Kidney Cancer
Overview of Contemporary Management

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Presenter Disclosure

- **Faculty/Speaker:** Jeffrey Graham

- **Relationships with financial sponsors:**
  - –Consulting/Honoraria: Ipsen, Pfizer, Janssen, Merck, EMD Serono, Bayer, AstraZeneca

Mitigating Potential Bias

- The information in this presentation was created without any external input from industry partners, and all content is based on published evidence

Equity Commitment

- In preparing for this presentation, I have considered the Health Equity Resource for Presenters provided by the conference planning committee.

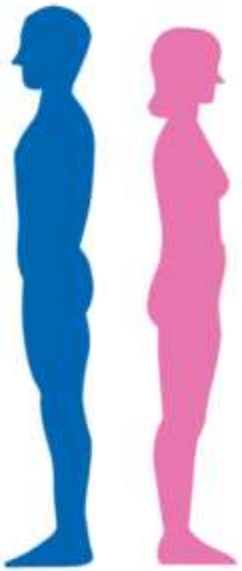
- This was provided to help presenters reflect on how these topics and content can have good effects or bad effects on people or populations that are underserved.

Learning Objectives

- Describe the epidemiology, pathology, and risk factors of kidney cancer
- Explain the staging of localized kidney cancer and the role of adjuvant therapy
- Describe a personalized approach to the management of advanced kidney cancer and the role of systemic therapy

Kidney Cancer - Epidemiology

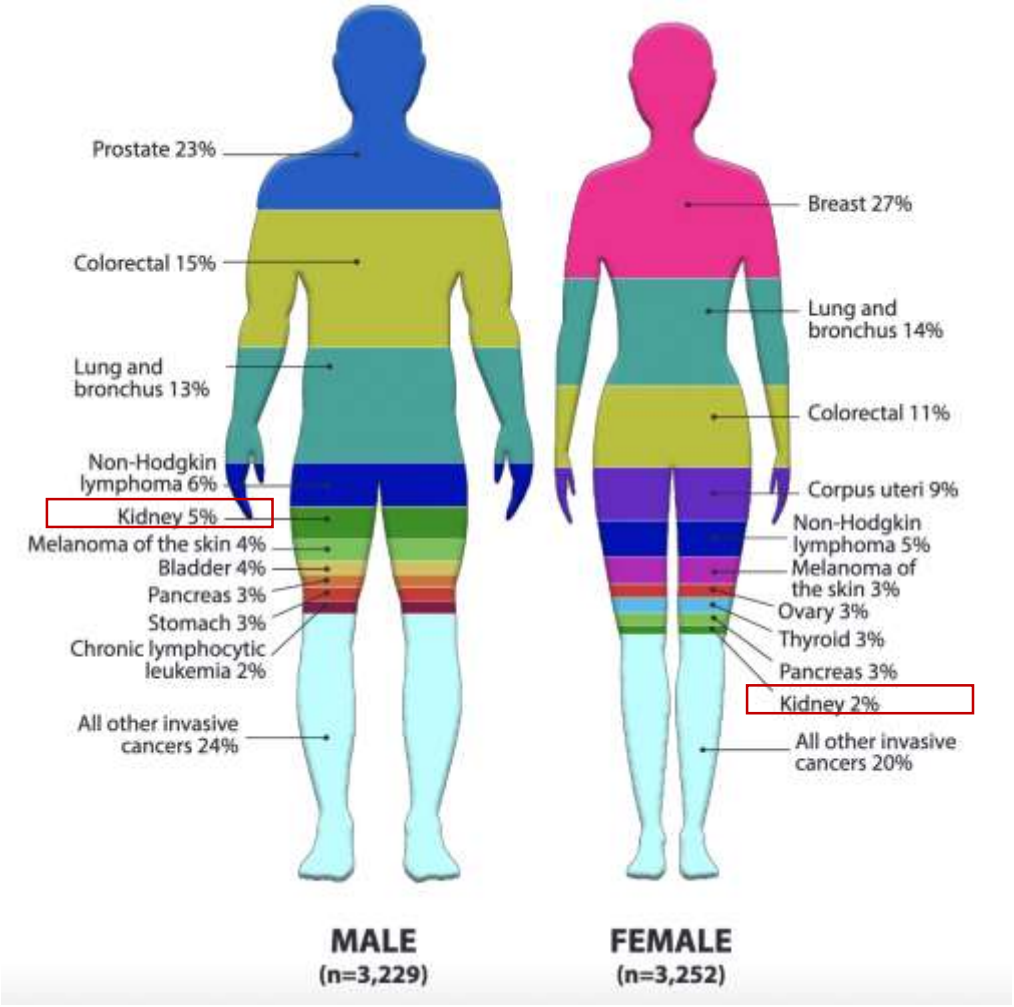
Males			Females		
Prostate	174,650	20%	Breast	268,600	30%
Lung & bronchus	116,440	13%	Lung & bronchus	111,710	13%
Colon & rectum	78,500	9%	Colon & rectum	67,100	8%
Urinary bladder	61,700	7%	Uterine corpus	61,880	7%
Melanoma of the skin	57,220	7%	Melanoma of the skin	39,260	4%
Kidney & renal pelvis	44,120	5%	Thyroid	37,810	4%
Non-Hodgkin lymphoma	41,090	5%	Non-Hodgkin lymphoma	33,110	4%
Oral cavity & pharynx	38,140	4%	Kidney & renal pelvis	29,700	3%
Leukemia	35,920	4%	Pancreas	26,830	3%
Pancreas	29,940	3%	Leukemia	25,860	3%
All Sites	**870,970**	**100%**	**All Sites**	**891,480**	**100%**



Siegel, et al. CA Cancer J Clin. 2019

Siegel, et al. CA Cancer J Clin. 2019

Distribution of cancer cases by primary site in Manitoba (2016)



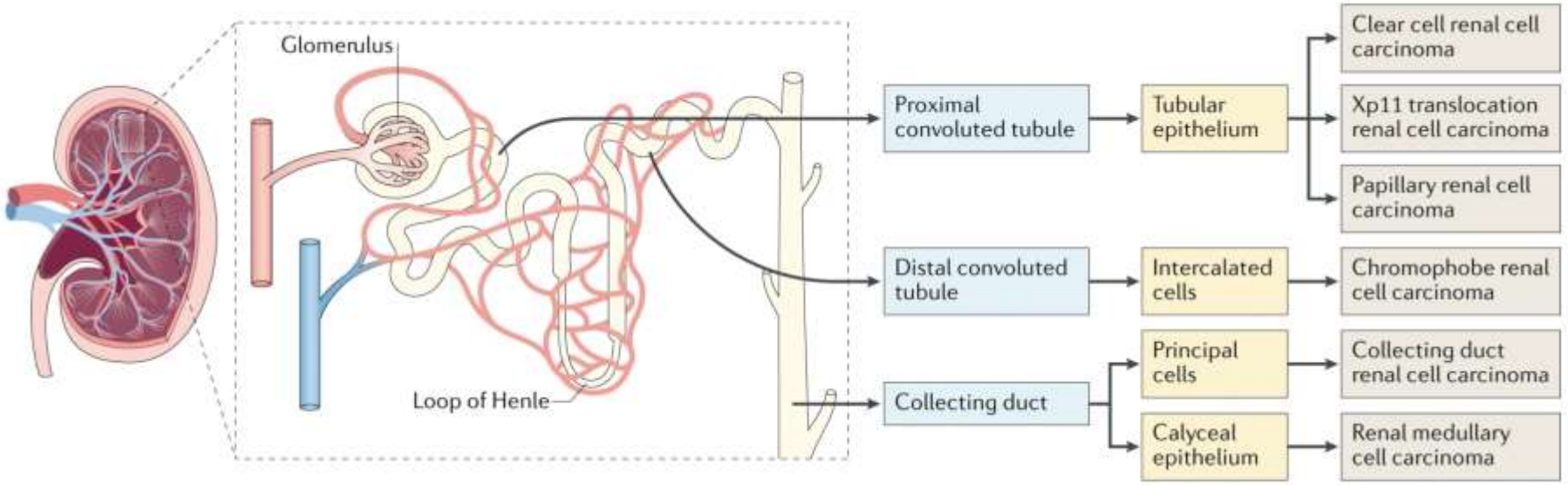
Kidney Cancer – Pathology

The most common type of primary tumor arising from the kidney is **renal cell carcinoma (RCC)**

Other less common kidney tumors – upper track urothelial carcinomas, lymphomas, sarcomas

RCC can be further divided into pathologic subtypes with clinical importance

RCC Subtypes – clear cell vs. non-clear cell



- **Clear cell RCC (ccRCC)** is the most common subtype of RCC (75% of cases) and collectively other subtypes are called **non-clear cell RCC**

Dizman Nature Reviews 2020

RCC - Risk Factors

Smoking	Male sex	Hypertension
Obesity	Chronic kidney disease	Genetic factors

Localized RCC

Approximately 80% of patients will present with local-regional disease

The detection of small renal masses (<4 cm) is increasing due to more widespread use of diagnostic imaging

Treatment is typically radical nephrectomy with curative intent

Nephron-sparing approaches or observation can be used for smaller masses

RCC – Staging

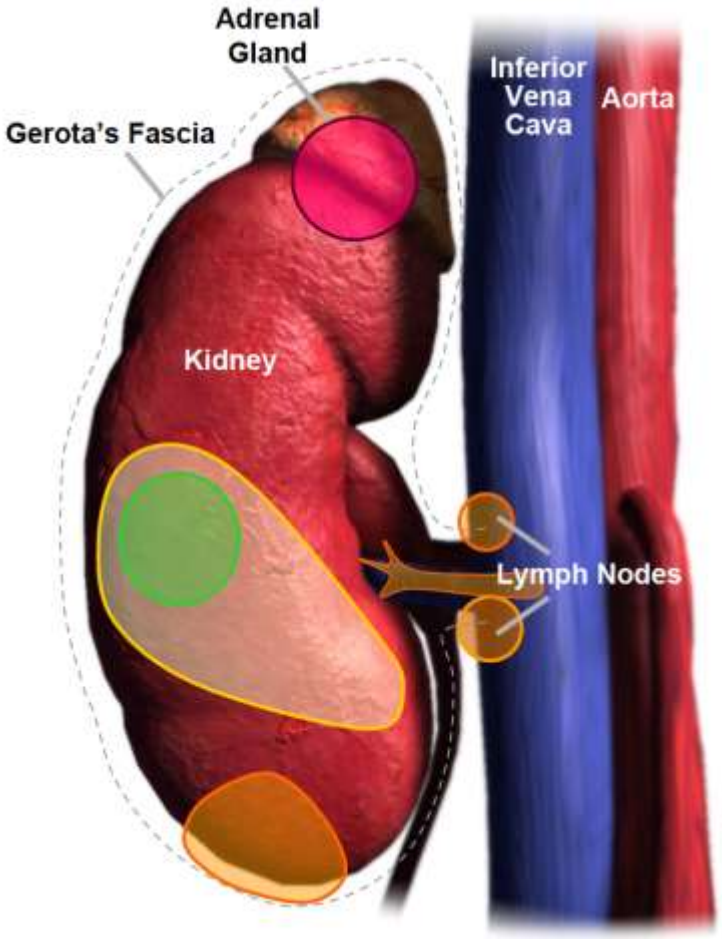
Stage I
Tumor < 7 cm in greatest dimension and limited to kidney

- **IA** < 4 cm
- **IB** > 4 to < 7 cm

Stage II
Tumor > 7 cm in greatest dimension and limited to kidney

Stage III
Tumor major veins, tumor within Gerota's fascia, or regional lymph node involved

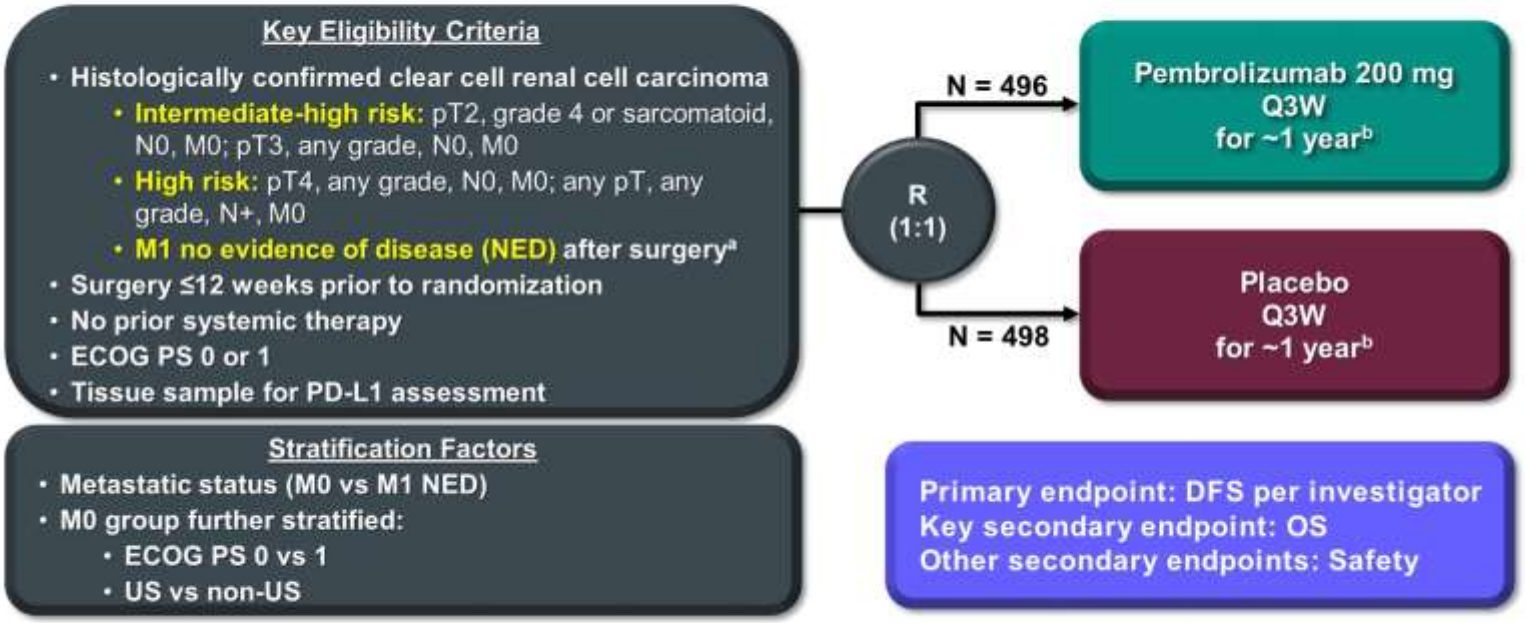
Stage IV
Tumor invasion beyond Gerota's fascia, adrenal or distant metastases



Adjuvant therapy in RCC

- Adjuvant therapy is designed to eliminate micro-metastatic disease and decrease risk of recurrence
- Multiple randomized trials have looked at adjuvant therapy post-nephrectomy
  - Sunitinib given for 1-year improved DFS
  - Not widely adopted due to toxicity and lack of OS benefit
- Focus has shifted towards adjuvant immune checkpoint inhibitors

KEYNOTE-564 (NCT03142334) Study Design

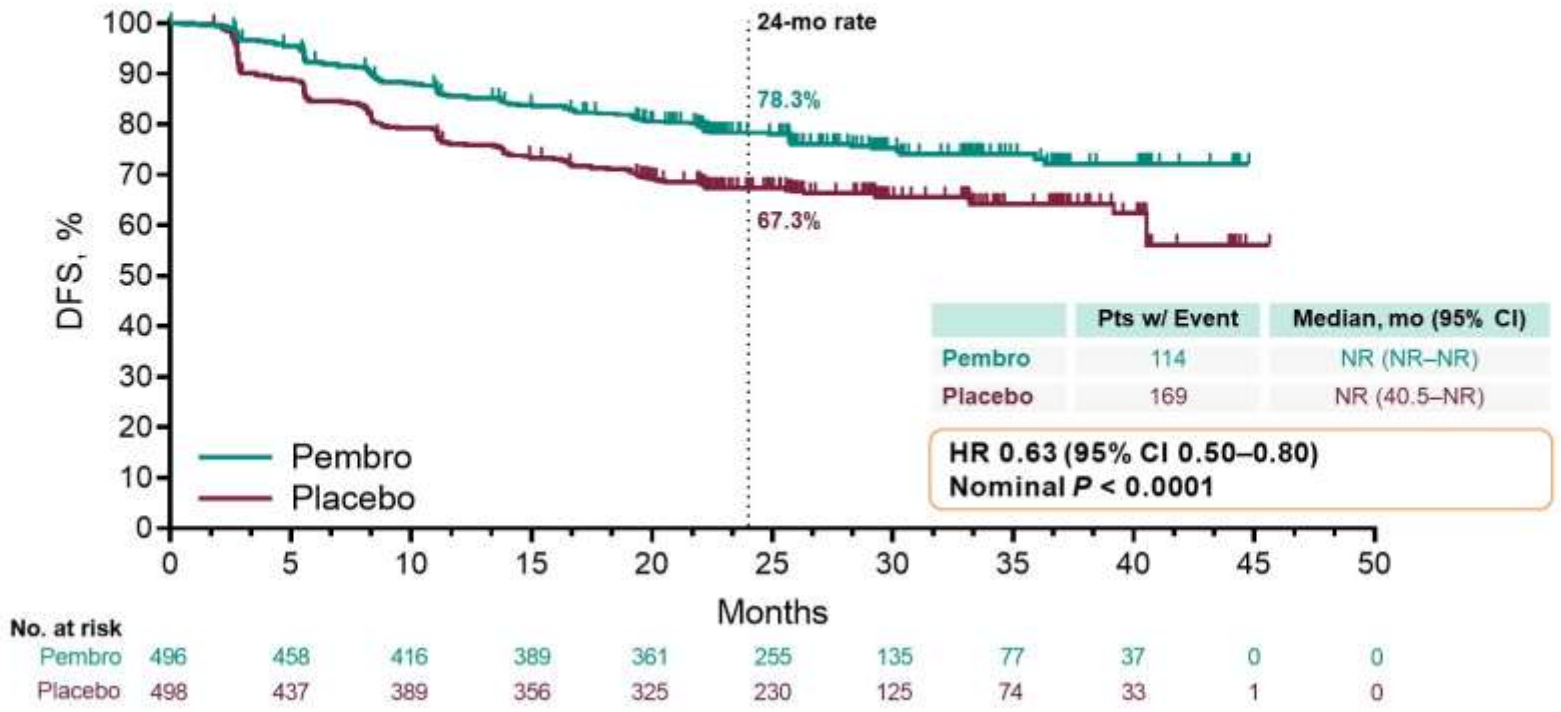


- Median (range) time from randomization to cutoff: 30.1 (20.8–47.5) months

Q3W, every 3 weeks
[a]M1 NED: no evidence of disease after primary tumor + soft tissue metastases completely resected ≤1 year from nephrectomy; [b]≤17 cycles of treatment were equivalent to ~1 year.
Data cutoff date: June 14, 2021

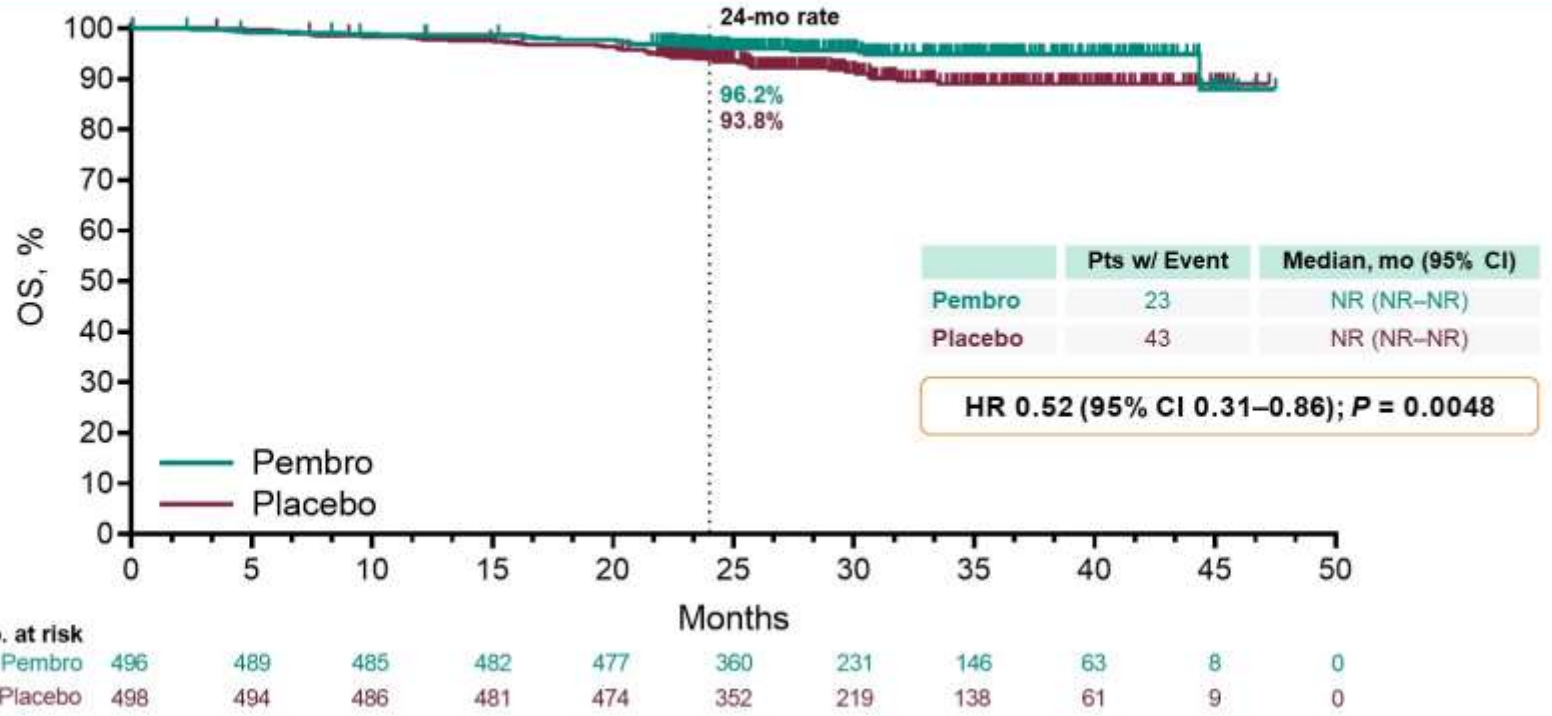
Intermediate-High Risk		High Risk		M1 NED
pT2 Grade 4 or sarcomatoid N0 M0	pT3 Any grade N0 M0	pT4 Any grade N0 M0	Any pT Any grade N+ M0	NED after resection of oligometastatic sites ≤1 year from nephrectomy
80% 5-year DFS UISS	55-80% 5-year DFS UISS	55% 5-year DFS UISS	32% 5-year DFS UISS	20% 3-year DFS E2810

Primary Endpoint: DFS, ITT Population



ITT population included all randomized participants. DFS, disease-free survival; NR, not reached. Data cutoff date: June 14, 2021.

Key Secondary Endpoint: OS, ITT Population



	Pts w/ Event	Median, mo (95% CI)
Pembro	23	NR (NR–NR)
Placebo	43	NR (NR–NR)

HR 0.52 (95% CI 0.31–0.86); *P* = 0.0048

- *P*-value did not cross the prespecified boundary for statistical significance of 0.000095 (one-sided)
- Final analysis for OS to occur after approximately 200 OS events; only 66 events had accrued for this updated analysis

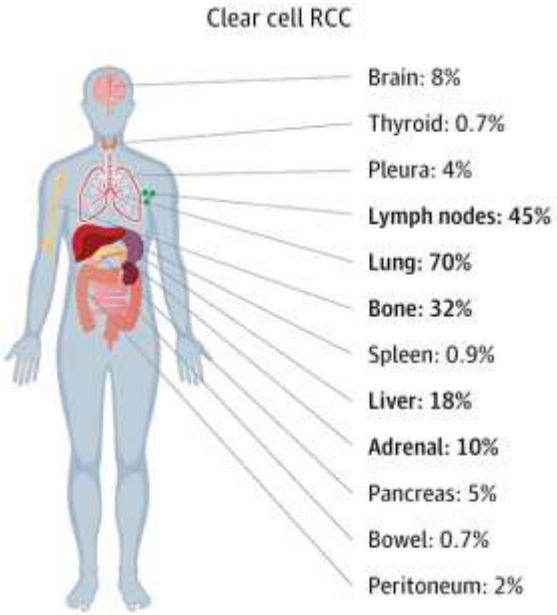
ITT population included all randomized participants. NR, not reached. Data cutoff date: June 14, 2021.

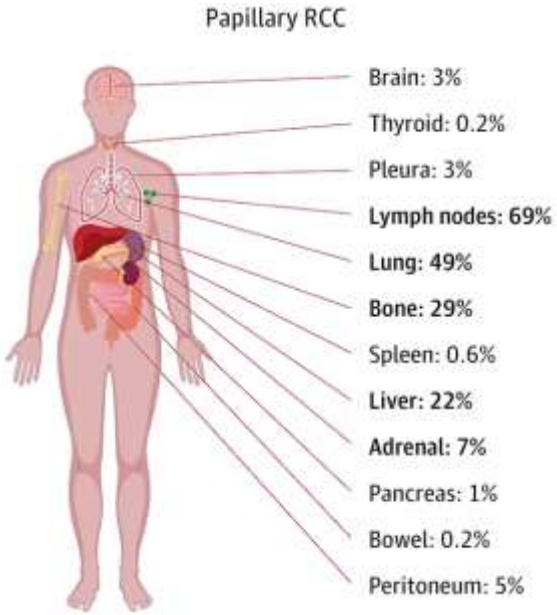
Metastatic RCC (mRCC)

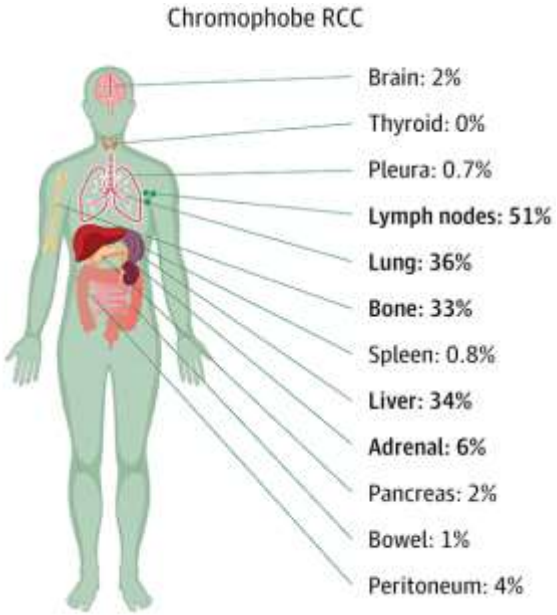
Approximately 15% of patients will present with advanced disease at the time of diagnosis (de novo) and others will develop metastatic recurrence after surgery

Given the expanding list of therapies in mRCC, developing a **personalized approach** to treatment selection is important

Sites of Metastatic Disease







Personalized Approach to mRCC

Patient Factors

- Performance status (ECOG, KPS)
- Comorbidities
- Symptoms
- Prognostic risk group
  - IMDC model

Tumor Factors

- Clear cell vs. non-clear cell
- Sarcomatoid features
- Synchronous vs. metachronous
- Sites and burden of metastatic disease
- Prognostic risk group
  - IMDC model

IMDC Prognostic Model

6 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

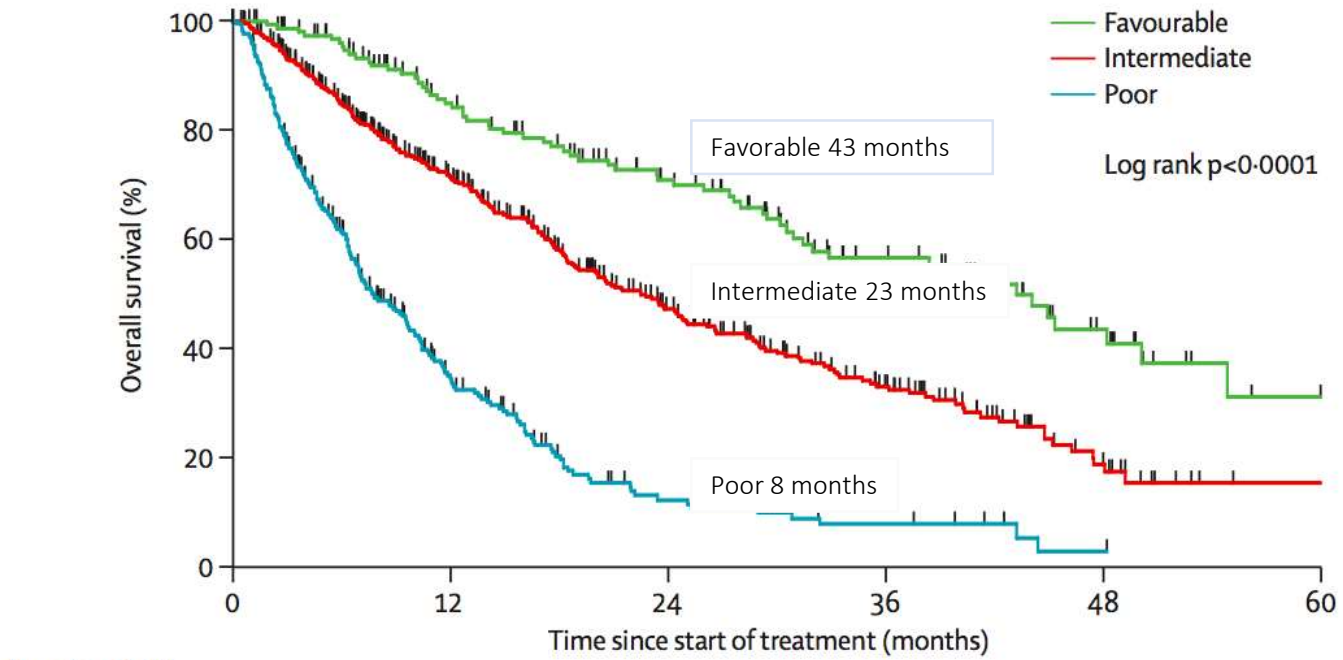
Favourable (0 factors)

Intermediate (1-2 factors)

Poor (3+ factors)

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

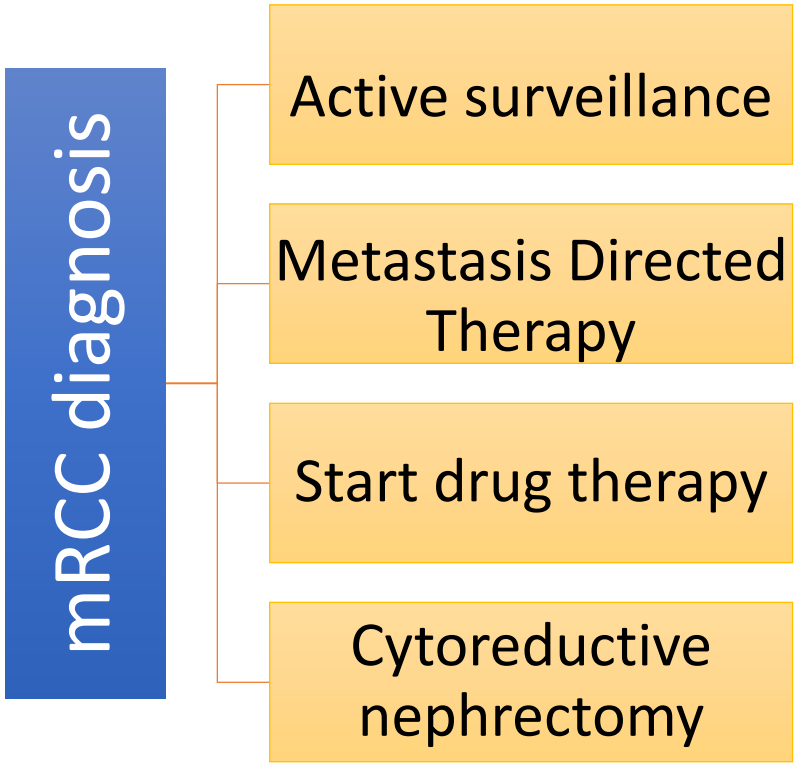
Updated OS = 52.1, 31.5, and 9.8 months in the favorable, intermediate, and poor risk groups, respectively



Number at risk						
Favourable	157	109	74	40	17	3
Intermediate	440	247	122	59	15	1
Poor	252	65	15	7	1	0

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

Personalized Approach to mRCC



Active surveillance in mRCC

- Metastatic RCC is a heterogeneous disease with variable natural history – both indolent and aggressive behavior

- Studies have shown that delaying the start of systemic therapy is safe in well selected patients

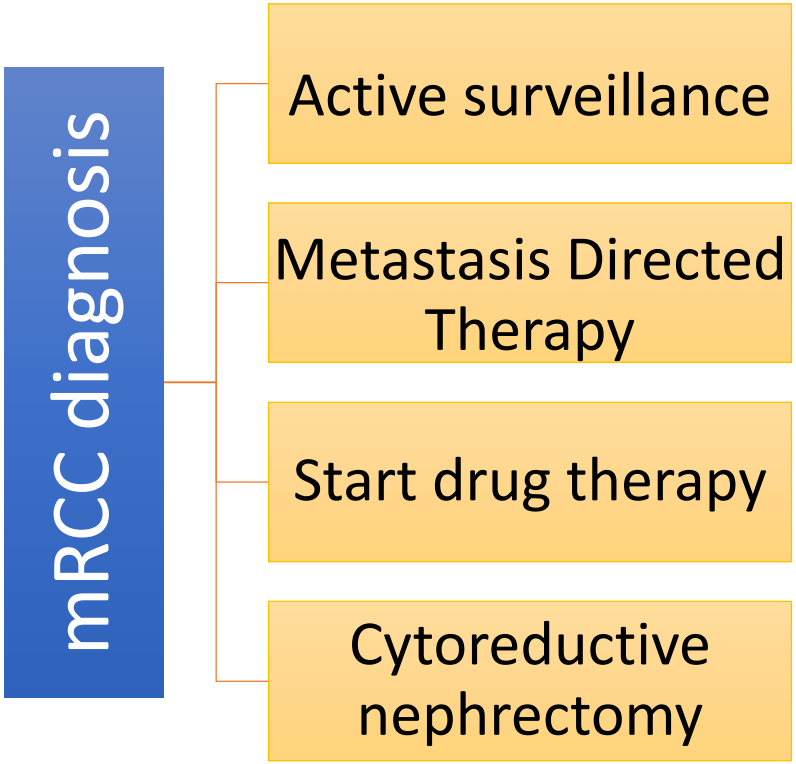
- Patients 0-1 IMDC risk factors, minimally symptomatic, with limited disease burden can be monitored with serial imaging – defer drug treatment until progression

Oligometastatic RCC

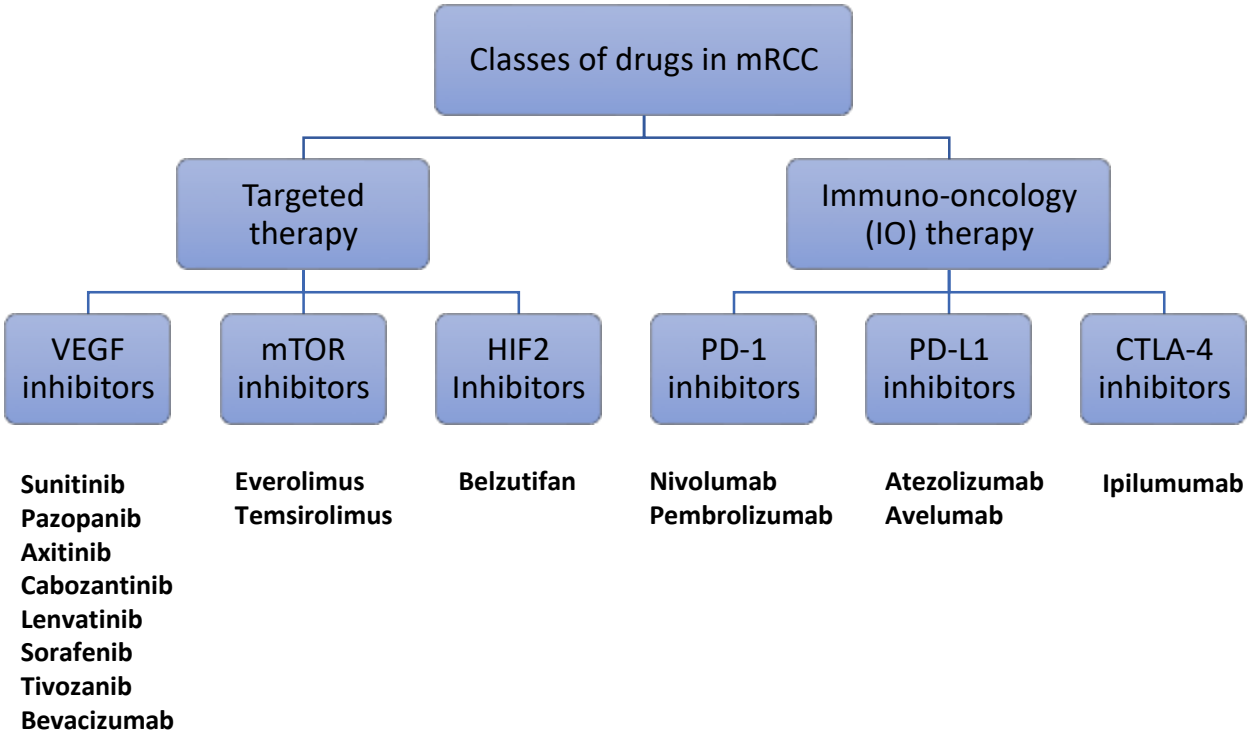
- There is evidence supporting **metastasis-directed therapy (MDT)** to isolated or limited sites of metastases (typically 1-5 lesions)
- Goal is to delay or avoid the need for systemic therapy by treating individual sites of disease
- Features associated with improved outcomes: disease-free interval > 12 months, solitary site, ECOG < 2, and certain sites of disease (pancreatic metastases)
- Less invasive techniques such as stereotactic radiation therapy
- Post-MDT - patients can be followed with active surveillance

Kavolius et al JCO 1998

Personalized Approach to mRCC



Current Systemic Therapy Landscape in mRCC



First-line therapy in mRCC

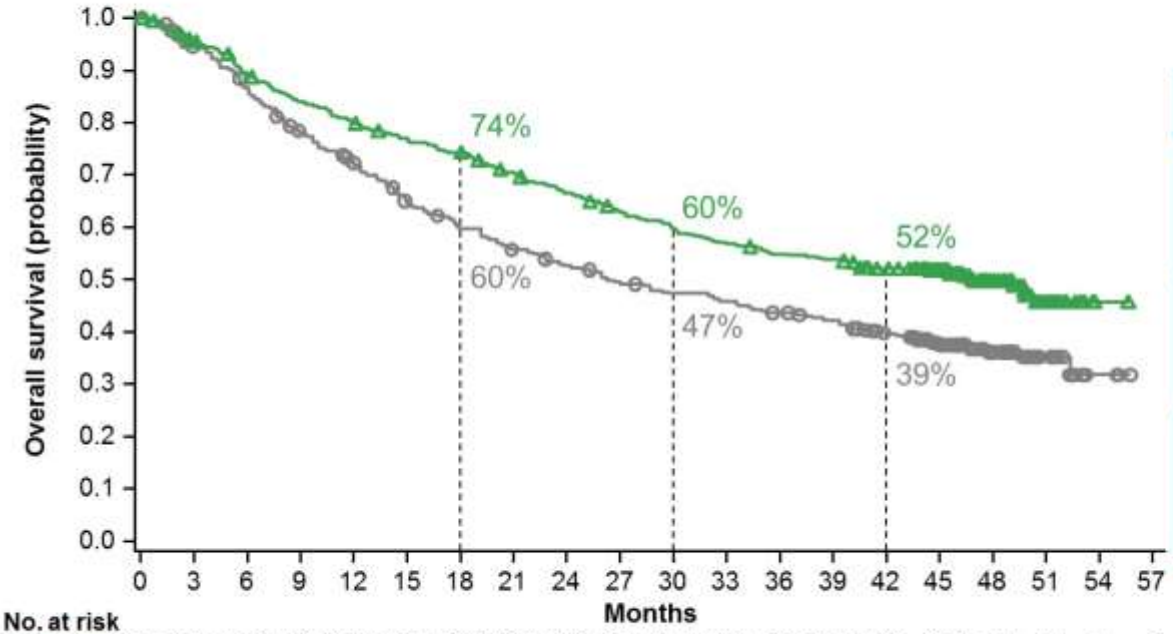
- **Previous standard of care** (pre-2018) - single agent VEGF targeted therapy: Sunitinib or Pazopanib
- **Current standard of care** - immune checkpoint inhibitor combination therapy:
  - Anti-PD-1 + Anti-CTLA-4
  - Anti-PD-1 + VEGF targeted therapy
- **Options in Manitoba:**
  - Nivolumab + Ipilumumab (CheckMate 214)
  - Pembrolizumab + Axitinib (KEYNOTE 426)
  - Pembrolizumab + Lenvatinib (CLEAR)

CheckMate 214 – Nivolumab + Ipilumumab vs. Sunitnib

CheckMate 214

Overall Survival

Primary efficacy population: Intermediate/poor-risk patients



Minimum follow-up	OS	NIVO+IPI N = 425	SUN N = 422
17.5 mo[1]	Median, mo (95% CI)	NR (28.2–NE)	26.0 (22.1–NE)
	HR (99.8% CI)	0.63 (0.44–0.89) $P < 0.001$	
30 mo[2]	Median, mo (95% CI)	NR (35.6–NE)	26.6 (22.1–33.4)
	HR (95% CI)	0.66 (0.54–0.80) $P < 0.0001$	
42 mo	Median, mo (95% CI)	47.0[a] (35.6–NE)	26.6 (22.1–33.5)
	HR (95% CI)	0.66 (0.55–0.80) $P < 0.0001$	

[a]With a minimum follow-up of 42 months, the median OS of 47.0 months in the NIVO+IPI arm could be unstable due to censoring.
NE, not estimable.

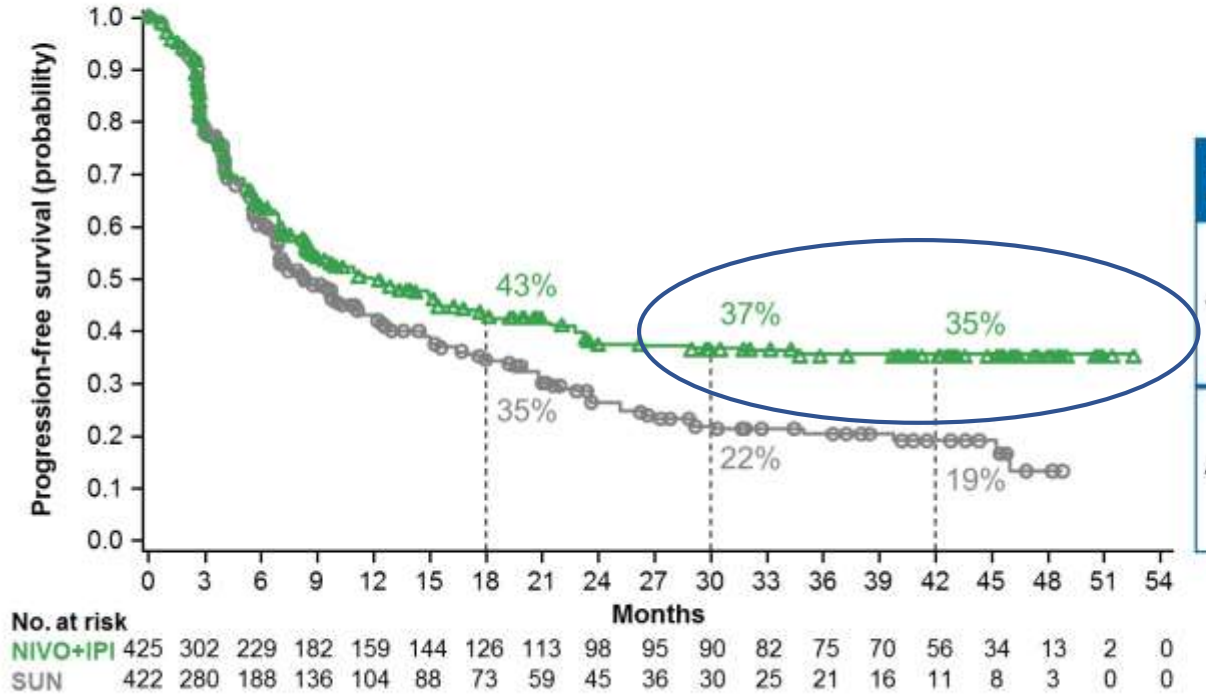
1. Motzer RJ, et al. *N Engl J Med* 2018;378:1277–1290. 2. Motzer RJ, et al. *Lancet Oncol* 2019;20:1370–1385.

CheckMate 214 – Nivolumab + Ipilumumab vs. Sunitnib

CheckMate 214

PFS per IRRC

Primary efficacy population: Intermediate/poor-risk patients



Minimum follow-up	PFS	NIVO+IPI N = 425	SUN N = 422
17.5 mo[1]	Median, mo (95% CI)	11.6 (8.7–15.5)	8.4 (7.0–10.8)
	HR (99.1% CI)	0.82 (0.64–1.05) $P = 0.03$	
42 mo	Median, mo (95% CI)	12.0 (8.7–15.5)	8.3 (7.0–11.1)
	HR (95% CI)	0.76 (0.63–0.91) $P < 0.01$	

1. Motzer RJ, et al. *N Engl J Med* 2018;378:1277–1290.

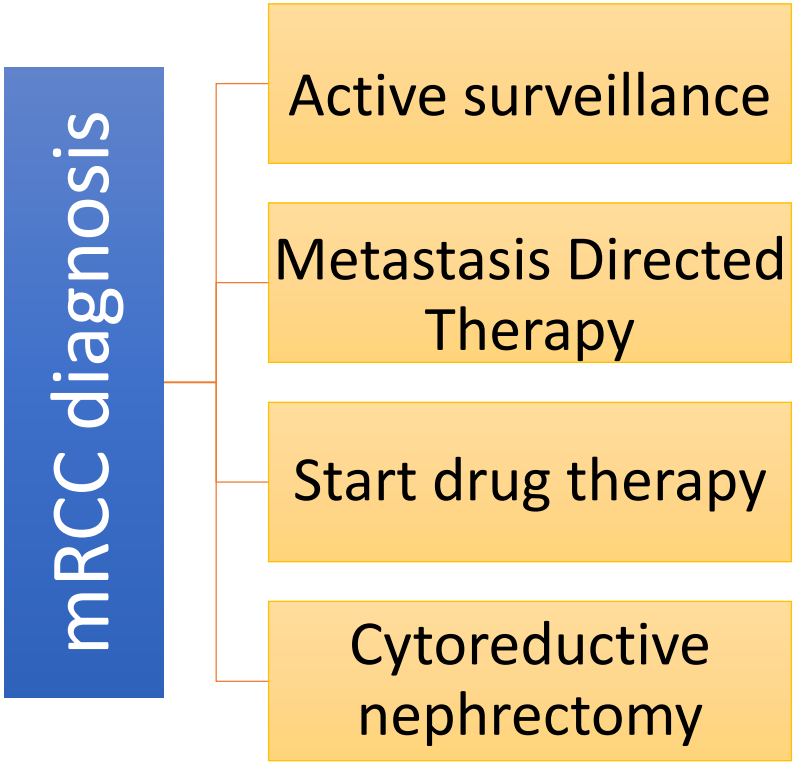
PD-1 + CTLA-4 combination

- Example - Nivolumab + Ipilumumab
- Improved PFS and OS vs. sunitnib
- Only approved for IMDC intermediate and poor risk
- Long term durable responses (30% PFS at 5 years)
- Lower response rate (42%), higher primary progression rate (20%)
- More immune mediated toxicity

PD-1 + VEGF TKI combination

- Example – Pembrolizumab + Axitinib
- Improved PFS and OS vs. sunitnib
- Approved for all IMDC risk groups
- Shorter follow-up - unclear if same degree of durable responses
- Higher ORR (60%), lower primary progression rate (11%)
- Overlapping ICI and TKI toxicity

Personalized Approach to mRCC



Cytoreductive Nephrectomy (CN)

- Does removal of the primary kidney tumor in the setting of metastatic disease improve outcomes?
- A large randomized trial showed that starting drug therapy first was non-inferior to upfront CN followed by drug treatment (CARMENA trial)
- There is a focus now on **deferred nephrectomy** – starting drug treatment and assessing the role for nephrectomy based on response

Take Home Messages

- Renal cell carcinoma is a relatively common malignancy and is associated with several modifiable risk factors
- The primary treatment of localized RCC is surgery, and there is emerging evidence that adjuvant immunotherapy can reduce the risk of recurrence
- A personalized approach to metastatic RCC is important
- The advent of immune based therapies has revolutionized the management of metastatic RCC, with a proportion of patients experiencing long-term, durable responses

Questions?

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