Checkpoint Inhibitors in the Treatment of Advanced Urothelial Cancer

This program is an accredited Group Learning Activity (Section 1) as defined by the Maintenance of Certification Program of the Royal College of Physicians and Surgeons of Canada, reviewed and approved by the Canadian Urological Association. Completion of this program enables participants to claim a maximum of one (1) Section 1 credit.

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- CMA Guidelines for Physician Interactions with Industry (2007)
- Innovative Medicines Canada Code of Ethical Practices (2016)

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Learning Objectives

Upon completion of this program, participants will be able to:

- Describe the rationale for the use of checkpoint inhibitors in the treatment of advanced urothelial cancer (UC)
- Review current data for checkpoint inhibitors in the first-line treatment of UC in cisplatin-ineligible patients and in second-line treatment following progression on platinum-based chemotherapies

Case Presentation:
Rapid progression after cystectomy and perioperative chemo

Mr. Patry: Presentation and History

- 74-year-old male diagnosed with high-grade UC of the bladder
- PMHx: Hypertension, dyslipidemia, type II diabetes
- Significant smoking history of 25 pack-years
- Normal renal function with eGFR of 75 mL/min/1.73m^2

eGFR = Estimated glomerular filtration rate
PMHx = Past medical history

Mr. Patry: TURBT Details

- High-grade papillary UC
- Muscularis propria present and involved by tumour
- Lymphovascular invasion present
- No CIS seen
- Examination under anesthesia: palpable mass, mobile and not fixed

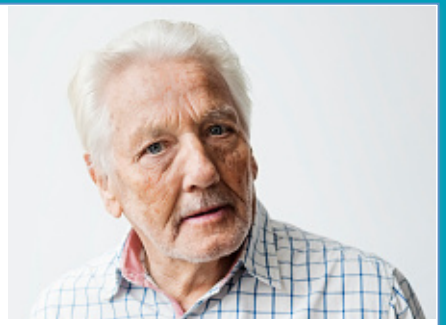
CIS = Carcinoma in situ; TURBT = Transurethral resection of bladder tumors

Mr. Patry: Staging

- CT C/A/P
- No pelvic or retroperitoneal lymphadenopathy
- No visceral metastases
- No hydronephrosis

CT C/A/P = Computed tomography of the chest/abdomen/pelvis

Discussion Question



- *Mr. Patry has agreed to undergo systemic therapy. What are his options?*

First-line Systemic Therapies for UC

- Muscle-invasive UC
  - Radical cystectomy ± preoperative cisplatin-based chemo
- Locally advanced/metastatic UC
  - Cisplatin + gemcitabine
    - Median OS 14 months[1,2]
  - HD-MVAC
    - Median OS 15.1 months[3]
  - Paclitaxel/cisplatin/gemcitabine
    - Median OS 15.8 months[4]

1. Bellmunt J, et al. Ann Oncol 2014;25(Suppl 3):iii40–iii48; 2. von der Maase H, et al. J Clin Oncol 2005;23:4602–8;
3. Sternberg CN, et al. Eur J Cancer 2006;42:50-4; 4. Bellmunt J, et al. J Clin Oncol 2012;30:1107-13

Mr. Patry: Treatment

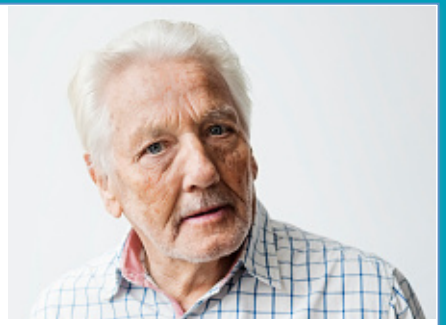
- Receives ddMVAC as neoadjuvant chemo
- Post-chemo assessment by CT and cystoscopy reveals partial response
- No additional biopsy is undertaken
- Undergoes cystectomy, pelvic lymphadenectomy and neobladder

ddMVAC = Dose-dense methotrexate + vinblastine + doxorubicin + cisplatin

Mr. Patry: Final Pathology

- pT3a high grade UC of bladder
- Lymph nodes: 35 assessed, 4 positive
- Negative soft tissue margins
- Negative urethral and ureteral margins

Mr. Patry: Medical Oncology Assessment



- Reassessed by medical oncology post-op and no further adjuvant chemo is recommended

Mr. Patry: Follow-up

- CT at 3 month follow-up clear
- CT at 6 months however shows multiple pulmonary lesions suspicious for metastatic disease
- Percutaneous biopsy of index 1.2 cm pulmonary nodule consistent with metastatic UC
- ECOG PS 0 and asymptomatic
- Renal function normal (eGFR 70 mL/min/1.73 m^2)

ECOG PS = Eastern Cooperative Oncology Group performance status

Discussion Question

- *What are the treatment options for Mr. Patry now that he has metastatic disease?*
  - *Retreatment with a cisplatin-based chemotherapy?*
  - *A taxane-based chemotherapy?*
  - *Single-agent gemcitabine?*
  - *Immunotherapy?*

Second-line Systemic Therapies for Locally Advanced or Metastatic UC

- Until recently there has been no standard second-line chemo option
- Single-agent chemotherapies studied in randomized trials:

Chemotherapy agent	n	ORR, %	mOS, months
Nab-paclitaxel vs. paclitaxel[1]	199	21 vs. 23	7.5 vs. 8.8
Vinflunine vs. BSC[2]	370	9	6.9 vs. 4.6
Cabazitaxel vs. vinflunine[3]	70	13 vs. 30	5.5 vs. 7.6

- Paclitaxel is a reasonable choice given no vinflunine access in Canada

But better options are needed

BSC = Best supportive care; mOS = Median OS;
ORR = Objective response rate

1. Sridhar SS, et al. J Clin Oncol 2018;36(suppl) Abstr 4505;
2. Bellmunt J, et al. J Clin Oncol 2009;27:4454–61.

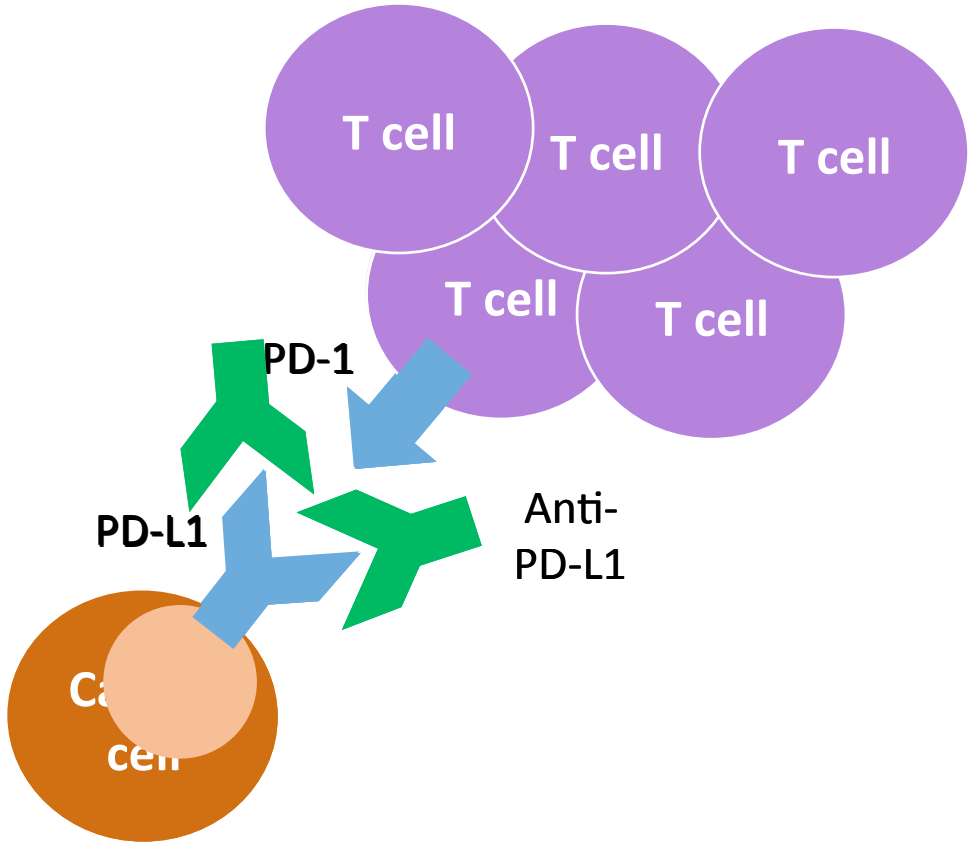
Immunotherapies for Advanced UC

- The immune-based treatment intravesical BCG has been used successfully in NMIBC for over 3 decades
- Immunotherapy for advanced UC has focused on 3 checkpoint targets:
  - PD-L1: Programmed death ligand-1
  - PD-1: Programmed cell death protein-1
  - CTLA-4: Cytotoxic T lymphocyte-associated protein 4
- Inhibitors of these checkpoint targets block negative co-signaling molecules that prevent an effective immune response
  - Reinvigorate T-cell–mediated antitumour activity

BCG = Bacillus Calmette-Guerin
NMIBC = Non-muscle invasive bladder cancer

Bellmunt J, et al. Cancer Treat Rev 2017;54:58-67

Blockade of Immune Checkpoints to Enhance T Cell Responses



Second-line Immunotherapies Approved in Canada for Advanced UC

- Notice of Compliance (NOC)
  - Pembrolizumab for post-platinum progression
- Notice of Compliance with conditions (NOC/c)*
  - Atezolizumab for post-platinum progression
  - Durvalumab for post-platinum progression
  - Avelumab for post-platinum progression
- No funded options but there are clinical trials and access programs

*The NOC/c policy facilitates earlier access to promising new medicines that treat, prevent or diagnose serious, life-threatening and/or severely debilitating diseases for which there is no alternative medicine available in Canada, or where the new medicine offers a significant improvement through its risk/benefit profile over existing medicines

Phase I/II Trials of Immunotherapy in Second-line Treatment of Locally Advanced and Metastatic UC

Trial	Drug	ORR, % (95% CI)	mOS, months (95% CI)
IMvigor210 – Cohort 2 (n = 310)[1]	Atezolizumab 1,200 mg IV q3w	15 (11–19)	7.9 (6.6-9.3)
Study 1108 (n = 191)[2]	Durvalumab 10 mg/kg q2w	17.8 (12.7-24.0)	18.2 (8.1 -NE)
JAVELIN (n = 241)[3]	Avelumab 10 mg/kg q2w	17 (11–24)	6.5 (4.8-9.5)

mOS = Median overall survival; NE = Not evaluable

1. Rosenberg JE, et al. Lancet 2016;387:1909-20; 2. Powles T, et al. JAMA Oncol 2017;3:e172411;
3. Patel MR, et al. Lancet Oncol 2018;19:51-64

IMvigor211: Phase III – 2nd-line Atezolizumab vs. Chemo in Locally Advanced or Metastatic UC

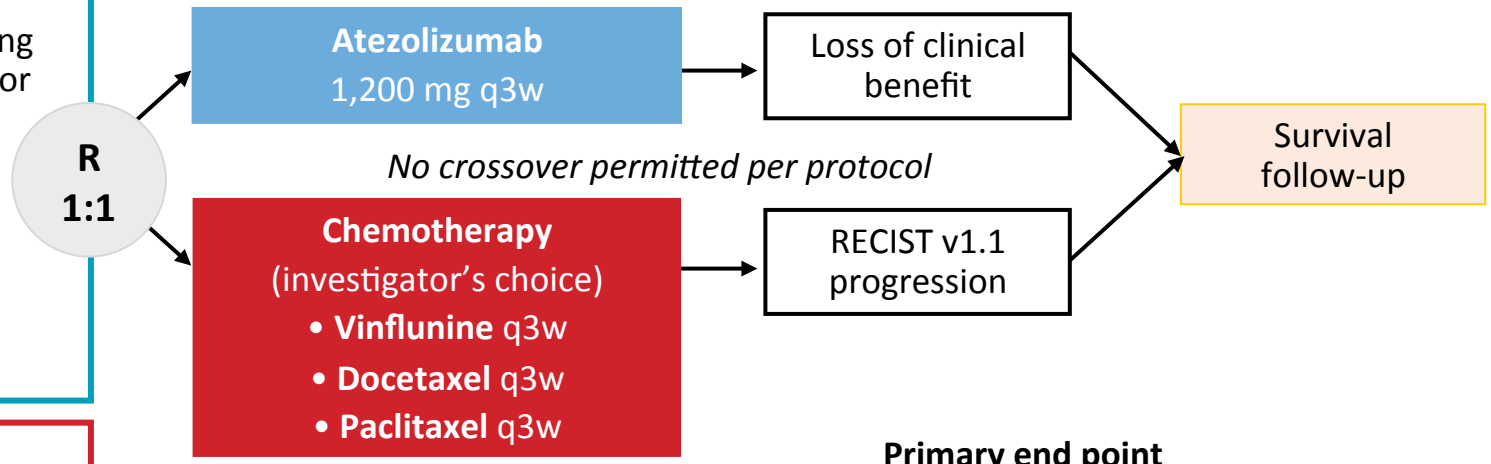
Key Eligibility Criteria

- mUC with progression during or following platinum-based chemotherapy – ≤ 2 prior lines of therapy
- Measurable disease per RECIST v1.1
- ECOG PS 0-1
- Evaluable sample for PD-L1 testing
- TCC histology as primary component

(n = 931)

Stratification Factors

- No. of risk factors (0 vs. 1/2/3)
- Liver metastases (yes vs. no)
- PD-L1 status (0/1 vs. 2/3)
- Chemotherapy (vinflunine vs. taxanes)



PD-L1 Subgroups:

% PD-L1–positive immune cells (ICs)	Subgroup
< 1%	IC0
≥ 1% but < 5%	IC1
≥ 5%	IC2/3

Primary end point

- OS, tested hierarchically in prespecified populations

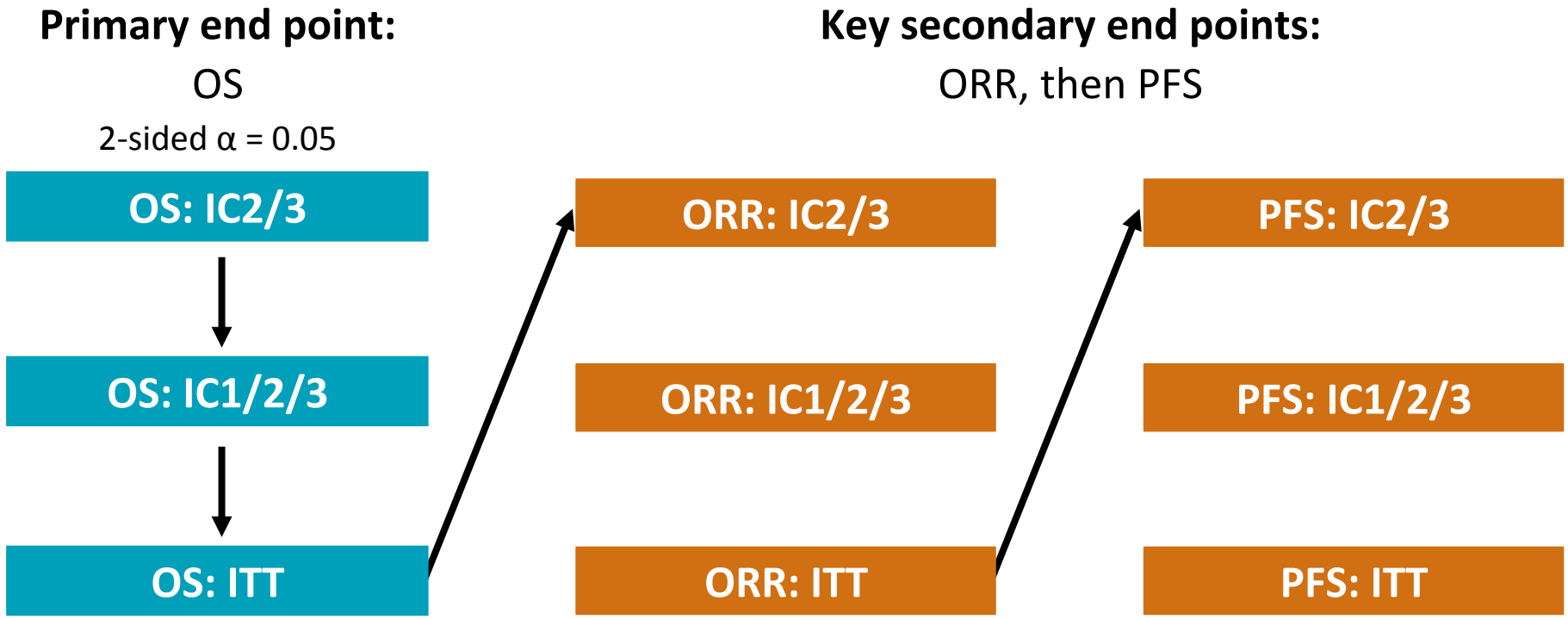
Additional end points

- Efficacy: RECIST v1.1 ORR, PFS and DOR
- Safety
- PROs: EORTC QLQ-C30

EORTC QLC-C30 = European Organization for Research and Quality of Life Core 30 Questionnaire; PRO = Patient-related outcomes; TCC = Transitional cell carcinoma

Powles T, et al. Lancet 2018;391:748-57

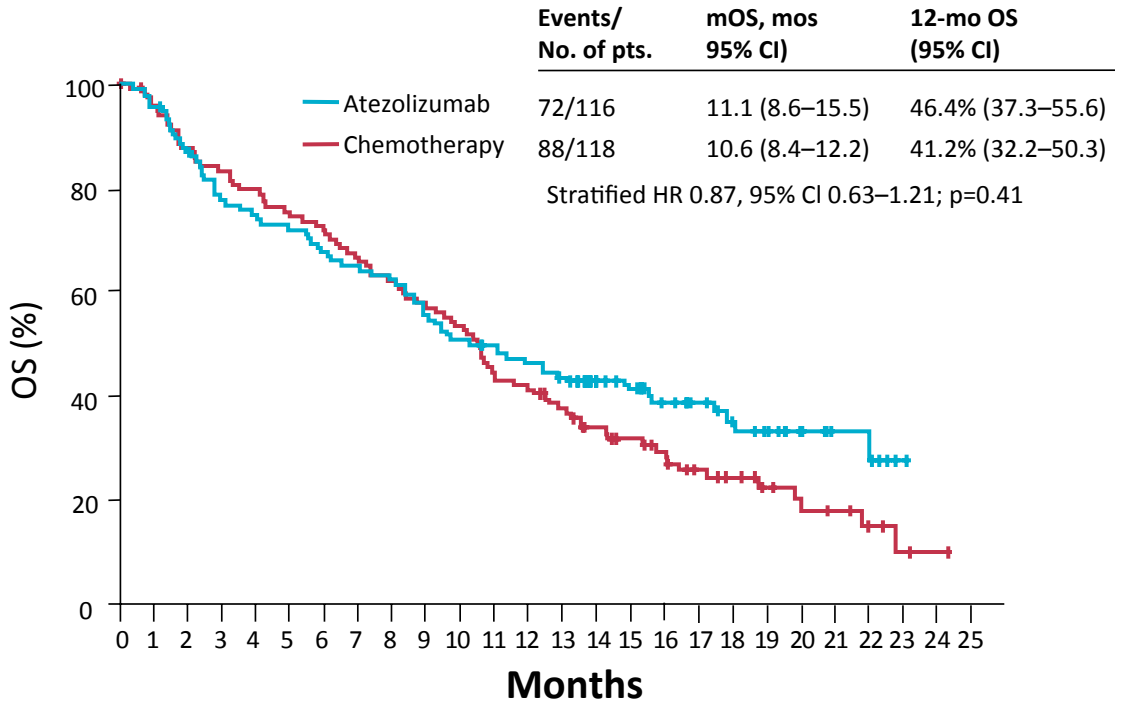
IMvigor211: Study Design



Powles T, et al. Lancet 2018;391:748-57

IMvigor211: Survival in the IC2/3 Population

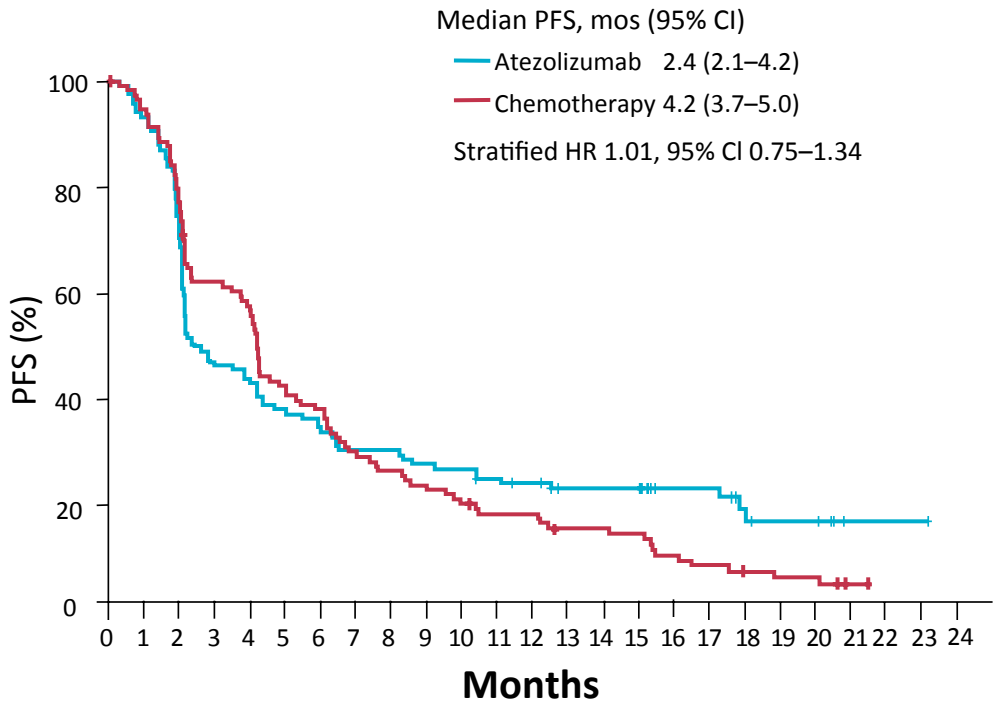
OS



Number at risk

Atezolizumab	116	112	100	88	85	82	77	73	71	63	58	55	51	47	39	35	27	23	19	15	11	6	6	1	..	..
Chemotherapy	118	109	100	95	91	85	82	75	71	65	61	51	47	41	32	28	24	18	15	11	9	7	5	2	1	..

PFS

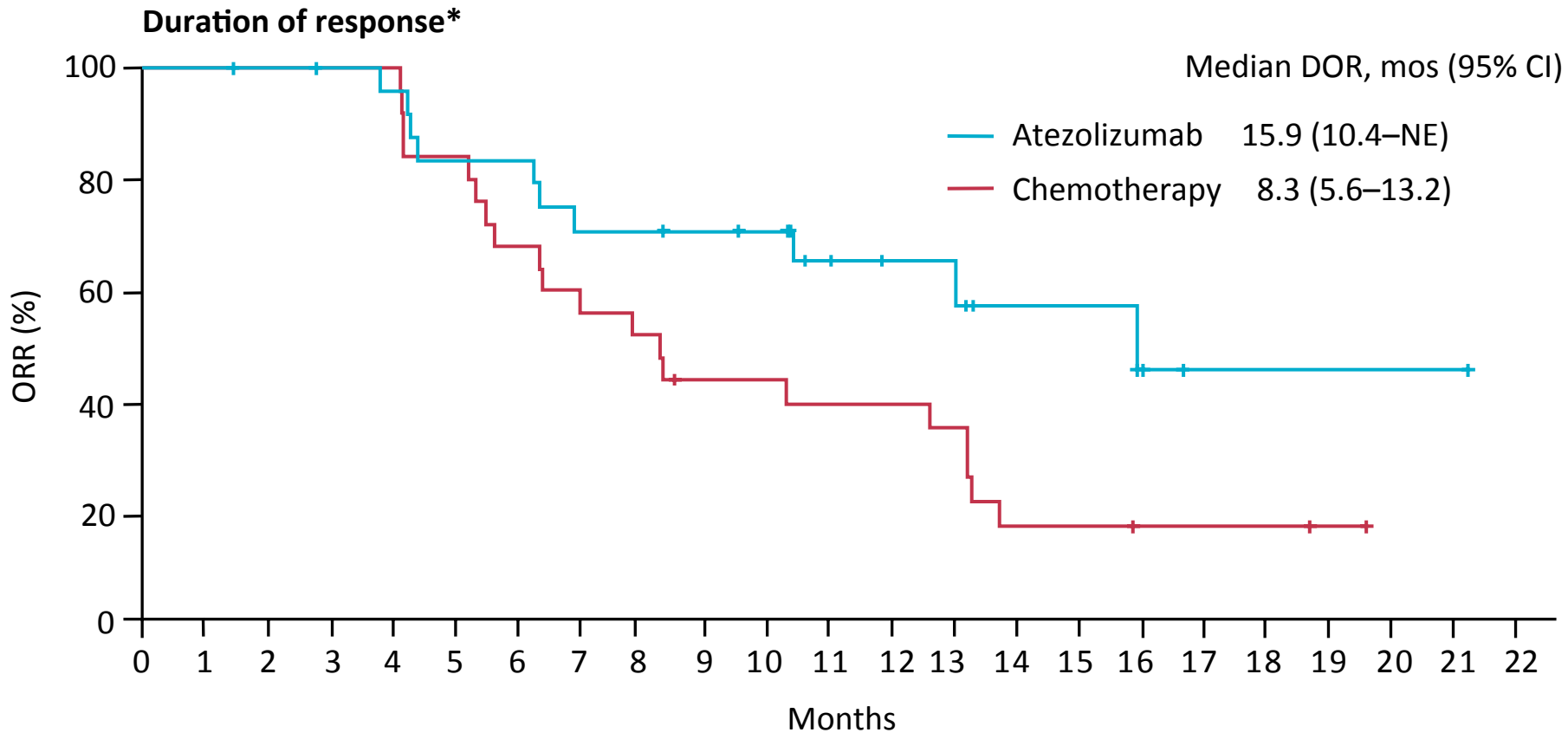


Number at risk

Atezolizumab	116	108	81	53	50	42	38	33	33	30	29	26	24	19	19	19	12	12	8	5	5	1	1	1	..
Chemotherapy	118	106	86	68	62	44	41	31	28	24	21	18	18	14	14	13	9	7	5	4	4	1	..	..	..

Powles T, et al. Lancet 2018;391:748-57

IMvigor211: Duration of Response in the IC2/3 Population



Number at risk

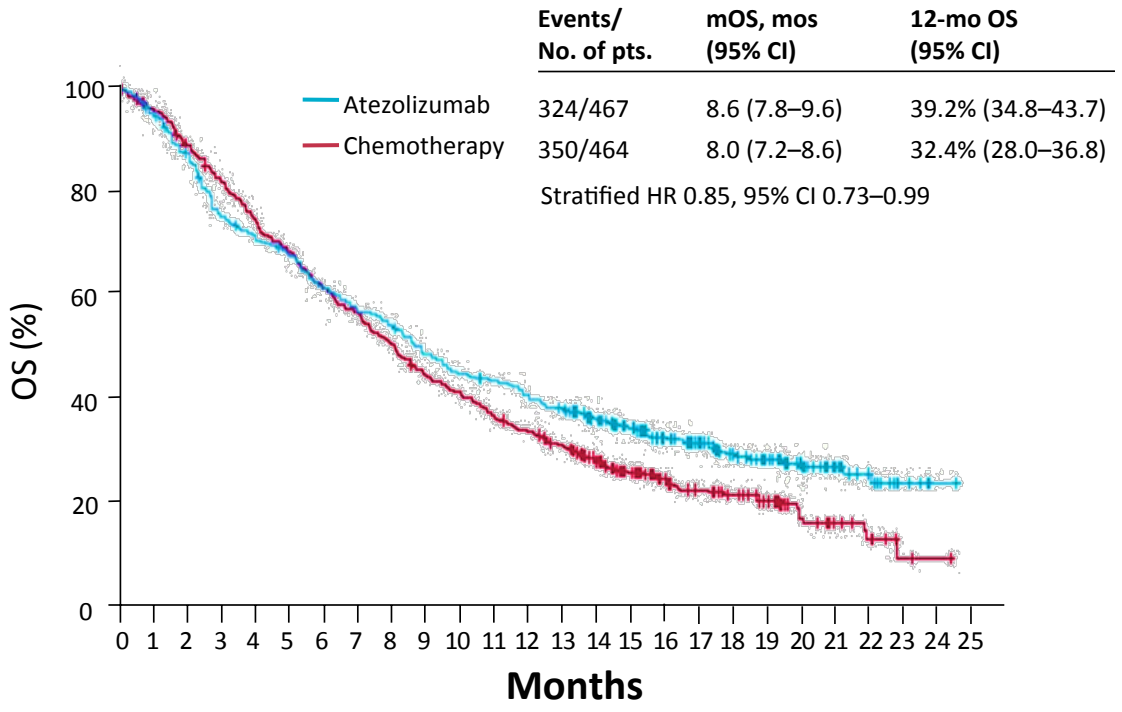
Atezolizumab	26	26	25	24	23	20	20	17	17	16	15	10	8	8	5	5	3	1	1	1	1	1	..
Chemotherapy	25	25	25	25	25	21	17	14	13	10	10	9	9	8	4	4	3	3	3	1	..	..	..

*In the subset of patients with objective response

Powles T, et al. Lancet 2018;391:748-57

IMvigor211: Survival and Duration of Response in the ITT Population

OS



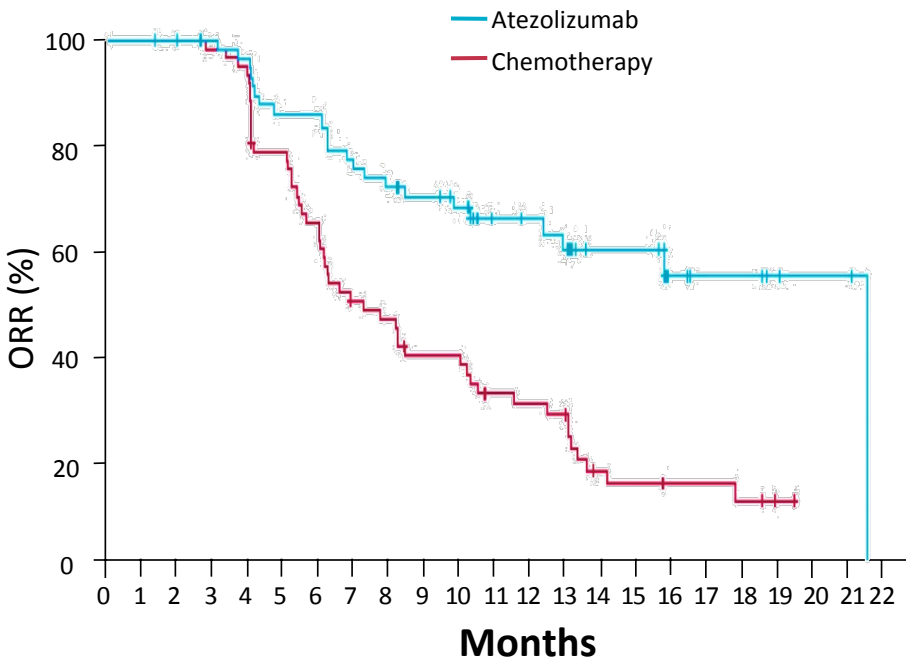
	Events/ No. of pts.	mOS, mos (95% CI)	12-mo OS (95% CI)
Atezolizumab	324/467	8.6 (7.8–9.6)	39.2% (34.8–43.7)
Chemotherapy	350/464	8.0 (7.2–8.6)	32.4% (28.0–36.8)

Stratified HR 0.85, 95% CI 0.73–0.99

Number at risk

Atezolizumab	467	443	405	348	327	309	280	259	245	218	201	192	177	166	138	113	90	76	59	47	34	20	13	5	1	–
Chemotherapy	464	428	397	364	330	299	268	244	219	191	175	156	140	126	99	78	60	49	42	30	17	11	7	2	1	–

Duration of Response*



Number at risk

Atezolizumab	62	62	61	58	56	50	50	45	42	38	35	25	23	22	14	14	9	5	5	3	2	2	–
Chemotherapy	62	62	62	61	59	48	40	30	28	23	23	17	16	15	8	7	5	5	4	2	–	–	–

*In the subset of patients with objective response

Powles T, et al. Lancet 2018;391:748-57

IMvigor211: Summary

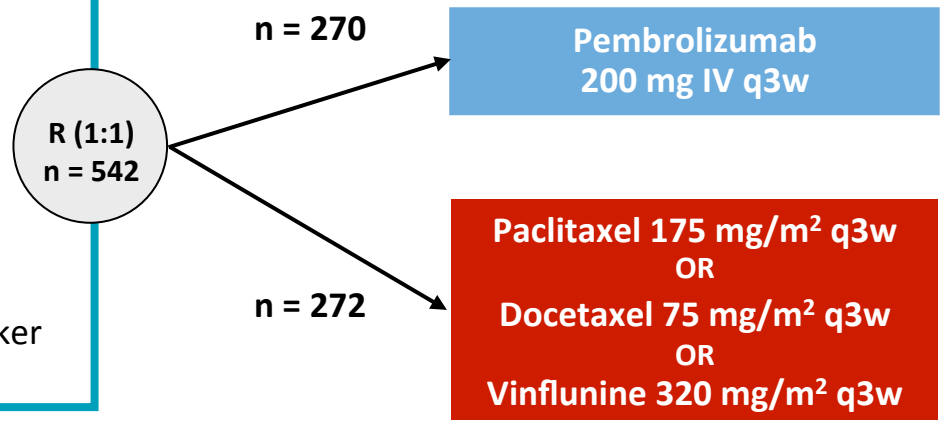
- Phase III trial negative for OS in the 2nd line setting
- Chemotherapy group did better than expected – benefit appears to be driven by vinflunine
- Vinflunine irrelevant – no Health Canada approval
- Further investigation of post-protocol treatment might be informative if there are differences based on what chemotherapy was given
- Atezolizumab still is a viable option in the Canadian context but funding will be an uphill battle with a negative phase III trial

Powles T, et al. Lancet 2018;391:748-57

KEYNOTE-045: Second-line Pembrolizumab in Advanced UC

Key Eligibility Criteria

- UC of the renal pelvis, ureter, bladder, or urethra
- Transitional cell predominant
- Progression after 1-2 lines of platinum-based chemo or recurrence < 12 months after perioperative platinum-based therapy
- ECOG PS 0–2
- Provision of tumour sample for biomarker assessment



Stratification Factors

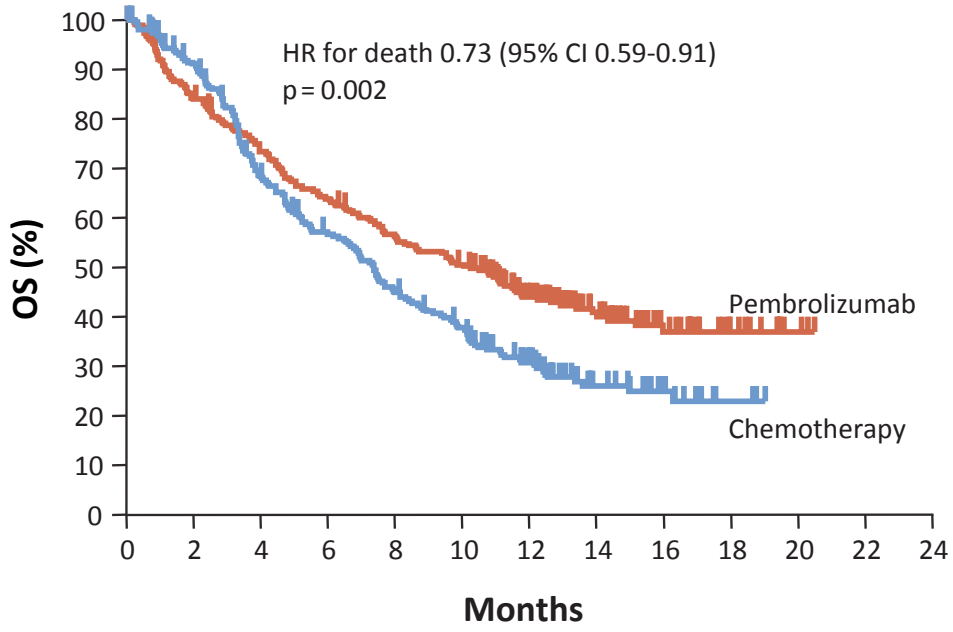
- ECOG PS (0/1 vs. 2)
- Hemoglobin level (< 10 vs. ≥ 10 g/dL)
- Liver metastases (yes vs. no)
- Time from last chemo dose (< 3 vs. ≥ 3 months)

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

Bellmunt J, et al. N Engl J Med 2017;376:1015-26

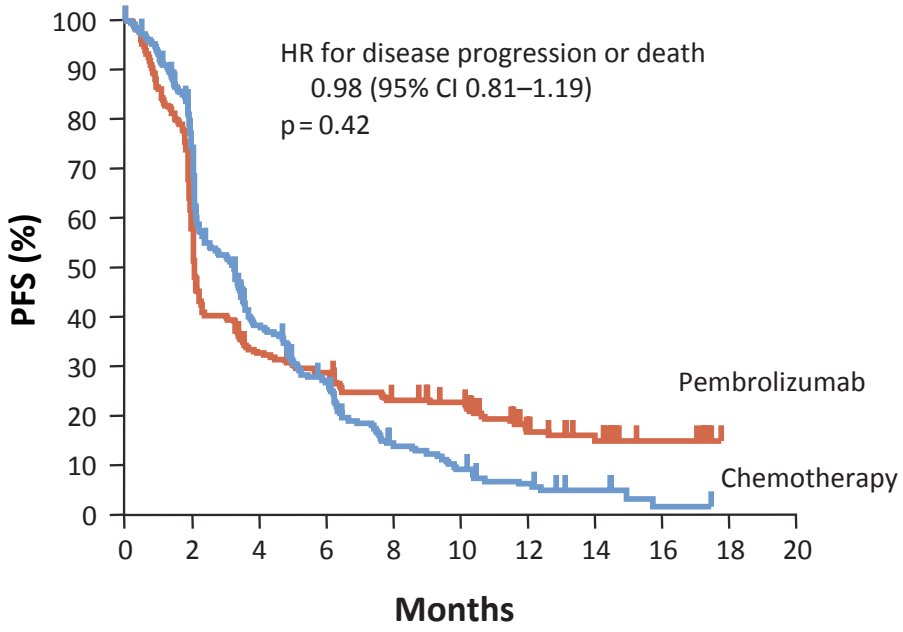
KEYNOTE-045: Survival

OS



No. at Risk												
Pembrolizumab	270	226	194	169	147	131	87	54	27	13	4	0	0
Chemotherapy	272	232	171	138	109	89	55	27	14	3	0	0	0

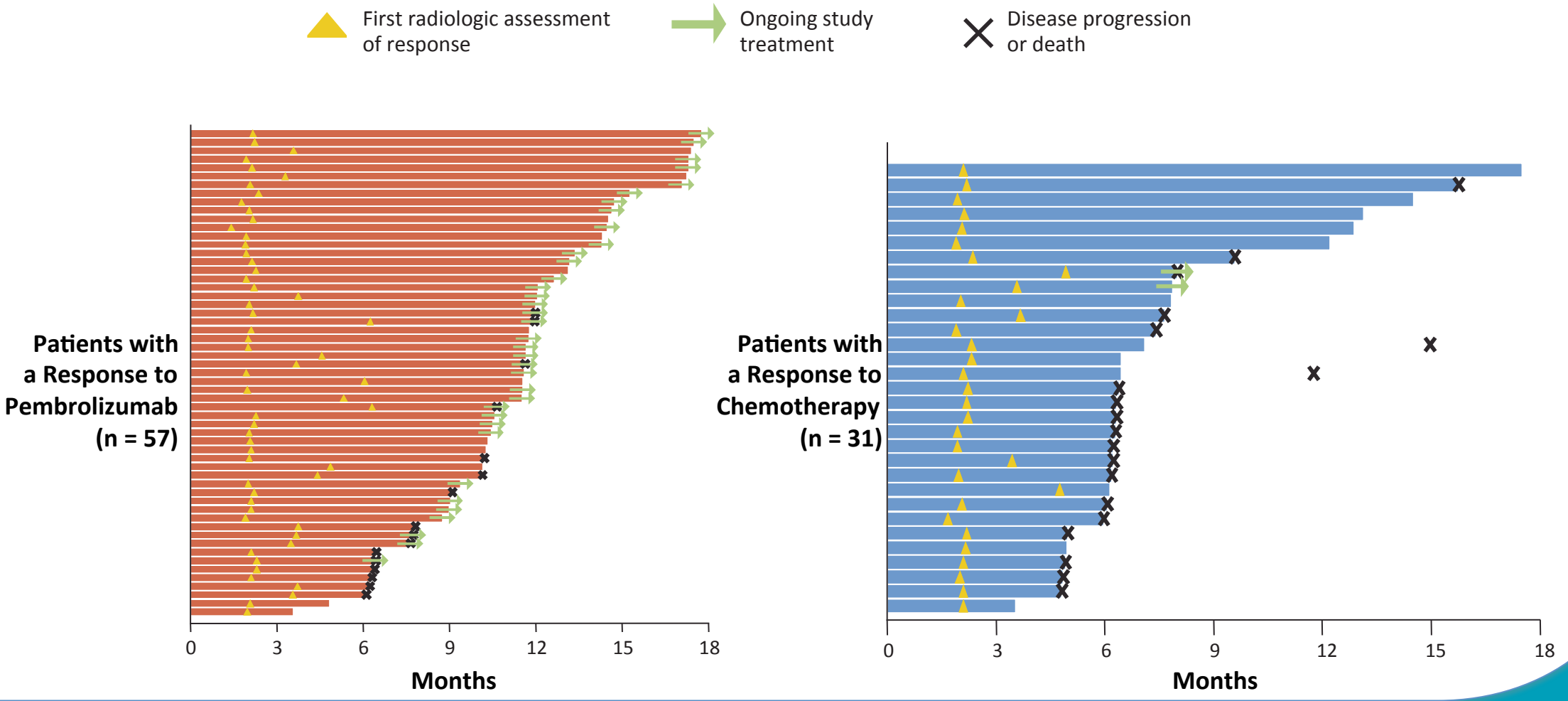
PFS



No. at Risk											
Pembrolizumab	270	165	85	73	56	51	23	16	7	0	0
Chemotherapy	272	188	85	56	27	17	10	5	1	0	0

Bellmunt J, et al. N Engl J Med 2017;376:1015-26.

KEYNOTE-045: Time to Response and Duration of Response



Bellmunt J, et al. N Engl J Med 2017;376:1015-26.

PD-L1 as a Biomarker of Response to PD-1/PD-L1 Inhibitors

- Several IHC biomarker assays have been developed to:
  - Screen for presence of PD-1/PD-L1 epitopes
  - Estimate % of PD-1– or PD-L1–expressing T cells/tumour cells
- BUT sensitivity and specificity are poor:
  - Average specificity = 58%
    - i.e., 42% of those not likely to respond are PD-L1–positive
  - Average sensitivity = 72%
    - i.e., 28% of those who are PD-L1–negative may benefit
- Additional factors may be involved in determining response to anti-PD-1/PD-L1

IHC = Immunohistochemistry

Diggs LP, Hsueh EC. Biomarker Res 2017;5:12.

Mr. Patry: Immunotherapy Treatment

- It’s decided that Mr. Patry is a good candidate for immunotherapy
- PD-L1 expression is not assessed
- He is started on pembrolizumab 200 mg Q3W

ECOG PS = Eastern Cooperative Oncology Group performance status

Discussion Question

- *Mr. Patry tolerated chemotherapy fairly well but did experience nausea and vomiting. He wonders what types of side effects he might expect with immunotherapy.*
  - *What do you tell him?*
  - *What additional monitoring is required?*

Chemotherapy vs. Immunotherapy

Chemotherapy

- Halt or interfere with cell division by damaging the DNA or RNA that controls the division process
- Faster-dividing cells (eg, cancer cells) more susceptible than slower-dividing, normal cells
- Trigger cancer cell apoptosis
- AEs: due to effects on fast-growing noncancer cells (eg, GI tract, scalp, mouth)

Checkpoint inhibitors

- Interfere with effects of checkpoint proteins that are preventing an effective immune response
- Restore T-cell–mediated anti-tumour activity
- AEs: autoimmune effects on normal tissue

Select Immunotherapy-related AEs

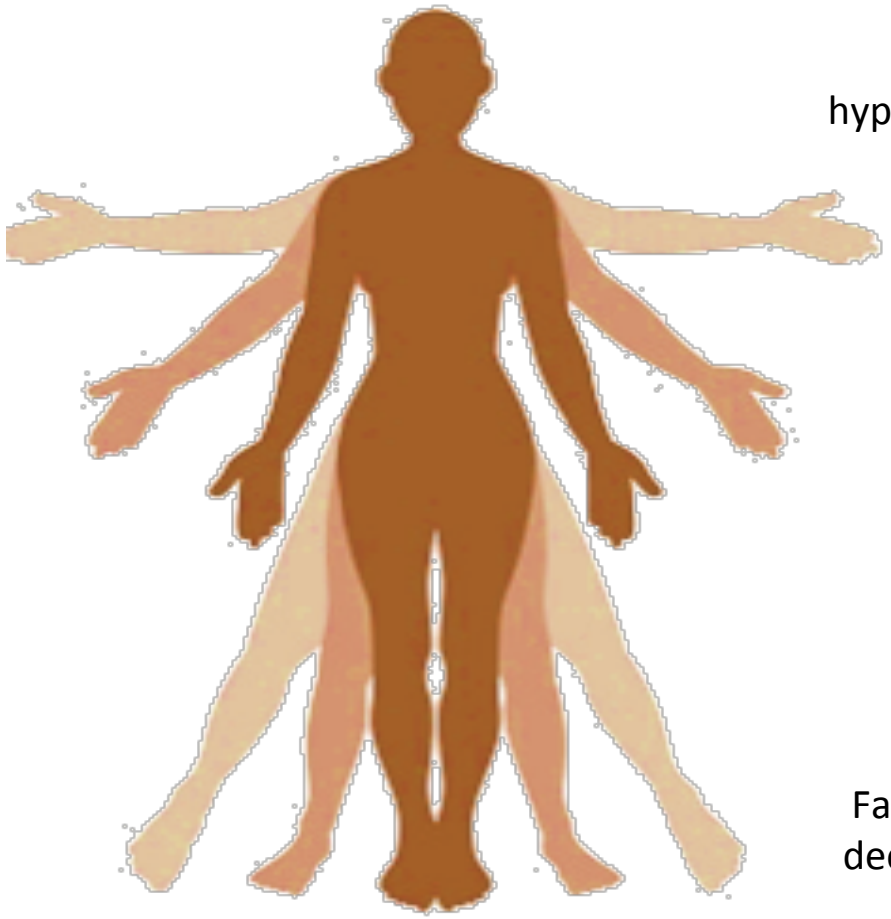
Ocular
Uveitis, episcleritis

Pulmonary
Pneumonitis

Hepatic
Increased liver function enzymes

Pancreatic
Elevated lipase levels

Infusion-related
Infusion-related reaction or hypersensitivity



Endocrine
Hypothyroidism, hyperthyroidism, hypopituitarism, hypophysitis, adrenal insufficiency

Dermatologic
Pruritus, rash, vitiligo, alopecia

Renal
Nephritis, renal failure

Gastrointestinal
Diarrhea, colitis, nausea

General
Fatigue, headache, decreased appetite, arthralgia

Kreamer KM. J Adv Pract Oncol 2014;5:418–31

KEYNOTE-045: Most Common AEs

	Pembrolizumab (n = 266)		Chemotherapy (n = 255)	
	Any Grade	Grade 3, 4, or 5	Any Grade	Grade 3, 4, or 5
Any event	162 (60.9)	40 (15.0)	230 (90.2)	126 (49.4)
Event leading to discontinuation of Tx	15 (5.6)	12 (4.5)	28 (11.0)	16 (6.3)
Event leading to death	4 (1.5)	4 (1.5)	4 (1.6)	4 (1.6)
Pruritus	52 (19.5)	0	7 (2.7)	1 (0.4)
Fatigue	37 (13.9)	3 (1.1)	71 (27.8)	11 (4.3)
Nausea	29 (10.9)	1 (0.4)	62 (24.3)	4 (1.6)
Diarrhea	24 (9.0)	3 (1.1)	33 (12.9)	2 (0.8)
Decreased appetite	23 (8.6)	0	41 (16.1)	3 (1.2)
Asthenia	15 (5.6)	1 (0.4)	36 (14.1)	7 (2.7)
Anemia	9 (3.4)	2 (0.8)	63 (24.7)	20 (7.8)
Constipation	6 (2.3)	0	52 (20.4)	8 (3.1)

Bellmunt J, et al. N Engl J Med 2017;376:1015-26.

Monitoring and Management of Immunotherapy-related AEs

- Thyroid function, blood counts, liver function, and metabolic panels should be tested/taken during treatment of checkpoint inhibitors.
- Most irAEs are mild–moderate and reversible, and occur within the first 3 months of treatment
- BUT some occur after the final dose of therapy
  - e.g., pneumonitis and endocrine events often occur later
- Early detection of irAEs is key
- Immunotherapy may need to be delayed or stopped in certain situations
  - Most (not all) grade 3/4 irAEs will require treatment discontinuation
  - After resolution of the irAE, immunotherapy can be restarted
- Mild cutaneous reactions can be managed with topical steroids

Eigentler TK, et al. Cancer Treat Rev 2016;45:7-18

Discussion Questions

- *8 weeks after starting pembrolizumab treatment, Mr. Patry returns with a rash on his torso, arms and legs:*
  - *Erythematous macules/papules/plaques*
  - *Pruritus*

- *How would you manage his rash?*
- *Does Mr. Patry need to discontinue his immunotherapy treatment?*

Management of Anti-PD-1 Inhibitor-induced Dermatologic AEs

	Maculopapular rash	Pruritus	Vitiligo
Grade 0	Gentle skin care instructions and sun-protective measures		
Grade 1	Topical corticosteroids bid **AND** oral antihistamines		Topical corticosteroids bid **AND** sun protection
	Continue drug at current dose and monitor for change in clinical severity of AE		
	Reassess after 2 weeks; if reactions worsen or remain stable, proceed to next step		

Belum VR, et al. Eur J Cancer 2016;60:12-25

Management of Anti-PD-1 Inhibitor-induced Dermatologic AEs (cont'd)

	Maculopapular rash	Pruritus	Vitiligo
Grade 2	Topical corticosteroids bid **AND** oral antihistamines **AND** oral corticosteroids (prednisone 0.5 mg/kg or equivalent	Topical moderate/high-potency corticosteroid bid **AND** Oral antihistamines	Topical corticosteroid bid **AND** Strict sun protection **AND** consider phototherapy

Reassess after 2 weeks. If reactions worsen or remain stable, counsel patient and encourage continuation of anticancer treatment (vitiligo); **OR** proceed to next step (pruritus, maculopapular rash) **AND** Strict sun protection

Belum VR, et al. Eur J Cancer 2016;60:12-25

Management of Anti-PD-1 Inhibitor-induced Dermatologic AEs (cont'd)

	Maculopapular rash	Pruritus	Vitiligo
Intolerable Grade 2 or Grade ≥ 3	Dose modifications as per package insert Topical corticosteroids bid AND Oral antihistamines AND Oral corticosteroids (prednisone 0.5 mg/kg or equivalent)	Dose modifications as per package insert; continue treatment of skin reaction with: Oral antihistamines AND Oral corticosteroids (prednisone 0.5-1mg/kg or equivalent for 5 days)	

Reassess after 2 weeks. If reactions worsen or remain stable, dose interruption or discontinuation of anticancer treatment as per package insert may be necessary (pruritus, maculopapular rash) **AND** Strict sun protection

Belum VR, et al. Eur J Cancer 2016;60:12-25

Discussion Questions

- *Can we add checkpoint inhibitors in earlier disease states?*
- *What if Mr. Patry had renal failure and was ineligible for cisplatin?*

Case Presentation: Cisplatin-ineligible patient

Mr. Anderson: Presentation and History

- 76-year-old male presents with gross hematuria
- US of pelvis reveals 2 cm bladder mass; no hydronephrosis
- Lab work unremarkable apart from mild anemia of 115 g/L
- Renal function demonstrates serum creatinine of 155 µmol/L and calculated GFR of 42 mL/min
- Comorbidities:
  - Prior CABG after MI, type II diabetes x 10 years, HTN
- Medications:
  - ASA 81 mg, rosuvastatin, metformin, perindopril, salbutamol puffer prn

ASA = Acetylsalicylic acid; CABG = Coronary artery bypass graft; US = Ultrasound

Mr. Anderson: Workup and Staging

- Cystoscopy reveals large tumour consistent with UC
- TURBT reveals muscle invasive UC
  - Perioperatively the patient develops congestive heart failure
  - Echocardiogram reveals ejection fraction of 40%
- Stabilized with diuresis and ACE inhibitor
- Staging investigations with CT scan of chest/abdomen/pelvis
  - Multiple perivesical and retroperitoneal lymph nodes up to 2 cm in size
  - 2 liver metastases, largest 2.5 cm in size
  - Multiple sub-centimeter pulmonary nodules

ACE inhibitor= Angiotensin-converting enzyme inhibitor

Discussion Question

- *What treatment options are available for this man with metastatic UC to liver/lung/node?*

First-line Systemic Therapies for UC

- Muscle-invasive UC
  - Radical cystectomy ± preoperative cisplatin-based chemo
- Locally advanced/metastatic UC
  - Cisplatin + gemcitabine
    - Median OS 14 months[1,2]
  - HD-MVAC
    - Median OS 15.1 months[3]
  - Paclitaxel/cisplatin/gemcitabine
    - Median OS 15.8 months[4]
- 30% to 50% are not eligible for cisplatin
  - Gemcitabine + carboplatin
    - Median OS 9 months[5,6]

1. Bellmunt J, et al. Ann Oncol 2014;25(Suppl 3):iii40–iii48; 2. von der Maase H, et al. J Clin Oncol 2005;23:4602–8;
3. Sternberg CN, et al. Eur J Cancer 2006;42:50-4; 4. Bellmunt J, et al. J Clin Oncol 2012;30:1107-13;
5. De Santis M, et al. J Clin Oncol 2012;30:191–9; 6. Bellmunt J, et al. J Clin Oncol 2009;27:4454–61

First-line Immunotherapy for Advanced UC in the Cisplatin-ineligible Population

- No immunotherapy is approved or available for first-line treatment of cisplatin-ineligible patients in Canada
- Pembrolizumab and atezolizumab have promising results in this population (single-arm phase II trials)
  - Approved in the US for these indications but not in Canada
- Only other options are clinical trials or carboplatin-based therapy
  - Carboplatin/gemcitabine is the most commonly used first-line therapy outside of a trial

Phase I/II Trials of Immunotherapy in First-line Treatment of Cisplatin-ineligible Advanced UC

Trial	Drug	ORR, % (95% CI)	mOS, mos (95% CI)
IMvigor210 – Cohort 1 (n = 119)[1]	Atezolizumab 1,200 mg IV q3w	23 (16–31)	15.9 (10.4-NE)
KEYNOTE-052 (n = 350)[2]	Pembrolizumab 200 mg q2w	24 (20–29)	NR

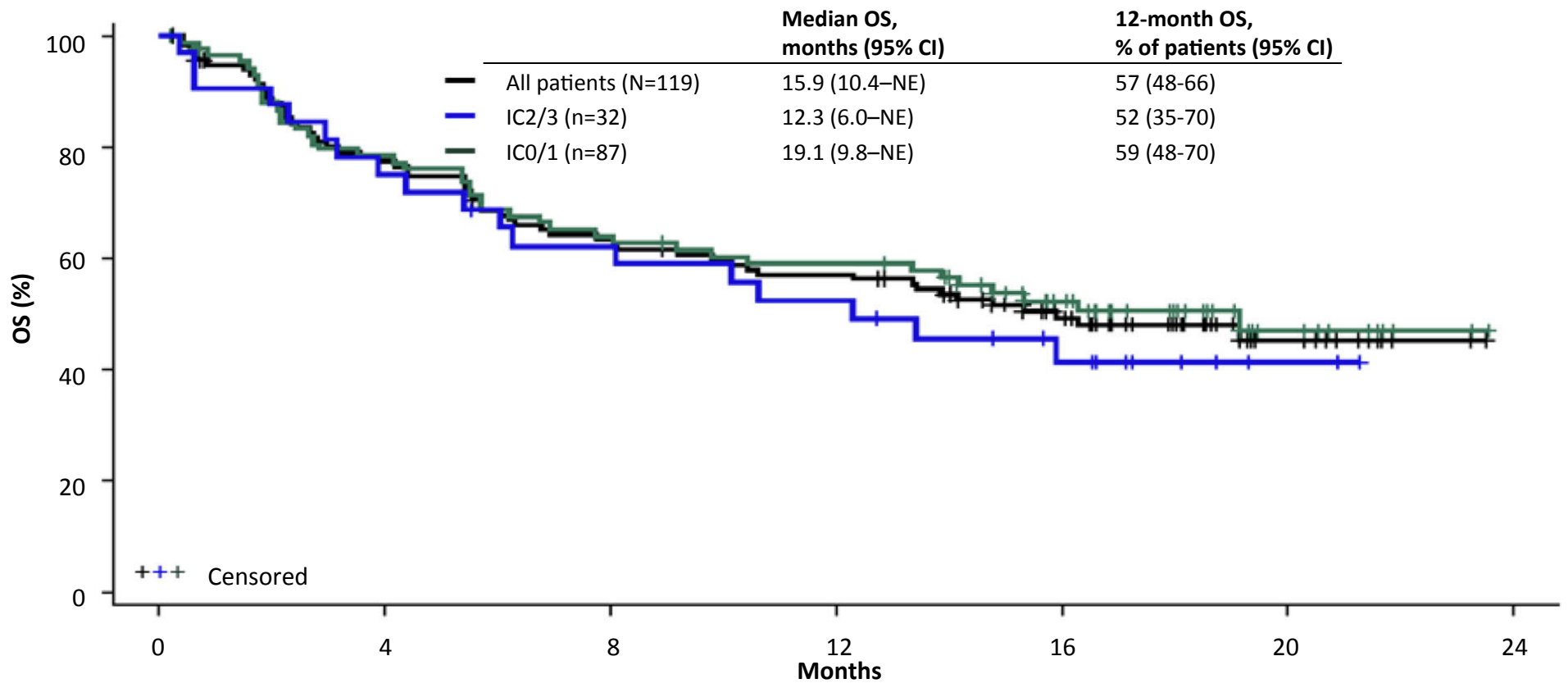
Carboplatin-based treatment in a phase III trial in the same setting:

EORTC Study 30986 (n = 238)[3]	Gemcitabine + carboplatin vs. M-CAVI	GC 41.2 (NR) M-CAVI 30.3 (NR)	GC 9.3 (NR) M-CAVI 8.1 (NR)

M-CAVI = Methotrexate + carboplatin + vinblastine ; Not evaluable;
NR = Not reported

1. Balar AV, et al. Lancet 2017;389:67-76; 2. Balar AV, et al. Lancet Oncol 2017;18:1483-92 ;
3. De Santis M, et al. J Clin Oncol 2012;30:191-9

IMvigor210 – Cohort 1: Overall Survival



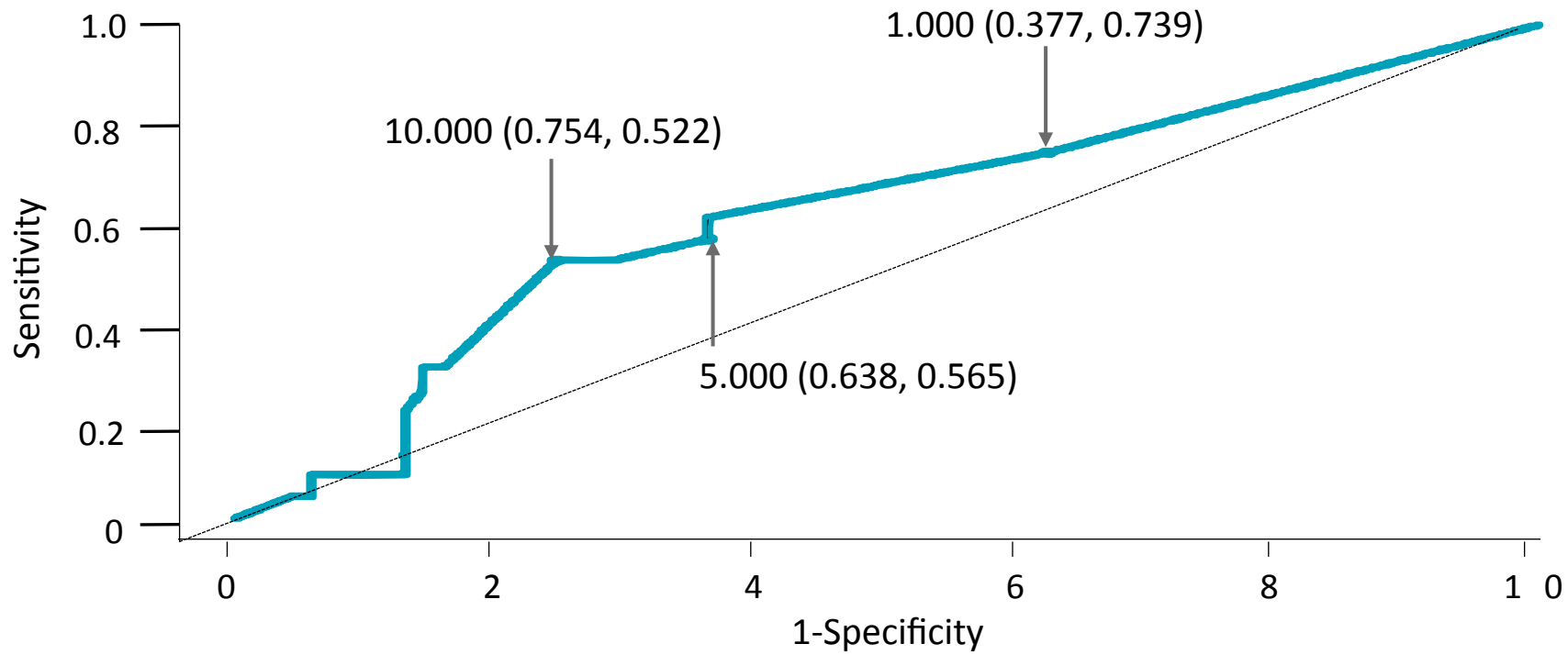
Number at risk

All Patients:	119	101	89	78	72	67	64	56	41	26	11	2	0
IC2/3	32	28	24	21	19	18	16	13	10	6	2	0	0
IC0/1	87	73	65	57	53	49	48	42	31	20	9	2	0

Balar AV, et al. Lancet 2017;389:67-76

KEYNOTE-052 – Specificity and Sensitivity of PD-L1 Expression Combined Positive Score Cut Points

ROC Curve



Although a combined positive score of ≥ 10% enriched for response to first-line pembrolizumab, low or absent PD-L1 expression did not preclude response.

ROC = Receiver operating characteristic

Balar AV, et al. Lancet Oncol 2017;18:1483-92

Mr. Anderson: Treatment Considerations

- He has de novo metastatic disease and multiple comorbidities
- Cisplatin contraindicated based on his renal and cardiac function
- Treatment options in the current environment would be carboplatin-based chemotherapy
- If immunotherapy were available in the cisplatin-ineligible space, atezolizumab or pembrolizumab could be considered
  - Enroll in clinical trial if possible
  - PD-L1 testing needed if considering monotherapy with a checkpoint inhibitor[1]
    - KEYNOTE-361 and IMvigor130 showed decreased OS in single-agent immunotherapy arms vs. chemo

FDA. https://www.fda.gov/Drugs/DrugSafety/ucm608075.htm

Discussion Questions

- *How would treatment differ if Mr. Anderson's renal and cardiac function were better?*
- *What if he had significant diabetic neuropathy?*
- *What if he had a history of ulcerative colitis?*

Mr. Anderson: Additional Treatment Considerations

- *How would treatment differ if Mr. Anderson's renal and cardiac function were better?*
  - → Combination cisplatin-based chemo is the choice
- *What if he had significant diabetic neuropathy?*
  - → Significant neuropathy would make cisplatin difficult; it would also make carboplatin an issue and second-line taxanes
- *What if he had a history of ulcerative colitis?*
  - → Active autoimmune disease would preclude routine use of immunotherapy, either as cisplatin-ineligible first-line or in second line

Case Presentation: BCG-unresponsive, High-risk NMIBC

Mr. Harris: Presentation and History

- 67-year-old male presented with irritative voiding symptoms and microhematuria
- 45 pack-year history of smoking – quit 7 years ago
- Obese, HTN, gout, type II diabetes, coronary artery disease

HTN = Hypertension

Mr. Harris: Workup

- Positive cytology
- CT-IVP normal (except for his 4.5 cm AAA)
- Cystoscopy shows red patches posterior wall
- TURBT: CIS of the bladder; prostatic urethra clear

AAA= Abdominal aortic aneurysm; CIS = Carcinoma in situ; CT-IVP = Computed tomography/Intravenous pyelogram;

Discussion Question

- *What treatment is indicated for Mr. Harris?*

Mr. Harris

- Receives induction BCG x 6
- Cytology now negative
  - Cystoscopy at 3 months – inflamed
- Receives maintenance BCG x 3
- Cytology negative
- Planned random bladder biopsy
  - Persistent CIS

Discussion Question

- *What treatment options are available for Mr. Harris in light of his persistent CIS?*
  - *Repeat BCG induction?*
  - *Radical cystectomy?*
  - *Intravesical chemotherapy?*
  - *Inclusion in a clinical trial?*

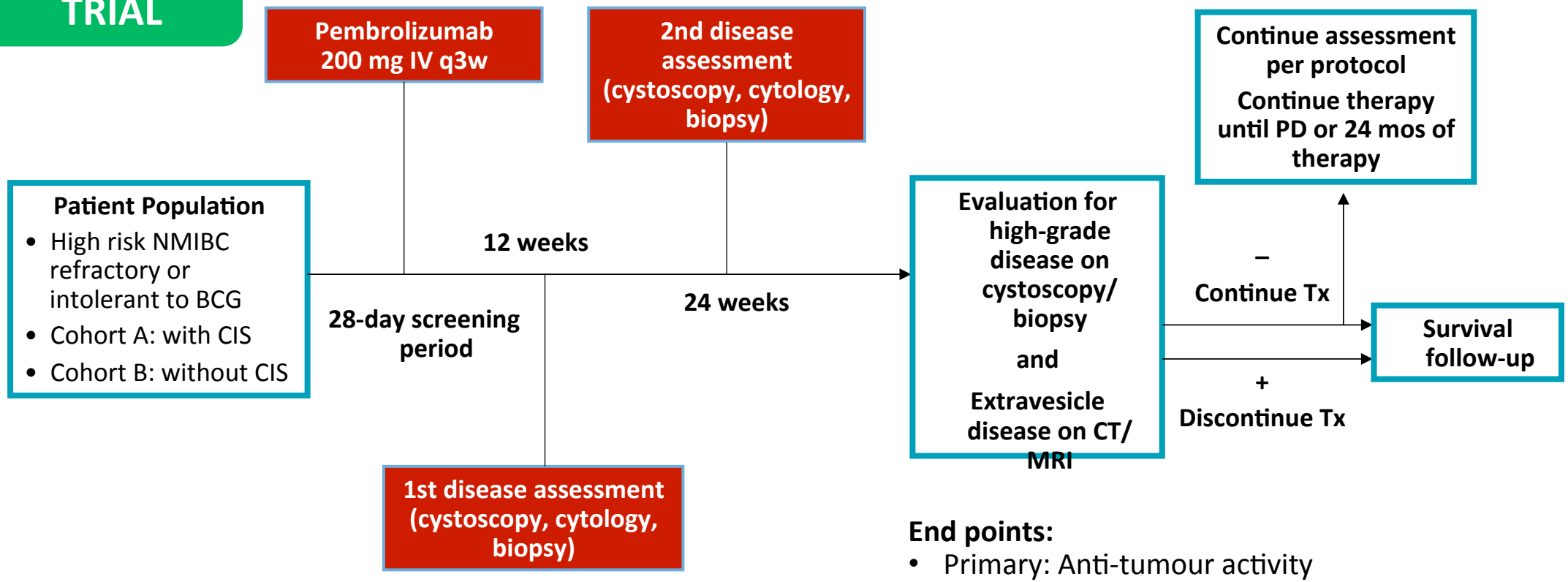
Treatment Options for BCG Failure

- Radical cystectomy recommended by CUA, AUA, and EAU guidelines[1-3]
- However, radical cystectomy is associated with morbidity and mortality:
  - 90-day rate of major complications = 17%[4]
  - 90-day mortality rate = 2% to 10%[5-7]
  - Considerations include: quality of life + duration of life + patient desire
- Salvage intravesicle chemo:[8]
  - < 30% recurrence free at 1 year
  - ~20% recurrence free at 2 years
- Consider clinical trial

1. Kassouf W, et al. Can Urol Assoc J 2015;9:E690-704; 2. Chang SS, et al. J Urol 2016;196:1021-9; 3. Babjuk M, et al. Eur Urol 2017;71:447-61;
4. Hara T, et al. Int J Urol 2009;16:293-8; 5. Sylvester RJ, et al. Eur Urol 2006;49:466-5; 6. Kamat AM, et al. J Urol 2006;175(3 Pt 1):881-5;
7. Fernandez-Gomez J, et al. Eur Urol 2008;53:992-1001; 8. Skinner EC, et al. J Urol 2013;190:1200–4

KEYNOTE-057: Pembrolizumab in Patients with BCG-Unresponsive High-risk NMIBC

ONGOING TRIAL



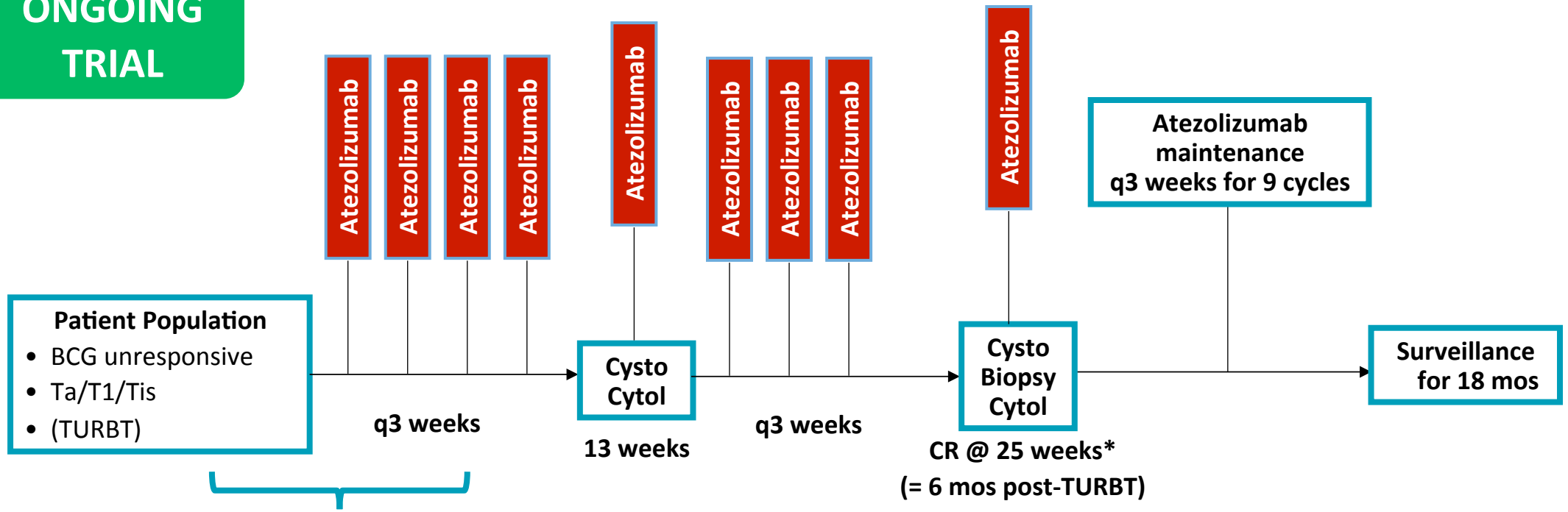
End points:

- Primary: Anti-tumour activity
- Secondary: CR, DOR, DFS, PFS, OS

Kamat AM, et al. ASCO 2016. Poster TPS4576

S1605 Trial: Atezolizumab in Patients with BCG-Unresponsive High-risk NMIBC

ONGOING TRIAL



- Registration within 6 weeks of TURBT
- Start therapy within 5 days of registration

End points:

- Primary: CR at 6 mos in the CIS subgroup; event-free survival at 18 mos in the overall population.
- Secondary: duration of CR, PFS, cystectomy-free survival, bladder cancer-specific survival, OS

*Time is relative to first dose of atezolizumab

Black P, et al. J Clin Oncol 2018;36(suppl). Abstr TPS527

The Future of Immunotherapy in UC

- First line trials are completed with some agents and underway with others
  - Immunotherapy monotherapy vs. combo vs. chemo
  - Chemo-immunotherapy
  - Other immune targets
- Adjuvant trials
- Neoadjuvant trials
- Trimodal therapies with checkpoint inhibitors (ie, chemoradiotherapy)
- NMIBC

Neoadjuvant Trials in MIBC: Interim Results Presented at ASCO 2018

- PURE-01[1]
  - 43 patients with MIBC
  - Pembrolizumab 200 mg q3w × 3 cycles before radical cystectomy
  - Pathologic CR in 39.5% (95% CI 26.3-54.4)
  - Pathologic downstaging to pT<2 in 51.2%
- ABACUS[2]
  - 69 patients with MIBC
  - Atezolizumab 1,200 mg q3w × 2 cycles before radical cystectomy
  - Pathologic CR in 29% (95% CI 18-42)
  - Downstaging to NMIBC in 39%

1. Necchi A, et al. ASCO 2018. Abstract 4507
2. Powles T, et al. ASCO 2018. Abstract 4506

Checkpoint Inhibitors in UC – Select Ongoing Phase III Trials

Trial	Treatments
First-line/cisplatin ineligible – locally advanced or metastatic UC	
IMvigor130	Atezolizumab ± gemcitabine/carboplatin vs. placebo + gemcitabine/ carboplatin
DANUBE	Durvalumab ± tremelimumab
KEYNOTE-361	Pembrolizumab ± chemo vs. chemo alone
CheckMate 901	Nivolumab + ipilimumab or nivolumab + gemcitabine/cisplatin vs. gemcitabine/cisplatin
Adjuvant	
IMvigor010	Adjuvant atezolizumab vs. observation in PD-L1–positive patients at high risk of recurrence following cystectomy
CheckMate 274	Adjuvant nivolumab vs. placebo following resection
AMBASSADOR	Adjuvant pembrolizumab in muscle invasive and locally advanced UC
Maintenance – locally advanced or metastatic UC	
JAVELIN Bladder 100	Avelumab following first-line platinum chemo

Conclusions

- First-line treatment for metastatic UC is still platinum-based chemotherapy if no trial is available
- Data in the second line and beyond suggest that immunotherapy is preferable to standard chemo
  - Best evidence is for pembrolizumab
- Chemo in the second-line setting has modest benefits but can be considered for immunotherapy ineligible or post-immunotherapy
- Multiple trials with immunotherapy are underway