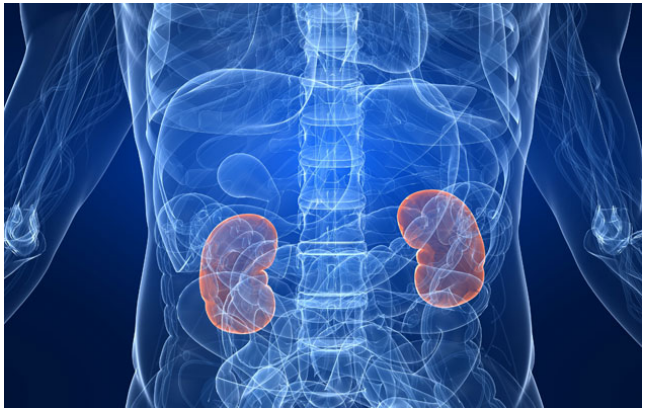
Immunotherapy in Genitourinary Malignancies



May 10th 2019

Dr. Jeffrey Graham MD
Medical Oncologist, CancerCare Manitoba
Assistant Professor, University of Manitoba

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Presenter Disclosure

- **Faculty / Speaker's name: Jeffrey Graham**

- **Relationships with commercial interests: None**

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Learning Objectives

1. Review the current landscape of immuno-oncology (IO) therapy in **kidney cancer**
2. Review the current landscape of IO therapy in **bladder cancer**

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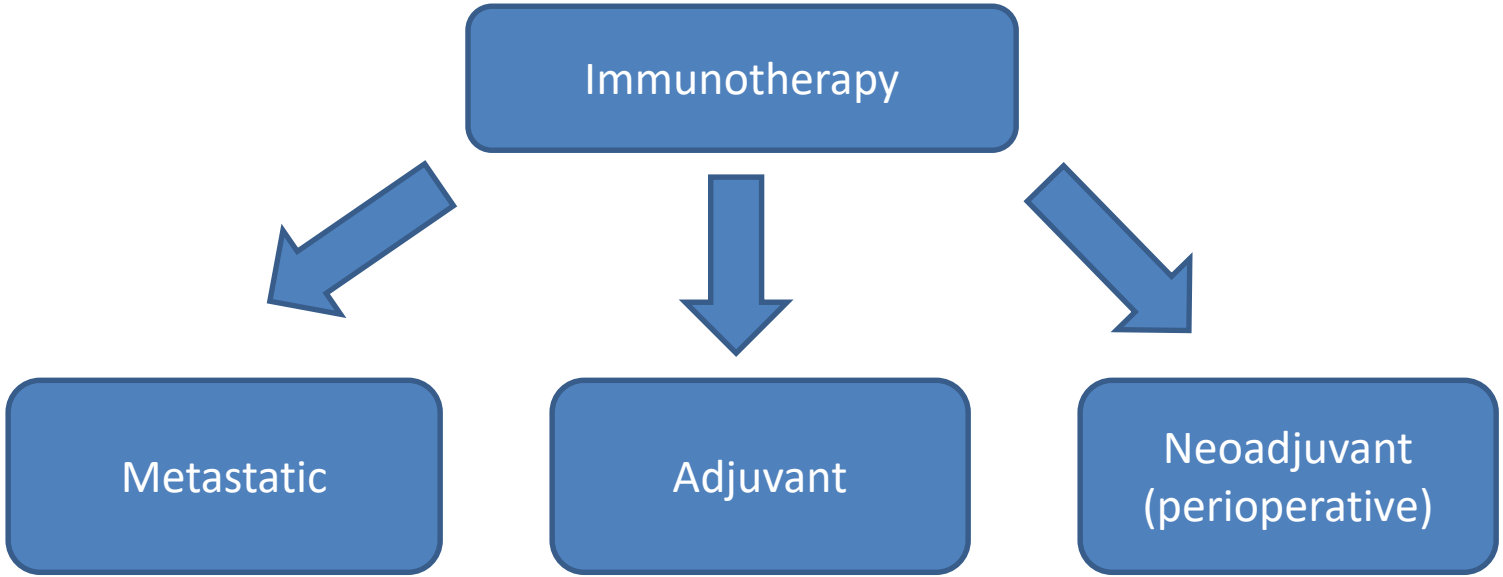
Kidney Cancer



First-line - IO combinations
Second-line - Nivolumab

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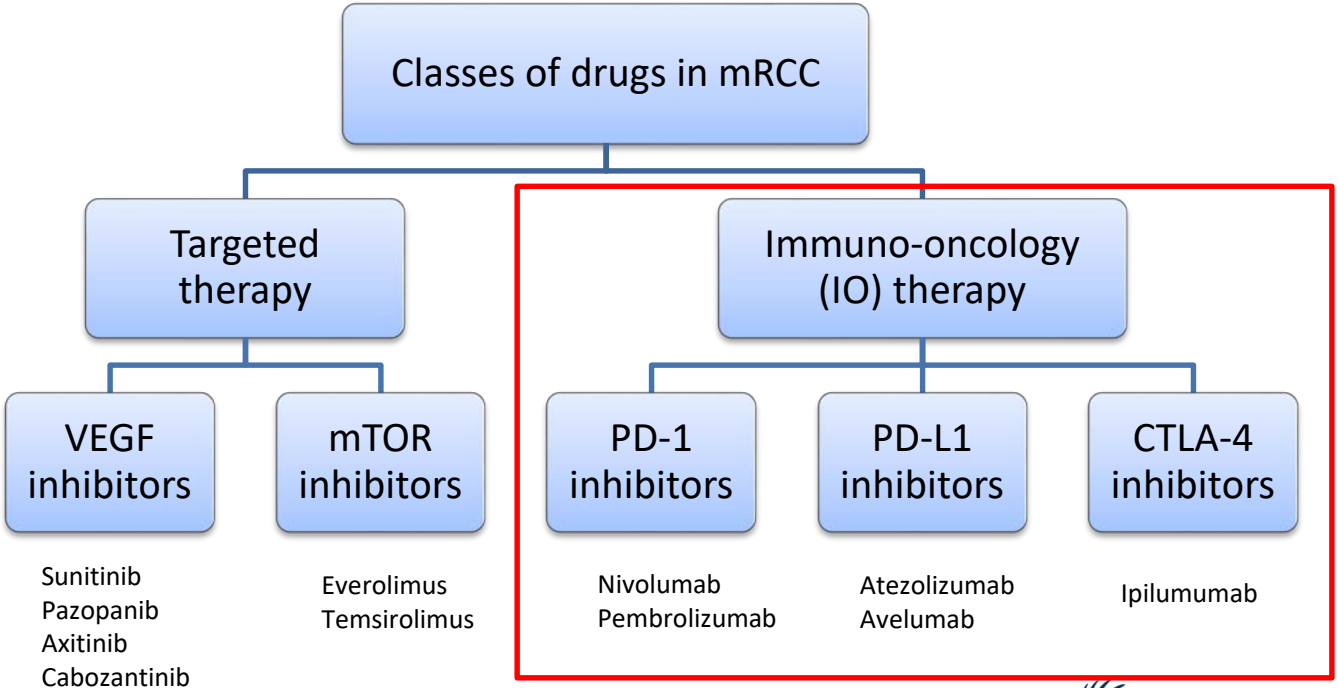
Systemic Therapy Landscape in Metastatic Renal Cell Carcinoma (mRCC)



*IL-2 in highly selected patients

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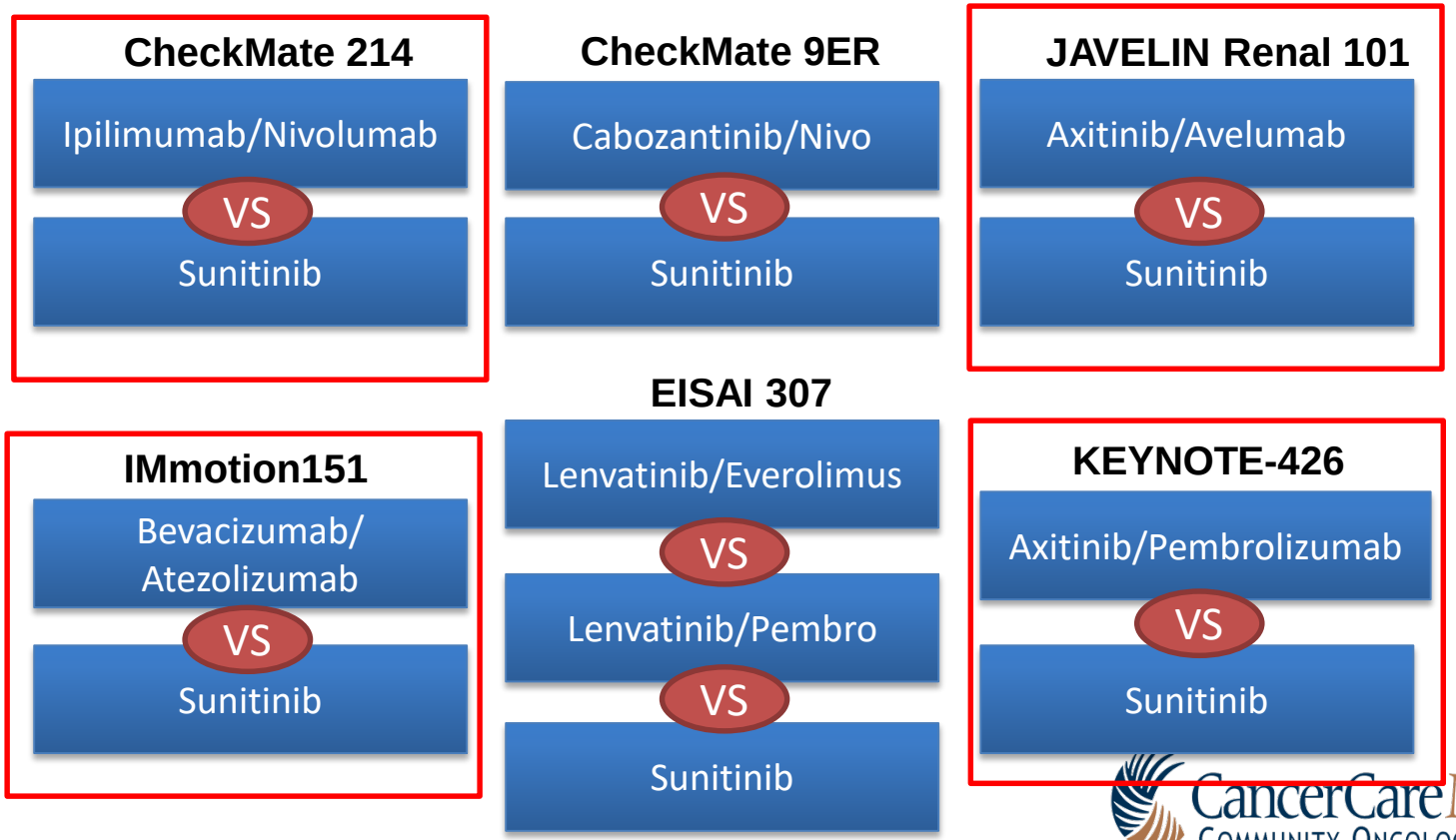
Phase III First-Line IO Combinations in mRCC



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IMDC Prognostic Model

International mRCC Database Consortium (IMDC) Prognostic Factors

Clinical:

- Low Karnofsky performance (<80%)
- Time from diagnosis to treatment <1 year

Laboratory:

- Low haemoglobin (<LLN)
- High corrected serum calcium (>ULN)
- High neutrophils (>ULN)
- High levels of platelets (>ULN)

Categorised into three risk groups

Favourable (0 factors)

Intermediate (1-2 factors)

Poor (3+ factors)

Heng DY, et al. *Lancet Oncol*. 2013

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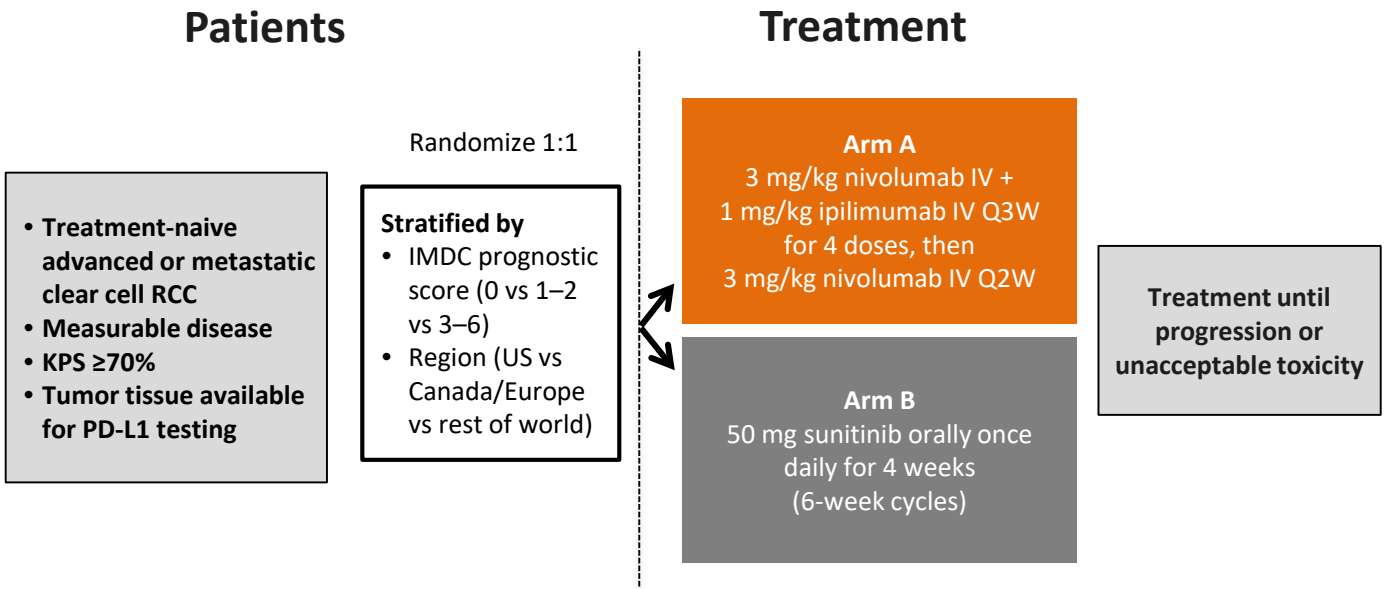
CheckMate 214: Study Design

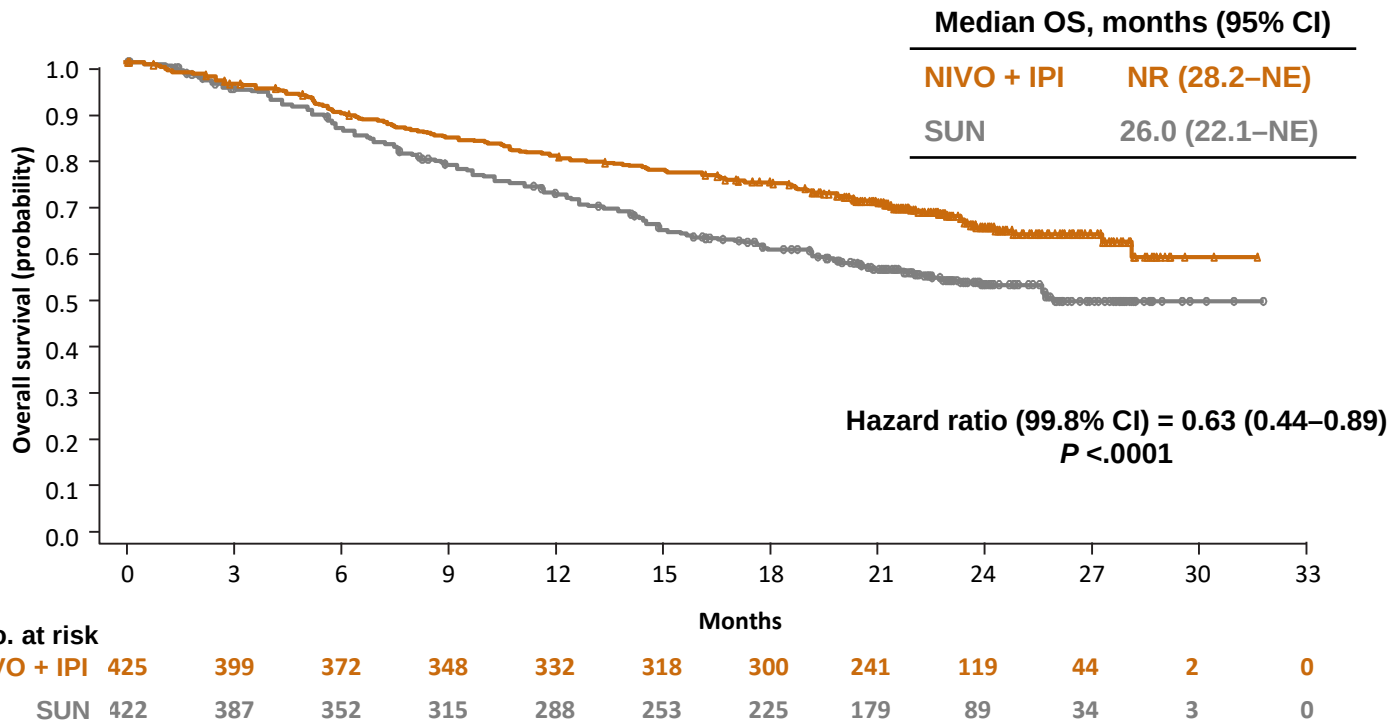


IMDC, International Metastatic RCC Database Consortium; KPS, Karnofsky performance status; Q2W, every 2 weeks; Q3W, every 3 weeks.

Escudier B, et al. *Ann Oncol.* 2017;28(suppl 5):v605-v649.

Co-primary endpoint

OS: IMDC Intermediate/Poor Risk



Escudier B, et al. *Ann Oncol.* 2017;28(suppl 5):v605-v649.

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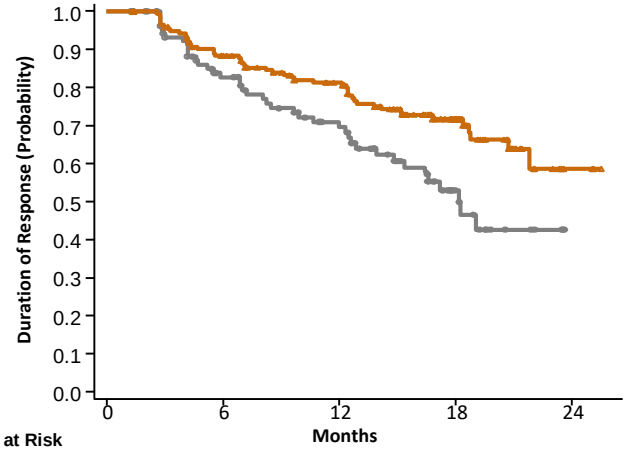
Co-primary endpoint: ORR

ORR and DOR: IMDC intermediate/poor risk

Outcome	N = 847	
	NIVO + IPI N = 425	SUN N = 422
Confirmed ORR,[a] % (95% CI)	**42 (37–47)**	**27 (22–31)**
	P < 0.0001	
Confirmed BOR,[a] %		
Complete response	**9**[b]	**1**[b]
Partial response	32	25
Stable disease	31	45
Progressive disease	20	17
Unable to determine/not reported	8	12

	Median duration of response, months (95% CI)	Patients with ongoing response, %
NIVO + IPI	NR (21.8–NE)	72
SUN	18.2 (14.8–NE)	63



No. at Risk					
NIVO + IPI	177	146	120	55	3
SUN	112	75	52	17	0

[a]IRRC-assessed ORR and BOR by RECIST v1.1; [b]*P* < 0.0001

MADRID 2017 ESMO

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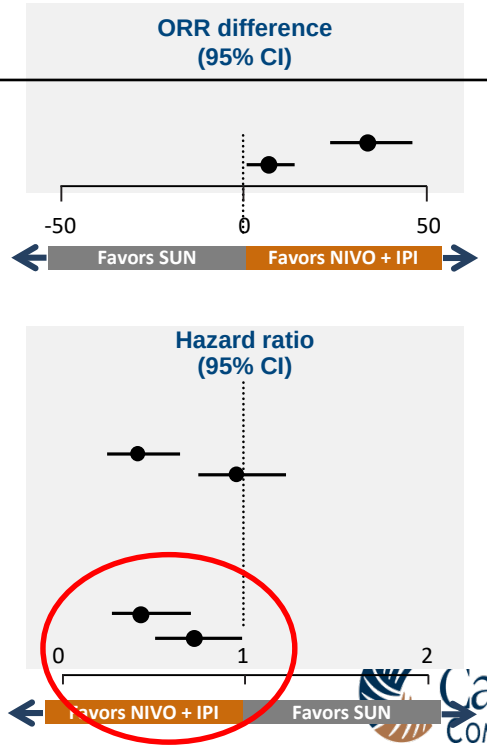
Efficacy by baseline PD-L1 expression: IMDC intermediate/poor risk

Subgroup	NIVO + IPI No. of patients	SUN No. of patients	ORR difference (95% CI)	*P* value
ORR				
Baseline PD-L1 expression				
≥1%	100	114		< 0.0001
<1%	284	278		0.0252
PFS			Hazard ratio (95% CI)	
Baseline PD-L1 expression				
≥1%	100	114		0.0003
<1%	284	278		0.9670
OS				
Baseline PD-L1 expression				
≥1%	100	114		<0.001
<1%	284	278		0.0249



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ORR and PFS: IMDC Favorable Risk

	N = 249*	
Outcome	**NIVO + IPI N = 125**	**SUN N = 124**
Confirmed ORR,† % (95% CI)	29 (21–38)	52 (43–61)
	P = .0002	
PFS,‡ median (95% CI), months	15.3 (9.7–20.3)	25.1 (20.9–NE)
	HR (99.1% CI) = 2.18 (1.29–3.68) P <.0001	

*Eleven percent of patients in both arms had tumor PD-L1 expression ≥1%.
†IRRC assessed by RECIST v1.1.
‡IRRC assessed.
Escudier B, et al. *Ann Oncol.* 2017;28(suppl 5):v605-v649.

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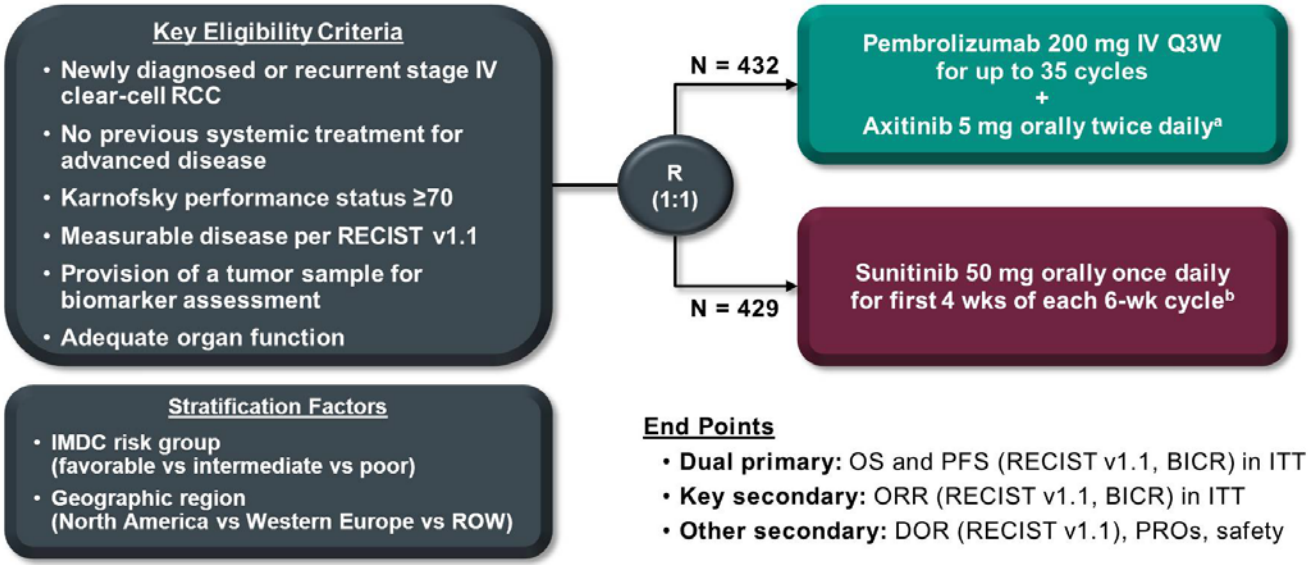
Immune-mediated adverse events: All treated patients

	NIVO + IPI N = 547	
Category, %	Any grade	Grade 3–4
Rash	17	3
Diarrhea/colitis	10	5
Hepatitis	7	6
Nephritis and renal dysfunction	5	2
Pneumonitis	4	2
Hypersensitivity/infusion reaction	1	0
Hypothyroidism	19	<1
Hyperthyroidism	12	<1
Adrenal insufficiency	8	3
Hypophysitis	5	3
Thyroiditis	3	<1
Diabetes mellitus	3	1

- **60% of patients treated with NIVO + IPI required systemic corticosteroids for an adverse event**
- Secondary immunosuppression with infliximab (3%) and mycophenolic acid (1%) was reported

Immune-mediated AE analyses included events, regardless of causality, occurring <100 days of the last dose. These analyses were limited to patients who received immune modulating medication for treatment of the event, except endocrine events that were included in the analysis regardless of treatment since these events are often managed without immunosuppression

KEYNOTE-426 Study Design

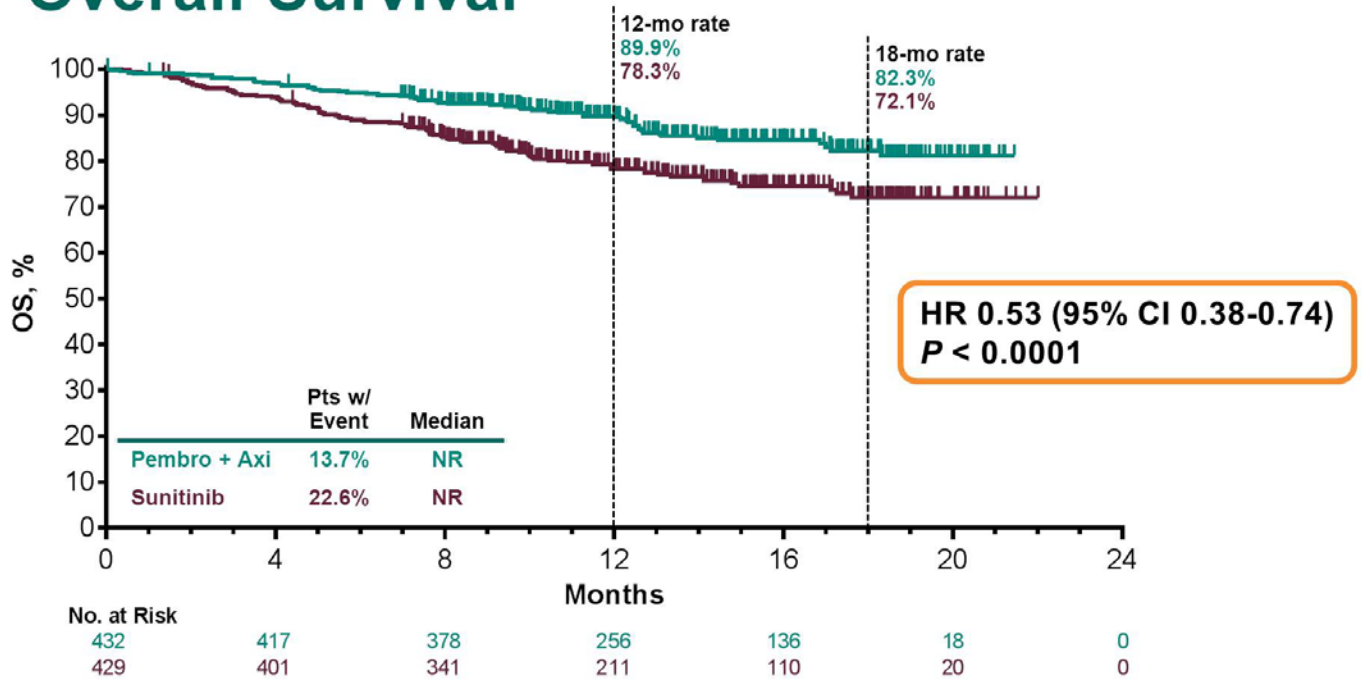


End Points

- **Dual primary:** OS and PFS (RECIST v1.1, BICR) in ITT
- **Key secondary:** ORR (RECIST v1.1, BICR) in ITT
- **Other secondary:** DOR (RECIST v1.1), PROs, safety

[a]Axitinib dose could be increased to 7 mg, then 10 mg, twice daily if safety criteria were met; dose could be reduced to 3 mg, then 2 mg, twice daily to manage toxicity.
[b]Sunitinib dose could be decreased to 37.5 mg, then 25 mg, once daily for the first 4 wks of each 6-wk cycle to manage toxicity.
BICR, blinded independent central radiologic review; DOR, duration of response; PROs, patient-reported outcomes; ROW, rest of world.
KEYNOTE-426 is a randomized, open-label, phase 3 study (ClinicalTrials.gov identifier NCT02853331).

Overall Survival



HR 0.53 (95% CI 0.38-0.74)
P < 0.0001

Data cutoff date: Aug 24, 2018.

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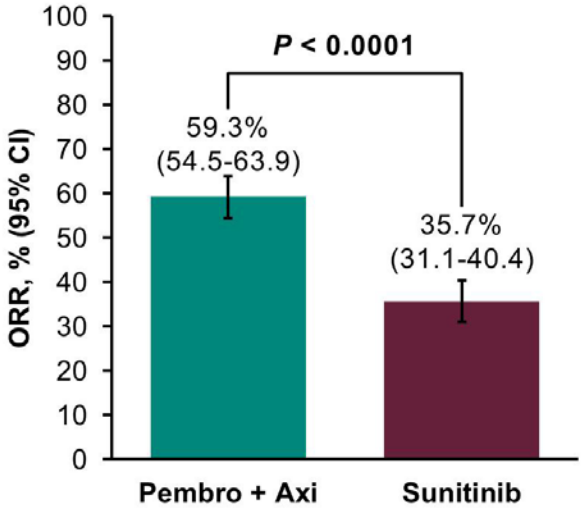
Confirmed Objective Response Rate



Best Response	Pembro + Axi N = 432	Sunitinib N = 429
CR	25 (5.8%)	8 (1.9%)
PR	231 (53.5%)	145 (33.8%)
SD	106 (24.5%)	169 (39.4%)
PD	47 (10.9%)	73 (17.0%)
NE[a]	8 (1.9%)	6 (1.4%)
NA[b]	15 (3.5%)	28 (6.5%)
Response Duration	**N = 256**	**N = 153**
Median (range), mo	NR (1.4+ to 18.2+)	15.2 (1.1+ to 15.4+)

[a]Patients who had ≥1 post-baseline imaging assessment, none of which were evaluable per RECIST v1.1 by BICR. [b]Patients who did not have ≥1 post-baseline imaging assessment.
Data cutoff date: Aug 24, 2018.

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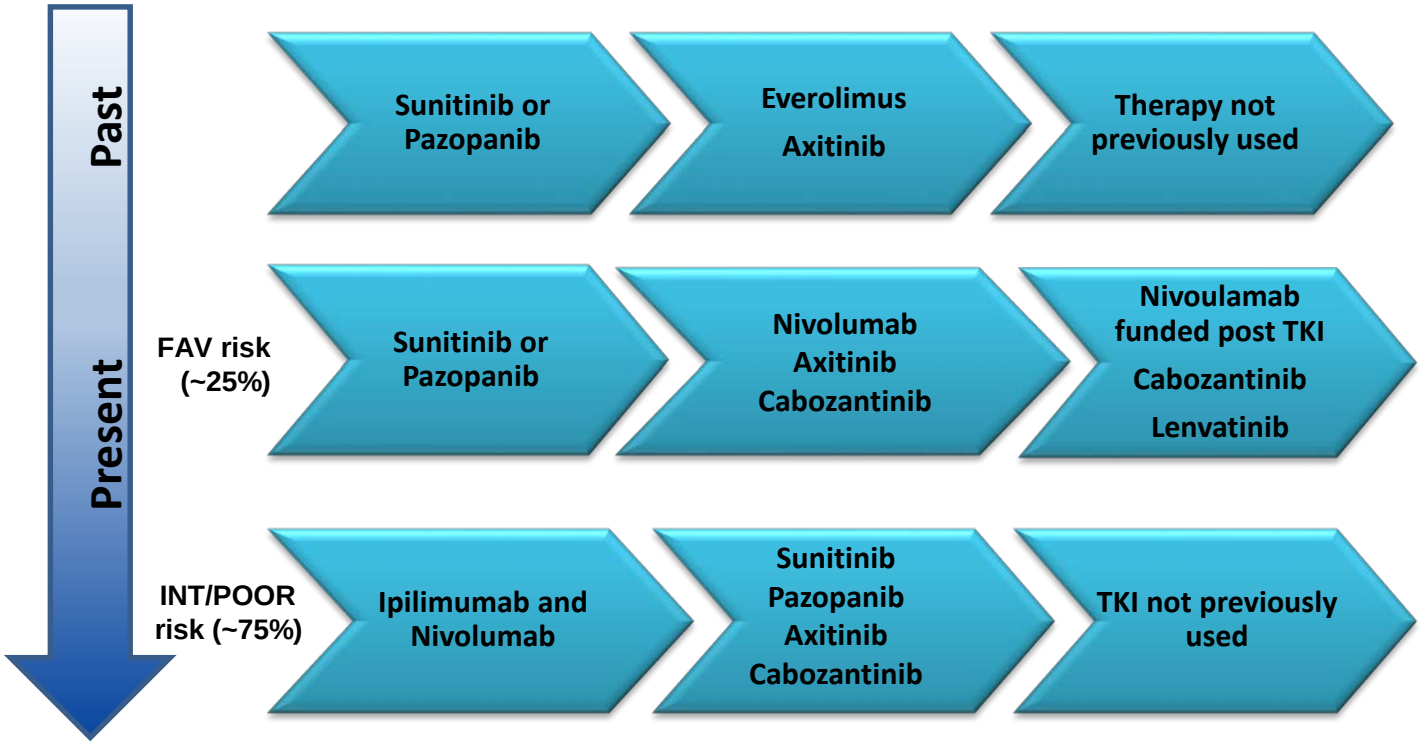
Summary of Adverse Events

	All Cause		Treatment Related	
	Pembro + Axi N = 429	Sunitinib N = 425	Pembro + Axi N = 429	Sunitinib N = 425
Any	98.4%	99.5%	96.3%	97.6%
Grade 3-5	75.8%	70.6%	62.9%	58.1%
Led to death	2.6%	3.5%	0.9%[a]	1.6%[b]
Led to discontinuation of any treatment	30.5%	13.9%	25.9%	10.1%
Led to discontinuation of both pembro and axi	10.7%	—	8.2%	—
Led to axi or sunitinib dose reduction	20.3%	30.1%	20.0%	28.5%
Led to interruption of any treatment	69.9%	49.9%	62.2%	40.2%

[a]One patient each from myasthenia gravis, myocarditis, necrotizing fasciitis, and pneumonitis.
[b]One patient each from acute myocardial infarction, cardiac arrest, fulminant hepatitis, gastrointestinal hemorrhage, intracranial hemorrhage, malignant neoplasm progression, and pneumonia.
Data cutoff date: Aug 24, 2018.



Clinical trial at any line

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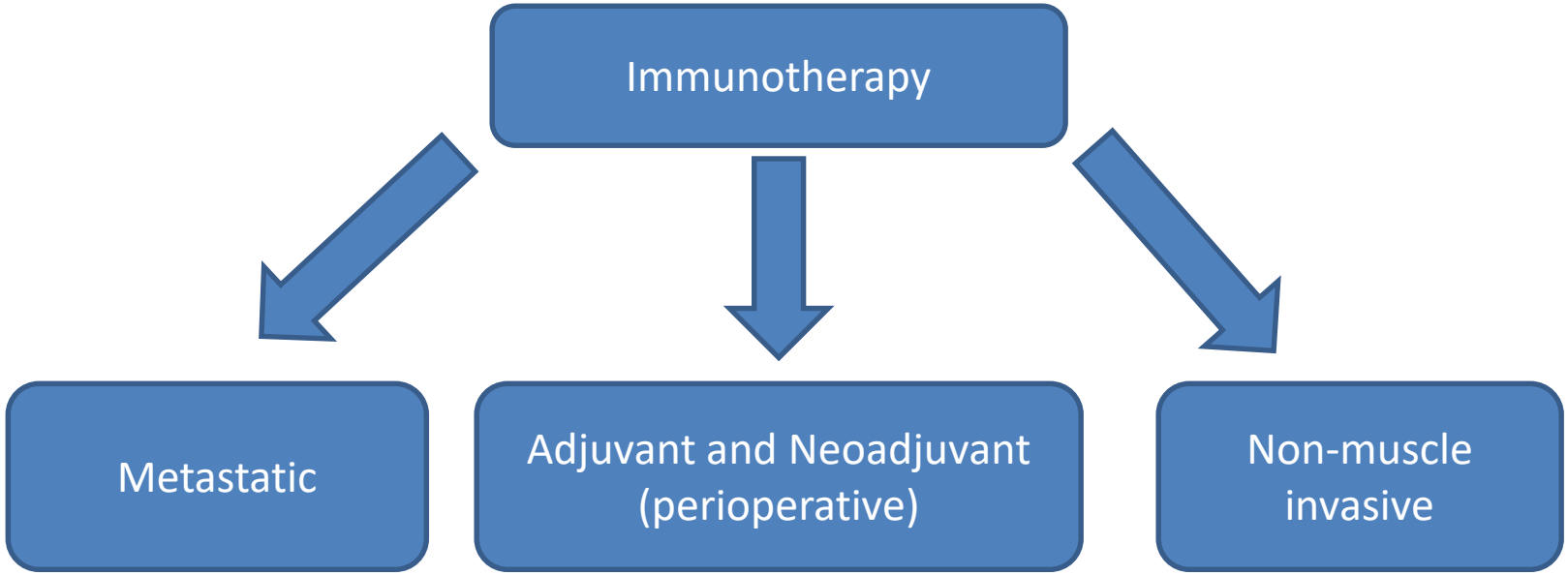
Summary – Kidney Cancer

- Immune checkpoint inhibitor nivolumab is already a standard treatment option post-TKI in mRCC
- IO-IO and IO-VEGF TKI combinations will replace first-line TKI for most patients
  - Nivo+Ipi in intermediate/poor risk mRCC already in use in Manitoba
- RCTs are investigating IO therapy in the adjuvant and neoadjuvant setting
  - RCT with adjuvant pembrolizumab is open at CCMB
- Biomarkers needed

Bladder Cancer



First-line - IO +/- chemo
Second-line - Pembrolizumab

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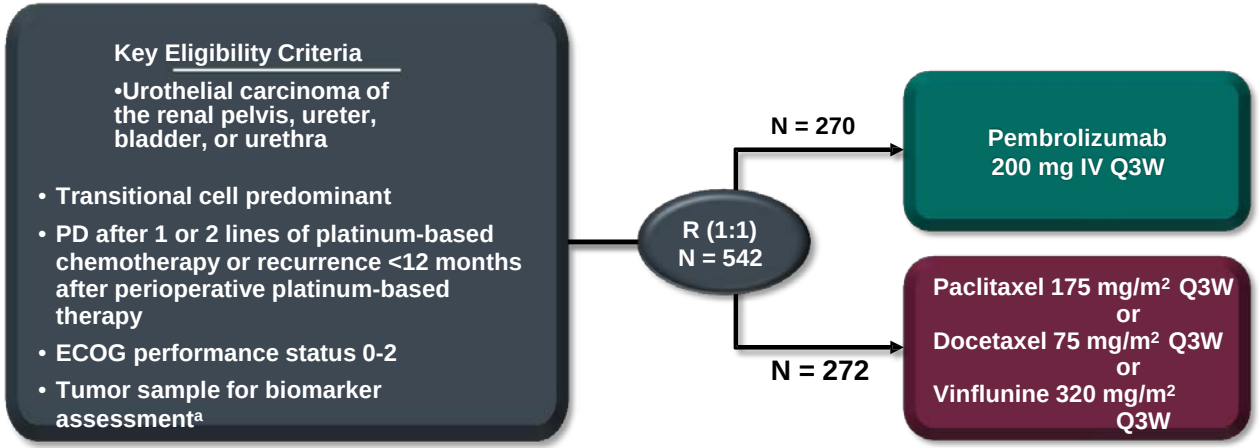
KEYNOTE-045 Study Design



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 months)

- **Dual primary end points: OS and PFS[b]**
- **Key secondary end points: ORR, DOR, safety**
- **Response: RECIST v1.1 by blinded, independent central review**
- **Unselected and biomarker-selected patients**
- **Data cutoff for this analysis was October 26, 2017**
- **Median follow-up, 27.7 months**

Bellmunt 2017 NEJM

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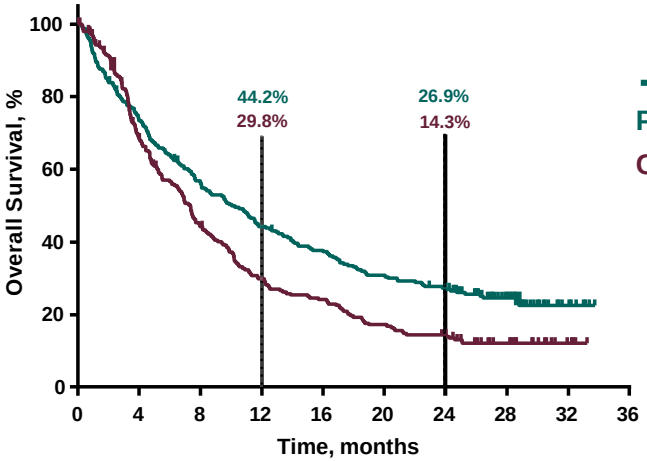
Overall Survival



No. at risk									
Pembrolizumab	195	148	116	98	80	67	33	7	0
270									
Chemotherapy	173	109	73	59	42	34	18	4	0
272									

	Events, n	HR (95% CI)[a]	*P*
Pembro	200	0.70 (0.57-0.85)	0.00015
Chemo	219		

Median (95% CI):

10.1 months (8.0-12.3 months)

7.3 months (6.1-8.1 months)

[a]Based on Cox regression model with treatment as a covariate stratified by ECOGperformance status (0/1 vs 2), liver metastases (yes vs no), hemoglobin (<10 vs ≥10 g/dL), and time from completion of chemotherapy (<3 vs ≥3 months). [b]One-sided *P* value based on stratified log-rank test. Data cutoff date: Oct 26, 2017.

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Immune Related Adverse Events (irAEs)

Table 2. Adverse Events in the As-Treated Population.*

Event	Pembrolizumab Group (N=266)		Chemotherapy Group (N=255)	
	Any Grade	Grade 3, 4, or 5	Any Grade	Grade 3, 4, or 5
	number of patients (percent)			
Event of interest§				
Any event	45 (16.9)	12 (4.5)	19 (7.5)	4 (1.6)
Hypothyroidism	17 (6.4)	0	3 (1.2)	0
Hyperthyroidism	10 (3.8)	0	1 (0.4)	0
Pneumonitis	11 (4.1)	6 (2.3)	1 (0.4)	0
Colitis	6 (2.3)	3 (1.1)	1 (0.4)	0
Infusion reaction	2 (0.8)	0	10 (3.9)	0
Nephritis	2 (0.8)	2 (0.8)	0	0
Severe skin reaction	2 (0.8)	1 (0.4)	3 (1.2)	3 (1.2)
Thyroiditis	2 (0.8)	0	0	0
Adrenal insufficiency	1 (0.4)	1 (0.4)	0	0
Myositis	0	0	1 (0.4)	1 (0.4)

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Current first-line metastatic IO trials

Trial	N	Opened Est. Complete	End Point
▪ Durvalumab (MEDI4736) [1] ▪ Durvalumab/tremelimumab ▪ Cisplatin or carboplatin/gemcitabine	1200	November 2015 September 2019	OS
▪ Atezolizumab [2] ▪ Atezolizumab + cisplatin or carboplatin/gemcitabine ▪ Cisplatin or carboplatin/gemcitabine	1200	June 2016 July 2020	PFS/OS/AE
▪ Pembrolizumab [3] ▪ Pembrolizumab + cisplatin or carboplatin/gemcitabine ▪ Cisplatin or carboplatin/gemcitabine	990	September 2016 May 2020	PFS/OS
▪ Ipilimumab + nivolumab [4] ▪ Nivolumab + cisplatin/gemcitabine* ▪ Cisplatin or carboplatin/gemcitabine†	897	March 2017 December 2022	PFS/OS

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Current neoadjuvant IO trials

Single-Agent Therapy	Country	Eligibility	Cisplatin Eligibility	Trial Identifier	Status
• Pembrolizumab (PURE-01)	Italy	T2-3bN0M0	Yes	NCT02736266	Has results
• Pembrolizumab + Epacadostat (PECULIAR)	Italy	T2-3bN0M0	Yes	NCT03832673	Not yet enrolling
• Pembrolizumab (PANDORE)	France	T2-4N0 or Nx	No	NCT03212651	Enrolling
• Atezolizumab	South Korea	T2-4aN0M0	N/A	NCT03577132	Enrolling
• Atezolizumab	United States	T<2, T2-4N0M0	No	NCT02451423	Enrolling
• Avelumab (BL-AIR)	United States	T2-4aN0M0	No	NCT03498196	Enrolling
• Atezolizumab (ABACUS)	Europe	T2-4aN0M0	No	NCT02662309	Has results
Immune Combination Therapy					
• Nivolumab/urelumab	United States	T2-4aN0M0	No	NCT02845323	Enrolling
• Nivolumab/ipilimumab (NABUCCO)	Netherlands	T3-4N0 or N+	No	NCT03387761	Enrolling
• Durvalumab/tremelimumab vs. chemotherapy (DUTRENEO)	Spain	T2-4N0 or N1	Yes	NCT03472274	Enrolling
• Durvalumab/tremelimumab (NITIMIB)	Switzerland	T2-4N0 or N+	No	NCT03234153	Enrolling
• Durvalumab/tremelimumab	MDACC	T2-4aN0M0	No	NCT02812420	Enrolling
• Nivolumab ± ipilimumab (CA209-9DJ)	MSKCC	T2-4aN0M0	No	NCT03520491	Enrolling
• Durvalumab + olaparib (NEODURVARIB)	Spain	T2-4aN0M0	No	NCT03534492	Enrolling
Chemoimmunotherapy Combinations					
• Nivolumab + gemcitabine/cisplatin (BLASST-1)	United States	T2-4aN0M0	Yes	NCT03294304	Enrolling
• Avelumab (AURA) ± chemotherapy	Belgium	T2-4N0 or N+	Yes/No	NCT03674424	Enrolling
• Pembrolizumab + gemcitabine/cisplatin	United States	T2-4N0 or Nx	Yes	NCT02690558	Enrolling
• Pembrolizumab + gemcitabine/cisplatin	Indiana University	T2-4aN0M0	Yes	NCT02365766	Has results
• Nivolumab + gemcitabine/cisplatin	Hoosier Cancer Research Network	T2-4aN0M0	Yes	NCT03558087	Enrolling
• Gemcitabine/cisplatin ± durvalumab (NIAGARA)	Multicenter international	T2-4aN0M0	Yes	NCT03732677	Enrolling
• Chemotherapy vs. chemotherapy + nivolumab, ± BMS-986205 (CA017-078)	Multicenter international	T2-4aN0M0	Yes	NCT03661320	Enrolling
• Durvalumab + tremelimumab + dose-dense MVAC (NEMIO)	French multicenter	T2-4aN0-1M0	Yes	NCT03549715	Not yet enrolling

Current adjuvant IO trials

IO Therapy/Study	Phase/N	Study Arms	Primary Endpoints	Secondary Endpoints	Estimated Primary Completion Date
Nivolumab[1] CheckMate 274 (NCT02632409)	Phase 3 N=700	• Nivolumab (adjuvant) • Placebo	• Disease-free survival	• Non-urothelial track recurrence-free survival • Disease-specific survival • OS	November 2020
Pembrolizumab[2] AMBASSADOR (NCT03244384)	Phase 3 N=739	• Pembrolizumab (adjuvant) • Observation	• Disease-free survival • OS (up to 5 years)	• Disease-free survival and OS in PD-L1$^+$ and PD-L1$^-$ patients	February 2019
Atezolizumab[3] IMvigor010 (NCT02450331)	Phase 3 N=809	• Atezolizumab (adjuvant) • Observation	• Disease-free survival	• Disease-specific survival • OS • Distant metastasis-free survival • Non-urinary tract recurrence-free survival • Safety, QoL • PK, immunogenicity	January 2020

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Summary – Bladder Cancer

- Immune checkpoint inhibitor pembrolizumab is standard second-line therapy in metastatic bladder cancer
- IO therapy will likely be used in the first-line for select patients, awaiting RCT results
- Multiple trials exploring the incorporation of IO therapy in neoadjuvant and adjuvant therapy
- Biomarkers needed

Thank You

- Questions?

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