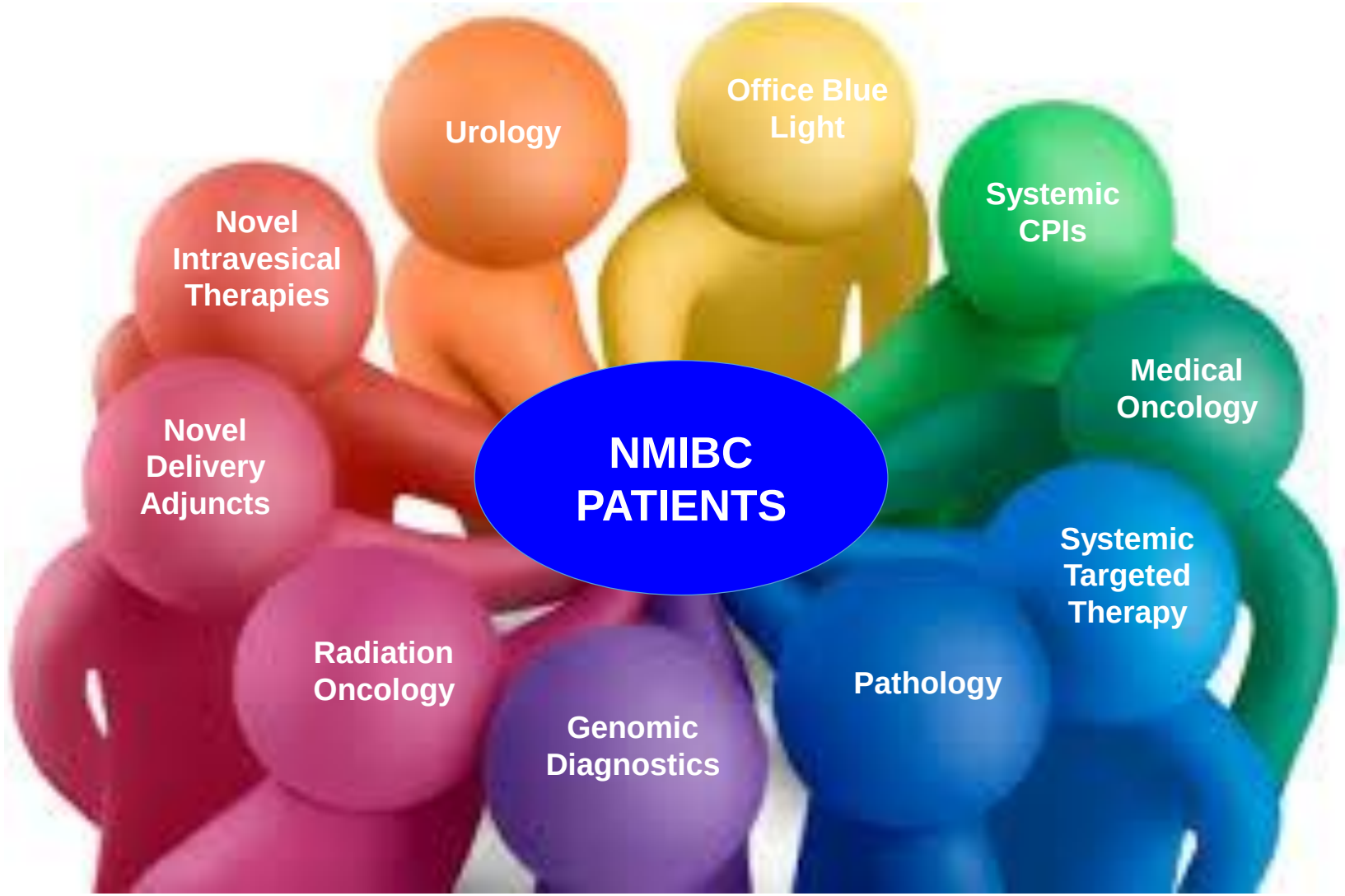
Pembro is just the beginning….

Giannarini G et al. Eur Urol Oncol. 2021;S2588-9311(21)00114-0.

NMIBC Registration/Practice-Changing Trials



The Future is Now for Multidisciplinary NMIBC Drug Development



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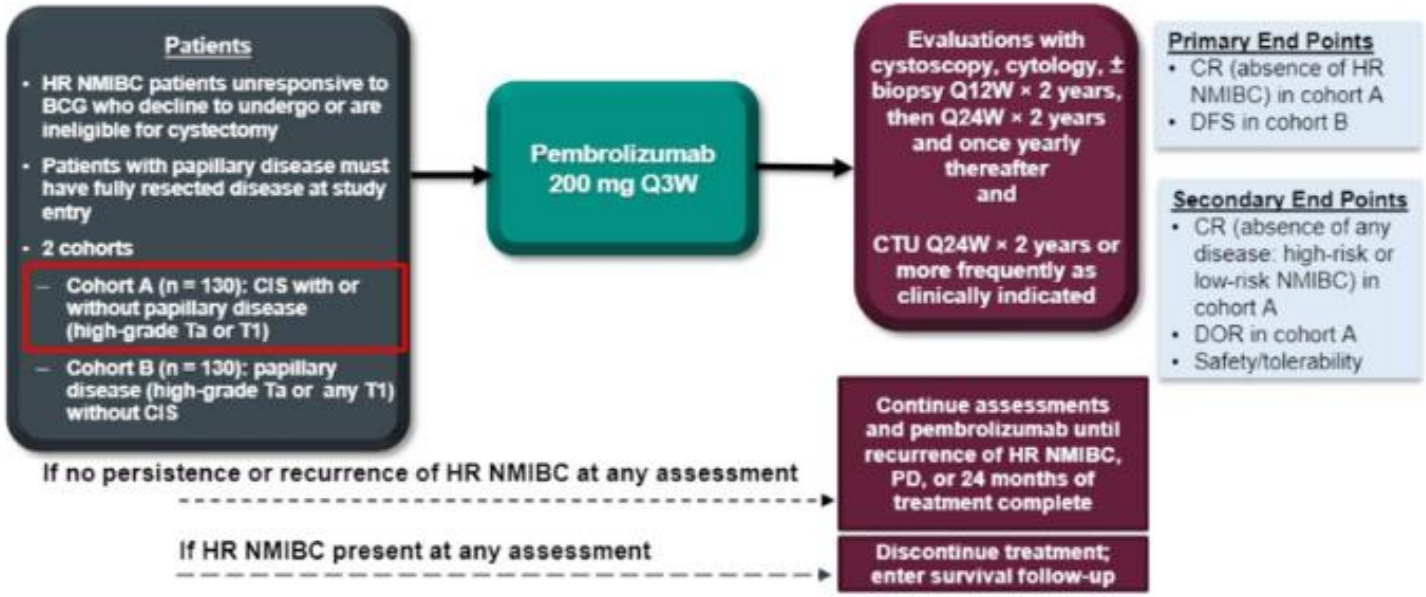
- Immunotherapy toxicities and management

Pembrolizumab monotherapy for the treatment of high-risk non-muscle-invasive bladder cancer unresponsive to BCG (KEYNOTE-057): an open-label, single-arm, multicentre, phase 2 study

Arjun V Balar, Ashish M Kamat, Girish S Kulkarni, Edward M Uchio, Joost L Boormans, Mathieu Roumiguié, Laurence E M Krieger, Eric A Singer, Dean F Bajorin, Petros Grivas, Ho Kyung Seo, Hiroyuki Nishiyama, Badrinath R Konety, Haojie Li, Kijoeng Nam, Ekta Kapadia, Tara Frenkl, Ronald de Wit

Lancet Oncol 2021; 22: 919–30

KEYNOTE-057: Single-Arm, Open-Label Phase 2 Study (NCT02625961)



Balar A et al. GU Symposium 2019
Slides from UroToday https://www.urotoday.com/conference-highlights/asco-gu-2019/asco-gu-2019-bladder-cancer/112879-asco-gu-2019-phase-ii-trial-of-pembrolizumab-for-patients-with-high-risk-non-muscle-invasive-bladder-cancer-unresponsive-to-bcg.html

Patient characteristics

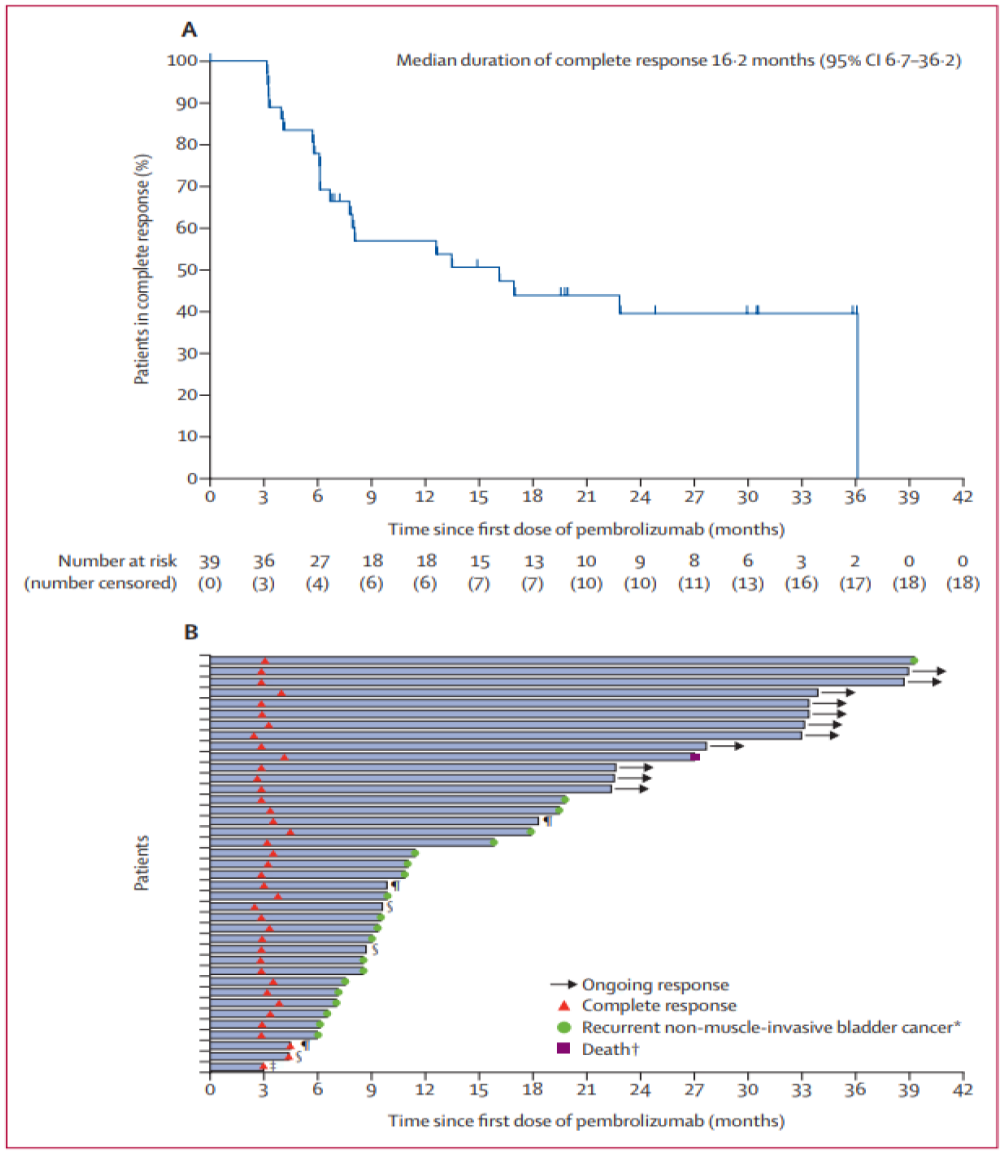
	Cohort A (n=101)
Age	
Median age, years (IQR)	73 (63–79)
≥65 years	71 (70%)
Sex	
Male	85 (84%)
Female	16 (16%)
ECOG performance status	
0	74 (73%)
1	27 (27%)
Previous BCG instillations, median (IQR)	12·0 (9·0–16·5)
Tumour stage	
Carcinoma in situ with T1	12 (12%)
Carcinoma in situ with high-grade Ta	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%)

Lancet Oncol 2021; 22: 919–30

Best Response at 3 months and durability of response

	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)

Lancet Oncol 2021; 22: 919–30



Toxicity

	Grade 1 or 2	Grade 3*	Grade 4†
Any	54 (53%)	11 (11%)	2 (2%)
Diarrhoea	11 (11%)	0	0
Fatigue	11 (11%)	0	0
Pruritus	10 (10%)	1 (1%)	0
Hypothyroidism	7 (7%)	0	0
Rash maculo-papular	6 (6%)	0	0
Hyperthyroidism	5 (5%)	0	0
Rash	5 (5%)	0	0
Nausea	5 (5%)	0	0
Arthralgia	4 (4%)	2 (2%)	0
Dry mouth	3 (3%)	0	0
Pneumonitis	3 (3%)	0	0
Rash pruritic	3 (3%)	0	0
Abdominal pain	2 (2%)	0	0
Alanine aminotransferase increased	2 (2%)	0	0
Asthaenia	2 (2%)	0	0
Blood thyroid-stimulating hormone decreased	2 (2%)	0	0
Colitis	2 (2%)	0	0
Constipation	2 (2%)	0	0
Eczema	2 (2%)	0	0
Haematuria	2 (2%)	0	0
Influenza-like illness	2 (2%)	0	0
Malaise	2 (2%)	1 (1%)	0
Myalgia	2 (2%)	0	0
Neuropathy peripheral	2 (2%)	0	0
Pyrexia	2 (2%)	0	0
Dermatitis	1 (1%)	1 (1%)	0
Hyponatraemia	0	2 (2%)	1 (1%)

Data are n (%). The table shows treatment-related adverse events that occurred in two or more patients. *In addition to the grade 3 events listed, one patient each experienced grade 3 adrenal insufficiency, cholestatic hepatitis, decreased lymphocyte count, syncope, adrenocorticotropic hormone deficiency, hypophosphataemia, and pulmonary embolism. †In addition to the grade 4 events listed, one patient experienced grade 4 type 1 diabetes.

***Table 3:* Treatment-related adverse events (n=101)**

22% with irAE, 3 pts with grade 3/4

7 pts received corticosteroids

No treatment related death

1 patient died of progressive disease

Pathologic staging of patients with PD who underwent cystectomy

3 upstaged to MIBC

2 node-positive

	Patients (n=38)*	N stage†	Achieved initial complete response	Interval between last dose of pembrolizumab and radical cystectomy, days	Number of pembrolizumab doses
Non-muscle-invasive bladder cancer					
pT0	6	N0=5, Nx=1	4	135 (91–138)	11·5 (7·0–14·0)
pTa	5	N0=5	0	103 (79–209)	5·0 (5·0–6·0)
pTis	18	N0=16, Nx=2	6	77 (61–176)	6·0 (6·0–7·0)
pT1	6	N0=6	0	133 (77–170)	6·5 (6·0–7·0)
Muscle-invasive bladder cancer					
pT2	2	N0=1, N1=1‡	0	60§,86§	3·5 (3·0–4·0)
PT3	1	N1	0	457§	6·0§

Data are n, or median (IQR). Tumour-node classification based on the guidelines in the American Joint Committee on Cancer Cancer Staging Manual, 8th edition.[25] *TNM staging was not available for two of the 40 participants who had undergone radical cystectomy. †Nx=lymph node dissection not performed. ‡In a patient with pT2N1 disease, a single perivesical lymph node was involved. §These data are only for one patient each, and therefore do not have IQR.

Table 4: **Pathological staging at time of radical cystectomy in patients who discontinued pembrolizumab by maximum T stage**

SITC guidelines for NMIBC immunotherapy

Table 2 NMIBC immunotherapy treatment algorithm

NMIBC risk category	Management		
Low-risk	BCG not recommended		
Intermediate-risk (BCG available)	BCG†-induction and 1-year maintenance		
Intermediate-risk (BCG unavailable)	Intravesical chemotherapy	If recurrence occurs	BCG†
High-risk*	BCG† induction and 3 years maintenance	If BCG-unresponsive high-risk CIS NMIBC with or without papillary tumors	Pembrolizumab

Individual rows represent treatment decision options that can be followed from left to right horizontally in adjacent columns.
*Including NMIBC high-risk cases with CIS or papillary tumors.
†BCG should not be administered to patients with active infection or gross hematuria, but BCG may be administered to patients experiencing asymptomatic bacteriuria. Best supportive measures should be employed to ensure that patients receive a full, adequate course of BCG.

BCG, Bacillus Calmette-Guérin; CIS, carcinoma in situ; NMIBC, non-muscle-invasive bladder cancer.

Clinical Characteristics

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjuvant Nivolumab versus Placebo in Muscle-Invasive Urothelial Carcinoma

D.F. Bajorin, J.A. Witjes, J.E. Gschwend, M. Schenker, B.P. Valderrama, Y. Tomita, A. Bamias, T. Lebret, S.F. Shariat, S.H. Park, D. Ye, M. Agerbaek, D. Enting, R. McDermott, P. Gajate, A. Peer, M.I. Milowsky, A. Nosov, J. Neif Antonio, Jr., K. Tupikowski, L. Toms, B.S. Fischer, A. Qureshi, S. Collette, K. Unsal-Kacmaz, E. Broughton, D. Zardavas, H.B. Koon, and M.D. Galsky

NEJM 2021

ypT2-4 or node positive or pT3-4 or node positive
Co-primary endpoints:
-Disease free survival - Intent to Treat

-Disease free survival - PD-L1 positive population

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)
Time from initial diagnosis to randomization — no. (%)		
<1 yr	325 (92.1)	324 (91.0)
≥1 yr	28 (7.9)	32 (9.0)
PD-L1 expression level of ≥1% by IVRS — no. (%)	140 (39.7)	142 (39.9)
Previous neoadjuvant cisplatin therapy — no. (%)	153 (43.3)	155 (43.5)
Pathological tumor stage and nodal status at resection — no. (%)§		
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 — no. (%)¶		
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 — no. (%)		
N0 or NX with <10 nodes removed	94 (26.6)	99 (27.8)

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Both primary endpoints statistically significant improvement with nivolumab

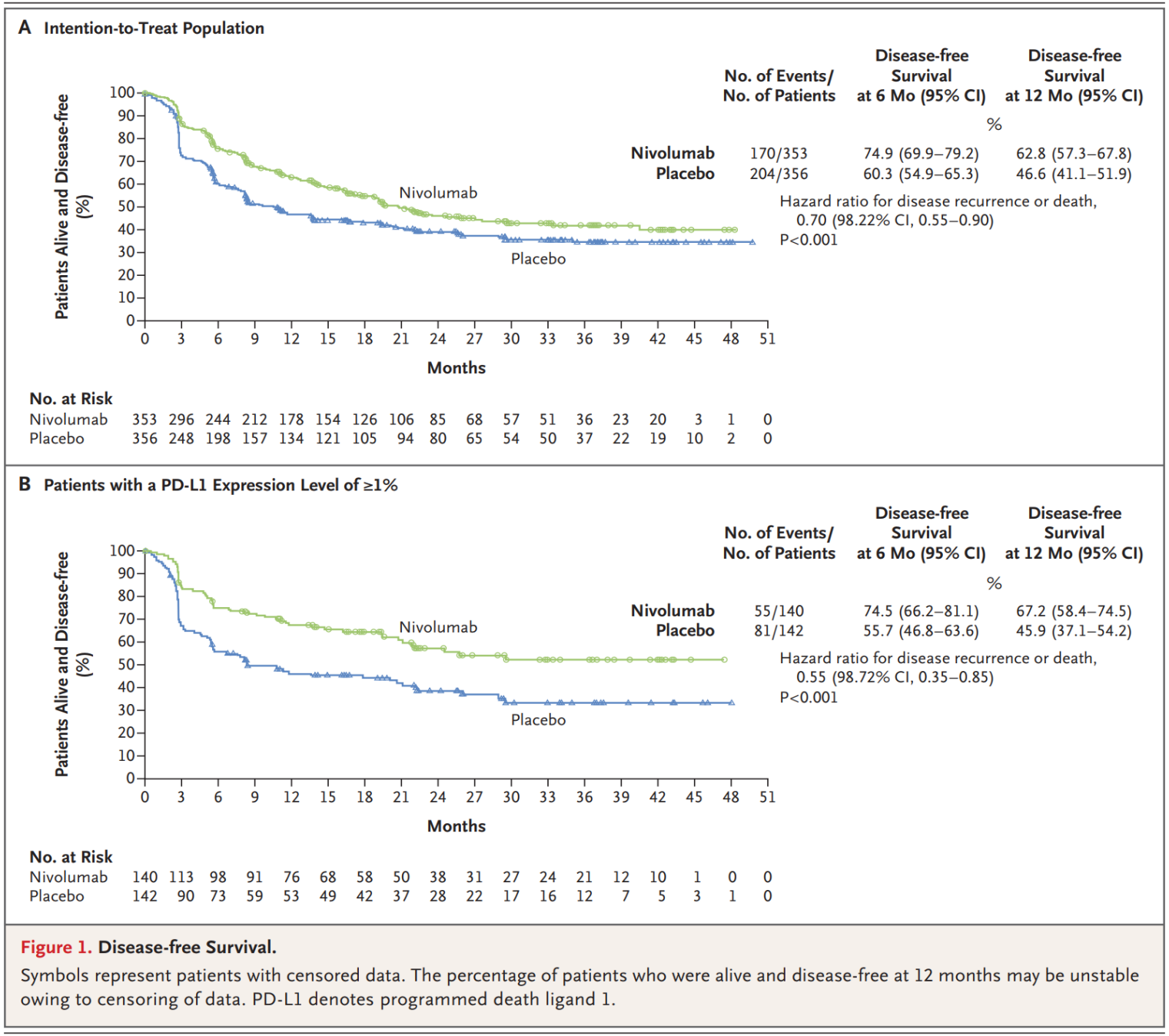


Figure 1. Disease-free Survival.

Symbols represent patients with censored data. The percentage of patients who were alive and disease-free at 12 months may be unstable owing to censoring of data. PD-L1 denotes programmed death ligand 1.

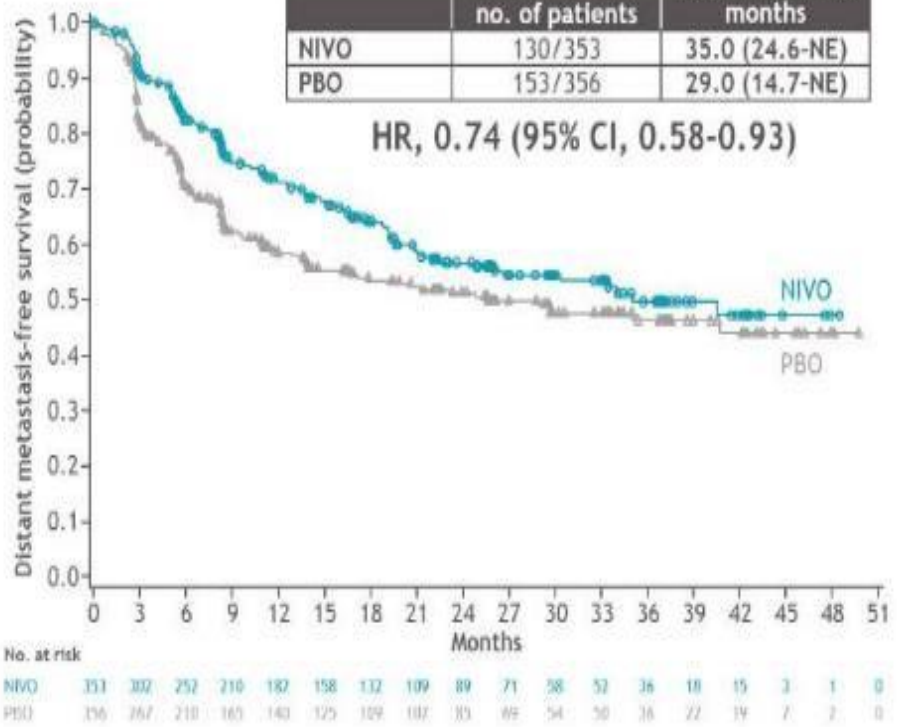
NEJM 2021

Distant metastasis-free survival

ITT

	No. of events/ no. of patients	Median (95% CI), months
NIVO	130/353	35.0 (24.6-NE)
PBO	153/356	29.0 (14.7-NE)

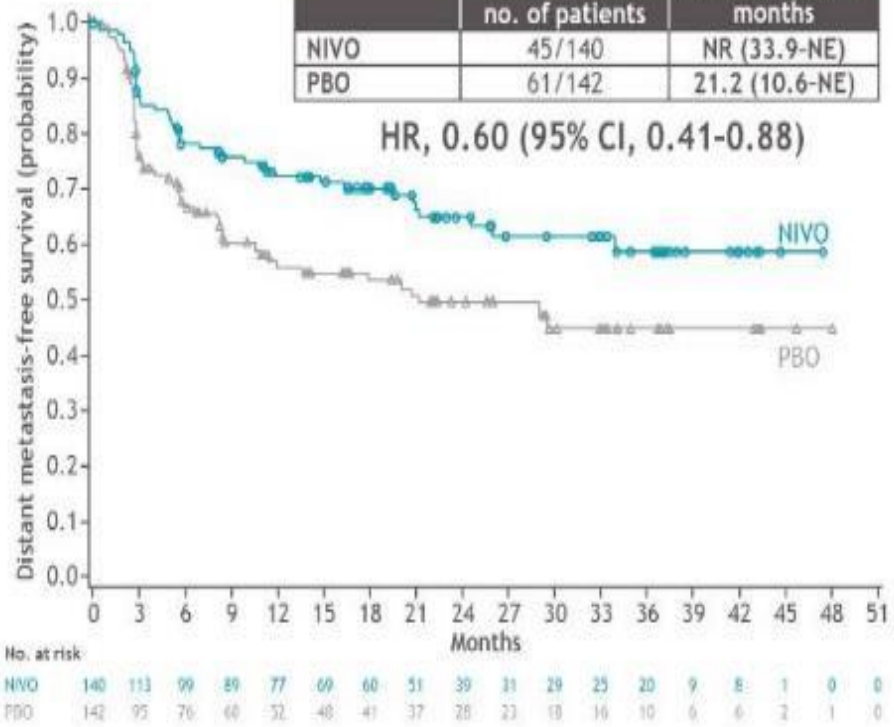
HR, 0.74 (95% CI, 0.58-0.93)



PD-L1 ≥ 1%

	No. of events/ no. of patients	Median (95% CI), months
NIVO	45/140	NR (33.9-NE)
PBO	61/142	21.2 (10.6-NE)

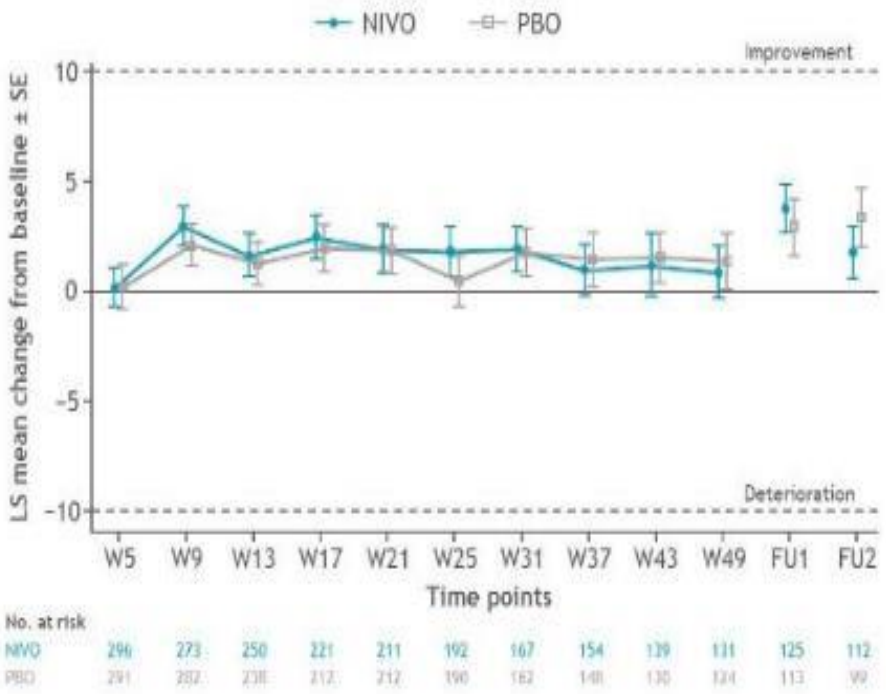
HR, 0.60 (95% CI, 0.41-0.88)



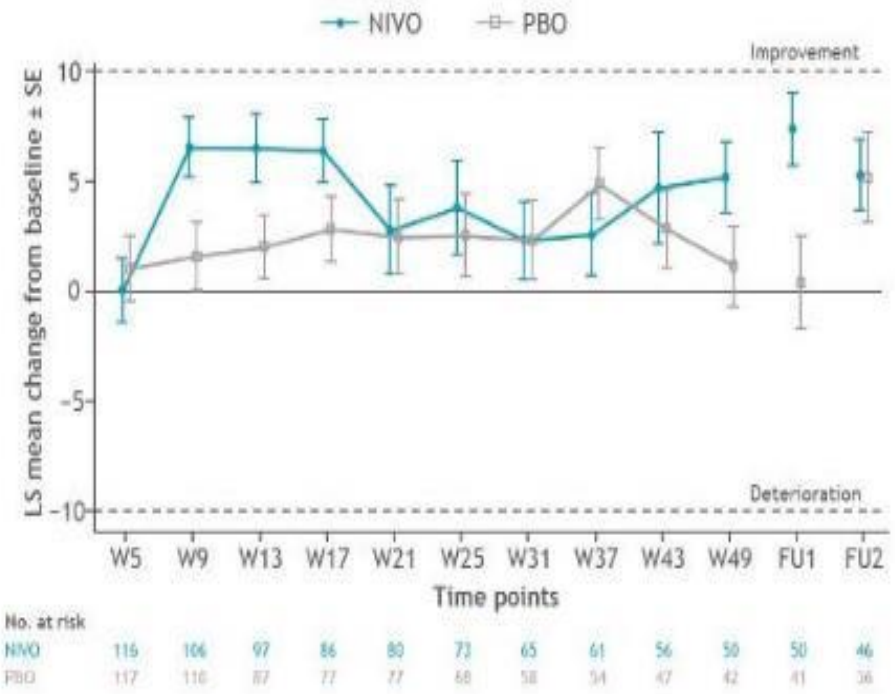
Minimum follow-up, 5.9 months.
DMFS was defined as the time between the date of randomization and the date of first distant recurrence (non-local) or date of death.

Health-related quality of life: change from baseline in EORTC-QLQ-C30 global health status score

ITT



PD-L1 ≥ 1%



- No deterioration in HRQoL with NIVO versus PBO was observed in either the ITT or PD-L1 ≥ 1% populations

Number of patients displayed is the number of patients included in the mixed effects linear regression for repeated measures analysis at each visit. SE is the robust SE calculated using empirical variance estimator.
FU, follow-up visit; LS, least square; SE, standard error.

Adverse Events

Table 2. Adverse Events.*

Adverse Event	Nivolumab (N = 351)		Placebo (N = 348)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Adverse event of any cause	347 (98.9)	150 (42.7)	332 (95.4)	128 (36.8)
Adverse event related to nivolumab or placebo†	272 (77.5)	63 (17.9)	193 (55.5)	25 (7.2)
Pruritus	81 (23.1)	0	40 (11.5)	0
Fatigue	61 (17.4)	1 (0.3)	42 (12.1)	0
Diarrhea	59 (16.8)	3 (0.9)	38 (10.9)	1 (0.3)
Rash	53 (15.1)	2 (0.6)	19 (5.5)	0
Increased lipase level	34 (9.7)	18 (5.1)	20 (5.7)	9 (2.6)
Hypothyroidism	34 (9.7)	0	5 (1.4)	0
Increased amylase level	33 (9.4)	13 (3.7)	20 (5.7)	5 (1.4)
Hyperthyroidism	33 (9.4)	0	3 (0.9)	0
Asthenia	24 (6.8)	2 (0.6)	17 (4.9)	0
Nausea	24 (6.8)	0	13 (3.7)	0
Decreased appetite	20 (5.7)	2 (0.6)	11 (3.2)	0
Increased blood creatinine level	20 (5.7)	1 (0.3)	11 (3.2)	0
Maculopapular rash	19 (5.4)	2 (0.6)	4 (1.1)	0

* Shown are events that were reported between the first dose and 30 days after the last dose of nivolumab or placebo.
† Shown are events that occurred in at least 5% of the patients in either trial group. There were two treatment-related deaths due to pneumonitis in the nivolumab group.

2 treatment related deaths due to pneumonitis

NEJM 2021

Adjuvant atezolizumab versus observation in muscle-invasive urothelial carcinoma (IMvigor010): a multicentre, open-label, randomised, phase 3 trial

*Joaquim Bellmunt, Maha Hussain, Jürgen E Gschwend, Peter Albers, Stephane Oudard, Daniel Castellano, Siamak Daneshmand, Hiroyuki Nishiyama, Martin Majchrowicz, Viraj Degaonkar, Yi Shi, Sanjeev Mariathasan, Petros Grivas, Alexandra Drakaki, Peter H O'Donnell, Jonathan E Rosenberg, Daniel M Geynisman, Daniel P Petrylak, Jean Hoffman-Censits, Jens Bedke, Arash Rezazadeh Kalebasty, Yousef Zakharia, Michiel S van der Heijden, Cora N Sternberg, Nicole N Davarpanah, Thomas Powles, for the IMvigor010 Study Group**

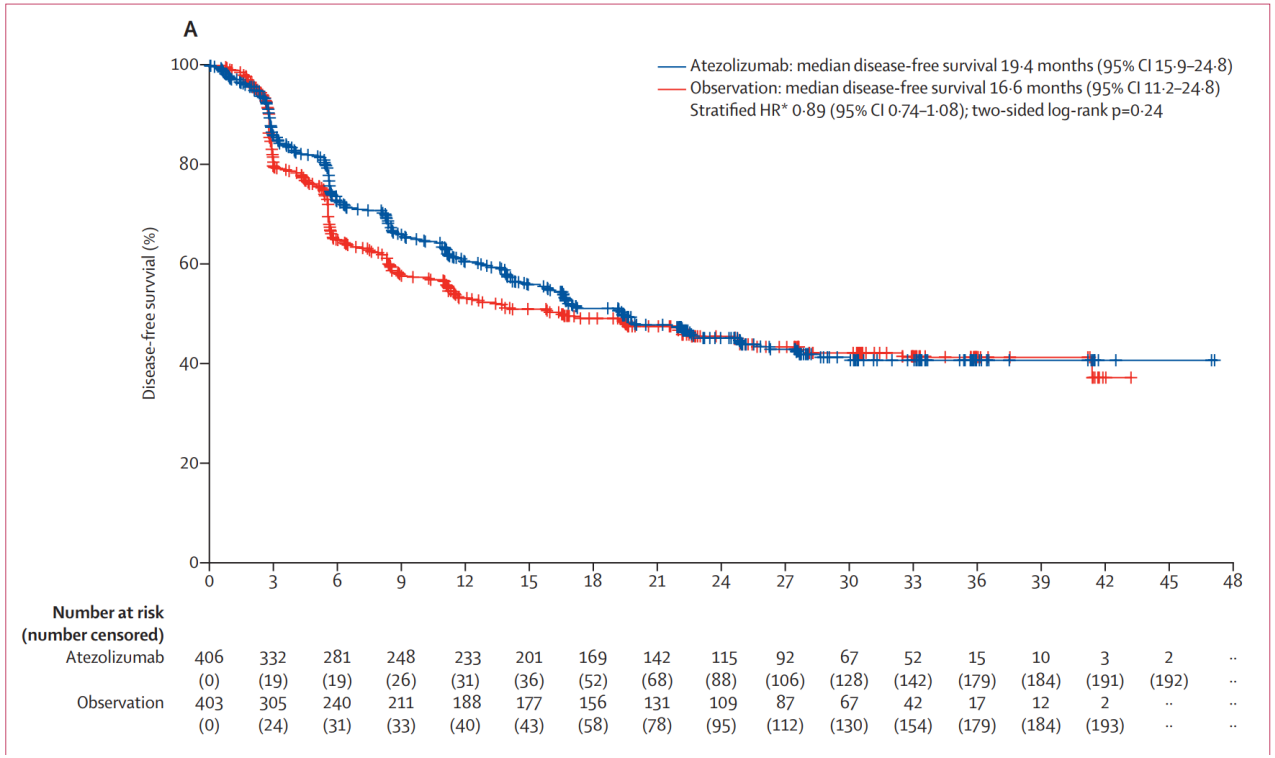
ypT2-4 or node positive or pT3-4 or node positive

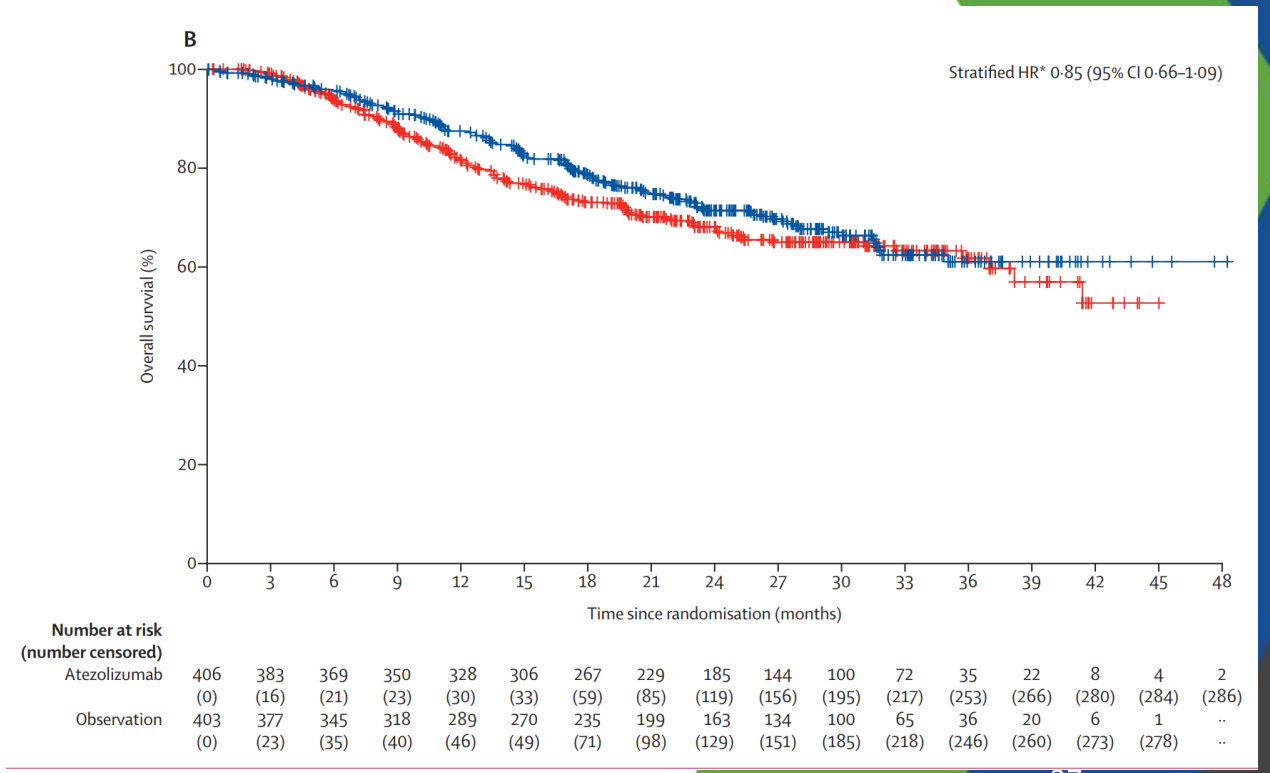
Primary endpoint: DFS for intent to treat population

Lancet Oncol 2021; 22: 525–37

	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%)
Pathological nodal status*		
Positive	212 (52%)	208 (52%)
Negative	194 (48%)	195 (48%)
Tumour stage and N0 nodal status†		
pT2N0	34 (8%)	39 (10%)
pT3N0	124 (31%)	119 (30%)
pT4N0	32 (8%)	33 (8%)
Number of lymph nodes resected*		
<10	95 (23%)	94 (23%)
≥10	311 (77%)	309 (77%)
Eastern Cooperative Oncology Group performance status		
0	248 (61%)	259 (64%)
1	142 (35%)	130 (32%)
2	16 (4%)	14 (3%)
Age-adjusted Charlson Comorbidity Index		
0–1	55/400 (14%)	61/401 (15%)
2–3	135/400 (34%)	150/401 (37%)
≥4	210/400 (53%)	190/401 (47%)
PD-L1 status on immune cells*‡		
IC0 or IC1	210 (52%)	207 (51%)
IC2 or IC3	196 (48%)	196 (49%)
Previous neoadjuvant chemotherapy*		
Yes	196 (48%)	189 (47%)
No	210 (52%)	214 (53%)

Disease free survival and overall survival





Lancet Oncol 2021; 22: 525–37

Toxicity

	Grade 1–2	Grade 3	Grade 4	Grade 5
All adverse events	212 (54%)	58 (15%)	5 (1%)	1 (<1%)
Pruritus	73 (19%)	2 (1%)	0	0
Fatigue	62 (16%)	1 (<1%)	0	0
Diarrhoea	34 (9%)	3 (1%)	0	0
Rash	32 (8%)	1 (<1%)	0	0
Arthralgia	22 (6%)	5 (1%)	0	0
Asthenia	20 (5%)	3 (1%)	0	0
Pyrexia	21 (5%)	2 (1%)	0	0
Infusion-related reaction	18 (5%)	2 (1%)	0	0
Alanine aminotransferase increased	14 (4%)	4 (1%)	0	0
Aspartate aminotransferase increased	12 (3%)	2 (1%)	0	0
Rash maculopapular	9 (2%)	2 (1%)	0	0
Anaemia	7 (2%)	2 (1%)	0	0
Pneumonitis	4 (1%)	2 (1%)	0	0
Colitis	1 (<1%)	4 (1%)	0	0
Lipase increased	2 (1%)	2 (1%)	1 (<1%)	0
Amylase increased	3 (1%)	2 (1%)	0	0
Acute kidney injury	1 (<1%)	2 (1%)	0	0
Urinary tract infection	1 (<1%)	2 (1%)	0	0
Autoimmune hepatitis	0	2 (1%)	0	0
Immune-mediated enterocolitis	0	2 (1%)	0	0
Systemic immune activation	0	2 (1%)	0	0
Small intestine ulcer	0	0	1 (<1%)	0
Bacterial sepsis	0	0	1 (<1%)	0
Neuroborreliosis	0	0	1 (<1%)	0
Hyperamylasaemia	0	0	1 (<1%)	0
Hyperlipasaemia	0	0	1 (<1%)	0
Acute respiratory distress syndrome	0	0	0	1 (<1%)
Myocardial infarction	0	1 (<1%)	0	0
Adrenal insufficiency	0	1 (<1%)	0	0
(Continued from previous column)				
Endocrine pancreatic disorder	0	1 (<1%)	0	0
Proctitis	0	1 (<1%)	0	0
Stomatitis	2 (1%)	1 (<1%)	0	0
Lithiasis	0	1 (<1%)	0	0
Hepatitis	0	1 (<1%)	0	0
Liver disorder	0	1 (<1%)	0	0
Hypersensitivity	1 (<1%)	1 (<1%)	0	0
Hepatic enzyme increased	0	1 (<1%)	0	0
Decreased appetite	17 (4%)	1 (<1%)	0	0
Diabetes	0	1 (<1%)	0	0
Hypokalaemia	2 (1%)	1 (<1%)	0	0
Arthritis	2 (1%)	1 (<1%)	0	0
Myalgia	10 (3%)	1 (<1%)	0	0
Polymyalgia rheumatica	1 (<1%)	1 (<1%)	0	0
Headache	16 (4%)	1 (<1%)	0	0
Peripheral neuropathy	3 (1%)	1 (<1%)	0	0
Autoimmune nephritis	0	1 (<1%)	0	0
Hydronephrosis	0	1 (<1%)	0	0
Nephritis	2 (1%)	1 (<1%)	0	0
Renal injury	0	1 (<1%)	0	0
Tubulointerstitial nephritis	0	1 (<1%)	0	0
Pulmonary embolism	1 (<1%)	1 (<1%)	0	0
Dermatitis allergic	0	1 (<1%)	0	0
Drug eruption	0	1 (<1%)	0	0
Palmar-plantar erythrodysaesthesia syndrome	0	1 (<1%)	0	0
Rash papular	1 (<1%)	1 (<1%)	0	0

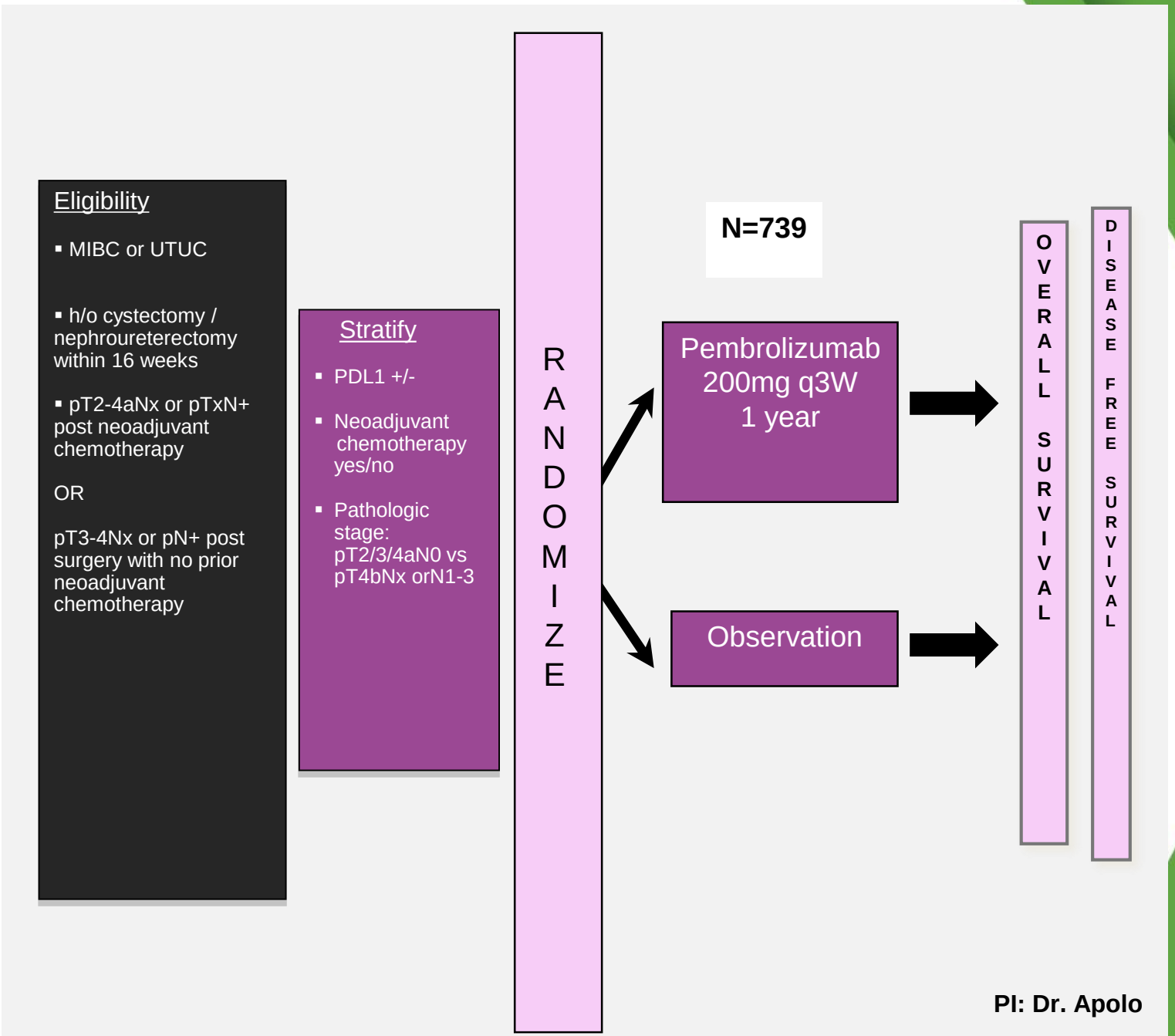
Data are n (%). Grade 1–2 treatment-related adverse events in at least 10% of patients in either group, and grade 3, 4, or 5 treatment-related adverse events in all patients are shown.

Table 2: **Treatment-related adverse events in the atezolizumab group (n=390)**

Lancet Oncol 2021; 22: 525–37

1 treatment related death due to ARDS

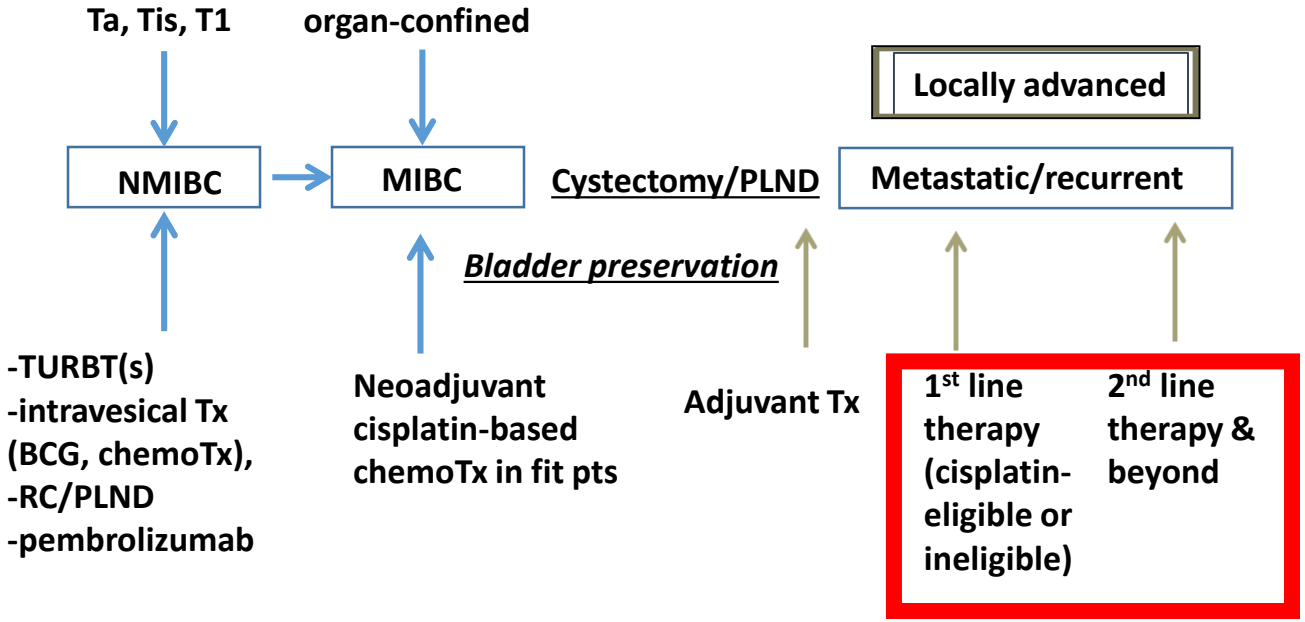
Phase III randomized “Adjuvant peMBrolizumAb in muScle invaSive & locAlly aDvanced urOthelial carcinoma” (AMBASSADOR) vs. observation



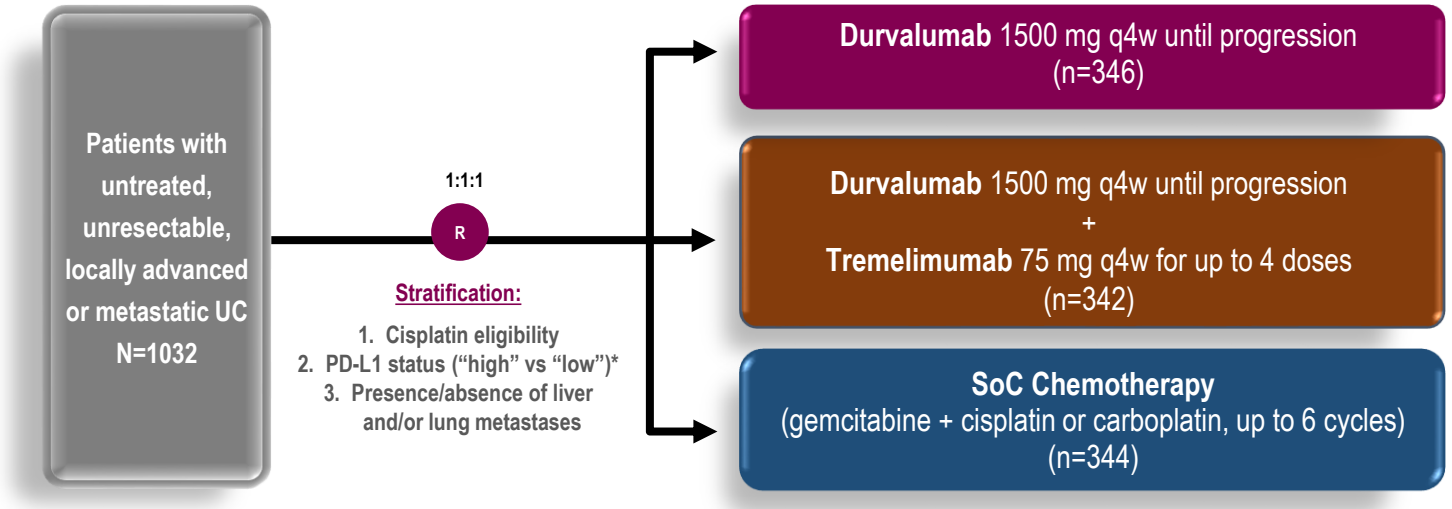
PI: Dr. Apolo

ClinicalTrials.gov: NCT03244384

Disease / treatment settings



DANUBE Study Design[1]



CO-PRIMARY ENDPOINTS

- OS (D vs SoC in PD-L1 high)
- OS (D+T vs SoC in all comers)

SELECT SECONDARY ENDPOINTS

- OS (D vs SoC in all comers)
- OS (D+T vs SoC in PD-L1 high)
- PFS, ORR, and DoR

Data cutoff date (final analysis): January 27 2020

Minimum follow-up from date last patient randomised: 34 months

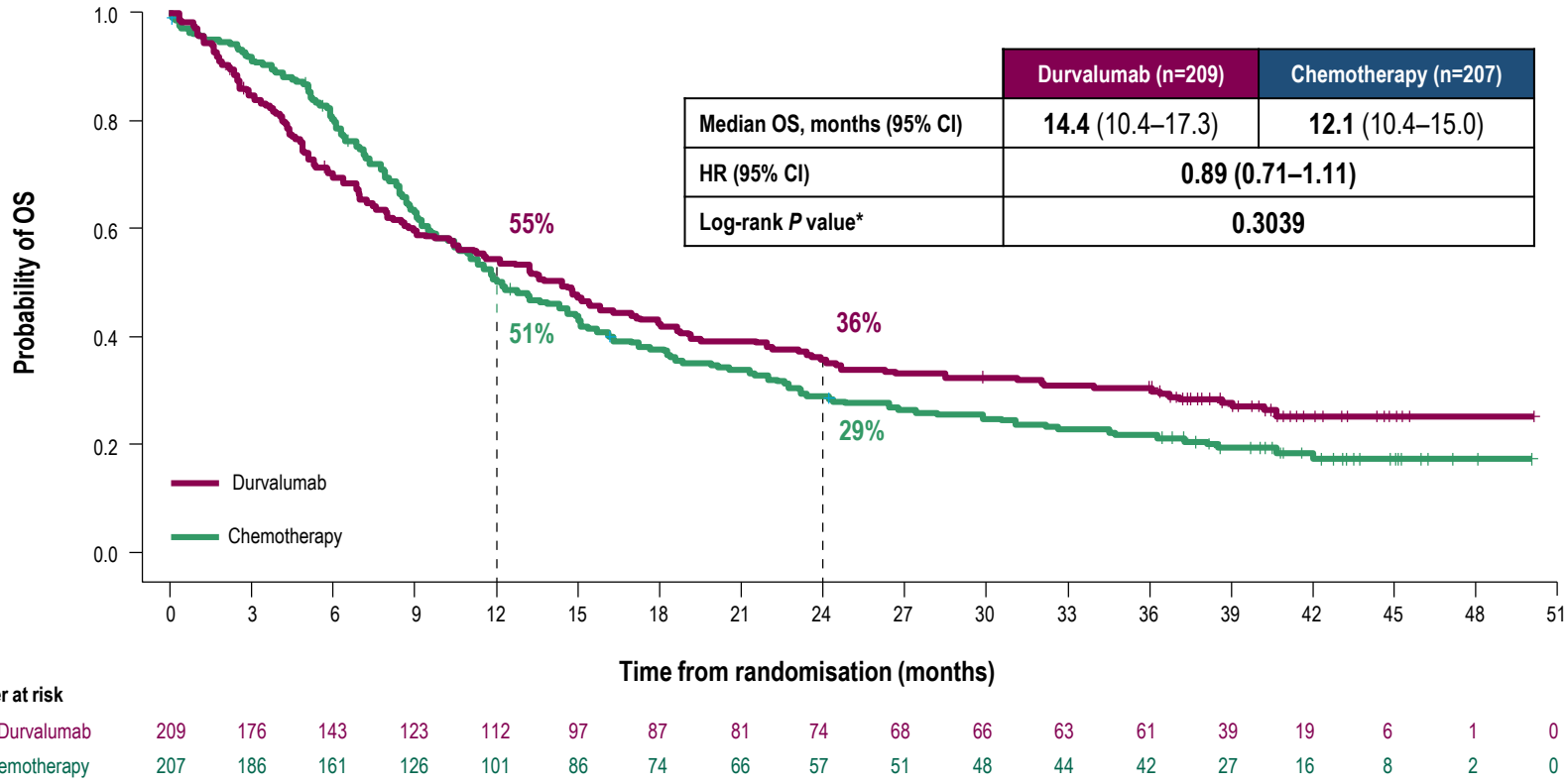
Median follow-up for survival: 41.2 months for all patients

*PD-L1 assessed using the VENTANA PD-L1 (SP263) Assay (Ventana Medical Systems, Tucson, AZ)[2]

- High PD-L1 expression:[3] either ≥25% of tumour cells (TCs) with membrane staining or ≥25% of immune cells (ICs) staining for PD-L1 at any intensity

1. Powles T, et al. Presented at ESMO 2020 697O; 2. Zajac M, et al. Arch Pathol Lab Med 2019;143:722–31; 3. Ventana Medical Systems. VENTANA PD-L1 (SP263) Assay. https://www.accessdata.fda.gov/cdrh_docs/pdf16/p160046c.pdf.

Co-primary Endpoint: OS With Durvalumab vs Chemotherapy in PD-L1 High Population



	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**	

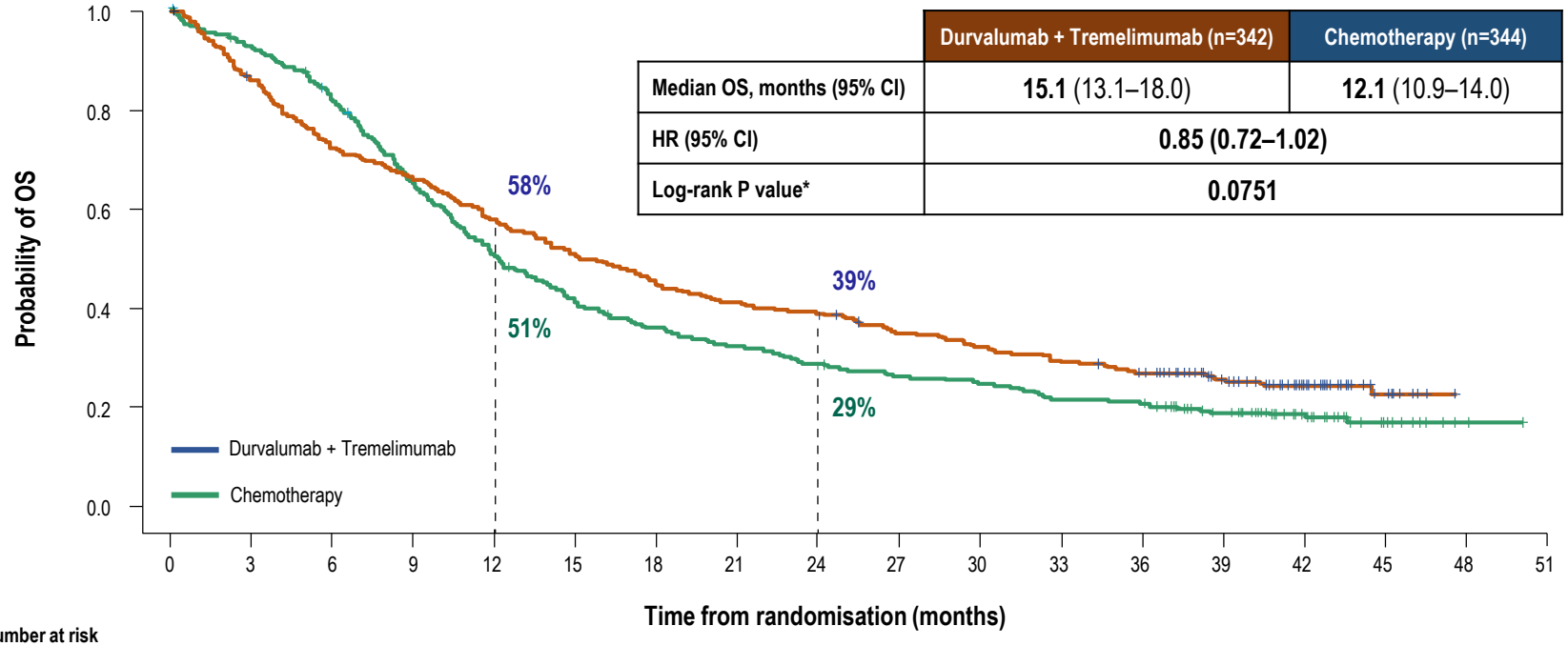
Number at risk

Durvalumab	209	176	143	123	112	97	87	81	74	68	66	63	61	39	19	6	1	0
Chemotherapy	207	186	161	126	101	86	74	66	57	51	48	44	42	27	16	8	2	0

*Considered statistically significant if p<0.0301.

Powles T, et al. Presented at ESMO 2020 697O.

Co-primary Endpoint – OS with Durvalumab + Tremelimumab vs Chemotherapy in ITT Population



	Durvalumab + Tremelimumab (n=342)	Chemotherapy (n=344)
Median OS, months (95% CI)	**15.1** (13.1–18.0)	**12.1** (10.9–14.0)
HR (95% CI)	**0.85 (0.72–1.02)**	
Log-rank P value*	**0.0751**	

Number at risk

Durvalumab + Tremelimumab	342	292	246	224	197	173	153	140	133	118	108	99	89	61	33	12	0	0
Chemotherapy	344	311	273	216	168	136	119	107	95	86	81	71	68	46	27	11	2	0

*Considered statistically significant if p<0.0301.

Powles T, et al. Presented at ESMO 2020 697O.

Safety Summary

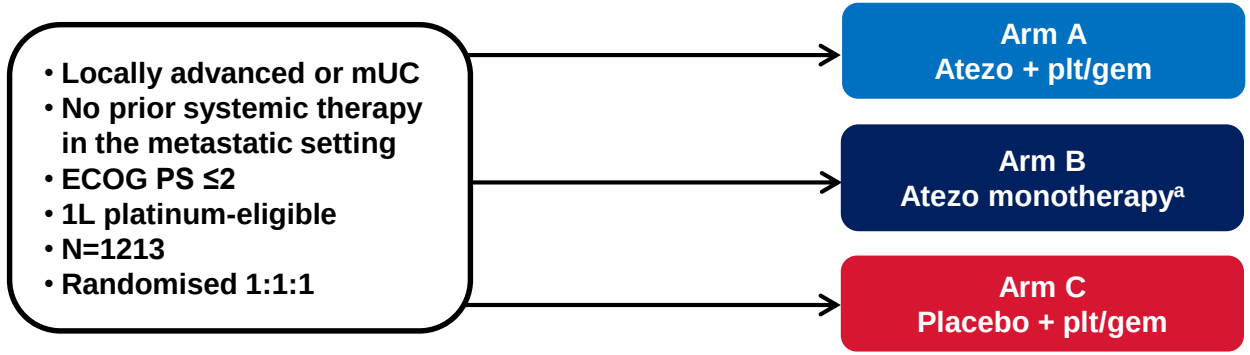
	Durvalumab n=345	Durvalumab + Tremelimumab n=340	Chemotherapy n=313
Treatment-related AEs			
Any grade	**56%**	**75%**	**90%**
Grade 3 or 4	**14%**	**28%**	**60%**
Grade 5	**1%**	**1%**	**<1%**
Treatment-related serious AEs	**9%**	**23%**	**16%**
Treatment-related AEs leading to discontinuation	**6%**	**16%**	**12%**
Treatment-related AEs of special interest*			
Any grade	**26%**	**49%**	**15%**
Grade 3 or 4	**6%**	**12%**	**2%**
Systemic corticosteroid use	**11%**	**26%**	**1%**

*Excluding infusion/hypersensitivity reactions.

Most common treatment-related AEs of Grade 3 or 4 was increased lipase (in both the durvalumab and durvalumab + tremelimumab groups) and neutropenia and anemia (in the chemotherapy group)

Powles T, et al. Presented at ESMO 2020 697O.

IMvigor130: chemo/atezo vs chemo; atezo vs chemo[1,2]



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 ± patients with liver metastases)
- Investigator choice of plt/gem (gem + carbo or gem + cis)

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

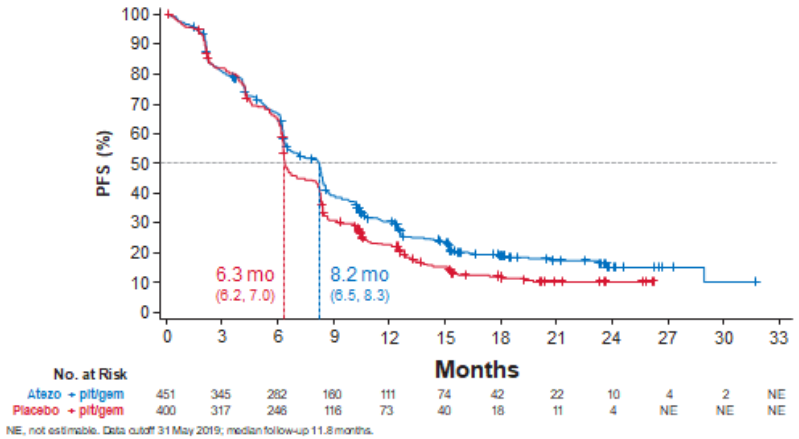
Key secondary endpoints:
- INV-ORR[b] and DOR
- PFS[b] and OS (Arm B vs C; PD-L1 IC2/3 subgroup)
- Safety

[a]The first 129 patients were randomised 2:1 to Arm A and Arm C per initial study design; Arm B enrolled later. PD-L1 status was unblinded in the final protocol amendment per IMDC recommendation, such that IC0/1 patients received atezo + plt/gem and IC2/3 patients received atezo monotherapy (n=6). [b]per RECIST 1.1.

Atezo, atezolizumab; carbo, carboplatin; cis, cisplatin; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; gem, gemcitabine; IC, immune cells; INV, investigator; KPS; Karnofsky performance status; mUC, metastatic urothelial carcinoma; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; plt, platinum; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumours. 1. Galsky MD et al. Lancet 2020;395:1547–57; 2. Grande E, et al. Presented at ESMO 2019 LBA14.

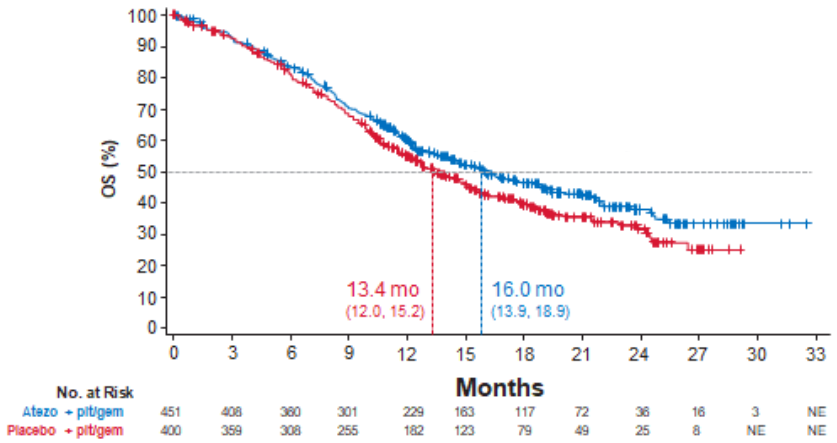
Progression free & overall survival (Arm A vs Arm C)[1,2]

Final PFS: ITT (Arm A vs Arm C)



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

Interim OS: ITT (Arm A vs Arm C)

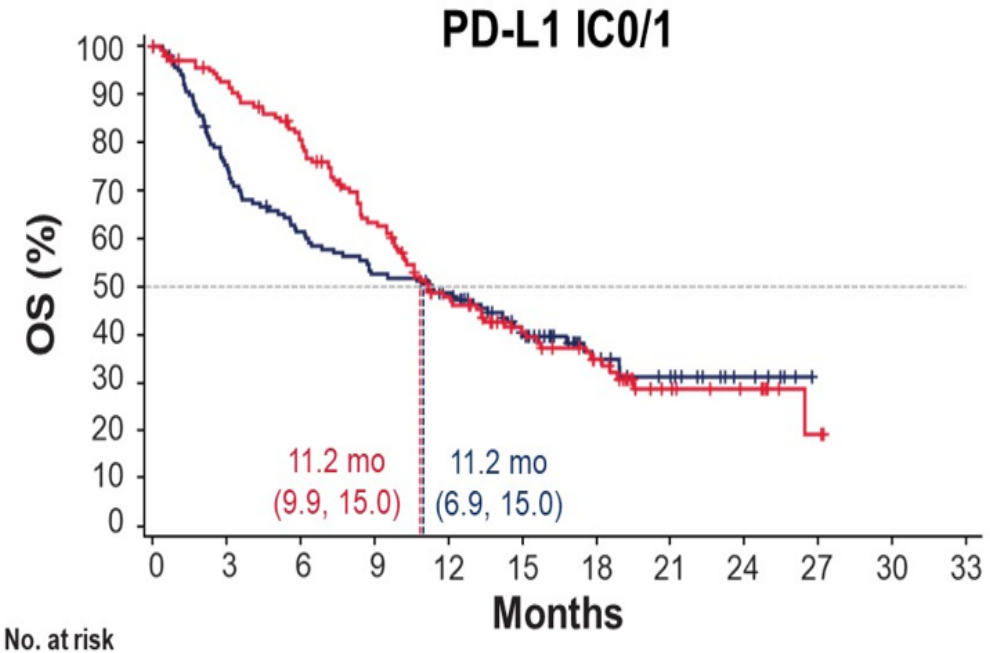


	Arm A Atezo + plt/gem (n=451)	Arm C Placebo + plt/gem (n=400)
OS events[a], n (%)	235 (52)	228 (57)
Stratified HR (95% CI)	**0.83 (0.69, 1.00)** P=0.027 (one-sided)[b]	

[b] Did not cross the interim efficacy boundary of 0.007 per the O'Brien-Fleming alpha spending function.

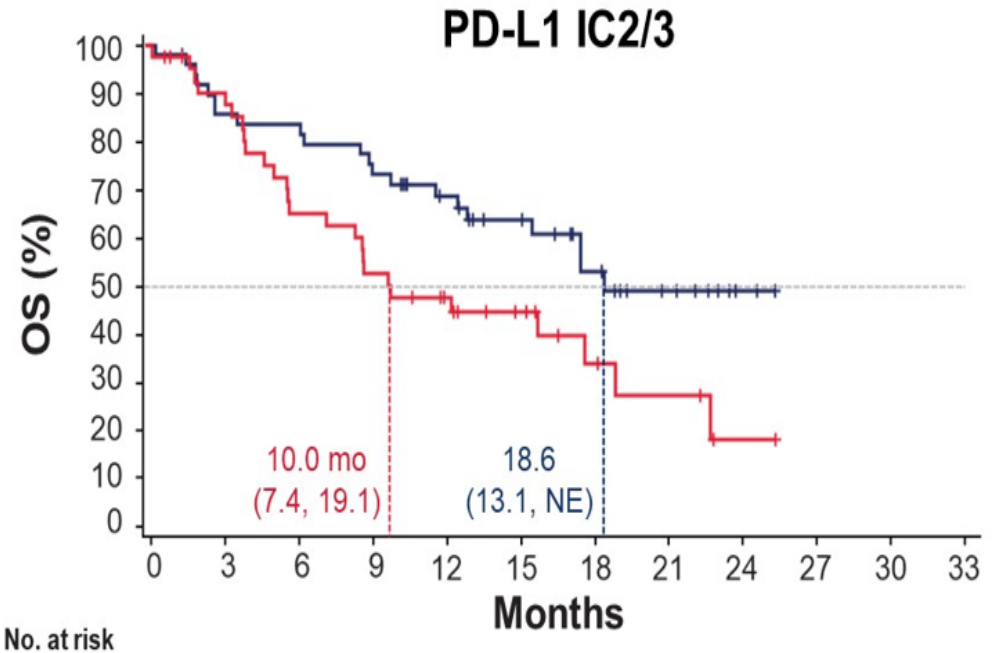
Atezo, atezolizumab; CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; mo, months; PFS, progression-free survival; plt/gem, platinum/gemcitabine; UC, urothelial carcinoma. 1. Galsky MD et al. Lancet 2020;395:1547–57; 2. Grande E, et al. Presented at ESMO 2019 LBA14.

Interim OS by PD-L1 status (cisplatin-ineligible patients)



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)

PD-L1–expressing immune cells covering ≥5% (IC2/3) or <5% (IC0/1) of the tumor area per VENTANA SP142 IHC assay. [a] For ORR, Arms B and C: n=139.

Galsky MD, et al. Virtual poster presentation at ASCO GU 2021; abstract 434

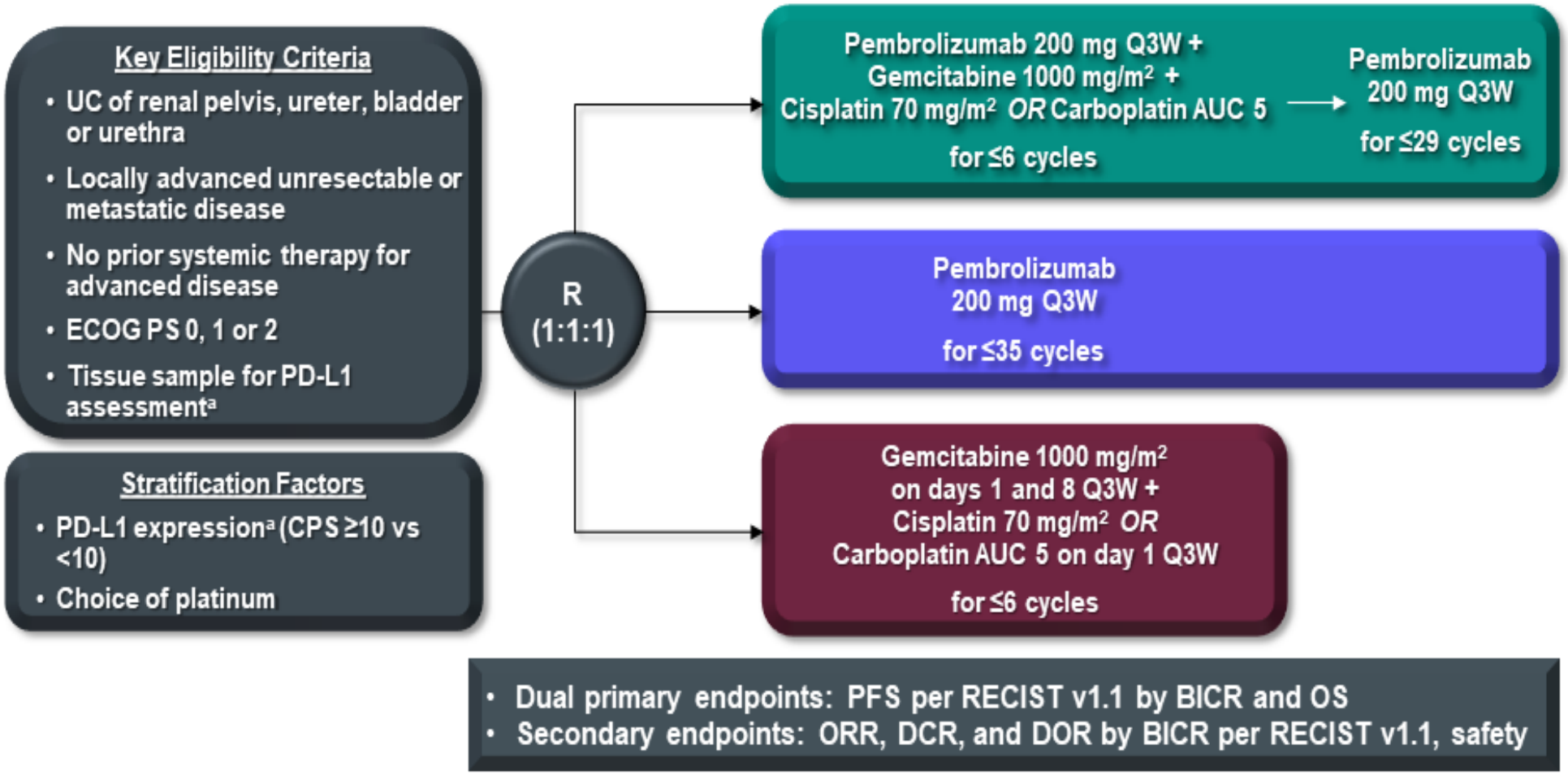
Safety summary

AE, n (%)	Atezo + plt/gem (n = 453)	Placebo + plt/gem (n = 390)	Atezo (n = 354)
Any grade, all cause	451 (100)	386 (99)	329 (93)
Grade 3-4	383 (85)	334 (86)	148 (42)
Grade 5	29 (6)	20 (5)	28 (8)
Any grade, treatment related	434 (96)	373 (96)	211 (60)
Grade 3-4	367 (81)	315 (81)	54 (15)
Grade 5	9 (2)	4 (1)	3 (1)
Any grade, serious	234 (52)	191 (49)	152 (43)
Treatment-related serious AEs	144 (32)	101 (26)	44 (12)
Any grade leading to any treatment discontinuation	156 (34)	132 (34)	22 (6)
Atezo or placebo discontinuation	50 (11)	27 (7)	21 (6)
Cisplatin discontinuation	53 (12)	52 (13)	0
Carboplatin discontinuation	90 (20)	79 (20)	1 (< 1)[a]
Gemcitabine discontinuation	117 (26)	100 (26)	1 (< 1)[a]
Any grade leading to any dose reduction or interruption	363 (80)	304 (78)	112 (32)

AE, adverse event. Safety-evaluable population.
Data cutoff, 31 May 2019; median survival follow-up 11.8 months (all patients).
[a] This patient was randomised to atezo + plt/gem and received atezo; they had an AE of pyrexia that day, and gemcitabine and carboplatin were marked as 'drug withdrawn'. Since no chemotherapy was given, this patient was included in the atezo monotherapy arm for safety analysis.

Galsky MD et al. Lancet 2020;395:1547–57.

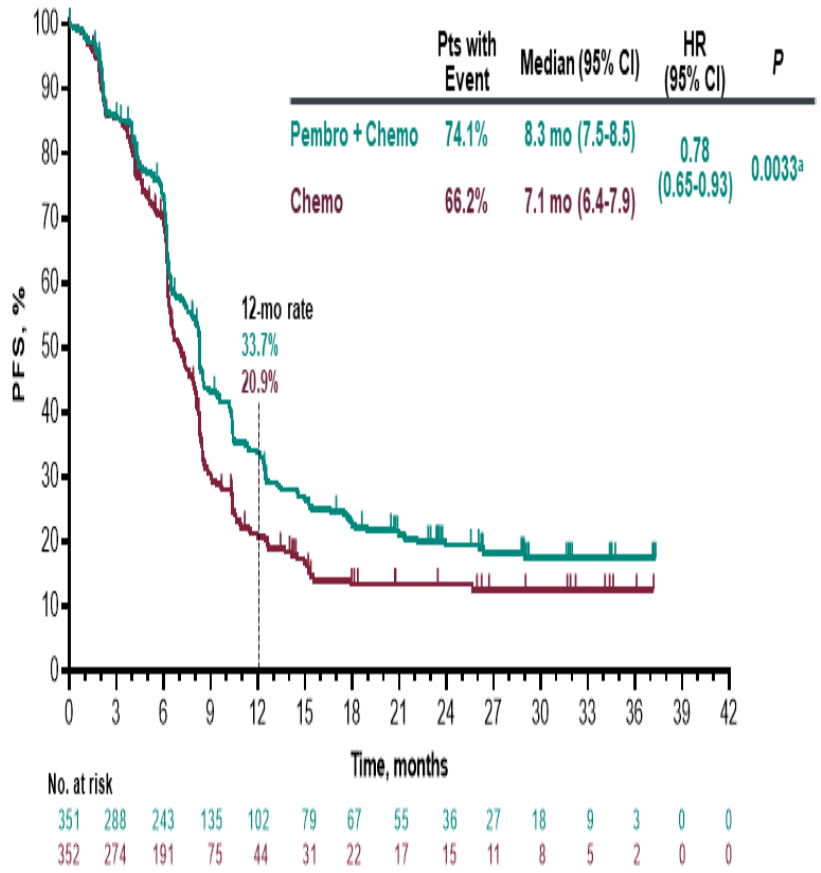
KEYNOTE-361 Study Design (NCT02853305)



[a]Assessed using the PD-L1 IHC 22C3 pharmDx assay. CPS (combined positive score) is the number of PD-L1–staining cells (tumor cells, lymphocytes, and macrophages) divided by the total number of viable tumor cells, multiplied by 100.
BICR, blinded independent central review.

Alva KN361 ESMO 2020

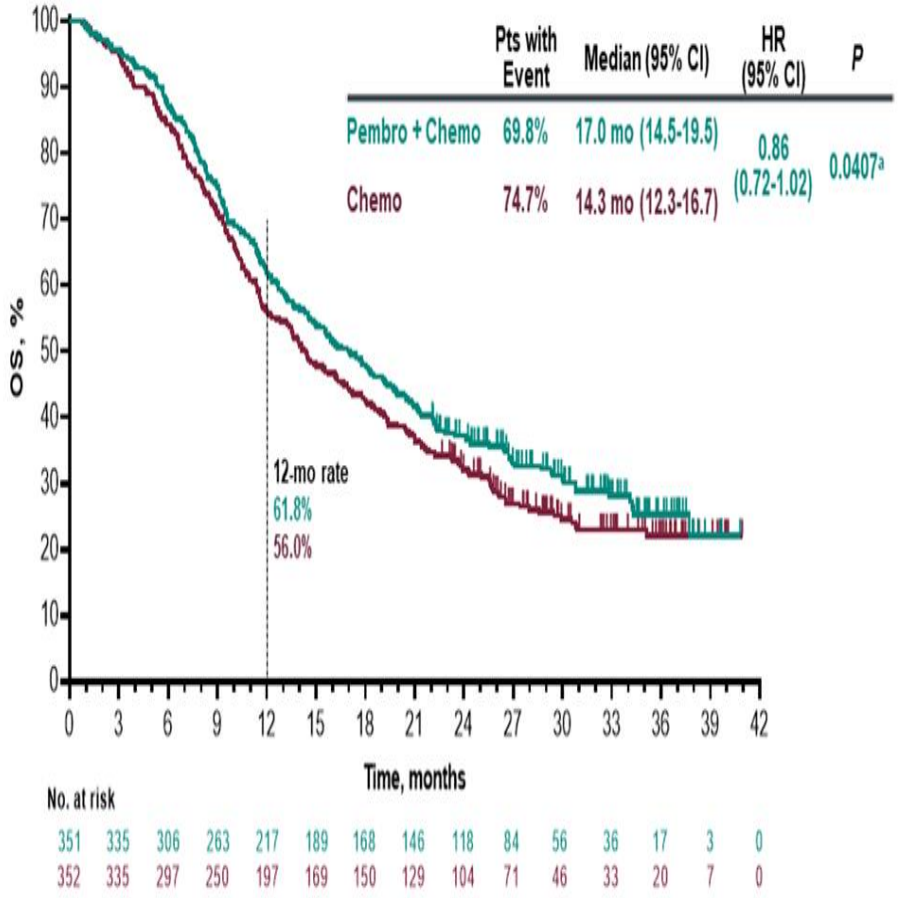
PFS by BICR: Pembro + Chemo vs Chemo, ITT Population (Primary Endpoint)



[a]*P*-value boundary of significance at final analysis ≤0.0019.
PFS assessed per RECIST v1.1. Data cutoff date: April 29, 2020.

Alva KN361 ESMO 2020

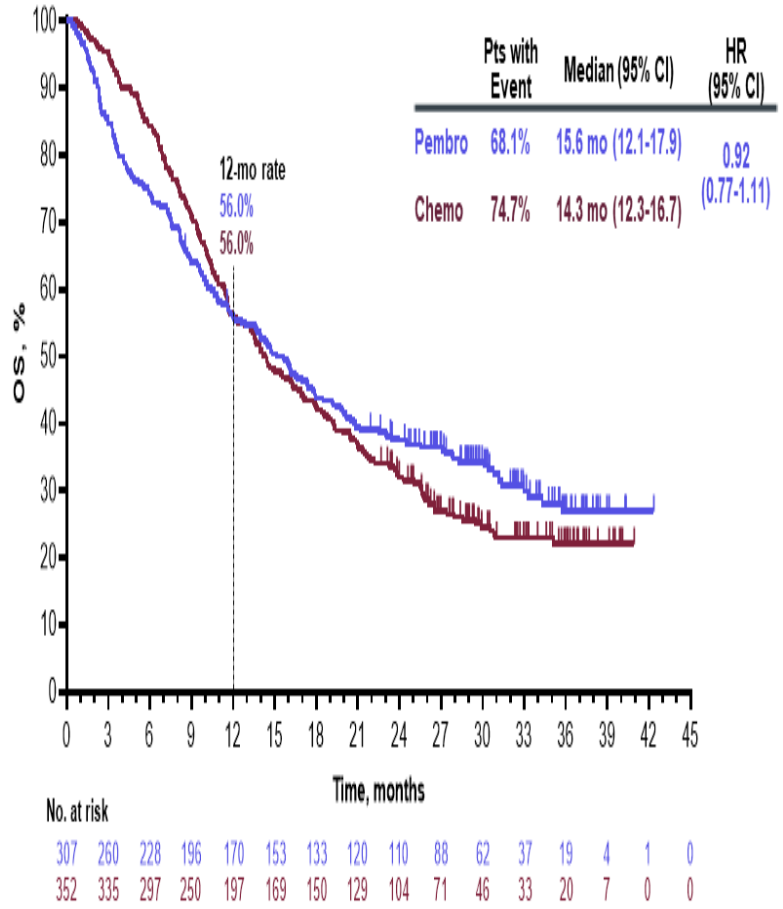
OS: Pembro + Chemo vs Chemo, ITT Population



[a]*P*-value boundary of significance at final analysis ≤0.0142. Per the statistical analysis plan, no further formal statistical testing was performed.
Data cutoff date: April 29, 2020.

Alva A, et al. Presented at ESMO 2020 LBA23.

OS: Pembro vs Chemo, ITT Population

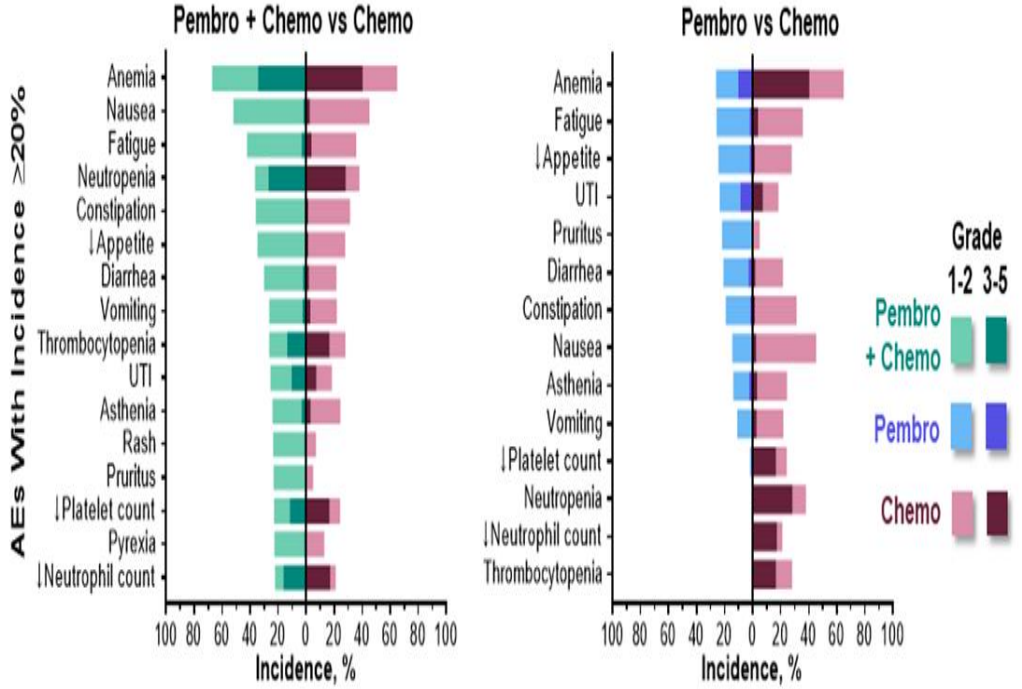


	Pts with Event	Median (95% CI)	HR (95% CI)
Pembro	68.1%	15.6 mo (12.1-17.9)	0.92 (0.77-1.11)
Chemo	74.7%	14.3 mo (12.3-16.7)	

Data cutoff date: April 29, 2020.

Alva KN361 ESMO 2020

All-Cause AEs, As-Treated Population



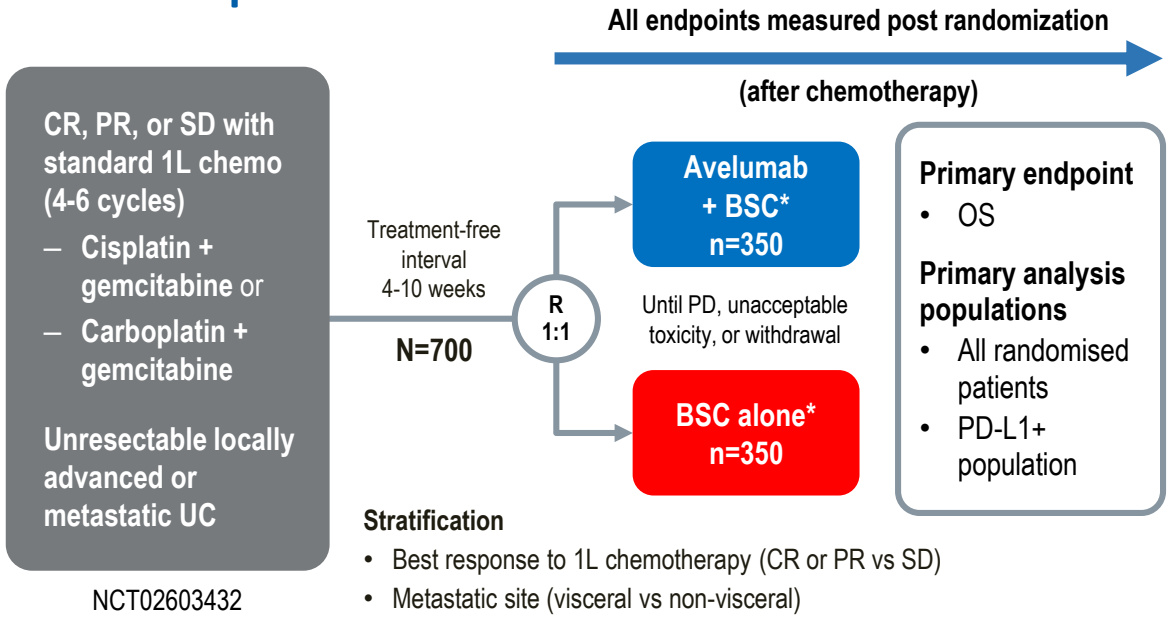
All AEs	Pembro + Chemo	Chemo
Any grade	99.7%	99.7%
Grade 3-5	87.4%	81.9%
Led to death	9.2%	2.6%
Led to discontinuation	30.9%	18.1%

All AEs	Pembro	Chemo
Any grade	95.7%	99.7%
Grade 3-5	62.9%	81.9%
Led to death	8.6%	2.6%
Led to discontinuation	15.9%	18.1%

Median (range) duration of treatment was 7.7 (0-27.8) months for pembro + chemo, 4.2 (0-28.1) months for pembro, and 3.7 (0-7.2) months for chemo. As-treated population includes all patients who received ≥1 dose of trial treatment. Data cutoff date: April 29, 2020.

Alva A, et al. Presented at ESMO 2020 LBA23.

Avelumab 1L maintenance + BSC significantly prolonged OS vs BSC alone in the JAVELIN Bladder 100 phase 3 trial[1]

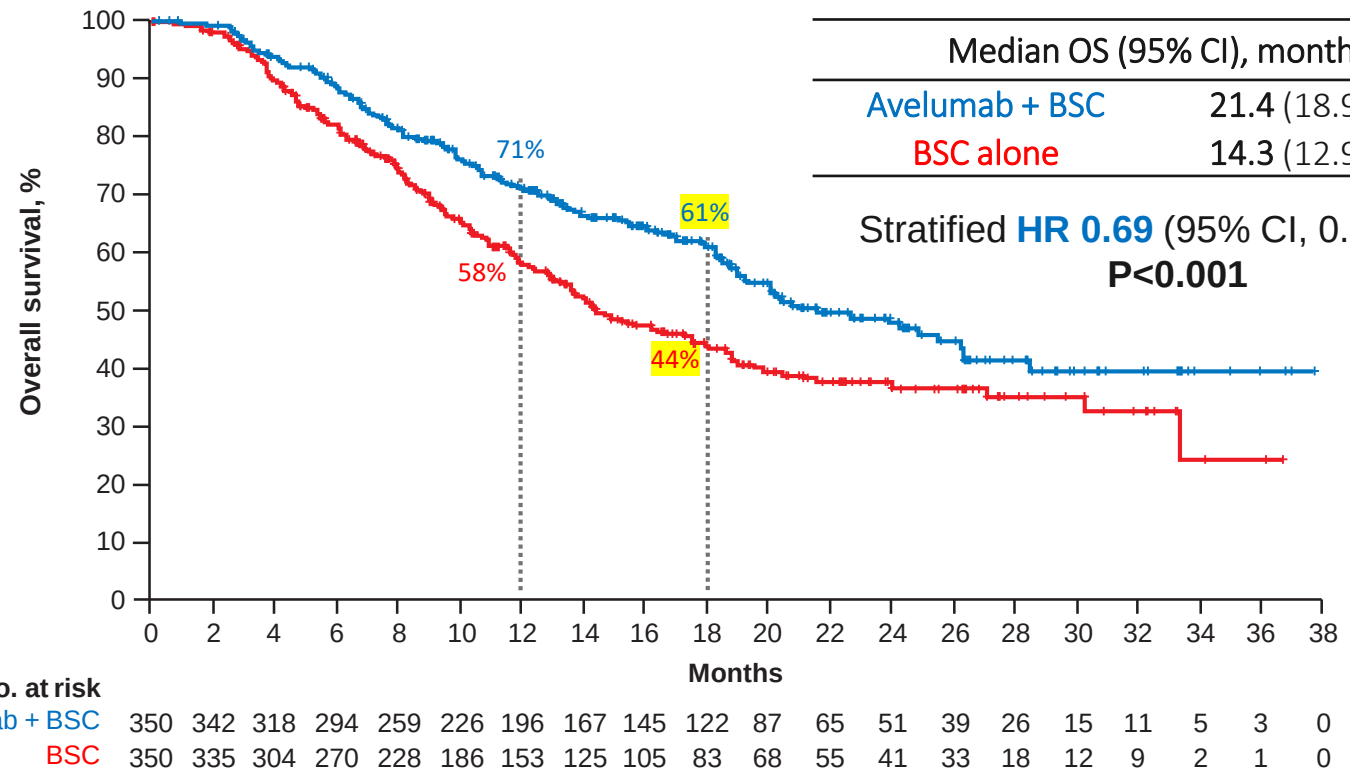


- Median OS in all randomised patients[1]
  - **Avelumab 1L maintenance + BSC**: **21.4 months** (95% CI, 18.9, 26.1)
  - **BSC alone**: **14.3 months** (95% CI, 12.9, 17.9)
  - **HR 0.69** (95% CI, 0.56, 0.86); P<0.001
- The safety profile of avelumab 1L maintenance was manageable and consistent with previous studies of avelumab monotherapy[1,2]

OS benefit with avelumab + BSC vs BSC alone were analysed in patient subgroups

1L, first line; BSC, best supportive care; CR, complete response; HR, hazard ratio; OS, overall survival; PR, partial response; R, randomisation; SD, stable disease; UC, urothelial carcinoma ·BSC (eg, antibiotics, nutritional support, hydration, or pain management) was administered per local practice based on patient needs and clinical judgment; other systemic antitumour therapy was not permitted, but palliative local radiotherapy for isolated lesions was acceptable. 1. Powles T, et al. New Engl J Med 2020.

JAVELIN Bladder 100: OS in the overall population



Median OS (95% CI), months	
Avelumab + BSC	**21.4** (18.9, 26.1)
BSC alone	**14.3** (12.9, 17.9)

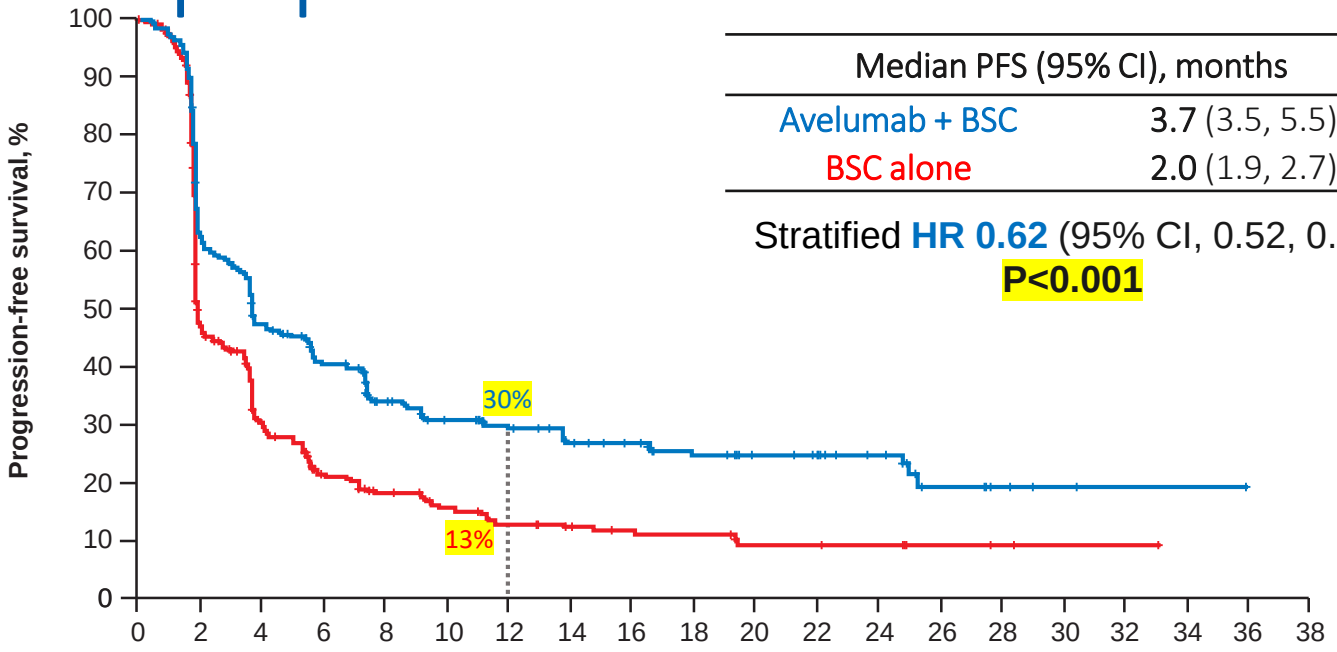
Stratified **HR 0.69** (95% CI, 0.56, 0.86)
P<0.001

No. at risk																				
Avelumab + BSC	350	342	318	294	259	226	196	167	145	122	87	65	51	39	26	15	11	5	3	0
BSC	350	335	304	270	228	186	153	125	105	83	68	55	41	33	18	12	9	2	1	0

OS was measured post randomisation (after chemotherapy); the OS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (P<0.0053)

BSC, best supportive care; CI, confidence interval; HR, hazard ratio; OS, overall survival.
Powles T, et al. New Engl J Med 2020.

JAVELIN Bladder 100: PFS by independent radiology review in the overall population



Median PFS (95% CI), months	
Avelumab + BSC	**3.7** (3.5, 5.5)
BSC alone	**2.0** (1.9, 2.7)

Stratified **HR 0.62** (95% CI, 0.52, 0.75)
P<0.001

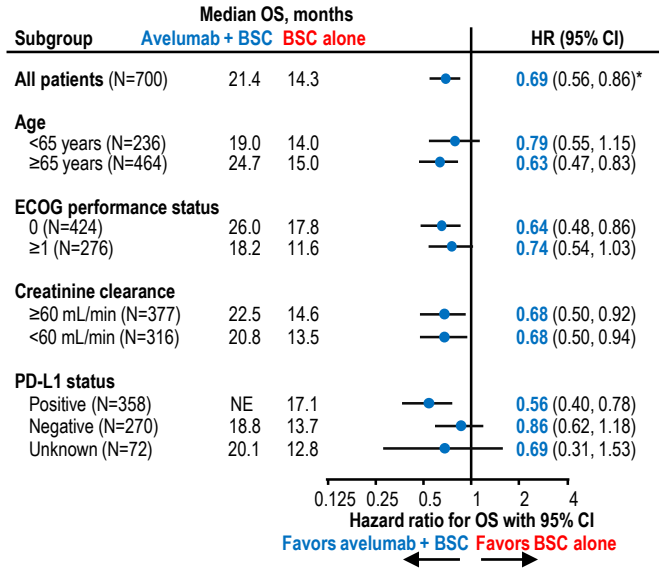
No. at risk																			
Avelumab + BSC	350	198	145	118	90	72	59	49	45	34	27	25	17	9	4	2	1	1	0
BSC	350	144	87	52	39	31	24	20	17	16	10	10	7	3	2	1	1	0	

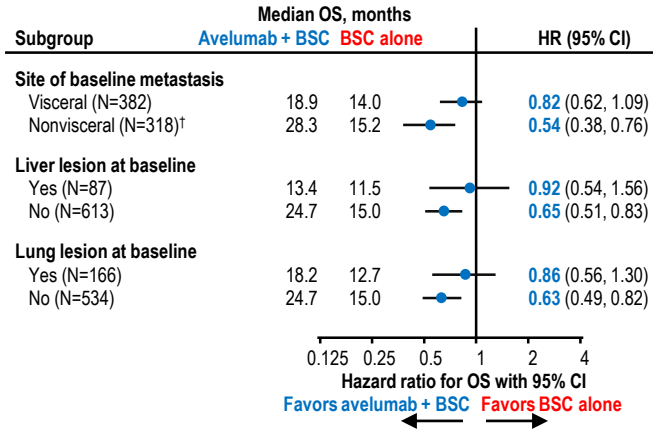
PFS was measured post randomisation (from end of chemotherapy)

BSC, best supportive care; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

Powles T, et al. New Engl J Med 2020.

OS benefit with avelumab 1L maintenance was observed across additional prespecified subgroups





No significant treatment-by-subgroup interaction (at 0.05 level) was observed for any subgroup variable

OS was measured post randomization (after chemotherapy)
* Stratified (all other analyses are unstratified)

† Nonvisceral includes patients with locally advanced disease or only nonvisceral disease, including bone metastasis

Treatment-emergent AEs (any causality)

	Avelumab + BSC (N=344)		BSC alone (N=345)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any TEAE, %	**98.0**	**47.4**	**77.7**	**25.2**
Fatigue	17.7	1.7	7.0	0.6
Pruritus	17.2	0.3	1.7	0
UTI	17.2	4.4	10.4	2.6
Diarrhea	16.6	0.6	4.9	0.3
Arthralgia	16.3	0.6	5.5	0
Asthenia	16.3	0	5.5	1.2
Constipation	16.3	0.6	9.0	0
Back pain	16.0	1.2	9.9	2.3
Nausea	15.7	0.3	6.4	0.6
Pyrexia	14.8	0.3	3.5	0
Decreased appetite	13.7	0.3	6.7	0.6
Cough	12.8	0.3	4.6	0
Vomiting	12.5	1.2	3.5	0.6
Hypothyroidism	11.6	0.3	0.6	0
Rash	11.6	0.3	1.2	0
Anemia	11.3	3.8	6.7	2.9
Hematuria	10.5	1.7	10.7	1.4
IRR	10.2	0.9	0	0

- TEAEs led to discontinuation of avelumab in 11.9%
- Death was attributed by the investigator to study treatment toxicity in 2 patients (0.6%) in the avelumab + BSC arm
  - Due to sepsis (in Cycle 10) and ischemic stroke (100 days after a single dose of avelumab)

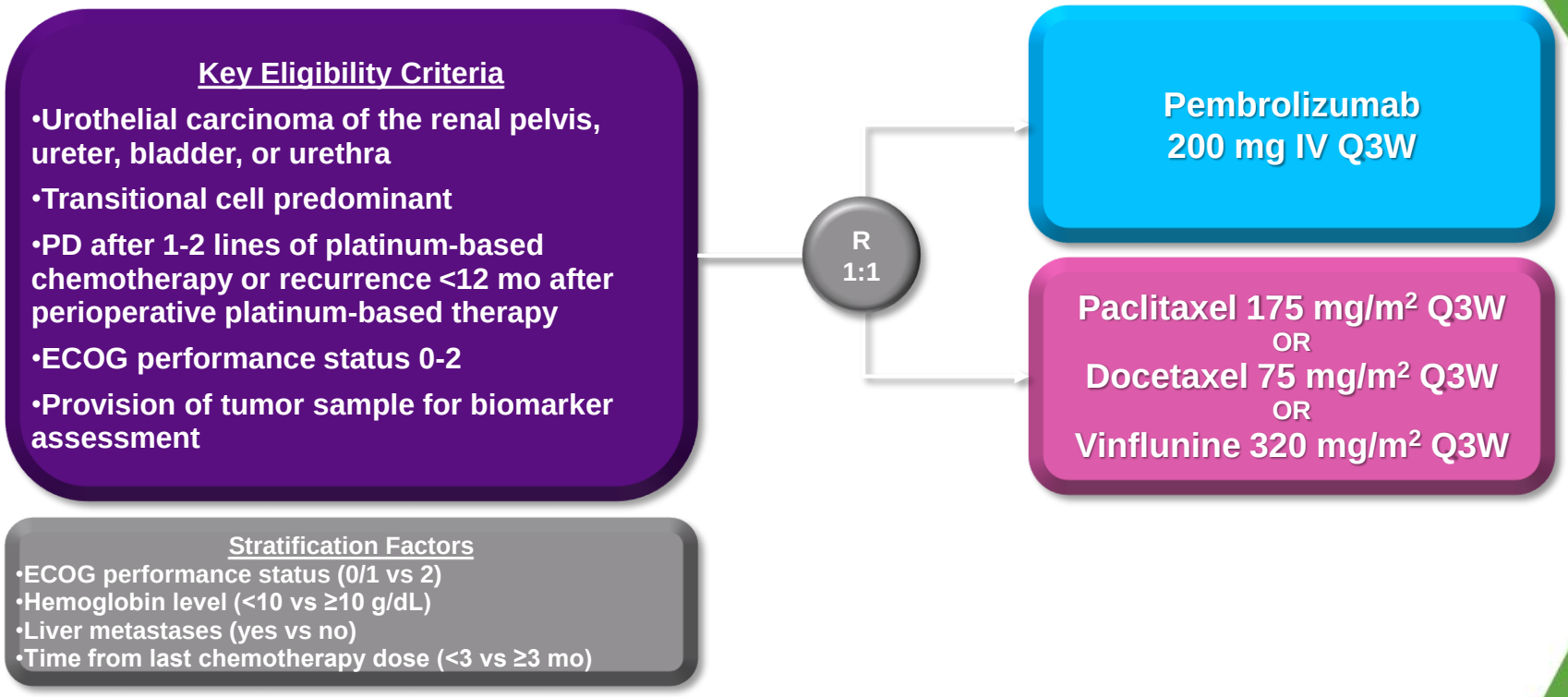
Table shows TEAEs of any grade occurring in ≥10% or grade ≥3 TEAEs occurring in ≥5% in either arm

AE, adverse event; **IRR**, infusion-related reaction; **TEAE**, treatment-emergent adverse event; **UTI,** urinary tract infection
Safety was assessed in all patients who received ≥1 dose of avelumab in the avelumab arm, or who completed the cycle 1 day 1 visit in the BSC arm (N=689)

	Atezolizumab[1]	Nivolumab[2]	Pembrolizumab[3]	Avelumab[4]	Durvalumab[5]
Phase	Phase III Randomized vs chemotherapy	Phase II Single Arm	Phase III Randomized vs Chemotherpay	Phase Ib	Phase I/II
Number of Patients	931	265	542	249 (161 pts ≥ 6 mos f/u)	191
Dosing	1200mg every 3 weeks	3mg/kg every 2 weeks	200mg every 3 weeks	10mg/kg every 2 weeks	10mg/kg every 2 weeks
ORR	13.4%	19.6%	21.1%	17%	17.8%
Duration of Response	63% of responses ongoing at median f/u of 21.7 mos	77% of responses ongoing at median f/u of 7 mos	72% of responses ongoing at median f/u of 14.1 mos	96% of responses ongoing at 6 mos f/u	50% of responses lasting ≥ 6 mos
Median OS	8.6 mos	8.7 mos	10.3 mos	6.5 mos	18.2 mos
Median PFS	2.1 mos	2.0 mos	2.1 mos	1.5 mos	1.5 mos
Rate of Grade 3/4 Treatment-related AEs	20%	18%	15%	8%	6.8%

1Powles T, et al. Lancet. 2018;391(10122):748-757.; 2Sharma P, et al. Lancet Oncol. 2017;18(3):312-322.; 3Bellmunt J, et al. N Engl J Med. 2017;376(11):1015-1026.; 4Patel MR, et al. Lancet Oncol. 2018;19(1):51-64.; 5Powles T, et al. JAMA Oncol. 2017;3(9):e172411

KEYNOTE-045 Study Design (NCT02256436)



eview

[a]In total ITT population and in patients with combined positive score ≥10%.

Presented by: **Dean Bajorin**

KEYNOTE-045 Study Design (NCT02256436)

Key Eligibility Criteria

- Urothelial carcinoma of the renal pelvis, ureter, bladder, or urethra
- Transitional cell predominant
- PD after 1-2 lines of platinum-based chemotherapy or recurrence <12 mo after perioperative platinum-based therapy
- ECOG performance status 0-2
- Provision of tumor sample for biomarker assessment

R 1:1

- Pembrolizumab 200 mg IV Q3W
- Paclitaxel 175 mg/m² Q3W OR Docetaxel 75 mg/m² Q3W OR Vinflunine 320 mg/m² Q3W

Stratification Factors

- ECOG performance status (0/1 vs 2)
- Hemoglobin level (<10 vs ≥10 g/dL)
- Liver metastases (yes vs no)
- Time from last chemotherapy dose (<3 vs ≥3 mo)

- Dual primary end points: OS and PFS[a]
- Key secondary end points: ORR, DOR, safety
- Response: RECIST v1.1 by blinded, independent central review
- Both unselected and biomarker-selected patients

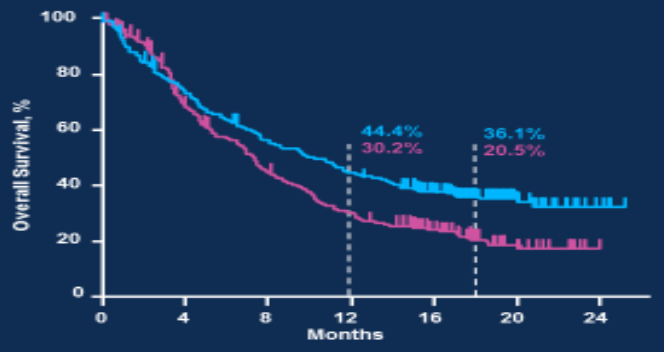
[a]In total ITT population and in patients with combined positive score ≥10%.

Abstract 4501: Survival analysis from phase 3, open-label study of pembrolizumab vs chemotherapy in advanced UC

- Longer follow up confirms initial data
- Objective responses occurred rapidly and were generally durable, with duration of response not yet reached
- Safety & tolerability support pembrolizumab over 2nd / 3rd line chemotherapy

	Events, n	HR (95% CI)[a]	P[b]
Pembro	170	0.70 (0.57-0.86)	0.0004
Chemo	196		

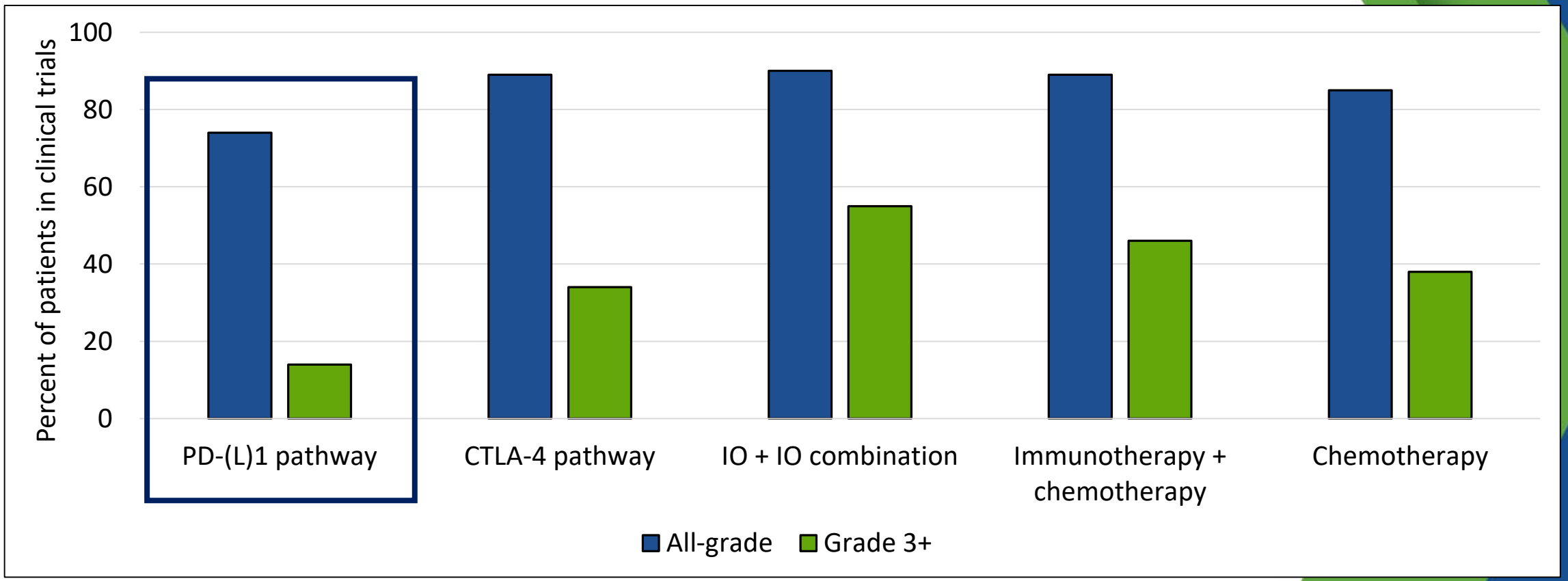
Median (95% CI):
10.3 mo (8.0-12.3)
7.4 mo (6.1-8.1)



Webinar outline

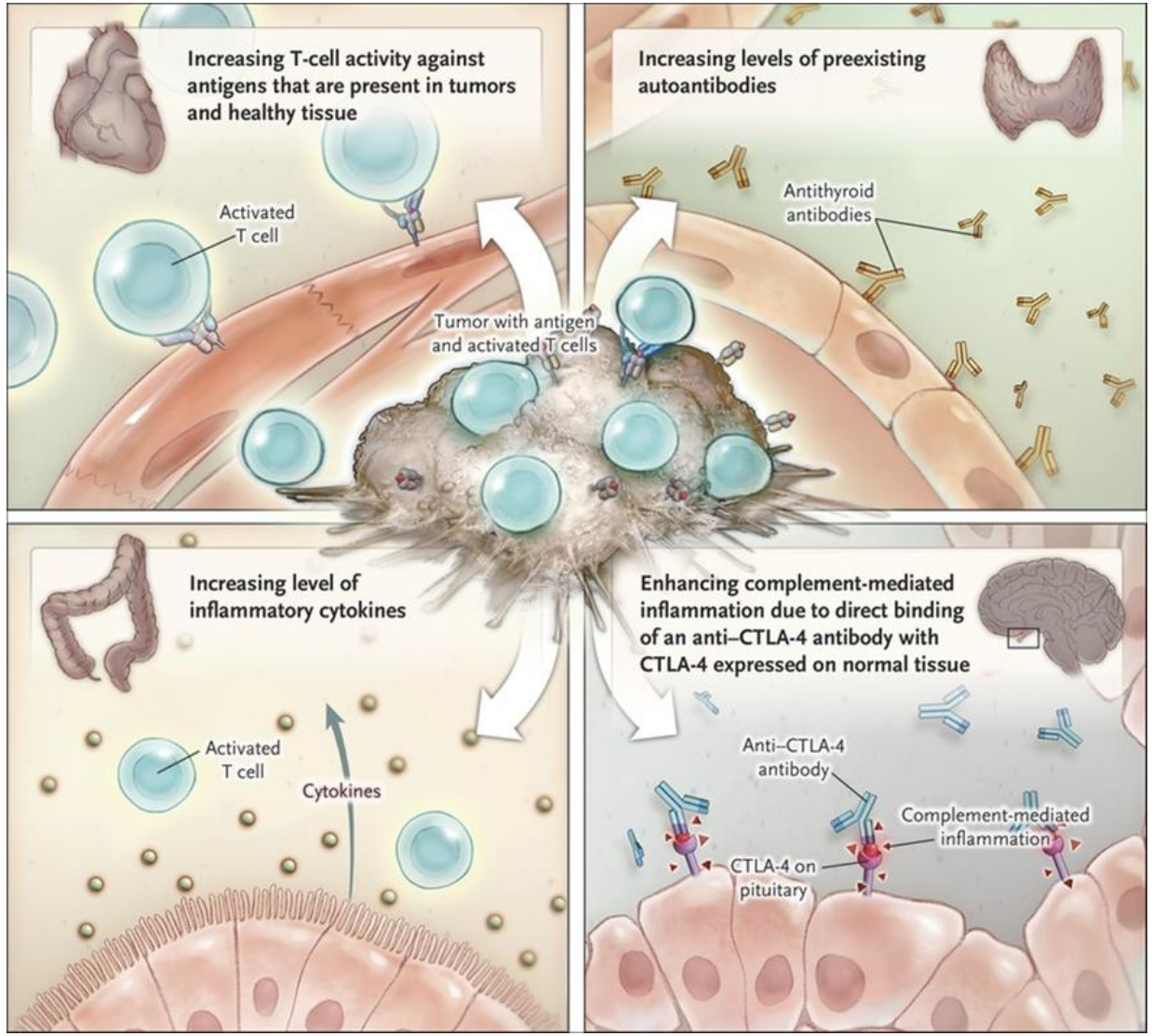
- Intravesical therapies in NMIBC
- Systemic therapies in UC
- Immunotherapy toxicities and management

Toxicity with immune checkpoint inhibitors (ICI)



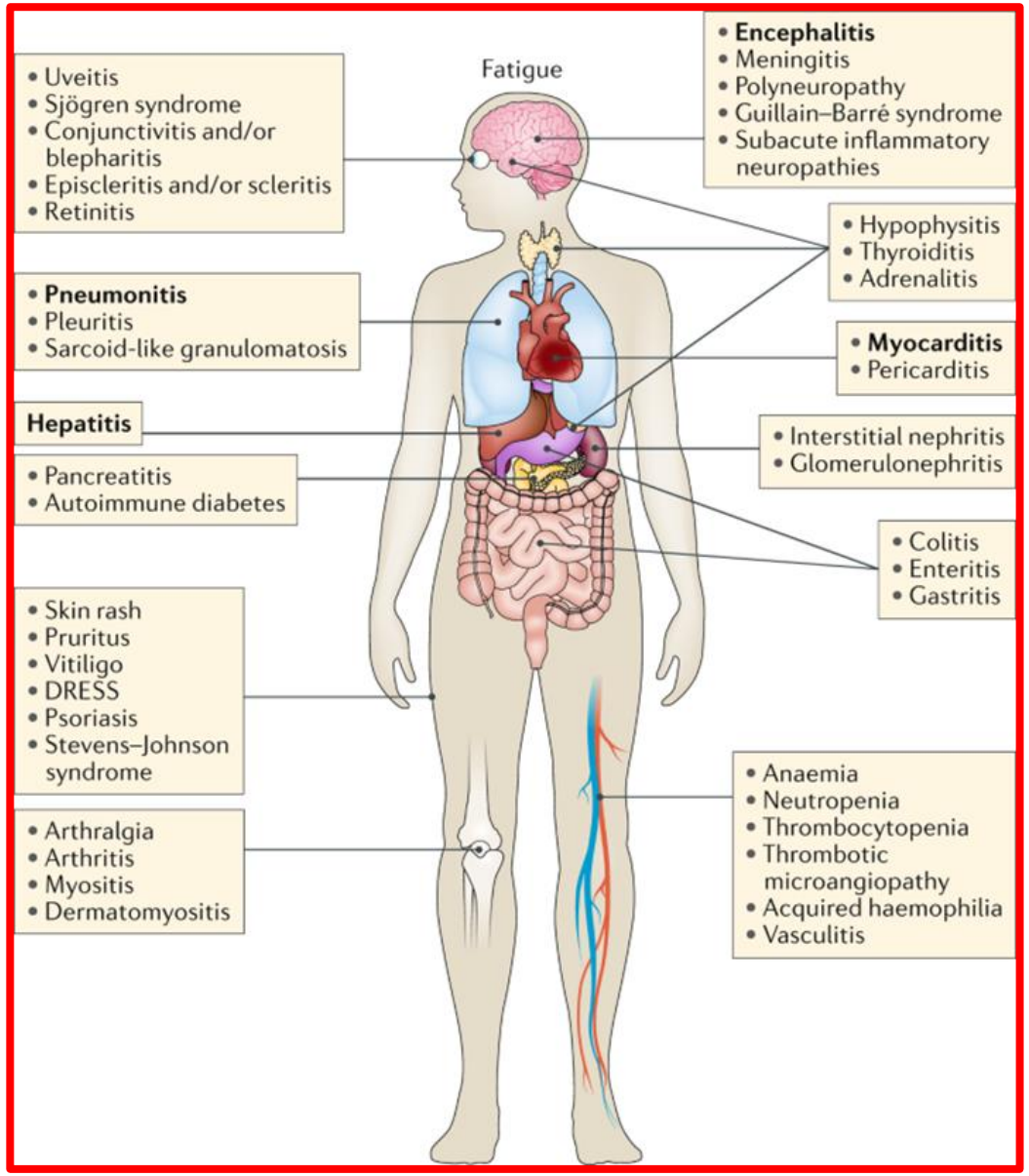
Wang, Front Pharmacol 2017.
Kelly, Cancer 2018.
Bertrand, BMC Med 2015.

Mechanism of action of irAE



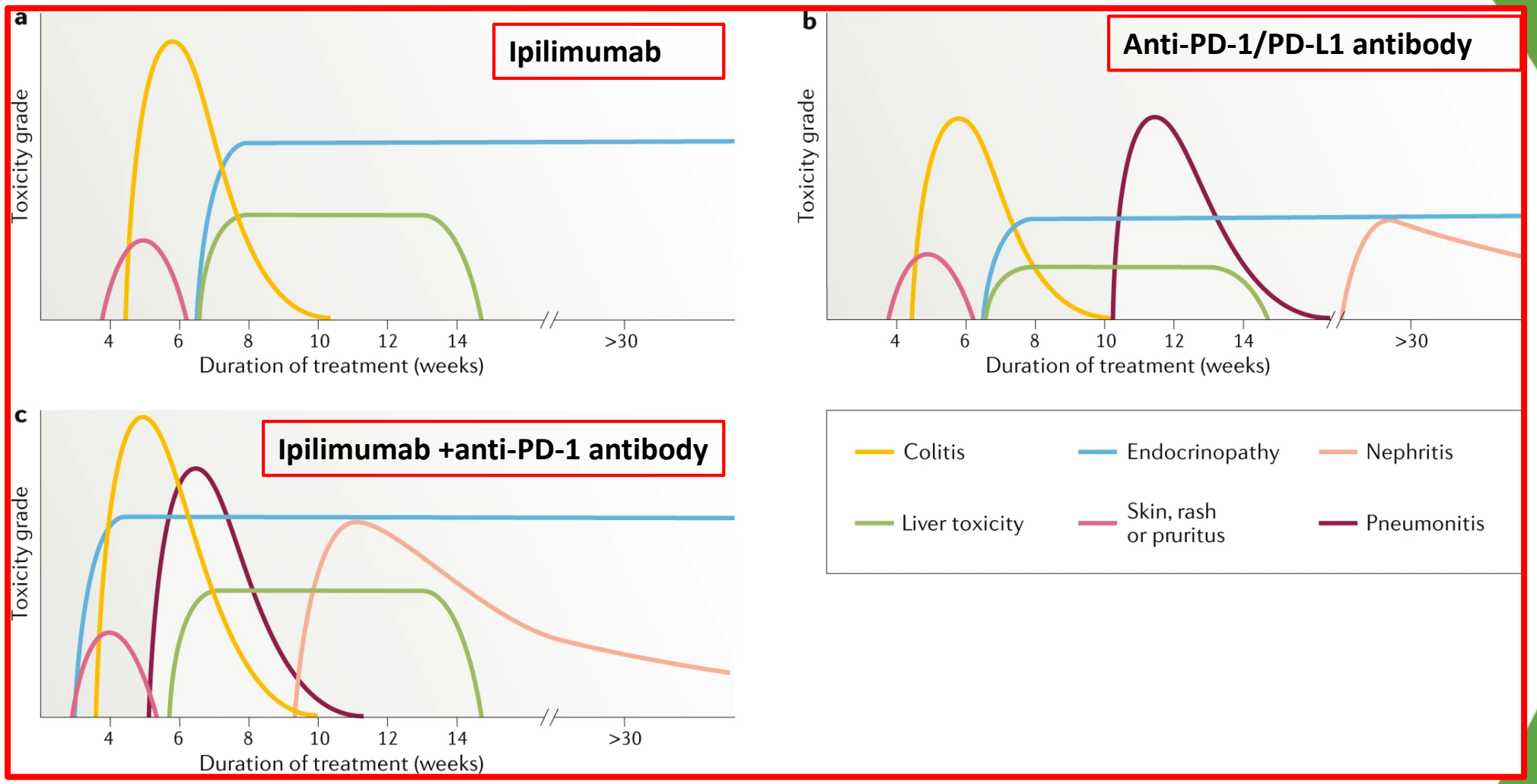
Postow MA et al NEJM 2018 2018;378(2):158-168.

Manifestation of irAEs



Martins F et al. Nat Rev Clin Oncol. 2019;16(9):563-580.

Timelines of irAEs

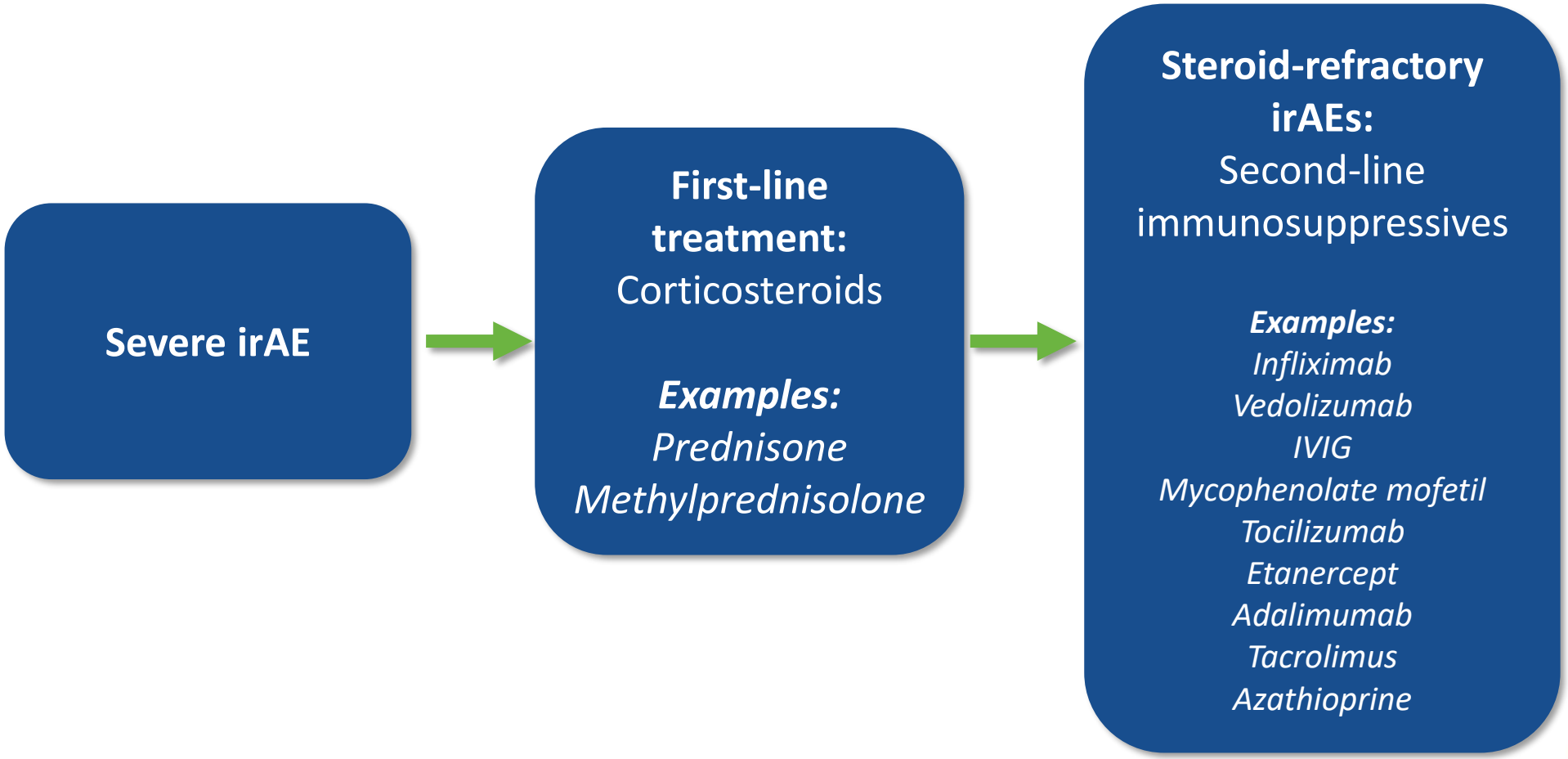


Martins F et al. Nat Rev Clin Oncol. 2019;16(9):563-580.

General Management of irAEs

Severity	Ambulatory Vs Inpatient	Corticosteroids	Continue IO
Grade 1	Ambulatory	Not recommended	Continue, monitor closely
Grade 2	Ambulatory	Oral 0.5-1 mg/kg/day	Hold until s/s resolve, down to prednisone 10 mg/day
Grade 3	Hospitalization	Oral/IV 1 mg/kg/day	Discontinue/discuss risk vs benefit of re-challenge
Grade 4	Hospitalization/ICU	IV 1-2 mg/kg/day	Permanently discontinue

Management of severe irAEs



Brahmer, J Immunother Cancer 2021

SITC's Guidelines on irAEs

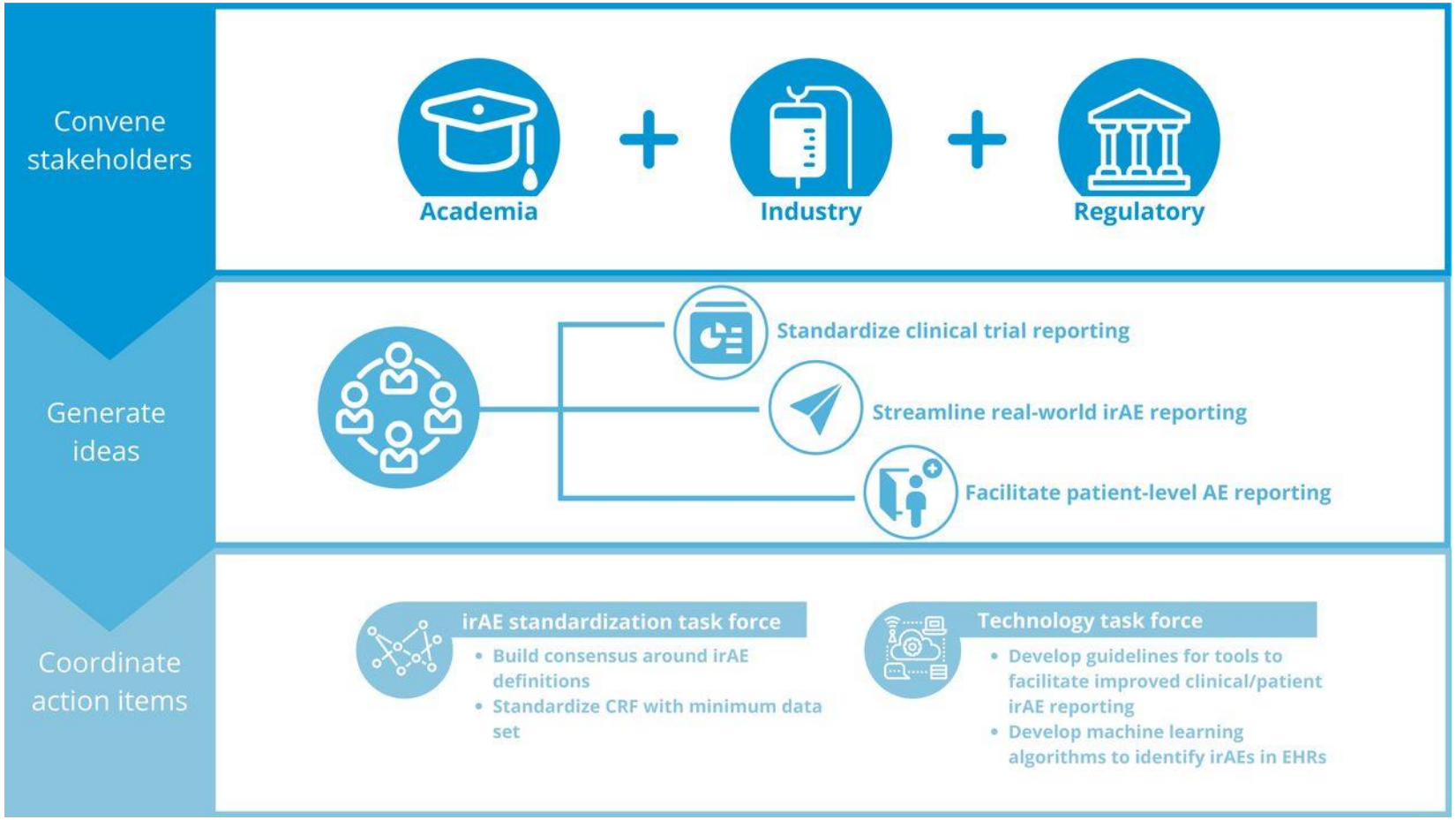
Open access Position article and guidelines

Journal for ImmunoTherapy of Cancer

Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events

Julie R Brahmer,[1] Hamzah Abu-Sbeih,[2] Paolo Antonio Ascierto ,[3] Jill Brufsky,[4] Laura C Cappelli,[5] Frank B Cortazar,[6,7] David E Gerber,[8] Lamya Hamad,[9] Eric Hansen,[10] Douglas B Johnson,[11] Mario E Lacouture,[12] Gregory A Masters,[13] Jarushka Naidoo,[1,14] Michele Nanni,[10] Miguel-Angel Perales,[12] Igor Puzanov,[10] Bianca D Santomasso,[15] Satish P Shanbhag,[5,16] Rajeev Sharma,[10] Dimitra Skondra,[17] Jeffrey A Sosman,[18] Michelle Turner,[1] Marc S Ernstoff [19]

Unmet need to standardize irAE definitions and reporting in clinical trials and streamline real-world irAE reporting



Kerry L Reynolds et al. J Immunother Cancer 2021;9:e002896

Conclusions

- Multi-disciplinary collaboration among oncologists, urologists, other internal medicine specialists is essential to monitoring and treating potentially life-threatening irAEs
- High-risk patients receiving ICI should have involvement of specialized multidisciplinary teams for a personalized surveillance strategy
- Re-challenge with ICI after the resolution of irAE depends on severity of the prior irAE, alternative treatment options and response to ICI
- Life-threatening irAE (cardiac, pulmonary, or neurologic) are absolute contraindications to re-challenge with ICI

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Thank you for attending the webinar!

Questions or comments: connectED@sitcancer.org

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