Practical Approaches to Managing Advanced Kidney Cancer

Version 2020

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Canadian Urological Association
The Voice of Urology in Canada

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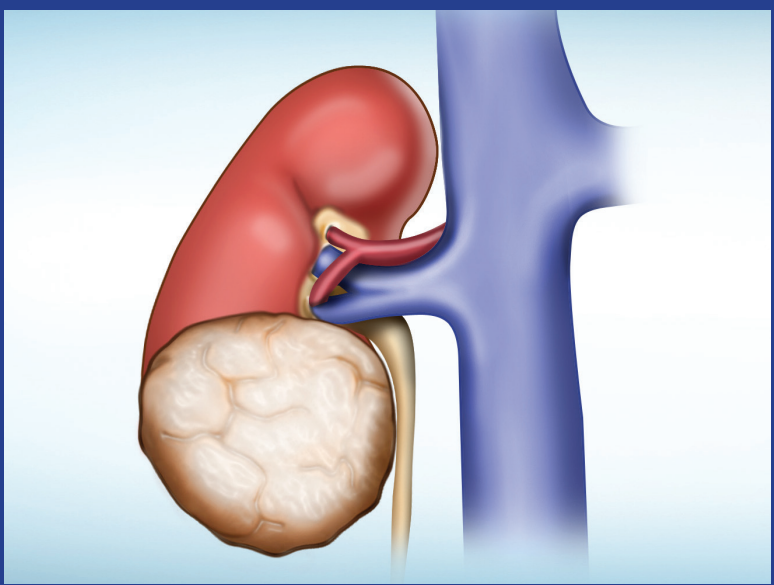
Introduction

In October 2019, the Kidney Cancer Research Network of Canada (KCRNC) published an updated consensus report on the management of advanced kidney cancer (Hotte SJ, et al. Can Urol Assoc J. 2019;13(10):343-54.) Advanced kidney cancer has seen an expansion in the treatment armamentarium from largely targeted systemic therapies to now include immunotherapy options. This shift in therapeutic strategy has implications for patient care in routine clinical practice, in terms of patient baseline assessment, evaluating disease response, as well as toxicity monitoring and management.

This handbook, *Practical Approaches to Managing Advanced Kidney Cancer*, aligns with the published consensus statements. Please note that unanimous consensus was not reached for all treatment options; the published recommendations reflect the majority position. With this in mind, this booklet aims to provide a concise overview of the practical aspects of patient management throughout the treatment continuum. The information presented in this handbook is not definitive guidance but rather is meant to support discussions with the patient and multidisciplinary team regarding both short- and long-term treatment planning and patient management.

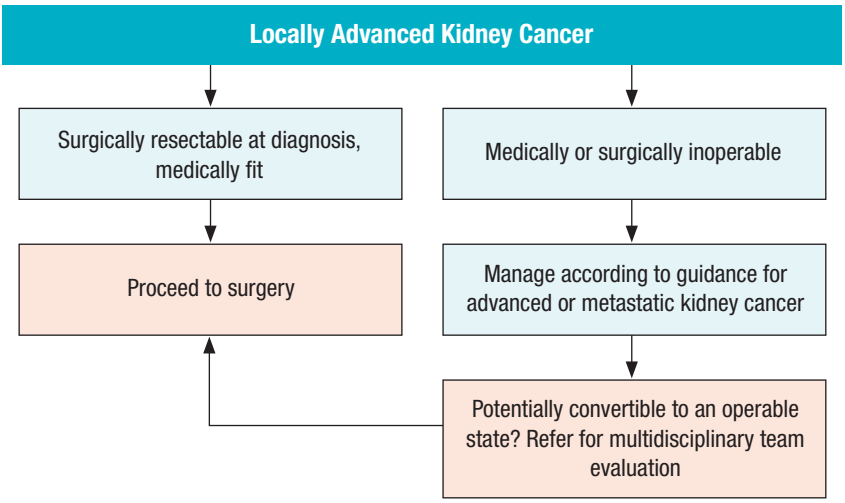
The Health Canada approval status of agents mentioned in this handbook reflects the products' indicated uses at the time of publishing. Please consult individual Product Monographs (through the Health Canada Drug Product Database) for the most current indicated uses. The Canadian Urological Association aims to update the content as the treatment landscape changes and new agents become available. We welcome your feedback to ensure this handbook serves as a helpful resource in your practice.

Locally Advanced Kidney Cancer



Management of Locally Advanced Kidney Cancer

Locally Advanced Kidney Cancer Management Algorithm



Management of Patients with Locally Advanced Kidney Cancer who are Surgical Candidates

- **Consensus Statement: There is no indication for neoadjuvant therapy prior to planned surgical resection outside the context of a clinical trial.**
  - Patients should proceed directly to surgery
  - There is currently insufficient evidence to support a general recommendation for neoadjuvant therapy
- **Consensus Statement: The use of adjuvant therapy following nephrectomy in non-metastatic renal cell carcinoma patients is not currently recommended outside the context of a clinical trial.**
  - To date, no clinical trial has demonstrated an overall survival (OS) advantage with adjuvant targeted therapy in patients with RCC after curative resection of the primary tumor
  - Patients with high-risk tumors who are candidates for complete resection should be encouraged to participate in clinical trials
  - Although not currently offered, adjuvant therapy is an exciting field for clinical trials

Completed Trials of Adjuvant Targeted Therapy					
Trial	N	Patient characteristics	Treatment arms	Treatment duration	Primary endpoint
S-TRAC[1]: Sunitinib trial in adjuvant renal cancer treatment	615	High-risk patients	Sunitinib Placebo	1 year	Disease-free survival (positive results)
ASSURE[2]: Adjuvant sorafenib or sunitinib for unfavourable RCC	1,943	Non-metastatic RCC; disease stage II-IV; high-risk	Sunitinib Sorafenib Placebo	1 year (9 treatment cycles)	Disease-free survival (negative results)
SORCE[3]: Sorafenib in patients with resected primary RCC at high/ intermediate risk of relapse	1,711	Patients with high- and intermediate-risk resected RCC	Sorafenib Sorafenib/Placebo Placebo	3 years	Disease-free survival (negative results)
EVEREST[4]: Everolimus for renal cancer ensuing surgical therapy	1,545	Pathological stage intermediate or very high-risk patients with full or partial nephrectomy	Everolimus Placebo	9 treatment cycles	Recurrence-free survival (results pending)
PROTECT[5]: Pazopanib as an adjuvant treatment for localized RCC	1,538	Patients with moderately high or high risk of relapse with nephrectomy of localized or locally advanced RCC	Pazopanib Placebo	1 year	Disease-free survival (negative results)
ATLAS[6]: Adjuvant axitinib therapy of renal cell cancer in high risk patients	724	High-risk, non-metastatic RCC with nephrectomy	Axitinib Placebo	3 years	Disease-free survival (negative results)

[1]Ravaud A, et al. N Engl J Med. 2016;375:2246-54.

[2]Haas NB, et al. Lancet. 2016;387:2008-2016.

[3]Eisen TQG, et al. Presented at: ESMO Congress 2019; September 27-October 3, 2019: Barcelona, Spain. Abstract LBA56.

[4]Clinicaltrials.gov. NCT01120249. Accessed: June 4, 2020.

[5]Motzer RJ, et al. J Clin Oncol. 2017;35:3916-3923.

[6]Gross-Goupil M, et al. Ann Oncol. 2018;29 :2371-2378.

Pending Trials of Adjuvant Targeted Therapy (Reference: ClinicalTrials.gov)					
Trial	Planned accrual	Eligibility	Treatment arms	Primary endpoint	Anticipated completion
IMmotion 010 (NCT03024996)	778	T2 (G4) N0 M0 T3a (G3-4) N0 M0 T3b-4 (G any) N0 M0 Tx (G any) N+ M0 M1 no evidence of disease	Atezolizumab Placebo	Disease-free survival	2022
KEYNOTE-564 NCT03142334)	950	T2 (G4) N0 M0 T3 (Gx) N0 M0 T4 (G any) N0 M0 Tx (G any) N+ M0 M1 no evidence of disease	Pembrolizumab Placebo	Disease-free survival	2022
PROSPER RCC (NCT03055013)	805	T2-4 Nx M0 Tx N1-2 M0	Nivolumab Standard of care	Recurrence-free survival	2023
CheckMate 914 (NCT03138512)	1600	T2a (G3-4) N0 M0 T2b-4 (G any) N0 Tx (G any) N1 M0	Nivolumab+ ipilimumab Placebo	Disease-free survival	2022

Management of Patients with Locally Advanced Kidney Cancer who are Medically or Surgically Inoperable

- There is currently insufficient evidence to support a general recommendation for neoadjuvant therapy
  - Some patients with advanced localized disease deemed medically or surgically inoperable at diagnosis may have a radiological and/or clinical response to systemic therapy
    - Many small studies have demonstrated a potential benefit of systemic neoadjuvant approaches (mostly with VEGF inhibitors)
- Patients who do not have the potential to be converted to an operable state should be managed according to the guidance for advanced or metastatic kidney cancer
- If there is a question that a patient may be converted to an operable state with systemic therapy, they should be re-evaluated by a multidisciplinary team
- For patients (particularly those with hematuria) who are symptomatic, other options such as angioembolization may be considered

Advanced/ Metastatic Kidney Cancer

Management of Advanced or Metastatic Kidney Cancer

Patient Identification and Multidisciplinary Evaluation

- Patients are best served by an oncologist specialist as the prescribing physician, who is knowledgeable about the disease, the drug and drug interactions, toxicities and monitoring
- A multidisciplinary team, including nursing care, dietary care and pharmacy support, should be involved in patient management
- Frequent patient evaluation is necessary to ensure toxicities are recognized and managed appropriately
- Information on prevention and management of potential side effects should be provided to patients/caregivers

Risk-Stratification

- Critical first step in therapeutic decision-making in patients who require systemic therapy for advanced or metastatic renal cell carcinoma (mRCC) is risk stratification
- Risk-stratification score based on information from the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) published by Heng and colleagues
  - Set of six IMDC criteria
  - Recommended tool for patient counselling and treatment selection
- IMDC classification is a prognostic classification tool (provides an estimate of survival) as well as a tool to determine eligibility for ipilimumab-nivolumab and other combinations

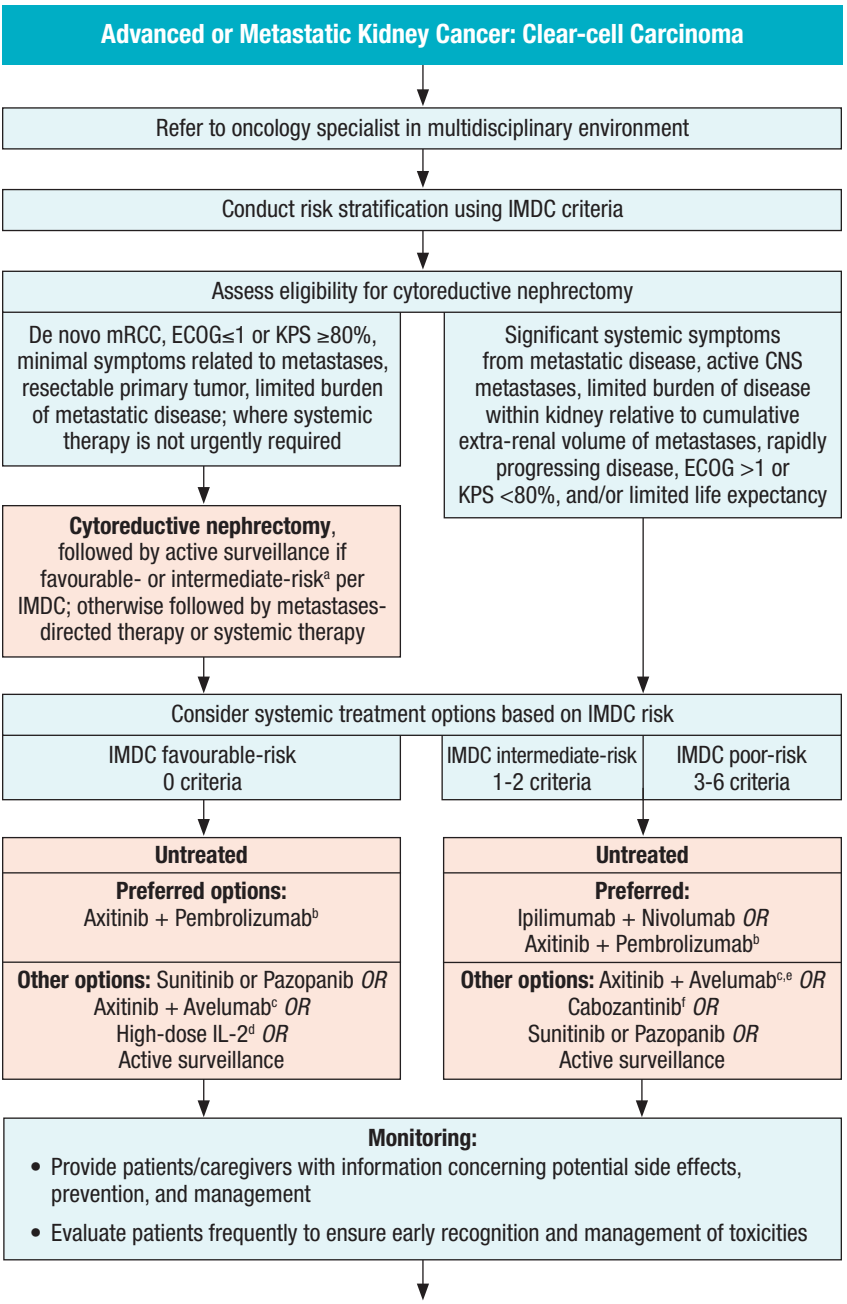
IMDC (International Metastatic Renal Cell Carcinoma Database Consortium) Criteria for Prognosis in mRCC (Heng 2009/2013)

Criterion	No (0) / Yes (+1)
<1 year from time of diagnosis to systemic therapy	0 / 1
Karnofsky Performance Status <80%	0 / 1
Hemoglobin < lower limit of normal	0 / 1
Corrected calcium > upper limit of normal	0 / 1
Neutrophils > upper limit of normal	0 / 1
Platelets > upper limit of normal	0 / 1
Number of criteria	

Number of criteria	Risk Group	Median overall survival
0	Favourable	43.2 months (95%CI: 31.4-50.1)
1-2	Intermediate	22.5 months (95%CI: 18.7-25.1)
3-6	Poor	7.8 months (95%CI: 6.5-9.7)

An online calculator can be found at IMDConline.com

Advanced/Metastatic Kidney Cancer Management Algorithm: Clear-cell Carcinoma



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Second-line and Beyond[g]		
Prior Immune Checkpoint Inhibitor	**Prior VEGF Inhibitor**	**Prior Immune Checkpoint Inhibitor and VEGF Inhibitor**
Preferred options: Cabozantinib[h] *OR* Axitinib[h]	**Preferred options:** Nivolumab *OR* Cabozantinib	**Preferred option:** Cabozantinib
Other options: Sunitinib *OR* Pazopanib[i] *OR* Lenvatinib + Everolimus[h]	**Other options:** Lenvatinib + Everolimus *OR* Everolimus *OR* Axitinib	**Other options:** Sunitinib *OR* Pazopanib *OR* Axitinib[e] *OR* Lenvatinib + Everolimus *OR* Everolimus

a. Some intermediate-risk patients are candidates for cytoreductive nephrectomy (per KCRNC)

b. Combination approved in Canada in December 2019

c. Awaiting mature overall survival data

d. No randomized control trial

e. Not approved in Canada (as of Mar. 2020)

f. Supported by phase II data only; approved for use but not funded in first line

g. If not used prior

h. In second or later lines, approved in Canada after one prior VEGF inhibitor therapy

i. Monitor closely for first 12 weeks for liver toxicity

Management of Advanced/Metastatic Kidney Cancer

Untreated/First-line Options: Clear-cell Carcinoma

- **Consensus Statement: Choice of initial systemic treatment is based in part on International Metastatic RCC Database Consortium (IMDC) risk status.**

IMDC Favourable-risk Patients

- **Consensus Statement: For IMDC favourable-risk patients, pembrolizumab + axitinib is the recommended treatment. Avelumab/axitinib and targeted therapy with sunitinib or pazopanib can be considered as alternative active treatment options.**
- **Consensus Statement: Active surveillance can also be considered in selected patients with favourable-risk, as some patients have slow-growing, low-volume, and/or asymptomatic disease.**
- Preferred therapy: Pembrolizumab + axitinib
  - Pembrolizumab in combination with axitinib was approved in Canada for use in advanced RCC; indication granted in December 2019 after the consensus guidelines were published
  - Axitinib, as single-agent therapy, is approved in Canada only after failure of a cytokine or sunitinib
  - Key evidence: KEYNOTE-426 study of pembrolizumab + axitinib vs. sunitinib
  - Candidates should undergo comprehensive baseline assessment
  - In rural areas with limited access to medical resources, physicians are encouraged to contact experienced centres for advice
  - Caution in:
    - Patients with pre-existing autoimmune diseases, particularly active disease under treatment
    - Patients with pre-existing comorbidities which make potential treatment with steroids challenging, eg, borderline-controlled diabetes
- Other options: Axitinib + avelumab
  - Axitinib, as single-agent therapy, is approved in Canada only after failure of a cytokine or sunitinib
  - Avelumab is not approved in Canada (as of March 2020) for use in RCC
  - Key evidence: JAVELIN Renal 101 study of avelumab + axitinib vs. sunitinib
    - Combination has yet to report an OS benefit
  - Candidates should undergo comprehensive baseline assessment

- In rural areas with limited access to medical resources, physicians are encouraged to contact experienced centres for advice
- Caution in:
  - Patients with pre-existing autoimmune diseases, particularly active disease under treatment
  - Patients with pre-existing comorbidities which make potential treatment with steroids challenging, eg, borderline-controlled diabetes

- Other options: Sunitinib
  - Key evidence: Motzer 2007/2009 study of oral sunitinib vs. interferon-alfa
    - Survival benefits observed in British Columbia and Alberta population-based studies since the introduction of sunitinib and sorafenib
  - Consider for patients who are ineligible for immunotherapy or patients who prefer TKI monotherapy
  - It is recommended to start with the monograph standard dosing schedule (4 weeks on/2 weeks off), then individualize schedule and/or dose to derive optimal benefit based on type and timing of toxicities
- Other options: Pazopanib
  - Key evidence: COMPARZ clinical trial of pazopanib vs. sunitinib (non-inferior)
    - Data from the Canadian Kidney Cancer information systems indicated longer OS with sunitinib vs pazopanib although other retrospective databases showed similar outcomes with either drug
  - Consider for patients who are ineligible for immunotherapy or patients who prefer TKI monotherapy
  - Pazopanib is associated with a higher incidence of hepatic transaminase elevations, while sunitinib treatment is associated with higher incidences of fatigue, hand-foot syndrome, and thrombocytopenia
- Other options: Initial observation
  - An initial period of observation is a reasonable option (to avoid the side effects of active treatment) in select patients likely to experience an indolent clinical course – those with stable or slow-growing, low-volume, and/or asymptomatic metastases
  - Key evidence: Prospective observational data (Rini, 2016)
  - Do not consider initial observation in patients with non-pulmonary visceral metastases, eg, bone, liver, brain

IMDC Intermediate- or Poor-risk Patients

- **Consensus Statement: For IMDC intermediate- or poor-risk patients, either ipilimumab + nivolumab or pembrolizumab + axitinib is the preferred first-line therapy; avelumab/axitinib and targeted therapy (sunitinib or pazopanib) remain alternative options, the latter especially for patients who have a contraindication to immunotherapy or who are felt to be unable to tolerate combination therapy.**
- **Consensus Statement: Active surveillance can also be considered in selected patients with intermediate-risk, as some patients have slow-growing, low-volume, and/or asymptomatic disease.**
- Preferred therapy: Ipilimumab + nivolumab
  - Key evidence: CheckMate 214 study of nivolumab + ipilimumab followed by nivolumab monotherapy vs. sunitinib (intermediate-poor risk patient cohort)
  - Candidates should undergo comprehensive baseline assessment
  - In rural areas with limited access to medical resources, physicians are encouraged to contact experienced centres for advice
  - Caution in:
    - Patients with pre-existing autoimmune diseases, particularly active disease under treatment
    - Patients with pre-existing comorbidities which make potential treatment with steroids challenging, eg, borderline-controlled diabetes
- Preferred therapy: Pembrolizumab + axitinib
  - Pembrolizumab in combination with axitinib was approved in Canada for use in advanced RCC; indication granted in December 2019 after the consensus guidelines were published
  - Axitinib is approved in Canada only as monotherapy after failure of a cytokine or sunitinib
  - Key evidence: KEYNOTE-426 study of pembrolizumab + axitinib vs. sunitinib
  - Candidates should undergo comprehensive baseline assessment
  - In rural areas with limited access to medical resources, physicians are encouraged to contact experienced centres for advice
  - Caution in:
    - Patients with pre-existing autoimmune diseases, particularly active disease under treatment
    - Patients with pre-existing comorbidities which make potential treatment with steroids challenging, eg, borderline-controlled diabetes

- Other option: Sunitinib or pazopanib
  - Non-preferred options in the first-line setting
  - Key evidence: Motzer 2007/2009 study and COMPARZ trial, respectively
  - Consider use preferentially in the following patients:
    - Patients with contraindications for immunotherapy
    - Patients with poor clinical condition due to extensive RCC
    - Patients who need a more rapid response to therapy
    - Patients who prefer TKI monotherapy
  - In sunitinib-intolerant, poor-risk patients, pazopanib remains an option
- Other option: Axitinib + avelumab
  - Axitinib, as single-agent therapy, is approved in Canada only after failure of a cytokine or sunitinib
  - Avelumab is not approved in Canada (as of March 2020) for use in RCC
  - Key evidence: JAVELIN Renal 101 study of avelumab + axitinib vs. sunitinib
    - Combination has yet to report an OS benefit
  - Candidates should undergo comprehensive baseline assessment
  - In rural areas with limited access to medical resources, physicians are encouraged to contact experienced centres for advice
  - Caution in:
    - Patients with pre-existing autoimmune diseases, particularly active disease under treatment
    - Patients with pre-existing comorbidities which make potential treatment with steroids challenging, eg, borderline-controlled diabetes
- Other option: Cabozantinib
  - Cabozantinib is approved for use in Canada in treat-naïve adults with intermediate or poor risk advanced RCC
  - Key evidence: CABOSUN phase 2 trial of cabozantinib vs. sunitinib
  - Consider for patients who are ineligible for immunotherapy or patients who prefer TKI monotherapy
- Other option: Initial observation
  - Selected patients with intermediate-risk with one IMDC risk factor may be candidates for active surveillance, as some patients have slow-growing, low-volume, and/or asymptomatic disease
  - Key evidence: Prospective observational data (Rini, 2016)
  - Do not consider initial observation in patients with non-pulmonary visceral metastases, eg, bone, liver, brain

Second-line (and Later) Options: Clear-cell Carcinoma

Following a First-line Immune Checkpoint Inhibitor-based Regimen

- **Consensus Statement: For patients who progress on, or who are intolerant of first-line immune checkpoint inhibitors, there is no prospective, randomized, phase 3 evidence available to select a preferred treatment option; options for patients in this situation include sunitinib, pazopanib, axitinib, cabozantinib, or lenvatinib/everolimus.**
- Axitinib and cabozantinib are listed as preferred options based on the AXIS and METEOR studies, which included patients who were previously treated with immunotherapy
- Preferred option: Axitinib
  - Axitinib, as a single agent, is approved in Canada only after failure of a cytokine or sunitinib
  - Key evidence: AXIS trial of axitinib vs. sorafenib as second-line therapy
  - The only prospective study in this setting has demonstrated the activity of axitinib after immunotherapy, therefore, axitinib is a preferred option post-immunotherapy progression
  - Axitinib was given on an individualized schedule, with significant inter-individual variation in the optimal dose and schedule (as shown with sunitinib)
- Preferred option: Cabozantinib
  - In second or later lines, cabozantinib is approved for use in Canada only in patients who have progressed on VEGF-targeted therapy
  - Key evidence: METEOR study of cabozantinib vs. everolimus following progression on VEGF-targeted therapy; a small minority of patients had also received a checkpoint inhibitor
  - Cabozantinib is also a preferred option post-immunotherapy progression
- Other options: Sunitinib or Pazopanib
  - Patients treated with pazopanib should be monitored closely for liver toxicity for the first 12 weeks
- Other options: Lenvatinib + Everolimus
  - Lenvatinib with everolimus is approved for use in Canada following one VEGF-targeted therapy only

Following First-line Sunitinib or Pazopanib: Intolerance

- **Consensus Statement: For patients who are intolerant to sunitinib or pazopanib, switching to the other VEGF inhibitor is a reasonable choice.**
  - If patients stop first-line therapy due to toxicity and not progression, another first-line therapy is very reasonable to try

Following First-line Sunitinib or Pazopanib: Progression

- **Consensus Statement: For patients who progress on first-line sunitinib or pazopanib, preferred options are nivolumab, axitinib, or cabozantinib.**
- **Consensus Statement: Other evidence-based options are lenvatinib/everolimus (based on a small phase 2 study demonstrating a PFS advantage over everolimus monotherapy) or everolimus monotherapy (although found to be inferior to alternatives such as nivolumab and cabozantinib).**
- Preferred option: Nivolumab
  - Key evidence: CheckMate 025 trial of nivolumab vs everolimus after failure of one or two lines of therapy
    - Benefit was observed independent of PD-L1 expression
    - A small minority of patients may experience pseudoprogression and delayed responses on immuno-oncology agents
    - Treatment beyond progression should be restricted to patients showing clinical benefit or stability
  - In rural areas with limited access to medical resources, physicians are encouraged to contact experienced centres for advice
  - Caution in:
    - Patients with pre-existing autoimmune diseases, particularly active disease under treatment
    - Patients with pre-existing comorbidities which make potential treatment with steroids challenging, eg, borderline-controlled diabetes
- Preferred option: Cabozantinib
  - Key evidence: METEOR trial of cabozantinib vs. everolimus following treatment with one or more VEGF-targeted TKIs
  - Caution in patients who experienced extensive toxicity on previous TKI, eg, uncontrolled hypertension
- Option (no consensus on Preferred vs Other): Axitinib
  - Key evidence: AXIS trial of axitinib vs sorafenib in patients progressing after first-line sunitinib (evidence not considered to be very strong)
  - Patients in CheckMate 025 and METEOR went on to receive axitinib in third or later lines

- Other option: Lenvatinib + Everolimus
  - Key evidence: Motzer 2015 phase 2 trial of lenvatinib + everolimus vs lenvatinib vs everolimus in patients who had progression on VEGF-targeted therapy
  - The combination of lenvatinib + everolimus is not currently funded in Canada (as of Mar. 2020)
- Other option: Everolimus
  - Key evidence: RECORD-1 trial of everolimus vs placebo in patients who had failed sunitinib or sorafenib or both
    - Note CheckMate 025, METEOR, and the lenvatinib-everolimus trial showed everolimus to be inferior to comparator arms in these trials

Following VEGF Inhibitor AND Immune Checkpoint Inhibitor Therapies

- **Consensus Statement: For patients who progress on, or who are intolerant of, both prior VEGF inhibitor and prior immune checkpoint inhibitor, there is no evidence base available to select a preferred treatment option; options for patients in this situation include any of the options that have not previously been tried among: sunitinib, pazopanib, axitinib, cabozantinib, or lenvatinib + everolimus.**
- Preferred option (given paucity of data): Cabozantinib
  - Key evidence: METEOR study of cabozantinib vs. everolimus following treatment with one or more VEGF-targeted TKIs
    - Note, only ~5% of patients in the trial received prior treatment with a VEGF inhibitor and an immune checkpoint inhibitor (ie, nivolumab), given in sequence not in combination
- Other options: Sunitinib, Pazopanib, Axitinib, Lenvatinib-Everolimus, Everolimus
  - In the absence of evidence-based recommendations, options include any of the therapies mentioned in the above sections with evidence in first or subsequent lines, that have not yet been used for a particular patient

Considerations for Baseline Assessment and Monitoring Patients During First-line Therapy

Immunotherapy-containing Regimens

- Candidates should undergo comprehensive baseline assessment
- Note the clinical trials with immunotherapy agents generally excluded patients with autoimmune disease and immunosuppressant use
- Provide patients and caregivers with information concerning potential side effects, prevention, and management
- Evaluate patients frequently to ensure early recognition and management of toxicities
- Closer monitoring may be required for patients with combination immunotherapy regimens; refer to product monographs for monitoring recommendations

Pre-Therapy Assessment and Monitoring During Therapy with Immune-Checkpoint Inhibitors (Adapted from NCCN v1.2020)

Pre-Therapy Assessment	Monitoring
Clinical • Physical examination • Comprehensive patient history of any autoimmune/organ-specific disease, endocrinopathy, or infectious disease • Neurologic examination • Bowel habits (typical frequency/consistency) • Infectious disease screening as indicated	• Clinical exam at each visit with AE symptom assessment • Follow-up testing based on findings, symptoms
Imaging • Cross-sectional imaging • Brain MRI if indicated	• Periodic imaging as indicated • Follow-up testing based on findings
General bloodwork • CBC with differential • Comprehensive metabolic panel	• Repeat prior to each treatment or every 4 weeks during immunotherapy, then in 6-12 weeks or as indicated • HbA1c for elevated glucose
Dermatologic • Examination of skin and mucosa if history of immune-related skin disorder	• Conduct/repeat based on symptoms
Pancreatic • Baseline testing is not required	• No routine monitoring if asymptomatic • If abnormal findings/symptoms: amylase, lipase, and consider abdominal CT with contrast or MRCP for suspected pancreatitis

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Pre-Therapy Assessment and Monitoring During Therapy with Immune-Checkpoint Inhibitors (Adapted from NCCN v1.2020)	
Pre-Therapy Assessment	**Monitoring**
Thyroid • TSH, free thyroxine (T4)	• If abnormal function suspected, measure T3 and free T4
Adrenal/Pituitary • Adrenal: Serum cortisol (morning preferred) • Pituitary: TSH, free thyroxine (T4)	• Repeat prior to each treatment or every 4 weeks during immunotherapy, then follow-up every 6-12 weeks • If abnormal findings/symptoms, LH, FSH, testosterone (males), estradiol (females), ACTH
Pulmonary • Oxygen saturation (resting and with ambulation) • Pulmonary function tests for high-risk patients	• Repeat oxygen saturation tests based on symptoms • If abnormal findings/symptoms, chest CT with contrast to evaluate for pneumonitis, biopsy if needed to exclude other causes
Cardiovascular • Consider baseline ECG • Individualize assessment in consultation with cardiology as indicated	• Consider periodic testing for those with abnormal baseline or symptoms • Individualize follow-up in consultation with cardiology as indicated
Musculoskeletal • Joint examination/functional assessment as needed for patients with pre-existing disease	• No routine monitoring if asymptomatic • If abnormal findings/symptoms, consider rheumatology referral • Depending on clinical situation, consider CRP, ESR or CPK

VEGF-targeted Therapies

- Baseline assessment and monitoring of patients receiving VEGF-targeted therapies should consider the common toxicities associated with these treatments, such as:
  - Cardiovascular effects, including hypertension and left ventricular dysfunction
  - Gastrointestinal toxicities, eg, diarrhea and nausea
  - Cutaneous effects including hand-foot syndrome
  - Thyroid dysfunction
  - Fatigue
  - Stomatitis
  - Myelosuppression
  - Hepatotoxicity
  - Impaired wound healing
- Provide patients and caregivers with information concerning potential side effects, prevention, and management

Role of Cytoreductive Nephrectomy in mRCC

Recommendations for Cytoreductive Nephrectomy (CN)

- **Consensus Statement: Cytoreductive nephrectomy can be considered in appropriately selected patients presenting with de novo mRCC, ideally after a multidisciplinary discussion. This is based on expert consensus of this authorship group.**
  - **Patients with a good performance status (Eastern Cooperative Oncology Group [ECOG] ≤1 or Karnofsky Performance Status [KPS] ≥ 80%), minimal symptoms related to metastases, a resectable primary tumor, and a limited burden of metastatic disease should be offered upfront cytoreductive nephrectomy followed by metastases-directed therapy, a period of surveillance, or systemic therapy.**
  - **Patients with significant systemic symptoms from metastatic disease, active central nervous system metastases, a limited burden of disease within the kidney relative to the cumulative extra-renal volume of metastases, rapidly progressing disease, a poor performance status (ECOG >1 or KPS <80%), and/or limited life expectancy should not undergo cytoreductive nephrectomy.**
  - **Patients with mRCC who don't fall within the two above categories should be offered initial treatment with systemic therapy, with consideration of cytoreductive nephrectomy given to those with a significant clinical response (deferred CN).**
- The recommendations for cytoreductive nephrectomy come from a recent KCRNC consensus statement by Mason and colleagues (2019)
  - Key evidence: CARMENA and SURTIME studies
    - Both studies from the VEGF-targeted therapy era
    - Applicability to treatment pathways including immune checkpoint inhibition requires investigation
  - Despite findings from CARMENA, some intermediate-risk patients may be candidates for CN as reflected in the KCRNC consensus

Patient Selection for Cytoreductive Nephrectomy		
	Consider CN	**Not Suitable for CN**
Performance Status/ Operative Candidacy	• ECOG PS 0 or 1, or KPS ≥ 80%	• ECOG PS ≥ 2 or KPS < 80% • Limited life expectancy • Not a surgical candidate / significant comorbidities
Symptoms	• No or minimal symptoms related to metastases • Patients requiring palliative nephrectomy for symptomatic control (eg, pain, bleeding, paraneoplastic syndrome)	• Significant symptoms from metastatic disease
IMDC Risk Status	• Favourable- or intermediate -risk mRCC who would otherwise be candidates for active surveillance	• Poor risk mRCC • Intermediate-risk mRCC requiring prompt initiation of systemic therapy (deferred CN may be considered on a case-by-case basis for patients exhibiting favourable response to initial systemic therapy)
Primary Tumor Burden	• Resectable primary tumor • Proportion of total tumor burden expected to be removed by CN favours surgery (>90-95% associated with best outcomes)	• Limited burden of disease with the kidney relative to cumulative extra-renal volume of metastases
Metastases / Disease Progression	• Limited burden of metastatic disease • Candidates for oligometastasectomy that will render them disease-free	• Active CNS metastases • Rapidly progressing disease

Post-Nephrectomy Management

- Patients that can undergo active surveillance may have CT scans every 3 months; systemic therapy should be initiated upon progression
- Post-operatively, wait at least 4 weeks before initiating TKIs or TKI-containing regimens

Key Trials

Key Trials in Advanced/Metastatic Renal Cell Carcinoma

New Trials Evaluating First-line Treatment of Advanced/Metastatic Renal Cell Carcinoma

KEYNOTE-426 (axitinib + pembrolizumab vs. sunitinib)

CheckMate 214 (ipilimumab + nivolumab vs. sunitinib)

JAVELIN Renal 101 (axitinib + avelumab vs. sunitinib)

Second-line (or Later) Treatment of Advanced/Metastatic Renal Cell Carcinoma

CheckMate 025 (nivolumab vs. everolimus)

METEOR (cabozantinib vs. everolimus)

AXIS (axitinib vs. sorafenib)

Lenvatinib + everolimus

Cytoreductive Nephrectomy

CARMENA

SURTIME

First-line Treatment of Advanced/Metastatic Renal Cell Carcinoma

- Choice of initial systemic treatment in advanced clear-cell renal cell carcinoma is based in part on International Metastatic RCC Database Consortium (IMDC) risk status
- Notable trials include KEYNOTE-426 (pembrolizumab + axitinib vs. sunitinib), CheckMate 214 (nivolumab + ipilimumab followed by nivolumab vs. sunitinib) and JAVELIN Renal 101 (avelumab + axitinib vs. sunitinib)
- At time of publication, the avelumab + axitinib regimen was not approved for use

KEYNOTE-426 NCT02853331

Phase and Design

- Phase 3, open label, randomized trial in patients with untreated advanced RCC
- Primary end points were OS and PFS in the ITT population; key secondary end point was ORR
- Median follow-up of 12.8 months for primary analysis[1]; minimum follow-up of 23 months for updated analysis[2]

Population, N=861

- ≥ 18 years of age with newly diagnosed or recurrent stage IV clear-cell RCC
- No prior systemic therapy for advanced disease
- Karnofsky PS ≥ 70
- ≥ 1 measurable lesion (RECIST criteria)

Exclusion criteria included:

- Symptomatic CNS metastases
- Active autoimmune disease
- Poorly controlled hypertension (SBP ≥ 150 or DBP ≥ 90); ischemic CV event or CHF (NYHA class III or IV) within 1 y of screening
- Receiving systemic immunosuppressive treatment

Intervention/Dosing

- Pembrolizumab (200 mg IV Q3W, max 35 cycles) + axitinib (5 mg PO BID), n=432
- Sunitinib (50 mg PO QD, first 4 wk of each 6-wk cycle), n=429

Primary Endpoints

- 12 mo OS[1], 89.9% vs 78.3%
  HR 0.53, (95%CI, 0.38-0.74; P<0.0001)
- Updated analysis 24 mo OS[2], 74% vs 66%
  HR 0.68, (95%CI, 0.55-0.85; P<0.001
- Median PFS[1]$_{BICR}$, 15.1 mo vs 11.1 mo
  HR 0.69, (95%CI 0.57-0.84; P<0.001)
- Updated analysis Median PFS[2], 15.4 mo vs 11.1 mo
  HR 0.71, (95%CI, 0.60-0.84; P<0.001)

Key Secondary Endpoints

- ORR[2], 60.2% vs 39.9% (P<0.0001)
  CR[2], 8.8% vs 3.0%
- Median Duration of Response[3], 23.5 mo vs 15.9 mo

Key Subgroup Outcomes[2]

- IMDC favourable risk (n=269): 24 mo OS, 85% vs 88%; HR 1.06 (95%CI, 0.60-1.86)
  Median PFS, 20.8 mo vs 18.0 mo; HR 0.79 (95%CI, 0.57-1.09)
  ORR, 69.6% vs 50.4%; CR 11% vs 6%
- IMDC intermediate/poor (n=592): 24 mo OS, 69% vs 56%; HR 0.63 (95%CI, 0.50-0.81)
  Median PFS, 12.7 mo vs 8.3 mo; HR 0.69 (95%CI, 0.56-0.84)
  ORR, 55.8% vs 35.2%; CR 8% vs 2%

Most Common AEs (> 30%), any grade[3]

- Diarrhea, 51.5% vs 42.6%
- Hypertension, 42.9% vs 43.5%
- Hypothyroidism, 33.8% vs 29.9%
- Fatigue, 31.2% vs 34.4%

Most Common (> 5%) AEs, grade 3+[1]

- Hypertension, 22.1% vs 19.3%
- ALT increased, 13.3% vs 3.1%
- Diarrhea, 9.1% vs 4.7%
- AST increased, 7.0% vs 2.4%

AEs of Interest, grade 3+[3]

- Severe skin reactions, 1.6% vs 0.7%
- Hepatitis, 1.4% vs 0%
- Colitis, 1.2% vs 0%
- Hyperthyroidism, 1.2% vs 0%
- Hypophysitis, 1.2% vs 0%

References

1. Rini BI, et al. N Engl J Med 2019;380:1116-1127.
2. Plimack ER, et al. J Clin Oncol. 2020;38 (suppl; abstr 5001).
3. Soulières D, et al. 18th International Kidney Cancer Symposium, 2019 Nov 15-16; Miami.

BICR = blinded, independent, central review

CheckMate 214 NCT02231749

Phase and Design

- Phase 3, open label, multicentre, randomized trial in patients with untreated clear-cell advanced RCC
- Coprimary endpoints were OS, ORR, and PFS among patients with intermediate or poor prognostic risk
- Minimum follow-up of 17.5 months for primary analysis[1] and 42 months for extended analysis[3]
- ITT population refers to primary patient population (intermediate or poor risk) and the exploratory group of favourable risk patients

Population, N=1096

- ≥ 18 years of age with previously untreated advanced RCC with a clear-cell component
- Karnofsky PS ≥ 70
- Measurable disease (RECIST criteria)

Exclusion criteria included:

- CNS metastases or autoimmune disease and glucocorticoid or immunosuppressant use

Intervention/Dosing

- Induction: nivolumab (3 mg/kg IV) + ipilimumab (1 mg/kg IV) Q3W for 4 doses; Maintenance: nivolumab (3 mg/kg IV Q2W), n=550
- Sunitinib (50 mg PO QD first 4-wk of each 6-wk cycle), n=546

Primary Endpoints[1]

IMDC intermediate risk (n=425) and IMDC poor risk (n=422)

- ORR_{IRRC}, 42% vs 27%; P<0.001
- Extended Analysis[3] ORR_{IRRC}, 42% vs 26%; P<0.0001
  CR_{IRRC}, 10% vs 1%
- Median OS, NR vs 26.0 mo
  HR 0.63 (99.8%CI, 0.44-0.89; P<0.001)
- Extended Analysis[a] Median OS[3], 47.0 mo vs 26.6 mo
  HR 0.66 (95%CI, 0.55-0.80; P<0.0001)
- Median PFS_{IRRC}, 11.6 mo vs 8.4 mo
  HR 0.82 (99.1%CI, 0.64-1.05; P=0.03)
- Extended Analysis Median PFS[3], 12.0 mo vs 8.3 mo
  HR 0.76 (95%CI, 0.63-0.91; P<0.01)

Key Secondary Endpoints[1]

- ORR_{ITT}, 39% vs 32%; P=0.02
- Extended Analysis[3] ORR_{ITT},
  39% vs 33%; P=0.02
  CR_{ITT}, 11% vs 2%
- Median OS_{ITT}, NR vs 32.9 mo
  HR 0.68 (99.8%CI, 0.49-0.95; P<0.001)
- Extended Analysis Median OS^{3}_{ITT},
  NR vs 38.4 mo
  HR 0.72 (95%CI, 0.61-0.86; P=0.0002)
- Median PFS_{ITT}, 12.4 mo vs 12.3 mo
  HR 0.98 (99.1%CI, 0.79-1.23; P=0.85)
- Extended Analysis Median PFS^{3}_{ITT},
  12.5 mo vs 12.3 mo
  HR 0.89 (95%CI, 0.76-1.05; P=0.16)

Key Subgroup Outcomes

- PD-L1 expression <1% (n=562): ORR, 37% vs 28% (P=0.03); Median PFS, 11.0 mo vs 10.4 mo (HR 1.00; 95%CI, 0.80-1.26); Median OS, NR vs NR (HR 0.73; 95%CI, 0.56-0.96)
- PD-L1 expression ≥1% (n=214): ORR, 58% vs 22% (P<0.001); Median PFS, 22.8 mo vs 5.9 mo (HR 0.46; 95%CI 0.31-0.67); Median OS, NR vs 19.6 mo (HR 0.45; 95%CI 0.29-0.71)
- IMDC favorable (n=249): ORR, 29% vs 52% (P<0.001); Median PFS, 15.3 mo vs 25.1 mo (HR 2.18; 99.1%CI, 1.29-3.68; P<0.001)

Most Common (> 30%) AEs, any grade

- Fatigue, 37% vs 49%
- Diarrhea, 27% vs 52%
- Nausea, 20% vs 38%
- Dysgeusia, 6% vs 33%
- Hypertension, 2% vs 40%
- PPES, <1% vs 43%

Most Common (> 5%) AEs, grade 3+

- Fatigue, 4% vs 9%
- Increased lipase level, 10% vs 7%
- Hypertension, <1% vs 16%
- PPES, 0 vs 9%
- Thrombocytopenia, 0 vs 5%

AEs of Interest, grade 3+

- None specified

References

1. Motzer RJ, et al. N Engl J Med 2018;378:1277-90.
2. Motzer RJ, et al. Lancet Oncol. 2019 Oct;20(10):1370-1385.
3. Tannir NM, et al. Genitourinary Cancers Symposium; 2020 Feb 13-15; San Francisco. Abstract 609.

IRRC = independent radiology review committee; ITT = intent-to-treat (included all randomized patients); NR = not reached; PPES = Palmar-plantar erythrodysesthesia.

[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.

JAVELIN Renal 101 NCT02684006

Phase and Design

- Phase 3, open label, multicentre, randomized trial in previously untreated patients with advanced RCC
- Two independent primary endpoints were PFS and OS among patients with PD-L1-positive tumors; a key secondary endpoint was PFS in the overall population

Population, N=886

- ≥ 18 years of age with advanced RCC with a clear-cell component
- ECOG PS 0-1
- Measurable disease (RECIST criteria)
- Fresh or archival tumor specimen; and adequate renal, cardiac, and hepatic function

Exclusion criteria included:

- Active CNS metastases or autoimmune disease and current or previous use of glucocorticoids or other immunosuppressants within 7 days before randomization

Intervention/Dosing

- Avelumab (10mg/kg IV Q2W) + axitinib (5mg PO BID), n=442
- Sunitinib (50 mg PO QD first 4-wk of each 6-wk cycle), n=444

Primary Endpoint

PD-L1-positive tumors, n=560

- Median PFS_{BICR}, 13.8 mo vs 7.2 mo HR 0.61 (95%CI, 0.47-0.79; P<0.001)
- Median OS: HR 0.82; (95%CI, 0.53-1.28; P=0.38)

Key Secondary Endpoints

Overall population, n=886

- Median PFS_{BICR}, 13.8 mo vs 8.4 mo HR 0.69 (95%CI, 0.56-0.84; P<0.001)
- OS, HR 0.78 (95%CI, 0.55-1.08; P=0.14)
- ORR, 51.4% vs 25.7% CR, 3.4% vs 1.8%

PD-L1-positive tumors, n=560

- ORR, 55.2% vs 25.5% CR, 4.4% vs 2.1%

Key Subgroup Outcomes

- IMDC favourable risk (n=111): PFS, HR 0.50 (0.26-0.97)
- IMDC intermediate risk (n=364): PFS, HR 0.64 (0.47-0.88)
- IMDC poor risk (n=83): PFS, HR 0.53 (0.30-0.93)

Most Common (> 30%) AEs, any grade

- Diarrhea, 62.2% vs 47.6%
- Hypertension, 49.5% vs 36.0%
- Fatigue, 41.5% vs 40.1%
- Nausea, 34.1% vs 39.2%
- PPES, 33.4% vs 33.7%
- Dysphonia, 30.6% vs 3.2%
- Dysgeusia, 13.1% vs 32.3%

Most Common (> 5%) AEs, grade 3+

- Hypertension, 25.6% vs 17.1%
- Diarrhea, 6.7% vs 2.7%
- Increased alanine aminotransferase level, 6.0% vs 2.5%
- PPES, 5.8% vs 4.3%
- Anemia, 1.6% vs 8.2%
- Neutropenia, 0.2% vs 8.0%
- Thrombocytopenia, 0.2% vs 6.2%
- Decreased neutrophil count, 0 vs 5.7%
- Decreased platelet count, 0 vs 5.0%

AEs of Interest, any grade

- Hypothyroidism, 24.9% vs 13.9%

References

1. Motzer RJ, et al. N Engl J Med 2019;380:1103-15.

BICR = blinded independent central review according to RECIST; PPES = Palmar-plantar erythrodysesthesia syndrome.

Second-line (or Later) Treatment of Advanced/Metastatic Renal Cell Carcinoma

- For patients who experience disease progression on, or are intolerant to, first-line immune checkpoint inhibitors, there is no prospective, phase 3 evidence available to guide treatment selection
- Key trials in second-line or later treatment options include: CheckMate 025 (nivolumab vs. everolimus), METEOR (cabozantinib vs. everolimus), AXIS (axitinib vs. sorafenib), and a small trial of lenvatinib + everolimus
- In this setting, cabozantinib is approved in Canada for use following VEGF-targeted therapy only; axitinib is approved for use after failure of a cytokine or sunitinib

CheckMate 025 NCT01668784

Phase and Design

- Phase 3, open label, multicentre, randomized trial in patients with RCC who had received previous treatment
- Primary endpoint was OS; secondary endpoints included ORR and safety
- Minimum follow-up of 14 months for interim analysis[1] and median follow-up of 72 months for final analysis[2]

Population, N=821

- ≥ 18 years of age with histologically confirmed advanced or metastatic RCC with a clear cell component
- Karnofsky PS ≥ 70
- Measurable disease (RECIST criteria)
- Received 1-2 previous regimens of antiangiogenic therapy
- ≤ 3 total previous regimens of systemic therapy, including cytokines and cytotoxic chemotherapy drugs, and disease progression during or after the last treatment regimen and within 6 months before study enrolment

Exclusion criteria included:

- CNS metastasis
- Previous mTOR inhibitor treatment
- Condition requiring treatment with glucocorticoids (equivalent to >10 mg of prednisone daily)

Intervention/Dosing

- Nivolumab (3mg/kg mg IV Q2W), n=410
- Everolimus (10 mg PO QD), n=411

Primary Endpoint

- Final Analysis Median OS[2], 25.8 mo vs 19.7 mo HR 0.73 (95%CI, 0.62-0.85; P<0.0001)

Key Secondary Endpoints

- ORR[2], 23% vs 4% (P<0.0001)
- Final Analysis Median PFS[2], 4.2 mo vs 4.5 mo HR 0.84 (95%CI 0.72-0.99; P=0.03)

Key Subgroup Outcomes

- PD-L1 expression <1% (n=575)[1]: Median OS, 27.4 mo vs 21.2 mo (HR 0.77; 95%CI, 0.60-0.97)
- PD-L1 expression ≥1% (n=181)[1]: Median OS, 21.8 mo vs 18.8 mo (HR 0.79; 95%CI 0.53-1.17)

Most Common (> 30%) AEs, any grade[2]

- Fatigue, 35% vs 35%

Most Common (> 5%) AEs, grade 3+[2]

- Anemia, 2% vs 9%
- Hypertriglyceridemia, 2 vs 5%

AEs of Interest, grade 3+

- None specified

References

1. Motzer RJ, et al. N Engl J Med 2015;373:1803-13.
2. Motzer RJ, et al. Genitourinary Cancers Symposium; 2020 Feb 13-15; San Francisco. Abstract 617.

METEOR NCT01865747

Phase and Design

- Phase 3, open label, randomized trial in patients with RCC that had progressed after VEGFR-targeted therapy
- Primary endpoint was PFS; secondary efficacy endpoints were OS and ORR

Population, N=658

- ≥ 18 years of age with advanced or metastatic RCC with a clear-cell component
- Karnofsky PS ≥ 70
- Measurable disease (RECIST criteria)
- Received ≥ 1 previous VEGFR TKI and disease progression during or within 6 mo of most recent dose of VEGFR inhibitor

Exclusion criteria included:

- Previous mTOR inhibitor or cabozantinib
- Uncontrolled hypertension or clinically significant CV, GI, wound healing, or infectious comorbidities

Intervention/Dosing

- Cabozantinib (60 mg PO QD), n=330
- Everolimus (10 mg PO QD), n=328

Primary Endpoint[1]

- Median PFS_{IRRC}, 7.4 mo vs 3.8 mo
  HR 0.58 (95%CI, 0.45-0.75; P<0.001)

Key Secondary Endpoints

- Median OS_{final}, 21.4 mo vs 16.5 mo[2]
  HR 0.66 (95%CI, 0.53-0.83; P=0.00026)
- ORR, 21% vs 5% (P<0.001)[1]

Key Subgroup Outcomes[2]

- 1 Prior VEGFR TKI (n=464): PFS, HR 0.52 (95%CI, 0.41-0.66); OS, HR 0.65 (95%CI, 0.50-0.85)
- ≥ 2 Prior VEGFR TKIs (n=194): PFS, HR 0.51 (95%CI, 0.35-0.74); OS, HR 0.73 (95%CI, 0.48-1.10)
- Previous PD-1 or PD-L1 (n=32):
  PFS, HR 0.22 (95%CI, 0.07-0.65); OS, HR 0.56 (95%CI, 0.21-1.52)

Most Common (> 30%) AEs, any grade[2]

- Diarrhea, 75% vs 28%
- Fatigue, 59% vs 47%
- Nausea, 53% vs 29%
- Decreased appetite, 47% vs 36%
- PPES, 43% vs 6%
- Weight decreased, 35% vs 13%
- Vomiting, 34% vs 15%

Most Common (> 5%) AEs, grade 3+[2]

- Hypertension, 15% vs 4%
- Diarrhea, 13% vs 2%
- Fatigue, 11% vs 7%
- PPES, 8% vs 1%
- Anemia, 6% vs 17%

AEs of Interest, grade 3+

- None specified

References

1. Choueiri TK, et al. N Engl J Med 2015;373: 1814–23.
2. Choueiri TK, et al. Lancet Oncol 2016;17: 917–27.

IRRC = independent radiology review committee; PPES = Palmar-plantar erythrodysesthesia syndrome.

AXIS — NCT00678392

Phase and Design

- Phase 3, open label, multicentre, randomized trial of second-line therapy in patients with metastatic renal cell cancer
- Primary endpoint was PFS and was assessed by a masked, independent radiology review

Population, N=723

- ≥ 18 years of age with histologically or cytologically confirmed RCC with a clear-cell component
- ECOG 0-1
- Measurable disease (RECIST criteria)
- RECIST-defined progressive disease after 1 previous regimen with a sunitinib-based, bevacizumab + interferon-alfa-based, temsirolimus-based, or cytokine-based regimen
- ≥ 2 weeks since end of previous treatment (≥ 4 weeks for bevacizumab + interferon-alpha)

Exclusion criteria included:

- Present use or anticipated need for CYP3A4-inhibiting, CYP3A4-inducing, or CYP1A2-inducing drugs
- CNS metastasis
- Uncontrolled hypertension; myocardial infarction, uncontrolled angina, CHF, or CVA within previous 12 months
- Deep vein thrombosis or pulmonary embolism within previous 6 months

Intervention/Dosing

- Axitinib (5 mg PO BID), n=361
- Sorafenib (400 mg PO BID), n=362

Primary Endpoint

- Median PFS_{IRRC}, 6.7 mo vs 4.7 mo HR 0.665 (95%CI, 0.544-0.812; P<0.0001)

Key Secondary Endpoints

- ORR, 19% vs 9%, P=0.0001
- Median OS[2], 20.1 mo vs 19.2 mo HR 0.969 (95%CI 0.800-1.174; P=0.3744)

Key Subgroup Outcomes

- Previous cytokine-based regimen: PFS, 12.1 mo vs 6.5 mo (HR 0.464, 95%CI 0.318-0.676; P<0.0001)
- Previous sunitinib-based regimen: PFS, 4.8 mo vs 3.4 mo (HR 0.741, 95%CI 0.573-0.958; P=0.0107)

Most Common (> 30%) AEs, any grade[2]

- Diarrhea, 54% vs 52%
- Hypertension, 42% vs 30%
- Fatigue, 37% vs 28%
- Decreased appetite, 31% vs 26%
- Nausea, 30% vs 19%
- Hand-foot syndrome, 28% vs 51%
- Rash, 13% vs 31%
- Alopecia, 4% vs 33%

Most Common (> 5%) AEs, grade 3+[2]

- Hypertension, 17% vs 12%
- Diarrhea, 11% vs 8%
- Fatigue, 10% vs 4%
- Hand-foot syndrome, 6% vs 17%

AEs of Interest, grade 3+

- None specified

References

1. Rini BI, et al. Lancet 2011;378:1931-9.
2. Motzer RJ, et al. Lancet Oncol 2013;14:552-62.

IRRC = independent radiology review committee

Lenvatinib + everolimus (Motzer 2015) NCT01136733

Phase and Design

- Phase 2, open label, multicentre, randomized trial of second-line treatment in patients with metastatic RCC
- Primary endpoint was PFS in the ITT population

Population, N=153

- ≥ 18 years of age with RCC and histologically verified clear-cell component
- ECOG 0-1
- Measurable disease (RECIST criteria)
- Radiographic evidence of progressive advanced or metastatic disease ≤ 9 months of stopping previous treatment
- One previous disease progression with VEGF-targeted treatment
- Adequately controlled blood pressure

Exclusion criteria included:

- Brain metastases
- Previous exposure to lenvatinib or mTOR inhibitors
- Received anticancer treatment or major surgery within 21 days before first dose of study drug

Intervention/Dosing

- Lenvatinib (18 mg/kg PO QD) + everolimus (5mg/day PO QD), n=51
- Lenvatinib (24 mg/kg PO QD), n=52
- Everolimus (10 mg/kg PO QD), n=50

Primary Endpoint

- Median PFS, 14.6 mo vs 7.4 mo vs 5.5 mo
  $HR_{LEN+EVE\ vs\ EVE}$ 0.40 (95%CI, 0.24-0.68; P=0.0005)
  $HR_{LEN+EVE\ vs\ LEN}$ 0.66 (95%CI, 0.39-1.10; P=0.12)
  $HR_{LEN\ vs\ EVE}$ 0.61 (95%CI, 0.38-0.98; P=0.048)

Key Secondary Endpoints

- ORR, 43% vs 27% vs 6%
- $RR_{LEN+EVE\ vs\ EVE}$ 7.2 (95%CI 2.3-22.5; P<0.0001)
- $RR_{LEN+EVE\ vs\ LEN}$ 1.6 (95%CI 0.9-2.8; P=0.10)
- $RR_{LEN\ vs\ EVE}$ 4.5 (95%CI 1.4-14.7; P=0.0067)
- Median OS, 25.5 mo vs 18.4 mo vs 17.5 mo
- $HR_{LEN+EVE\ vs\ EVE}$ 0.55 (95%CI, 0.30-1.01; P=0.062)
- $HR_{LEN+EVE\ vs\ LEN}$ 0.74 (95%CI, 0.40-1.36; P=0.30)
- $HR_{LEN\ vs\ EVE}$ 0.74 (95%CI, 0.42-1.31; P=0.29)

Key Subgroup Outcomes

- None reported

Continued on next page

Lenvatinib + everolimus (Motzer 2015) NCT01136733

Most Common (> 30%) AEs, grade 1-2

- Diarrhea, 65% vs 60% vs 32%
- Decreased appetite, 45% vs 54% vs 18%
- Fatigue or asthenia, 45% vs 42% vs 36%
- Vomiting, 37% vs 35% vs 10%
- Nausea, 35% vs 54% vs 16%
- Cough, 37% vs 15% vs 30%
- Hypercholesterolemia, 31% vs 10% vs 16%
- Decreased weight, 29% vs 42% vs 8%
- Stomatitis, 29 vs 23% vs 40%
- Hypertension, 27% vs 31% vs 8%
- Hypothyroidism, 24% vs 35% vs 2%
- Dysphonia, 20% vs 37% vs 4%
- Constipation, 12% vs 37% vs 18%

Most Common (> 5%) AEs, grade 3-4

- Diarrhea, 20% vs 12% vs 2%
- Decreased appetite, 6% vs 4% vs 0
- Fatigue or asthenia, 14% vs 8% vs 2%
- Vomiting, 8% vs 4% vs 0
- Nausea, 6% vs 8% vs 0
- Hypertriglyceridemia, 8% vs 4% vs 8%
- Hypertension, 14% vs 17% vs 2%
- Dyspnea, 2% vs 2% vs 8%
- Proteinuria, 4% vs 19% vs 2%
- Hyperglycemia, 0 vs 0 vs 10%
- Anemia, 8% vs 2% vs 12%
- Lower-respiratory-tract infection, 0 vs 8% vs 2%

AEs of Interest, grade 3-4

- None specified

References

1. Motzer RJ, et al. Lancet Oncol 2015;16:1473-82.

RR = rate ratio

Cytoreductive Nephrectomy

- Two randomized controlled studies were published in 2018, CARMENA and SURTIME
- The studies reflect clinical practice during the era of VEGF-targeted therapy
- Applicability of these findings to the era of immune checkpoint inhibition requires investigation

CARMENA NCT00930033

Phase and Design

- Phase 3, open label, multicentre, randomized trial to assess the role of nephrectomy in patients with metastatic RCC who were receiving targeted therapies
- Primary endpoint was OS

Population, N=450

- ≥ 18 years of age with clear-cell RCC confirmed on mandatory biopsy and documented metastatic disease
- ECOG 0-1
- Suitable candidates for nephrectomy and eligible for treatment with sunitinib
- Absence of brain metastases or treated brain metastases without recurrence 3 weeks after treatment, and acceptable organ function

Exclusion criteria included:

- Received previous systemic treatment for kidney cancer (including VEGF-targeted therapy) or anticoagulants
- Any medical condition, including cardiovascular disease, that ruled them out as candidates for treatment

Intervention/Dosing

- Sunitinib alone immediately, n=224
- Nephrectomy + sunitinib, n=226

Primary Endpoint
(sunitinib alone vs nephrectomy-sunitinib)

- Median OS_{ITT}[1], 18.4 mo vs 13.9 mo
  HR 0.89 (95%CI, 0.71-1.10)[a]
- Median OS_{ITT}, updated[2], 19.8 mo vs 15.6
  $HR_{(MSKCC\ stratified)}$ 0.933 (95%CI, 0.76- 1.15)
  $HR_{(IMDC\ stratified)}$ 0.957 (95%CI, 0.78-1.18)

Key Secondary Endpoints
(sunitinib alone vs nephrectomy-sunitinib)

- Median PFS[1], 8.3 mo vs. 7.2 mo
  HR 0.82 (95%CI, 0.67-1.00)
- ORR[1], 29.1% vs 27.4%

Key Subgroup Outcomes (sunitinib alone vs nephrectomy-sunitinib)

- Median $OS_{(MSKCC\ intermediate\text{-}risk)}$[1], 23.4 mo vs 19.0 mo; HR 0.92 (95%CI, 0.68-1.24)
- Median $OS_{(MSKCC\ poor\ risk)}$[1], 13.3 mo vs 10.2 mo; HR 0.86 (95%CI, 0.62-1.17)

Most Common (> 30%) AEs, any grade

- Only severe AEs presented

Most Common (> 5%) AEs, grade 3+

- Asthenia, 9.9% vs 8.6%
- Hand foot syndrome, 5.6% vs 4.3%
- Anemia, 5.2% vs 2.7%

AEs of Interest, grade 3+ (nephrectomy arm)

- Clavien-Dindo postoperative complications grade 3+, 15.9%
- Post-operative death, N=4

References

1. Méjean A, et al. N Engl J Med 2018;379: 417-427.
2. Méjean A, et al. J Clin Oncol 2019;37(no. 15_suppl):4508-4508.

[a] Upper boundary of the 95% confidence interval for noninferiority, ≤1.20
MSKCC, Memorial Sloan Kettering Cancer Center prognostic model

SURTIME	NCT01099423
Phase and Design • Phase 3, open label, multicentre, randomized trial to examine whether a period of sunitinib therapy before CN improves outcome compared with immediate CN followed by sunitinib • Primary endpoint was PFS; secondary endpoints included OS, adverse events, and post-operative progression	
Population, N=99 • ≥ 18 years of age with histologically confirmed, untreated clear cell mRCC with a resectable asymptomatic primary tumor in situ and required therapy with sunitinib • WHO PS 0 or 1 • Measurable disease (RECIST criteria) • No clinical signs of CNS involvement • ≤ 3 surgical risk factors	
Intervention/Dosing • Deferred nephrectomy: 3 cycles of sunitinib followed by CN + sunitinib by minimization (variance method), n=49 • Immediate nephrectomy: CN + sunitinib, n=50	
Primary Endpoint • Median PFS: not met due to poor accrual HR 0.88 (95%CI, 0.56-1.37; P=0.57) • 28-wk PFR_{IDMC}, 43% vs 42% P=0.61	**Key Secondary Endpoints** • OS, 32.4 mo vs 15.0 mo HR 0.57 (95%CI, 0.34-0.95; P=0.03) • Progression at Restaging (4 wk post-surgery): Confirmed, 23.5% vs 19.6% Unconfirmed, 2.9% vs 8.7%
Treatment Deferred CN arm: • Presurgical sunitinib, 98%; PR, 23%; PD 29% • CN per protocol, 34/48; CN off protocol, 6/48	Immediate CN arm: • CN, 92% (46/50) • Sunitinib, 80% (40/50)
Safety • Surgical complications, 53% vs 52% • Grade 3+ AEs, 58% vs 52%	
References 1. Bex A, et al. JAMA Oncol. 2019;5(2):164–170. CN = cytoreductive nephrectomy; IDMC = independent data monitoring committee; PFR = progression free rate.	

Conference Highlights


HEALTH CARE
• INVENTION
• HEALTH
• INSPIRATION
TREATMENT
• INVENTORS
• CREATIVITY
• DISCOVERY

Conference Highlights

Key Trials from ASCO 2020 Conference

- Summaries from noteworthy clinical trial presentations and posters from the ASCO 2020 conference are summarized below

KEYNOTE-426	NCT02853331

Study Design

- Updated analysis of phase 3, open label, randomized trial in patients with untreated advanced RCC, Karnofsky PS ≥ 70, and measurable disease
- Primary endpoints: OS, PFS; secondary endpoints: ORR, DOR and safety
- Median follow-up was 27.0 months

Intervention/Dosing

- Pembrolizumab (200 mg IV Q3W, max 35 cycles) + axitinib (5 mg PO BID), n=432
- Sunitinib (50 mg PO QD, 4-week on/2-week off), n=429

Key Results

- OS, NYR vs 35.7 mo; HR 0.68 (95%CI, 0.55-0.85); P<0.001; 24 mo OS, 74% vs 66%
- PFS, 15.4 vs 11.1 mo; HR, 0.71 (95%CI, 0.60-0.84); P<0.001; 24 mo PFS, 38% vs 27%
- ORR, 60% vs 40% (P<0.0001); CR, 9% vs 3%; Median DOR, 23.5 vs 15.9 mo
- Benefit observed in all tested subgroups, including IMDC risk and PD-L1 expression subgroups

Conclusions and Implications for Canadian Practice

- Benefit of axitinib-pembrolizumab was maintained with increased CR rate; however, longer follow-up is needed to conclusively assess duration of response and durability of CR
- It is unknown which regimen (axitinib-pembrolizumab vs ipilimumab-nivolumab) is better in the intermediate and poor risk population as they are both standards of care
  - They may be differentiated based on toxicity profiles (VEGF vs IO toxicities) or pre-existing autoimmune disease
- Axitinib-pembrolizumab is a standard of care for favourable risk individuals; it is unknown if all favourable risk individuals require combination therapy but until there are biomarkers that better differentiate this issue, axitinib-pembrolizumab remains a standard of care

References

Plimack ER, et al. J Clin Oncol. 2020;38 (suppl; abstr 5001).

OMNIVORE — NCT03203473

Study Design

- Phase II, response-adaptive trial in patients with advanced RCC with no prior checkpoint inhibitor exposure
- Primary endpoints: proportion with PR/CR at 1 year after nivolumab discontinuation and proportion of nivolumab non-responders who convert to PR/CR after adding ipilimumab
- Median follow-up was 17.0 mo

Intervention/Dosing

- All patients: nivolumab induction (240 mg q2W or 480 mg Q4W), N=83
- Confirmed CR/PR within 6 months → Stop treatment (Arm A), n=12
- Confirmed stable disease or progressive disease → Add ipilimumab (1 mg/kg Q3W x 2) (Arm B), n=57

Key Results

- Confirmed PR at 6 months with induction nivolumab, 11% (n=9/83)
- 12 patients (14%) allocated to Arm A; 5 (42%) remained off nivolumab at ≥ 1 year
- 57 patients (69%) allocated to Arm B; 2 (4%) converted to PR with addition to ipilimumab; no CRs
- Grade 3-4 treatment-related AEs: 7% (6/83) on induction nivolumab; 23% (13/57) in Arm B

References

McKay RR, et al. J Clin Oncol. 2020;38 (suppl; abstr 5005).

HCRN GU16-260 — NCT03117309

Study Design

- Phase II trial in patients with treatment-naïve RCC

Intervention/Dosing

- All patients: nivolumab induction (240 mg q2W x 6; 360 mg Q3W x 4; 480 mg Q4W)
- CR/PR (RECIST) → Continue nivolumab (up to 96 total weeks) (Part A)
- PD or best response SD at 48 weeks → nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W x 4 then nivolumab (up to 48 weeks) (Part B)

Key Results

- 123 patients evaluable for response: ORR, 31.7% (CR, 5.7%, PR, 26.0%); SD, 37.4%; PD, 30.9%
  Median duration of response: 19.3 mo
  Median PFS, 8.3 mo
- 65 patients (59 PD, 6 SD) eligible for salvage nivolumab/ipilimumab (31 did not enroll); 30 of 34 Part B patients evaluable for efficacy; best response to nivolumab/ipilimumab: PR, 13.3%; SD, 23.3%; PD, 63.3%
  ORR (irRECIST), 13.3%
- Treatment-related AEs (grade ≥3): 38/123 (31%) on nivolumab; 12/30 (40%) on nivolumab/ipilimumab

References

Atkins MB, et al. J Clin Oncol. 2020;38 (suppl; abstr 5006).

Continued on next page

OMNIVORE	NCT03203473
HCRN GU16-260	NCT03117309

Conclusions and Implications for Canadian Practice

- Based on the low conversion rate of nivolumab non-responders to PR/CR (4%), the strategy of single-agent nivolumab followed by response-based ipilimumab cannot be recommended at this time
- First-line nivolumab has limited activity and low CR rate
- "Salvage" concept with nivolumab/ipilimumab at progression or insufficient response is not a valid management strategy
- Upfront nivolumab/ipilimumab remains standard of care and the preferred approach whenever possible

Oligoprogression – Stereotactic RT Study

Study Design

- Prospective, phase II, multicentre study in patients with mRCC who develop oligoprogression while receiving TKI therapy
- Included patients with IMDC favourable/intermediate risk with previous stability or response on ≥3 months of TKI and radiographic progression (≤5 metastases)
- Endpoints: local control of irradiated lesions, PFS, OS and cumulative incidence of changing systemic therapy after study entry
- Median follow-up was 11.6 months

Intervention/Dosing

- Oligoprogressive tumors: SRT (TKI temporarily stopped) same TKI resumed
- Other metastases (stable or responding to TKI): no SRT

Key Results

- 37 patients (IMDC favourable, 12; intermediate, 25) with 57 oligoprogressive tumors
- Oligoprogressive tumors treated with stereotactic RT: solitary, 21 patients; 2-3 tumors, 17 patients
- 2-year local control of irradiated tumors, 96%
- Median PFS, 9.6 mo with majority of progression outside irradiated areas; 2-year OS, 77%
- Cumulative incidence of changing systemic therapy, 47% (at 1 year); 75% (at 2 years); median time to change in systemic therapy, 12.6 mo
- No grade 3-5 stereotactic RT toxicities

Conclusions

- Local control of irradiated oligoprogressive mRCC tumors was high; patients did not require a change in systemic therapy for a median of 1 year after

References

Cheung P, et al. J Clin Oncol. 2020;38 (suppl; abstr 5065).

Immune Checkpoint Inhibitors in Older Adults – IMDC Analysis

Study Design

- Real-world evidence in older adults with mRCC treated with immune checkpoint inhibitors (ICIs)
- Efficacy assessment: OS, time to treatment failure (TTF), ORR

Intervention

- PD-1 or PD-L1 ICI either as monotherapy or combination therapy, N=1427
  - Older adults (≥70 years), n=397 (28%)
  - Younger adults (<70 years), n=1,030 (72%)

Key Results

- ICI used in: 1st line, 40%; 2nd line, 48.5%; 3rd line, 11.5%
- ICI use in 1st line: 32.2% (older adults) vs 43% (younger adults), P<0.01
- Median OS (older vs younger), 25.1 vs 30.8 mo (P<0.01); median TTF, 6.9 vs 6.9 mo (P=0.40)
- Multivariate analyses: OS, HR 1.02 (P=0.86); TTF, HR 0.95 (P=0.59)
- Older vs younger: ORR, 24% vs 31% (P=0.01); response in 1st line, 31% vs 44% (P=0.02); response in 2nd/3rd line, 20% vs 20% (P=0.86)

Conclusions

- Older age is not an independent risk factor for survival; treatment selection should not be based solely on chronological age

References

Araujo DV, et al. J Clin Oncol. 2020;38 (suppl; abstr 5068).

Sequencing


PE OR PRINT ALL
CAN STATE
PATIENT IS BEING TREATED FOR:
HYPOGLYCEMIA
DIABETES
LAPSES OF CONSCIOUSNESS
ORTHOPEDIC
OVASCULAR
PSY
Patient?
date of last examination:
equency of any of the patients signs or symptoms, especially those that might affect the safe

Treatment Sequencing

Considerations for Treatment Selection

- With the drug therapies now available, patients may be treated with multiple lines of therapy over the course of disease
- The optimal sequence of available options is unknown
- Consider a patient's treatment history
- Preference should be given to agents with a different mechanism of action from the prior line; however, the efficacy of TKI followed by TKI has been demonstrated
- Consider the implications of the treatments' toxicity profiles

Real-world Evidence

- The International Metastatic Renal-cell Carcinoma Database Consortium (IMDC) provides the opportunity to gather insights into practice patterns
  - A retrospective analysis of first-line combination therapy options and sequential treatment is summarized on the following pages

International Metastatic Renal-cell Carcinoma Database Consortium (Dudani, 2019)

Design

- Using the IMDC dataset and data from 38 international centres, retrospective analysis of patients treated with any first-line IO-VEGF combination compared with ipilimumab-nivolumab (ipi-nivo)
- Objective: to compare efficacy of IO-VEGF combinations vs ipi-nivo in first-line mRCC; to describe practice patterns and effectiveness of second-line therapies
- Outcome measurements:
  - Response rates (first- and second-line)
  - Time to treatment failure (first- and second-line)
  - Time to next treatment
  - Overall survival

First-line Interventions

- IO-VEGF combinations (n=113) vs ipi-nivo (n=75)
- IO-VEGF combinations:
  - IO agents: atezolizumab, avelumab, nivolumab, pembrolizumab
  - VEGF-directed treatments: axitinib, bevacizumab, cabozantinib, sunitinib

Key Efficacy Outcomes with First-Line IO Combination Therapy

Outcome	IO-VEGF (n=113)	Ipi-nivo (n=75)	P value
Response rate (%)	33	40	0.4
Time to treatment failure (mo)	14.3	10.2	0.2
Time to next treatment (mo)	19.7	17.9	0.4
Overall survival (mo)	Not reached	Not reached	0.17
Adjusted hazard ratios (IO-VEGF vs ipi-nivo)			
Time to treatment failure	0.71 (0.46-1.12)		0.14
Time to next treatment	0.65 (0.38-1.11)		0.11
Overall survival	1.74 (0.82-3.68)		0.14

Second-line interventions

- 64 (34%) of patients received second-line treatment
  - 34 patients (30%) in IO-VEGF cohort
  - 30 patients (40%) in the ipi-nivo cohort

Second-line treatments	IO-VEGF (n=34)	Ipi-nivo (n=30)
Axitinib	5 (15%)	2 (7%)
Cabozantinib	9 (26%)	2 (7%)
Lenvatinib+everolimus	2 (6%)	0 (0%)
Nivolumab	5 (15%)	0 (0%)
Pazopanib	2 (6%)	9 (30%)
Sunitinib	9 (26%)	15 (50%)
Other (includes carboplatin+gemcitabine, temsirolimus, high-dose IL-2, pazopanib+Rad223)	2 (6%)	2 (7%)

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International Metastatic Renal-cell Carcinoma Database Consortium (Dudani, 2019)

Key Efficacy Outcomes with Second-Line Treatment

Outcome (with second-line VEGF-based therapy)	Prior IO-VEGF (n=27)	Prior ipi-nivo (n=28)	P value
Response rate	3/20 (15%)	9/20 (45%)	0.04
Time to treatment failure (mo)	3.7	5.4	0.4

- Response in patients who received first-line IO-VEGF followed by second-line nivolumab (5 patients, first-line IO-VEGF exposure was < 3 mo): PR, 1/5 ; SD, 1/5 ; PD, 3/5

Author Insights/Conclusions

- No significant differences in first-line outcomes between IO-VEGF combinations and ipi-nivo
- Most patients received VEGF-based therapy in the second line; in this group, second-line response rate was greater in patients who initially received ipi-nivo
  - Biologically plausible that VEGF-based second-line therapy would be more effective in VEGF-naïve ipi-nivo cohort
- Although patient numbers are small, the 60% rate of progressive disease observed in this study does not support the practice of treatment with IO agents following progression on first-line IO-VEGF combinations
- Given no clearly superior strategy in terms of efficacy, differences in toxicity, cost, logistics, prognostic categories, and patient preferences may be key factors when deciding between various first-line IO combination regimens

References

1. Dudani S, et al. European Urology. 2019;76:861-867.

IMDC = International Metastatic Renal-cell Carcinoma Database Consortium; IL-2 = interleukin 2; IO = immuno-oncology; IO-VEGF = immuno-oncology and vascular endothelial growth factor; ipi-nivo = ipilimumab and nivolumab; Rad-223 = radium 223; VEGF = vascular endothelial growth factor.

Drug Therapy

Drug Therapy

Immunotherapy Agents

Avelumab (BAVENCIO®)

Class

- Fully human immunoglobulin G1 (lgG1) monoclonal antibody directed against programmed death ligand 1 (PD-L1)

Indications

- No current Health Canada indication for RCC

Precautions

- Immune-mediated pneumonitis, hepatitis and colitis have been reported; monitor for signs and symptoms of immune-mediated events and administer corticosteroids for grade ≥2 events
- Immune-mediated thyroid disorders may occur during treatment; monitor for changes in thyroid function and for signs and symptoms of thyroid disorders; manage with replacement therapy (hypothyroidism) or anti-thyroid drug (hyperthyroidism)
- Immune-mediated adrenal insufficiency may occur in patients; monitor for signs and symptoms during and after treatment and administer corticosteroids for grade ≥3 events
- Type 1 diabetes mellitus may occur in patients; monitor for hyperglycemia and other signs and symptoms and treat with insulin
- May cause immune-mediated nephritis; monitor for elevated serum creatinine prior to and periodically during treatment and administer corticosteroids for grade ≥2 events

Dosing

- RCC (FDA in combination with axitinib): 800 mg IV over 60 minutes every 2 weeks with axitinib 5 mg PO BID, until disease progression or unacceptable toxicity
- RCC (JAVELIN Renal 101): 10 mg/kg IV over 60 minutes every 2 weeks with axitinib 5 mg PO BID
- Hepatic impairment
  - Mild/moderate impairment: no clinically important effects on clearance
  - Not studied in severe impairment
- Renal impairment
  - Mild/moderate/severe: no clinically important effects on clearance

Drug-drug Interactions

- Consult a pharmacist for a BPMH (best possible medication history) and drug interaction database check
- No known significant interactions

Drug-food Interactions

- None reported

Continued on next page

Avelumab (BAVENCIO®)

Common Toxicities*

- Fatigue
- Musculoskeletal pain
- Diarrhea
- Constipation
- Abdominal pain
- Nausea/vomiting
- Anemia
- Thrombocytopenia
- Infusion-related reaction
- Rash
- Peripheral edema
- Decreased appetite/weight
- Cough
- Dyspnea
- Urinary tract infection
- Elevated ALT/AST

Other Notable Toxicities

- Immune-mediated adverse reactions (pneumonitis, hepatitis, colitis, endocrinopathies, nephritis/renal dysfunction, myocarditis, pancreatitis)

Monitoring

- Monitor for signs and symptoms of immune-mediated adverse drug reactions such as pneumonitis, hepatitis, colitis, thyroid disorders, adrenal insufficiency, type 1 diabetes, nephritis
- Patients should be monitored for signs and symptoms of infusion reactions including pyrexia, chills, flushing, dyspnea, wheezing, back pain, abdominal pain, and urticaria

Dose Reductions and Discontinuation

- Dose escalation or reduction is not recommended; dosing delay or discontinuation may be required based on individual safety and tolerability
- Immune-mediated pneumonitis and hepatitis
  - Withhold for grade 2 immune-mediated events until resolution to grade 1 or less
  - Permanently discontinue for grade ≥3 events
- Immune-mediated colitis
  - Withhold for grade 2 or 3 events until resolution to grade 1 or less
  - Permanently discontinue for grade 4 or recurrent grade 3 immune-related events
- Immune-mediated thyroid disorders, adrenal insufficiency and hyperglycemia
  - Withhold for grade ≥3 events until resolution to grade 1 or less
- Immune-mediated nephritis and renal dysfunction
  - Withhold for grade 2 or 3 nephritis until resolution to grade 1 or less
  - Permanently discontinue for grade 4 nephritis
- Infusion reactions
  - Interrupt or slow the rate of infusion for grade 1 or grade 2 reactions
  - Permanently discontinue for grade 3 or 4 reactions

*Based on most common adverse reactions listed in Product Monograph for Merkel cell carcinoma and urothelial carcinoma clinical trials.

References

BAVENCIO (avelumab) Product Monograph. November 6, 2019
Avelumab: Drug Information. UpToDate. 2020. Topic 112481 Version 54.0

Ipilimumab (YERVOY®)

Class

- Fully human monoclonal antibody that binds to and blocks human cytotoxic T lymphocyte-associated antigen 4 (CTLA-4)

Indications

- Indicated, in combination with nivolumab (OPDIVO), for the treatment of adult patients with intermediate/poor-risk advanced or metastatic renal cell carcinoma

Precautions

- Immune-mediated enterocolitis, intestinal perforation, hepatitis, dermatitis, and neuropathies have been reported; monitor for signs and symptoms of immune-mediated events and administer corticosteroids for grade 3 or 4 events
- Immune-mediated endocrinopathies have been reported; monitor for signs and symptoms of hypophysitis, adrenal insufficiency, and hyper/hypothyroidism; corticosteroids and hormone replacement therapy should be initiated when pituitary imaging or laboratory tests of endocrine function are abnormal

Dosing

- RCC: 1 mg/kg IV over 30 minutes every 3 weeks for the first 4 weeks in combination with 3 mg/kg IV nivolumab administered intravenously over 30 minutes, followed by nivolumab single agent phase
- Hepatic impairment
  - Not studied in patients with hepatic impairment
  - Mild: no dose adjustment is considered necessary
- Renal impairment
  - Not studied in patients with renal impairment
  - Mild/moderate: no dose adjustment is considered necessary
  - Data are insufficient in severe renal impairment

Drug-drug Interactions

- Consult a pharmacist for a BPMH (best possible medication history) and drug interaction database check
- Impact of other drugs on metabolism of ipilimumab
  - Except for treatment of immune-mediated adverse reactions, systemic immunosuppressants (including systemic corticosteroids) should be avoided as they could interfere with the pharmacodynamic activity of ipilimumab
- Impact of ipilimumab on metabolism of other drugs
  - May enhance the hepatotoxic effect of vemurafenib

Drug-food Interactions

- None reported

Common Toxicities*

- Diarrhea
- Rash
- Pruritus
- Fatigue
- Headache
- Nausea
- Vomiting
- Decreased appetite
- Abdominal pain
- Elevated ALT/AST

Continued on next page

Ipilimumab (YERVOY®)

Other Notable Toxicities

- Immune-mediated adverse reactions (enterocolitis, hepatitis, dermatitis, neuropathy, endocrinopathy)

Monitoring

- Liver function tests must be assessed at baseline and before each dose
- Thyroid function test should be performed and electrolytes monitored before each dose
- Closely monitor patients for signs and symptoms of immune-mediated adverse events including, but not limited to, adrenal insufficiency, hypophysitis, enterocolitis, hepatitis, muscle weakness, sensory alterations, paresthesia, mental status changes, visual disturbances

Dose Reductions and Discontinuation

- Immune-mediated gastrointestinal adverse reactions
  - Withhold for uncontrolled, persistent or recurrent moderate diarrhea or colitis until resolution to grade 1 or less and management of corticosteroids is complete
  - Permanently discontinue for grade 3 or 4 diarrhea or colitis or if resolution to grade 1 or less does not occur
- Immune-mediated hepatitis
  - Withhold for grade 2 elevation in AST, ALT or total bilirubin until resolution to grade 1 or less and management of corticosteroids is complete
  - Permanently discontinue for grade 3 or 4 elevation in AST, ALT or total bilirubin
- Immune-mediated endocrinopathy
  - Withhold for symptomatic endocrinopathy until resolution to grade 1 or less and management of corticosteroids is complete
- Immune-mediated dermatologic adverse reactions
  - Withhold for grade 3 rash or widespread/intense pruritus until resolution to grade 1 or less and management of corticosteroids is complete
  - Permanently discontinue for grade 4 rash or grade 3 pruritus
- Immune-mediated neuropathy
  - Withhold for grade 2 unexplained motor neuropathy, muscle weakness, or sensory neuropathy (lasting >4 days) until resolution to grade 1 or less and management of corticosteroids is complete
  - Permanently discontinue for grade 3 or 4 motor or sensory neuropathy
- Discontinue for grade ≥3 immune-related reactions involving any other organ system (eg, nephritis, pneumonitis, pancreatitis, myocarditis)
- Discontinue for grade ≥2 immune-related eye disorders not responding to topical immunosuppressive therapy

*Based on most common adverse reactions listed in Clinical Trial Adverse Drug Reactions of Product Monograph.

References

YERVOY (ipilimumab) Product Monograph. January 13, 2020.

Ipilimumab Drug Information. UpToDate. 2020. Topic 16084 Version 170.0

Nivolumab (OPDIVO®)

Class

- Fully human immunoglobulin G4 (IgG4) monoclonal antibody directed against programmed death 1 (PD-1) receptor

Indications

- Indicated as monotherapy for the treatment of adult patients with advanced or metastatic renal cell carcinoma who have received prior anti-angiogenic therapy
- Indicated, in combination with ipilimumab (YERVOY), for the treatment of adult patients with intermediate/poor-risk advanced or metastatic renal cell carcinoma

Precautions

- Immune-mediated endocrinopathies have been reported; monitor for signs and symptoms of hypothyroidism, adrenal insufficiency, hypophysitis and diabetes; corticosteroids and hormone replacement therapy may be required as clinically indicated
- Immune-mediated gastrointestinal, hepatic, pulmonary and renal adverse reactions have been reported; monitor for signs and symptoms of immune-mediated events and administer corticosteroids for grade ≥2 events
- Immune-mediated skin adverse events have been reported; monitor patients for rash and administer corticosteroids for severe or life-threatening events
- May cause immune-mediated encephalitis; evaluate patient and administer corticosteroids
- Immune-mediated adverse reactions have occurred at higher frequencies when nivolumab was administered in combination with ipilimumab compared with nivolumab monotherapy
- Cases of myotoxicity have been reported; symptomatic patients should undergo prompt diagnostic workup to evaluate for myocarditis with close monitoring; initiate high dose steroids if myocarditis is suspected and seek cardiology consultation

Dosing

- RCC, as monotherapy: 3 mg/kg every 2 weeks or, 240 mg every 2 weeks or, 480 mg every 4 weeks, administered IV over 30 minutes
- RCC, in combination: 3 mg/kg IV over 30 minutes followed by 1 mg/kg IV ipilimumab over 30 minutes on same day every 3 weeks for first 4 doses; after completion of combination phase, administer nivolumab as single agent
- Hepatic impairment
  - Mild: no dose adjustment is considered necessary
  - Not studied in patients with moderate or severe hepatic impairment
- Renal impairment
  - Mild/moderate: no dose adjustment is considered necessary
  - Data are insufficient in severe renal impairment

Drug-drug Interactions

- Consult a pharmacist for a BPMH (best possible medication history) and drug interaction database check
- Impact of other drugs on metabolism of nivolumab
  - Except for treatment of immune-mediated adverse reactions, systemic immunosuppressants (including systemic corticosteroids) should be avoided as they could interfere with the pharmacodynamic activity of nivolumab

Drug-food Interactions

- None reported

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Nivolumab (OPDIVO®)

Common Toxicities*

- Fatigue/malaise
- Headache
- Rash
- Pruritus
- Diarrhea
- Nausea
- Decreased appetite
- Increased serum triglycerides
- Elevated ALT/AST/Alk Phos
- Asthenia
- Musculoskeletal pain

Other Notable Toxicities

- Immune-mediated adverse reactions (dermatitis, endocrinopathy, gastrointestinal, hepatic, pulmonary, renal, cardiac)

Monitoring

- Liver function tests, thyroid function tests, blood glucose and electrolytes should be monitored prior to and periodically during treatment
- Closely monitor patients for signs and symptoms of immune-mediated adverse events including, but not limited to, gastrointestinal, hepatic, renal, dermatologic, and neurologic reactions
- Continuously monitor for cardiac and pulmonary reactions

Dose Reductions and Discontinuation

- Endocrinopathy
  - Withhold for grade 2 or 3 hypo/hyperthyroidism, grade 2 hypophysitis or adrenal insufficiency, or grade 3 diabetes until symptoms resolve and management with corticosteroids is complete
  - Permanently discontinue for grade 4 hypo/hyperthyroidism, grade 3 or 4 hypophysitis or adrenal insufficiency, or grade 4 diabetes
- Gastrointestinal adverse events
  - Withhold for grade 2 or 3 diarrhea or colitis until symptoms resolve and management with corticosteroids is complete
  - Permanently discontinue for grade 4 diarrhea colitis (or grade 3 if in combination with ipilimumab)
- Hepatic adverse events
  - Withhold for grade 2 elevation in AST, ALT or bilirubin until lab values return to baseline and management with corticosteroids is complete
  - Permanently discontinue for grade 3 or 4 elevation in AST, ALT or bilirubin
- Pneumonitis
  - Withhold for grade 2 events until symptoms resolve, radiographic abnormalities improve and management with corticosteroids is complete
  - Permanently discontinue for grade 3 or 4 events
- Renal impairment
  - Withhold for grade 2 creatinine elevation until lab values return to baseline and management with corticosteroids is complete
  - Permanently discontinue for grade 3 or 4 creatinine elevation
- Dermatologic adverse events
  - Withhold for grade 3 rash until symptoms resolve and management with corticosteroids is complete

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Nivolumab (OPDIVO®)

- Dermatologic adverse events (con't'd)
  - Withhold for suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)
  - Permanently discontinue for grade 4 rash or confirmed SJS/TEN
- Encephalitis
  - Withhold for new-onset moderate or severe neurologic signs or symptoms until symptoms resolve and management with corticosteroids is complete
  - Permanently discontinue for immune-mediated encephalitis
- Myocarditis
  - Withhold for grade 2 myocarditis until symptoms resolve and management with corticosteroids is complete; retreatment may be considered after recovery
  - Permanently discontinue for grade 3 myocarditis

*Based on most common adverse reactions listed in UpToDate and Clinical Trial Adverse Drug Reactions of Product Monograph.

References

Nivolumab (OPDIVO) Product Monograph. February 13, 2020.

Nivolumab Drug Information. UpToDate. 2020. Topic 98764 Version 133.0

Pembrolizumab (KEYTRUDA®)

Class

- Selective humanized immunoglobulin G4 (IgG4) kappa monoclonal antibody directed against programmed death 1 (PD-1) receptor

Indications

- Indicated for the treatment of patients with advanced or metastatic renal cell carcinoma in combination with axitinib, in adults with no prior systemic therapy for metastatic RCC

Precautions

- Immune-mediated pneumonitis, colitis, hepatitis, and nephritis have been reported; monitor for signs and symptoms of immune-mediated events and administer corticosteroids for grade ≥2 events
- Immune-mediated endocrinopathies have been reported; monitor for signs and symptoms of adrenal insufficiency, hypophysitis, diabetes and thyroid disorders; corticosteroids and hormone replacement therapy may be required as clinically indicated
- Immune-mediated skin adverse events have been reported; monitor patients for severe skin reactions and administer corticosteroids depending on severity
- When given with axitinib, higher than expected frequencies of grade 3 and 4 liver enzyme elevations have been reported in patients with advanced RCC; monitor liver enzymes before and frequently throughout treatment; corticosteroids may be considered depending on severity

Dosing

- RCC: 200 mg IV over 30 minutes every 3 weeks until unacceptable toxicity, disease progression, or for up to 24 months or 35 doses, whichever is longer, in combination with:
  - Axitinib 5 mg PO twice daily until unacceptable toxicity or disease progression
  - Per KEYNOTE-426, axitinib dose escalation may be considered for patients who tolerated the initial 5 mg dose, at intervals of 6 weeks or longer (at least 2 treatment cycles)
- Hepatic impairment
  - Mild: no dose adjustment is considered necessary
  - Not studied in patients with moderate or severe hepatic impairment
- Renal impairment
  - Mild/moderate: no dose adjustment is considered necessary
  - Not studied in patients with severe renal impairment

Drug-drug Interactions

- Consult a pharmacist for a BPMH (best possible medication history) and drug interaction database check
- Impact of pembrolizumab on metabolism of other drugs
  - May enhance adverse/toxic effect of thalidomide analogues; avoid combination

Drug-food Interactions

- None reported

Common Toxicities*

- Hyper/hypothyroidism
- Diarrhea
- Nausea
- Stomatitis
- PPES
- Hypertension
- Elevated ALT/AST
- Mucosal inflammation
- Proteinuria
- Dysphonia
- Pruritus
- Rash

Continued on next page

Pembrolizumab (KEYTRUDA®)

Common Toxicities* (con't'd)

- Asthenia
- Fatigue
- Decreased appetite
- Arthralgia

Other Notable Toxicities

- Immune-mediated adverse reactions (endocrinopathy, pneumonitis, colitis, hepatitis, nephritis)
- Myasthenia gravis, myocarditis, necrotising fasciitis, pneumonitis

Monitoring

- Liver function tests, thyroid function tests, and serum electrolytes should be monitored at start of treatment, periodically during treatment and as clinically indicated
- Closely monitor patients for signs and symptoms of immune-mediated adverse events including, but not limited to, dyspnea, hypoxia, gastrointestinal reactions, hepatic or renal abnormalities, skin reactions, and neurologic disturbances

Dose Reductions and Discontinuation

- Pneumonitis
  - Withhold for grade 2 events until resolution to grade 0 or 1
  - Permanently discontinue for grade 3 or 4 events or recurrent grade 2 events
- Colitis
  - Withhold for grade 2 or 3 events until resolution to grade 0 or 1
  - Permanently discontinue for grade 4 or recurrent grade 3 events
- Nephritis
  - Withhold for grade 2 events (creatinine >1.5 to ≤3 times ULN) until resolution to grade 0 or 1
  - Permanently discontinue for grade 3 or 4 events (creatinine >3 times ULN)
- Endocrinopathy
  - Withhold for grade 3 or 4 hypophysitis, diabetes associated with grade >3 hyperglycemia or ketoacidosis, or grade ≥3 hyperthyroidism until resolution to grade 0 or 1
  - Permanently discontinue for grade 4 or recurrent grade 3 events
- Hepatitis (for pembrolizumab + axitinib)
  - Withhold both pembrolizumab and axitinib for ALT or AST ≥3 times ULN but <10 times ULN without concurrent total bilirubin ≥2 times ULN until resolution to grade 0 or 1
  - Permanently discontinue both pembrolizumab and axitinib for ALT or AST ≥10 times ULN or >3 times ULN with concurrent total bilirubin ≥2 times ULN
- Dermatologic reactions
  - Withhold for grade 3 skin reactions or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) until resolution to grade 0 or 1
  - Permanently discontinue for grade 4 skin reactions or confirmed SJS/TEN
- Permanently discontinue for grade 3 or 4 myocarditis, encephalitis, or Guillain-Barré syndrome
- Permanently discontinue for grade 3 or 4 infusion-related reactions
- Permanently discontinue for other immune-related adverse reactions of grade 4 or recurrent grade 3 severity

*Based on most common adverse reactions listed in UpToDate and Clinical Trial Adverse Drug Reactions of Product Monograph.

References

Pembrolizumab (KEYTRUDA) Product Monograph. December 27, 2019.
Pembrolizumab Drug Information. UpToDate. 2020. Topic 96957 Version 159.0

Anti-angiogenic Therapy (VEGF Receptor TKIs)

VEGF Receptor TKIs

Axitinib (INLYTA®)

Class

- VEGF receptor-tyrosine kinase inhibitor

Indications

- Indicated for treatment of patients with metastatic renal cell carcinoma of clear cell histology after failure of prior systemic therapy with either a cytokine or the VEGFR-TKI, sunitinib

Precautions

- Hypertension is a common adverse event; ensure blood pressure is well controlled prior to starting treatment
- Congestive heart failure/cardiomyopathy has been reported; monitor for signs and symptoms at baseline and periodically throughout treatment
- Arterial and venous thromboembolism have been reported; use with caution in patients at risk or who have history of these events
- Hypo- and hyperthyroidism have been reported; monitor thyroid function prior to starting treatment and periodically throughout
- Events of gastrointestinal perforation or fistula have occurred; monitor for symptoms periodically throughout treatment
- Use with caution in patients with significant risk for hemorrhage
- Reversible posterior leukoencephalopathy syndrome has been reported

Dosing

- RCC: Starting dose of 5 mg PO twice daily
  - Increase to 7 mg and 10 mg twice daily if tolerating lower dose
- May be taken with or without food; swallow whole with glass of water
- Hepatic impairment
  - Mild (Child-Pugh A): no dose adjustment
  - Moderate (Child-Pugh B): decrease starting dose by half in patients
  - Severe (Child-Pugh C): not studied, avoid use in this population
- Renal impairment
  - Not studied in patients with renal impairment
  - Mild to severe: no dose adjustments based on renal function are required
  - Caution in patients with end-stage renal disease

Drug-drug Interactions

- Consult a pharmacist for a BPMH (best possible medication history) and drug interaction database check
- Impact of other drugs on metabolism of axitinib
  - Substrate of CYP3A4/5 (major); avoid strong inducers and inhibitors
  - Substrate of CYP1A2 (minor), CYP2C19 (minor), UGT1A1(minor)

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Axitinib (INLYTA®)

- Notable/select drug interactions (not a complete list):
  - Co-administration with drugs that increase gastric pH (eg, proton pump inhibitors, H2-receptor antagonists, antacids) may decrease axitinib exposure

Drug-food Interactions

- May be taken with or without food
- Grapefruit, grapefruit juice and products containing grapefruit extract may increase concentrations and should be avoided
- St John's Wort may decrease concentration of axitinib

Common Toxicities*

- Diarrhea
- Nausea
- Vomiting
- Constipation
- Fatigue
- Asthenia
- Weight loss
- Decreased appetite
- Dysphonia
- Palmar-plantar erythrodysesthesia syndrome
- Hypertension

Other Notable Toxicities

- Congestive heart failure/cardiomyopathy
- Thrombotic events
- Cardiac dysfunction
- Hemorrhagic events
- Gastrointestinal perforation/fistula formation
- Elevated ALT/AST/Alk Phos

Monitoring

- Prior and during course of treatment, monitor for:
  - Hypertension
  - Signs/symptoms of congestive heart failure/cardiomyopathy
  - Decreased heart rate
  - Thyroid dysfunction
  - Increased hemoglobin/hematocrit
  - Symptoms of GI perforation or fistula formation
  - Proteinuria
  - Elevated liver enzymes
  - Elevated creatinine

Dose Reductions and Discontinuation

- Management of some adverse reaction may require temporary or permanent discontinuation and/or dose reduction
- If dose reduction to manage adverse reactions is necessary, the dose may be reduced from 5 mg to 3 mg twice daily and further to 2 mg twice daily

*Based on most common adverse reactions listed in Clinical Trial Adverse Drug Reactions of Product Monograph.

References

Axitinib (INLYTA) Product Monograph. January 3, 2020.

Axitinib Drug Information. UpToDate. 2020. Topic 17141 Version 153.0

Cabozantinib (CABOMETYX™)

Class

- VEGF receptor tyrosine kinase inhibitor

Indications

- Indicated for treatment of advanced renal cell carcinoma:
  - In treatment-naïve adults with intermediate or poor risk
  - In adult patients who have received prior VEGF-targeted therapy

Precautions

- Arterial and venous thromboembolism have been reported; use with caution in patients at risk or who have history of these events
- Increased incidence of treatment-emergent hypertension, including hypertensive crisis; ensure blood pressure is well controlled prior to starting treatment and monitor regularly during treatment
- QTc prolongation; monitor patients who have risk factors for Torsades de pointes or taking medications known to prolong QT interval
- PR prolongation; exercise caution in patients with low baseline heart rate, history of syncope or arrhythmia, sick sinus syndrome, sinoatrial block, AV block, ischemic heart disease or congestive heart failure
- Hypothyroidism has been reported; monitor thyroid function prior to starting treatment and periodically throughout
- Events of gastrointestinal perforation or fistula have occurred; monitor for symptoms periodically throughout treatment
- Hepatotoxicity has been reported; monitor liver enzymes before initiation and periodically throughout treatment
- Use with caution in patients with significant risk for hemorrhage

Dosing

- RCC: 60 mg PO daily
- Do not administer with food; instruct patients to not eat for at least 2 hours before and at least 1 hour after administration
- Hepatic impairment
  - Mild/moderate: reduce starting dose to 40 mg daily
  - Severe: not recommended
- Renal impairment
  - Mild/moderate: use with caution
  - Severe: not recommended

Drug-drug Interactions

- Consult a pharmacist for a BPMH (best possible medication history) and drug interaction database check
- Impact of other drugs on metabolism of cabozantinib
  - Substrate of CYP3A4 (major); avoid strong inducers and inhibitors
  - Substrate of CYP2C9 (minor)

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Cabozantinib (CABOMETYX™)

- Impact of cabozantinib on metabolism of other drugs
  - P-glycoprotein inhibition
- Notable/select drug interactions (not a complete list):
  - May enhance the toxic effects of bisphosphonate derivatives

Drug-food Interactions

- Do not administer with food; patients should not eat for at least 2 hours before and at least 1 hour after taking cabozantinib
- Grapefruit or grapefruit juice may increase concentrations and should be avoided
- St John's Wort may decrease concentration of cabozantinib

Common Toxicities*

- Diarrhea
- Fatigue
- Hypertension
- Decreased appetite
- Palmar-plantar erythrodysesthesia syndrome
- Nausea
- Vomiting
- Weight loss
- Elevated ALT/AST
- Dysgeusia
- Thrombocytopenia
- Stomatitis
- Anemia
- Dyspepsia
- Constipation

Other Notable Toxicities

- Thrombotic events
- Acute renal failure
- Hyponatremia
- Hypophosphatemia

Monitoring

- Monitor heart rate and blood pressure; ECG should be performed prior to initiating treatment and periodically throughout to monitor QTc and PR interval prolongation
- Assess electrolyte levels, liver function and thyroid function at baseline/before start of treatment and regularly during treatment

Dose Reductions and Discontinuation

- If dose reduction to manage adverse reactions is necessary, the dose may be reduced to 40 mg daily, and then to 20 mg daily
- Dose interruptions are recommended for grade ≥3 or intolerable grade 2 reactions
- Discontinue for:
  - Development of unmanageable fistula or GI perforation
  - Severe hemorrhage
  - Arterial thromboembolic event
  - Hypertensive crisis or severe hypertension
  - Nephrotic syndrome
  - Reversible posterior leukoencephalopathy syndrome

*Based on most common adverse reactions listed in Clinical Trial Adverse Drug Reactions of Product Monograph.

References

Cabozantinib (CABOMETYX) Product Monograph. November 7, 2019.

Cabozantinib Drug Information. UpToDate. 2020. Topic 87299 Version 152.0

Lenvatinib (LENVIMA®)

Class

- VEGF receptor-tyrosine kinase inhibitor

Indications

- Indicated in combination with everolimus for the treatment of patients with advanced renal cell carcinoma following one prior VEGF-targeted therapy

Precautions

- Hypertension is a common adverse event; ensure blood pressure is well controlled prior to starting treatment and regularly monitor during treatment
- Cardiac failure has been reported; monitor for signs and symptoms of cardiac decompensation
- Arterial thromboembolism has been reported; use with caution in patients at risk or who have history of these events
- QTc prolongation; monitor patients who have risk factors for Torsades de pointes; not recommended in patients with congenital long QT syndrome or who are taking medications known to prolong QT interval
- Hypothyroidism has been reported; monitor thyroid function prior to starting treatment and monthly throughout
- Initiate prompt medical management for the development of diarrhea
- Events of gastrointestinal perforation or fistula have occurred; monitor for symptoms periodically throughout treatment and discontinue treatment if development occurs
- Hemorrhagic events have been reported; use with caution in patients with significant risk for hemorrhage
- Hepatoxicity has been reported; monitor liver function prior to starting treatment and regularly thereafter
- Reversible posterior leukoencephalopathy syndrome has been reported

Dosing

- RCC: 18 mg (one 10 mg capsule and two 4 mg capsules) in combination with everolimus 5 mg PO daily
- Taken at the same time each day, with or without food; should be swallowed whole with water
- Hepatic impairment, RCC
  - Mild/moderate: no dose adjustment is required
  - Severe (Child-Pugh C): recommended dose in 10 mg daily
- Renal impairment, RCC
  - Mild/moderate: no dose adjustments are required
  - Severe: recommended dose is 10 mg daily
  - Not studied in patients with end-stage renal disease, use is not recommended

Drug-drug Interactions

- Consult a pharmacist for a BPMH (best possible medication history) and drug interaction database check
- Impact of other drugs on metabolism of lenvatinib
  - Substrate of CYP3A4 (minor)
  - Substrate of BCRP/ABCG2 and P-glycoprotein/ABCB1
- Impact of lenvatinib on metabolism of other drugs
  - UGT1A9 inhibition
- Notable/select drug interactions (not a complete list):
  - May enhance QT-prolonging effect of other drugs

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Lenvatinib (LENVIMA®)

Drug-food Interactions

- May be taken with or without food

Common Toxicities*

- Diarrhea
- Fatigue
- Arthralgia/myalgia
- Decreased appetite
- Nausea
- Vomiting
- Weight loss
- Hemorrhagic events
- Stomatitis/oral inflammation
- Hypertension
- Peripheral edema
- Cough
- Abdominal pain
- Dyspnea
- Rash
- Proteinuria

Other Notable Toxicities

- Renal failure
- Hyponatremia

Monitoring

- Regularly monitor blood pressure, complete blood count, electrolytes, electrocardiogram, urine protein
- Monitor for clinical signs and symptoms of cardiac decompensation
- Check TSH level before treatment and monthly throughout
- Monitor liver function before starting treatment and then regularly during treatment

Dose Reductions and Discontinuation

- Dose interruptions are recommended for the following adverse reactions until resolution to grade 0, 1 or baseline:
  - Grade 3 hypertension, cardiac dysfunction, hepatotoxicity, nausea, vomiting, diarrhea, renal failure/impairment, hemorrhage
  - Any grade thrombotic event
  - Proteinuria >2 g/24 hours
  - QTc prolongation >500 ms
- Hold or discontinue for reversible posterior leukoencephalopathy syndrome
- Discontinue for the following adverse reactions
  - Grade 4 hypertension, cardiac dysfunction, hepatoxicity, nausea, vomiting, diarrhea, renal failure/impairment, hemorrhage
  - Grade 3 or 4 hepatic failure, fistula
  - Nephrotic syndrome
  - Any grade gastrointestinal perforation
- Dose modifications for other persistent and intolerable grade 2 or 3 adverse reactions or grade 4 lab abnormalities:
  - Hold until resolved to grade 0, 1 or baseline
  - First occurrence: 14 mg PO daily
  - Second occurrence: 10 mg PO daily
  - Third occurrence: 8 mg PO daily

*Based on most common adverse reactions listed in Clinical Trial Adverse Drug Reactions of Product Monograph.

References

Lenvatinib (LENVIMA) Product Monograph. September 19, 2019.

Lenvatinib Drug Information. UpToDate. 2020. Topic 99962 Version 116.0

Pazopanib (VOTRIENT®)

Class

- VEGF receptor tyrosine kinase inhibitor

Indications

- Indicated for the treatment of patients with metastatic renal cell (clear cell) carcinoma as first-line systemic therapy or as second-line systemic therapy after treatment with cytokines for metastatic disease

Precautions

- Cases of hepatic failure and increases in serum transaminases and bilirubin have been reported; monitor hepatic function; dose interruption, reduction or discontinuation may be required; pazopanib should not be used in patients with baseline plasma bilirubin >1.5 times ULN (with direct bilirubin >35%) and ALT elevations of >2 times ULN, or who have moderate or severe hepatic impairment
- Hypertension is a common adverse event; ensure blood pressure is well controlled prior to starting treatment and regularly monitor during treatment; pazopanib should not be used in patients with uncontrolled hypertension
- Cardiac dysfunction has been reported; monitor for signs and symptoms of congestive heart failure and perform baseline and periodic evaluation of left ventricular ejection fraction in patients at risk of cardiac dysfunction
- QTc prolongation; exercise caution in patients with a history of QT prolongation, those taking antiarrhythmics and other medications that may prolong QT interval; baseline and periodic ECG monitoring should be performed, and electrolytes should be maintained within normal limits
- Arterial and venous thromboembolism and thrombotic microangiopathy have been reported; use with caution in patients at risk or who have history of thrombotic events
- Hypothyroidism has been reported; proactively monitor thyroid function
- Events of gastrointestinal perforation or fistula have occurred; exercise caution in patients at risk and monitor for signs and symptoms periodically throughout treatment
- Use with caution in patients with significant risk for hemorrhage
- Reversible posterior leukoencephalopathy syndrome/reversible posterior leukoencephalopathy has been reported

Dosing

- RCC: 800 mg PO daily
- Not to be taken with food
- Hepatic impairment
  - Mild: not studied in patients with mild impairment, caution recommended
  - Moderate/severe: not recommended
  - Baseline plasma bilirubin >1.5 x ULN and ALT elevations >2 x ULN: not recommended
- Renal impairment
  - Mild/moderate: no dose adjustments recommended
  - Severe: not recommended

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Pazopanib (VOTRIENT®)

Drug-drug Interactions

- Consult a pharmacist for a BPMH (best possible medication history) and drug interaction database check
- Impact of other drugs on metabolism of pazopanib
  - Substrate of CYP3A4 (major); avoid strong inhibitors and inducers
  - Substrate of CYP1A2 (minor)
  - Substrate of P-glycoprotein/ABCB1
  - Substrate of BCRP/ABCG2
- Impact of pazopanib on metabolism of other drugs
  - CYP3A4 inhibition (weak)
  - CYP2D6 inhibition (weak)
  - CYP2C8 inhibition (weak)
  - UGT1A1 inhibition
- Notable/select drug interactions (not a complete list):
  - Co-administration with drugs that increase gastric pH (eg, proton pump inhibitors, H2-receptor antagonists, antacids) may decrease pazopanib exposure and should be avoided

Drug-food Interactions

- Should be not be taken with food (at least 1 hour before or 2 hours after a meal)
- Grapefruit, grapefruit juice and products containing grapefruit extract may affect CYP3A4 and PgP activity and should be avoided
- St John's Wort may decrease concentration of pazopanib

Common Toxicities*

- Diarrhea
- Nausea
- Vomiting
- Hypertension
- Hair colour changes
- Anorexia

Other Notable Toxicities

- Hepatic effects
- QT prolongation/Torsade de Pointes
- Thrombotic events
- Cardiac dysfunction
- Hemorrhagic events
- Gastrointestinal perforation/fistula

Monitoring

- Monitor for hypertension prior to and during course of treatment
- Baseline and periodic evaluation of left ventricular ejection fraction is recommended for patients at risk of cardiac dysfunction
- Complete blood counts, clinical chemistries, urinalyses should be measured at baseline and periodically throughout treatment
- Perform ECG evaluations at baseline and periodically throughout treatment
- Proactive monitoring of thyroid function is recommended
- Monitor for sign/symptoms of tumor lysis syndrome at baseline and during treatment for patients at risk; monitor hydration status closely
- Monitor liver function before start of treatment and regularly during treatment (at weeks 2, 4, 6 and 8, at month 3 and at month 4, and as clinically indicated); periodic monitoring should then continue after month 4

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Pazopanib (VOTRIENT®)

- Baseline and periodic urinalyses during treatment are recommended and patients should be monitored for worsening proteinuria with measurement of 24-hour urine protein as clinically indicated
- Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis

Dose Reductions and Discontinuation

- Dose modification should be in 200 mg increments in a stepwise fashion based on individual tolerability in order to manage adverse reactions
- See product monograph for dose modifications (interruption and reinitiation, discontinuation) for:
  - Cardiac dysfunction
  - Hepatic dysfunction, ALT elevations with/without bilirubin elevations
  - Thrombotic complications
  - Proteinuria
  - Pulmonary complications

*Based on most common adverse reactions listed in Clinical Trial Adverse Drug Reactions of Product Monograph.

References

Pazopanib (VOTRIENT) Product Monograph. February 28, 2020.

Pazopanib Drug Information. UpToDate. 2020. Topic 9524 Version 223.0

Sunitinib (SUTENT®)

Class

- VEGF receptor-tyrosine kinase inhibitor

Indications

- Indicated for the treatment of metastatic renal cell carcinoma of clear cell histology

Precautions

- Hypertension is a common adverse event; monitor blood pressure and treat as appropriate with standard anti-hypertensive medication
- Cardiovascular events including heart failure, myocardial disorders and cardiomyopathy have been reported; carefully monitor for signs and symptoms of heart failure; consider baseline and periodic evaluations of left ventricular function
- QTc prolongation; monitor patients who have risk factors for Torsades de pointes or taking medications known to prolong QT interval
- Arterial and venous thromboembolism and thrombotic microangiopathy have been reported; use with caution in patients at risk or who have history of thrombotic events
- Hypothyroidism has been reported; measure baseline thyroid function and monitor routinely every 3 months; observe closely for signs and symptoms of thyroid dysfunction
- Events of gastrointestinal perforation or fistula have occurred; monitor for symptoms periodically throughout treatment
- Use with caution in patients with significant risk for hemorrhage
- Associated with hepatoxicity; monitor liver function tests before starting treatment and during each treatment cycle

Dosing

- RCC: 50 mg PO daily on schedule of 4 weeks on treatment followed by 2 weeks off
- May be taken with or without food
- Hepatic impairment
  - Mild (Child-Pugh Class A)/moderate (Child-Pugh Class B): dose adjustment might not be necessary
  - Severe: not studied in severe (Child-Pugh Class C) impairment
- Renal impairment
  - Mild to severe: no adjustment to starting dose
  - End-stage renal disease on hemodialysis: no adjustment to starting dose

Drug-drug Interactions

- Consult a pharmacist for a BPMH (best possible medication history) and drug interaction database check
  - Impact of other drugs on metabolism of sunitinib
  - Substrate of CYP3A4 (major); avoid potent inducers and inhibitors
- Notable/select drug interactions (not a complete list):
  - Concomitant use with another QT-prolonging drug is discouraged
  - Use with caution in combination with drugs that prolong PR interval

Drug-food Interactions

- May be taken with or without food
- Grapefruit or grapefruit juice may increase concentrations and should be avoided
- St John's Wort may decrease concentration of sunitinib; do not take concomitantly

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Sunitinib (SUTENT®)

Common Toxicities*

- Fatigue
- Diarrhea
- Nausea
- Stomatitis
- Vomiting
- Dyspepsia
- Anorexia
- Dysgeusia
- Constipation
- Hypertension
- Rash
- Hand-foot syndrome
- Skin discoloration
- Ejection fraction decline

Other Notable Toxicities

- Left ventricular dysfunction
- QT interval prolongation
- Hemorrhage
- Thyroid dysfunction
- Adrenal dysfunction

Monitoring

- Perform complete blood count and serum chemistries before starting each treatment cycle
- Baseline laboratory measurement of thyroid function is recommended; routine monitoring should be performed every 3 months and observe for signs and symptoms of thyroid dysfunction during treatment
- Baseline urinalysis is recommended; monitor for development or worsening proteinuria
- ECG should be performed at baseline and periodically during treatment
- Check blood glucose levels regularly

Dose Reductions and Discontinuation

- Dose modification of 12.5 mg based on individual safety and tolerability

*Based on most common adverse reactions listed in Clinical Trial Adverse Drug Reactions of Product Monograph.

References

Sunitinib (SUTENT) Product Monograph. July 11, 2019.

Sunitinib Drug Information. UpToDate. 2020. Topic 10305 Version 217.0

mTOR Targeted Agents

Everolimus (AFINITOR®)

Class

- Inhibitor of mTORC1

Indications

- Indicated for the treatment of patients with metastatic renal cell carcinoma of clear cell morphology, after failure of initial treatment with either of the VEGF-receptor TKIs sunitinib or sorafenib

Precautions

- Co-administration with strong inhibitors of CYP3A4 and/or PgP should be avoided
- Increased risk of angioedema in patients taking concomitant ACE inhibitor
- Hyperlipidemia and hyperglycemia have been reported; monitor fasting lipid profile and serum glucose prior to start of therapy and periodically thereafter
- Stomatitis is common and usually occurs within the first 8 weeks of treatment; topical treatments are recommended
- Hematologic abnormalities have been reported; monitor complete blood count prior to start of therapy and periodically thereafter
- Hemorrhage (all grades) has been reported; exercise caution with concomitant use of active substances that increase risk of bleeding and monitor for signs and symptoms
- May predispose patients to infections, including those with opportunistic pathogens
- There are unconfirmed reports of rhabdomyolysis; monitor for signs and symptoms especially if concomitant statin is being used
- Elevated serum creatinine and proteinuria have been reported; monitor renal function prior to start of therapy and periodically thereafter
- Non-infectious pneumonitis is a class effect of rapamycin derivatives; advise patients to promptly report any new or worsening respiratory symptoms

Dosing

- RCC: 10 mg once daily; administer consistently with or without food
- Hepatic impairment
  - Mild (Child-Pugh A): recommended dose is 7.5 mg daily; decrease to 5 mg if not well-tolerated
  - Moderate (Child-Pugh B): recommended dose is 5 mg daily; decrease to 2.5 mg if not well-tolerated
  - Severe (Child-Pugh C): if benefit outweighs risk, 2.5 mg daily may be used but must not be exceeded
- Renal impairment
  - Not studied in patients with renal impairment
  - No adjustment is recommended in renal impairment given renal metabolism and clearance is < 5% total

Drug-drug Interactions

- Consult a pharmacist for a BPMH (best possible medication history) and drug interaction database check
- Impact of other drugs on metabolism of everolimus
  - Substrate of CYP3A4 and PgP; avoid strong inducers or inhibitors

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Everolimus (AFINITOR®)

- Impact of everolimus on metabolism of other drugs
  - CYP3A4 inhibitor (weak)
- Notable/select drug interactions (not a complete list):
  - May inhibit metabolism of substrates of CYP3A4 including statins; exercise caution with concomitant administration
  - Patients taking concomitant ACE inhibitor may be at increased risk of angioedema
  - Immunosuppressants may enhance the adverse/toxic effect of live vaccines and may diminish the therapeutic effect of live vaccines; avoid use of live vaccines; live-attenuated vaccines should not be given for at least 3 months after immunosuppressants

Drug-food Interactions

- Administer consistently with or without food
- Grapefruit, grapefruit juice, star fruit, Seville oranges, and other inhibitors of cytochrome P450 and PgP activity may increase everolimus exposure; avoid use during treatment
- St. John's wort induces CYP3A4 and may decrease everolimus blood levels; avoid use

Common Toxicities*

- Stomatitis
- Infections
- Fatigue
- Diarrhea
- Anemia
- Asthenia
- Cough

Other Notable Toxicities

- Dyspnea
- Edema
- Hypercholesterolemia
- Hyperglycemia
- Pneumonitis
- Elevated ALT/AST/Alk Phos

Monitoring

- CBC, serum chemistry and urinary protein should be performed at start of treatment and periodically thereafter

Dose Reductions and Discontinuation

- Non-infectious pneumonitis
  - Withhold for grade 2 or 3 events until symptoms resolve to grade ≤1
  - Discontinue for grade 4 events and consider corticosteroid treatment
- Stomatitis
  - Withhold for grade 2 or 3 events until resolution to grade ≤1
  - Discontinue for grade 4 events
- Other non-hematologic toxicities
  - Withhold for intolerable or recurrent grade 2 events or grade 3 events until resolution to grade ≤1
  - Discontinue for grade 4 events
- Metabolic events
  - Temporary dose interruption for grade 3 events
  - Discontinue for grade 4 events
- Hepatic impairment
  - Dose adjustments should be made if Child-Pugh status changes

*Based on most common adverse reactions listed in Clinical Trial Adverse Drug Reactions of Product Monograph.

References

Everolimus (AFINITOR) Product Monograph. November 16, 2017.

Everolimus Drug Information. UpToDate. 2020. Topic 9078 Version 243.0

Managing Toxicities

Managing Toxicities

Immune-related Adverse Events (IrAEs)

General IrAE Management Principles

- Provide patient and caregivers with timely and up-to-date education about immunotherapy, including mechanism of action and possible IrAEs prior to and throughout treatment
- Counsel patient and caregivers to report IrAEs to their oncologist to avoid delays in AE management (ie, treatment with steroids)
- Providing patients with a wallet card can help them alert other physicians such as emergency department staff, that they are receiving immunotherapy, that IrAE management algorithms must be followed, and that the on-call oncologist should be contacted for treatment advice
- Suspect that new symptoms are treatment related
- In general, continue immunotherapy with close monitoring for grade 1 toxicities
- Hold immunotherapy for most grade 2 toxicities
  - May resume when symptoms/lab values resolve to grade ≤1
  - Corticosteroids (initial dose: 0.5-1 mg/kg/day prednisone or equivalent) may be administered
- Hold immunotherapy for grade 3 toxicities and initiate high-dose corticosteroids (1-2 mg/kg/day prednisone or IV methylprednisolone)
  - Involve specialists early, eg, endocrinologists, gastroenterologists
  - Infliximab may be offered if symptoms do not improve within 48-72 hours of high-dose steroid
  - Taper steroids over course of at least 4-6 weeks
  - Consider other immunosuppressants if experiencing difficulties with steroid tapering
- May re-challenge with immunotherapy once symptoms/lab values resolve to grade ≤1
  - Proceed with caution in patients with early-onset IrAEs
- Permanently discontinue immunotherapy for grade 4 toxicities
  - Exception applies to endocrinopathies that may be controlled with hormone replacement

Baseline Assessment

See page 22:
Pre-Therapy Assessment and Monitoring During Therapy with Immune-Checkpoint Inhibitors (Adapted from NCCN v1.2020)

Guidance for Rash/Inflammatory Dermatitis IrAE

Diagnostic Work-up	
• Pertinent history and physical exam • Rule out other etiologies of the skin disorder • Biologic checkup (blood cell count, liver and kidney tests), as required • Directed serologic studies if autoimmune condition is suspected • Skin biopsy, clinical photography when indicated • Review medication list to rule out other drug-induced causes for photosensitivity	
Grading	**Management**
Grade 1: Symptoms do not affect quality of life or controlled with topical regimen and/or oral antipruritic	• Continue immunotherapy • Treat with topical emollients and/or mild-moderate potency topical corticosteroids • Counsel patients to avoid skin irritants and sun exposure
Grade 2: Inflammatory reaction that affects quality of life and requires intervention based on diagnosis	• Consider holding immunotherapy and monitor weekly for improvement • If no improvement, interrupt treatment until skin AE resolution to grade 1 • Consider initiating 1 mg/kg prednisone (or equivalent) – Taper over at least 4 weeks • Treat with topical emollients, oral antihistamines, and medium- to high-potency topical corticosteroids
Grade 3: As grade 2 but with failure to respond to indicated interventions for a grade 2 dermatitis	• Hold immunotherapy and consult with dermatology • Treat with topical emollients, oral antihistamines, and high-potency topical corticosteroids • Initiate IV (methyl)prednisolone (or equivalent) 1-2 mg/kg, tapering over at least 4 weeks
Grade 4: All severe rashes unmanageable with prior interventions and intolerable	• Immediately hold immunotherapy • Consult dermatology to determine appropriateness of resuming immunotherapy upon resolution of skin toxicity and once corticosteroids are reduced to prednisone (or equivalent) ≤10 mg • Systemic corticosteroids: 1-2 mg/kg IV (methyl) prednisolone (or equivalent) – Slow tapering when the toxicity resolves • Monitor closely for progression to severe cutaneous adverse reaction • Admit patient immediately with direct oncology involvement and with an urgent consult by dermatology • Consider alternative antineoplastic therapy over resuming immunotherapy if the skin IrAE does not resolve to grade ≤1 – If immunotherapy is the patient's only option, consider restarting once these adverse effects have resolved to grade 1
Reference: Brahmer JR, et al. J Clin Oncol. 2018. 36:1714-1768.	

Guidance for Colitis IrAE

Diagnostic Work-up	
Grade 2 • Work-up of blood and stool • Consider testing for lactoferrin and calprotectin • Screening laboratories (HIV, hepatitis A and B, blood quantiferon for TB) as required • Imaging (CT abdomen/pelvis, GI endoscopy) • Consider repeating endoscopy for patients not responsive to immunosuppressive agents – Repeat endoscopy for disease monitoring when clinically indicated or when planning to resume immunotherapy **Grade 3-4** • Work-up listed for grade 2 (complete immediately) • Consider repeating endoscopy for patients not responsive to immunosuppressive agents – Repeat endoscopy for disease monitoring when clinically indicated or when planning to resume immunotherapy	
Grading	**Management**
Grade 1: Increase of <4 stools per day over baseline; mild increase in ostomy output compared with baseline	• Continue immunotherapy – Alternatively, hold immunotherapy temporarily and resume if toxicity grade ≤1 • Monitor for dehydration and recommend dietary changes • Obtain gastroenterology consult for prolonged grade 1 cases
Grade 2: Increase of 4-6 stools per day over baseline; moderate increase in ostomy output compared with baseline	• Hold immunotherapy temporarily until patient's symptoms resolve to grade ≤1 – Consider permanently discontinuing CTLA-4 agents and may restart PD-1, PD-L1 agents if resolution to grade ≤1 • Concurrent immunosuppressant maintenance therapy (<10 mg prednisone equivalent dose) offered only if clinically indicated • Supportive care with medications (eg, loperamide) if infection is ruled out • Consult with gastroenterology for grade ≥2 • Administer corticosteroids, unless diarrhea is transient, starting with initial dose of 1 mg/kg/day prednisone or equivalent • When symptoms improve to grade ≤1, taper corticosteroids over at least 4-6 weeks before resuming treatment • EGD/colonoscopy, endoscopy evaluation is highly recommended • Consider testing for stool inflammatory markers (lactoferrin and calprotectin) – Use calprotectin to monitor treatment response • Repeat colonoscopy is optional

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Grading	Management
Grade 3: Increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared with baseline, limiting self-care ADL	• Consider permanently discontinuing CTLA-4 agents and may restart PD-1, PD-L1 agents if resolution to grade ≤1 • Administer corticosteroids (initial dose of 1-2 mg/kg/d prednisone or equivalent) • Consider hospitalization or outpatient facility for patients with dehydration or electrolyte imbalance • If symptoms persist ≥3-5 days or recur after improvement, administer IV corticosteroid or non-corticosteroid (eg, infliximab) • Consider colonoscopy for patients on immunosuppression and at risk for opportunistic infections and for those who are anti-TNF or corticosteroid refractory
Grade 4: Life-threatening consequences; urgent intervention indicated	• Permanently discontinue treatment • Admit patient when clinically indicated – Closely monitor outpatients • Administer 1-2 mg/kg/day methylprednisolone or equivalent until symptoms improve to grade 1 – Start taper over 4-6 weeks • Consider early infliximab 5-10 mg/kg if symptoms are refractory to corticosteroid within 2-3 days • Consider lower GI endoscopy if symptoms are refractory despite treatment or there is concern of new infections
Reference: Brahmer JR, et al. J Clin Oncol. 2018. 36:1714-1768.	

Guidance for Pneumonitis IrAE

Diagnostic Work-up

- Chest x-ray, CT, pulse oximetry
- For grade ≥2: infectious work-up including nasal swab, sputum/blood/urine culture and sensitivity

Grading	Management
Grade 1: Asymptomatic, confined to one lobe of the lung or <25% parenchyma, clinical or diagnostic observations only	• Hold immunotherapy with radiographic evidence of pneumonitis progression • Repeat CT in 3-4 weeks – In patients with baseline testing, may offer repeat spirometry/DLCO in 3-4 weeks • Resume immunotherapy with radiographic evidence of improvement or resolution – Treat as grade 2 if no improvement • Monitor patients weekly with history and physical examination and pulse oximetry; consider chest x-ray
Grade 2: Symptomatic, involves >1 lobe of the lung or 25%-50% parenchyma, medical intervention indicated, limiting instrumental ADL	• Hold immunotherapy until resolution to grade ≤1 • Prednisone 1-2 mg/kg/d and taper by 5-10 mg/week over 4-6 weeks • Consider bronchoscopy with bronchoalveolar lavage • Consider empirical antibiotics • Monitor every 3 days with history and physical examination and pulse oximetry; consider chest x-ray • Treat as grade 3 if no clinical improvement after 48-72 hours
Grade 3: Severe symptoms, hospitalization required, involves all lung lobes or >50% parenchyma, limited self-care ADL, oxygen indicated **Grade 4:** Life-threatening respiratory compromise, urgent intervention indicated (intubation)	• Permanently discontinue immunotherapy • Empirical antibiotics • (Methyl)prednisolone IV 1-2 mg/kg/d – If no improvement after 48 hours, add infliximab 5 mg/kg or mycophenolate mofetil IV 1 g twice a day or IVIG for 5 days or cyclophosphamide – Taper corticosteroids over 4-6 weeks • Pulmonary and infectious disease consults if necessary • Bronchoscopy with bronchoalveolar lavage ± transbronchial biopsy • Hospitalization

Additional considerations:

- GI and *Pneumocystis* prophylaxis with proton pump inhibitor and sulfamethoxazole/trimethoprim may be offered to patients on prolonged corticosteroid use (>12 weeks)
- Calcium and vitamin D supplementation with prolonged corticosteroid use
- Bronchoscopy + biopsy; if clinical picture is consistent with pneumonitis, no need for biopsy

Reference: Brahmer JR, et al. J Clin Oncol. 2018. 36:1714-1768.

Guidance for Hypothyroidism IrAE

Diagnostic Work-up	
• Thyroid-stimulating hormone (TSH) and free thyroxine (T4) levels every 4-6 weeks (routine clinical monitoring on therapy or case detection in symptomatic patients)	
Grading	**Management**
Grade 1: TSH <10 mIU/L and asymptomatic	• Continue immunotherapy with close follow-up and monitoring of TSH, free T4
Grade 2: Moderate symptoms; able to perform ADL; TSH persistently <10 mIU/L	• Hold immunotherapy until symptoms resolve to baseline • Consider endocrine consultation • Prescribe hormone supplementation in symptomatic patients with any degree of TSH elevation or in asymptomatic patients with TSH levels that persist > 10 mIU/L (measured 4 weeks apart) • Monitor TSH every 6-8 weeks while titrating hormone replacement to normal TSH • Free T4 can be used in the short term (2 weeks) to ensure adequacy of therapy in those with frank hypothyroidism where the free T4 was initially low • Once adequately treated, monitor thyroid function every 6 weeks while on active immunotherapy or as needed for symptoms • Repeat testing annually or as indicated by symptoms once stable
Grade 3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL	• Hold immunotherapy until symptoms resolve to baseline with appropriate supplementation • Endocrine consultation • Admit for IV therapy if signs of myxedema (bradycardia, hypothermia) • Thyroid supplementation and reassessment as in grade 2
Additional considerations: • For patients without risk factors, full replacement can be estimated with an ideal body weight-based dose of approximately 1.6 µg/kg/day • Extreme elevations of TSH can be seen in the recovery phase of thyroiditis – Watch in asymptomatic patients to determine whether there is recovery to normal within 3-4 weeks • Under endocrinologist guidance, consider tapering hormone replacement and retesting in patients with a history of thyroiditis • Adrenal dysfunction, if present, must always be replaced before thyroid hormone therapy is initiated	
Reference: Brahmer JR, et al. J Clin Oncol. 2018. 36:1714-1768.	

Guidance for Inflammatory Arthritis IrAE

Diagnostic Work-up

Grade 1

- Complete rheumatologic history and examination of all peripheral joints for tenderness, swelling, and range of motion; examination of the spine
- Consider plain x-ray/imaging to exclude metastases and evaluate joint damage, if appropriate
- Consider autoimmune blood panel and anti-inflammatory markers if symptoms persist

Grade 2

- Complete history, examination, lab tests as above
- Consider ultrasound ± MRI of affected joints if clinically indicated
- Consider early rheumatology referral for joint swelling (synovitis) or if symptoms of arthralgia persist >4 weeks

Grade 3

- As for grade 2
- Seek rheumatology consultation

Monitoring

- Monitor with serial rheumatologic examinations, including inflammatory markers, every 4-6 weeks after treatment is instituted

Grading	Management
All grades	• Report new joint pain to determine whether inflammatory arthritis is present; question whether symptom is new since receiving immunotherapy
Grade 1: Mild pain with inflammation, erythema, or joint swelling	• Continue immunotherapy • Initiate analgesia with acetaminophen and/or NSAIDs
Grade 2: Moderate pain with signs of inflammation, erythema, or joint swelling, limiting instrumental ADL	• Hold immunotherapy and resume upon symptom control and prednisone ≤10 mg/day • Escalate analgesia and consider higher doses of NSAIDS as needed – If inadequately controlled, initiate prednisone or prednisolone 10-20 mg/day or equivalent for 4-6 weeks ▪ If improvement, slowly taper according to response during the next 4-6 weeks ▪ If no improvement after initial 4-6 weeks, treat as grade 3 – Consider DMARD if unable to lower corticosteroid dose to <10 mg/day after 3 months – Consider intra-articular corticosteroid injections for large joints – Referral to rheumatology

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Grading	Management
Grade 3-4: Severe pain associated with signs of inflammation, erythema, or joint swelling; irreversible joint damage; disabling; limiting self-care ADL	• Hold immunotherapy temporarily and resume in consultation with rheumatology if resolution to grade ≤1 • Initiate oral prednisone 0.5-1 mg/kg • If failure to improve or worsening after 4 weeks, consider synthetic or biologic DMARD • Test for viral hepatitis B, C, and latent/active TB test prior to DMARD treatment • Referral to rheumatology
Additional considerations: • Early recognition is critical to avoid erosive joint damage • Corticosteroids can be used as part of initial therapy in inflammatory arthritis, but due to likely prolonged treatment requirements, physicians should consider starting corticosteroid-sparing agents earlier than one would with other IrAEs • Oligoarthritis can be treated early with intra-articular corticosteroids; consider early referral • Consider PCP prophylaxis for patients treated with high dose of corticosteroids for >12 weeks	
Reference: Brahmer JR, et al. J Clin Oncol. 2018. 36:1714-1768.	

Other IrAEs to Watch For

- Skin toxicities: bullous dermatoses; severe cutaneous adverse reactions
- Gastrointestinal toxicities: hepatitis
- Endocrine toxicities: hyperthyroidism; adrenal insufficiency; hypophysitis; diabetes
- Musculoskeletal toxicities: myositis; polymyalgia-like syndrome
- Renal toxicities: nephritis; symptomatic nephritis
- Nervous system toxicities: myasthenia gravis; Guillain-Barré syndrome; peripheral neuropathy; autonomic neuropathy; aseptic meningitis; encephalitis; transverse myelitis
- Hematologic toxicities: autoimmune hemolytic anemia; acquired thrombotic thrombocytopenia purpura; hemolytic uremic syndrome; aplastic anemia; lymphopenia; immune thrombocytopenia; acquired hemophilia
- Cardiovascular toxicities: myocarditis; pericarditis; arrhythmias; impaired ventricular function with heart failure and vasculitis; venous thromboembolism
- Ocular toxicities: uveitis/iritis; episcleritis; blepharitis

For management details, refer to Brahmer JR, et al. J Clin Oncol. 2018. 36:1714-1768.

Resources

Resources

Prognostic Scoring – IMDC criteria

IMDC (International Metastatic Renal Cell Carcinoma Database Consortium) Criteria for Prognosis in mRCC (Heng 2009/2013)

Criterion	No (0) / Yes (+1)
<1 year from time of diagnosis to systemic therapy	0 / 1
Karnofsky Performance Status <80%	0 / 1
Hemoglobin < lower limit of normal	0 / 1
Corrected calcium > upper limit of normal	0 / 1
Neutrophils > upper limit of normal	0 / 1
Platelets > upper limit of normal	0 / 1
Number of criteria	

Number of criteria	Risk Group	Median overall survival
0	Favourable	43.2 months (95%CI: 31.4-50.1)
1-2	Intermediate	22.5 months (95%CI: 18.7-25.1)
3-6	Poor	7.8 months (95%CI: 6.5-9.7)

An online calculator can be found at IMDConline.com

ECOG Performance Status

Grade	ECOG Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

Oken M, et al. Am J Clin Oncol. 1982. https://ecog-acrin.org/resources/ecog-performance-status

Acronyms and Abbreviations

ACE	Angiotensin-converting enzyme
ACTH	Adrenocorticotropic hormone
ADL	Activities of daily living
AE	Adverse event
Alk Phos	Alkaline phosphatase
ALT	Alanine aminotransferase
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
BICR	Blinded independent central review
BPMH	Best possible medication history
CBC	Complete blood count
CHF	Congestive heart failure
CN	Cytoreductive nephrectomy
CNS	Central nervous system
CPK	Creatine phosphokinase
CR	Complete response
CRP	C-reactive protein
CT	Computed tomography
CTLA-4	Cytotoxic T lymphocyte-associated antigen 4
CVA	Cerebrovascular accident
DLCO	Diffusing capacity of the lungs for carbon monoxide
DMARD	Disease-modifying anti-rheumatic drug
DOR	Duration of response
ECOG PS	Eastern Cooperative Oncology Group performance status
EGD	Esophagogastroduodenoscopy
ECG	Electrocardiogram
ESR	Erythrocyte sedimentation rate
FSH	Follicle-stimulating hormone
HR	Hazard ratio
ICI	Immune checkpoint inhibitor
IL-2	Interleukin-2
IVIG	Intravenous immunoglobulin
IMDC	International Metastatic Renal Cell Carcinoma Database Consortium
IO	Immuno-oncology
IO-VEGF	Immunotherapy-VEGF
ipi-nivo	ipilimumab-nivolumab
IrAE	Immune-related adverse event

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IRRC	Independent radiology review committee
ITT	Intent-to-treat
KC	Kidney cancer
KCRNC	Kidney Cancer Research Network of Canada
KPS	Karnofsky performance status
LH	Luteinizing hormone
mRCC	Metastatic renal cell carcinoma
MRCP	Magnetic resonance cholangiopancreatography
mTOR	Mammalian target of rapamycin
NE	Not evaluable
NR	Not reached
NYHA	New York Heart Association
ORR	Overall response rate
OS	Overall survival
PCP	Pneumocystis pneumonia
PD	Progressive disease
PD-1	Programmed death 1
PD-L1	Programmed death ligand 1
PFS	Progression-free survival
PgP	P-glycoprotein
PPES	Palmar-plantar erythrodysesthesia syndrome
PR	Partial response
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria In Solid Tumors
RT	Radiotherapy
SD	Stable disease
SJS	Stevens-Johnson syndrome
SRT	Stereotactic radiotherapy
T3	Triiodothyronine
T4	Thyroxine
TB	Tuberculosis
TEN	Toxic epidermal necrolysis
TKI	Tyrosine kinase inhibitor
TNF	Tumor necrosis factor
TSH	Thyroid stimulating hormone
TTF	Time to treatment failure
ULN	Upper limit of normal
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor

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