I Kid(ney) You Not: Updates on Renal Cell Carcinoma

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Disclosures

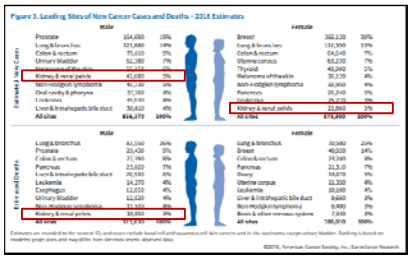
- Nothing to disclose

Objectives

- Review the pathophysiology and risk stratification of renal cell carcinoma (RCC)
- Evaluate literature supporting the use of adjuvant therapy for non-metastatic RCC
- Analyze new first-line and subsequent treatment options for metastatic RCC (mRCC)
- Discuss future directions for treatment of mRCC

Background

Incidence & Mortality



American Cancer Society. Cancer Stats & Figures 2018. https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/

Incidence & Mortality

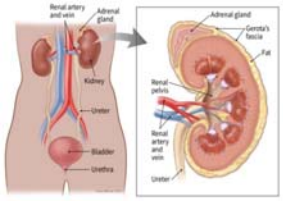
- 2018 estimates
  - 63,340 new cases (42,680 men/22,660 women)
  - 14,970 deaths (10,010 men/4,960 women)
- Median age at diagnosis = 64
- Male > female (2:1)

Stage	Percent by Stage	5-year Relative Survival
Localized	65%	92.6%
Regional	16%	68.7%
Distant	16%	11.6%
Unknown/Unstaged	3%	38%

National Cancer Institute: SEER Program. http://seer.cancer.gov/statfacts/html/mulmy.html
American Cancer Society. Cancer Stats & Figures 2018. https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/.

Anatomy & Pathophysiology

- 90% of kidney cancers are renal cell carcinoma
  - Arise from renal tubular epithelial cells
  - 70-80% clear-cell (cc) histology
  - 20-30% non-clear cell histology
- 5-10% of kidney cancers are transitional cell carcinomas



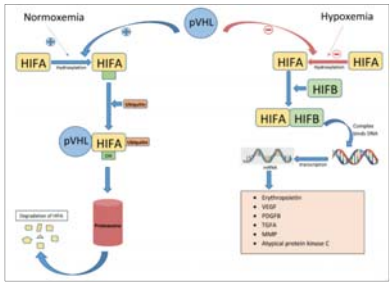
Jonasch E et al. *BMJ*. 2014;349:g4797. // Nabi S et al. F1000Res. 2018;7:307.
American Cancer Society. Kidney Cancer. 2018; https://www.cancer.org/cancer/kidney-cancer.html.

Pathophysiology: Genetic Alterations

- Inherited or sporadic
  - Inherited associated with autosomal dominant alterations in von Hippel-Lindau (*VHL*), a tumor suppressor gene
  - Up to 90% of sporadic RCC are associated with somatic alterations in *VHL*
- Several other genes involved in RCC pathogenesis
  - *PBRM-1, SETD2, BAP1, mTOR, KDM5C*
- 95% of ccRCC are associated with the loss of chromosome 3p

Nabi S et al. F1000Res. 2018;7:307.

Pathophysiology: Genetic Alterations



Nabi S et al. F1000Res. 2018;7:307.

Risk Factors

- Tobacco use
- Obesity
- Hypertension
- Workplace exposures
- Family history
- Advanced CKD
- Male > female
- Genetic disorders
  - Von Hippel-Lindau disease
  - Hereditary papillary RCC
  - Hereditary leiomyoma-renal cell carcinoma
  - Birt-Hogg-Dube (BHD) syndrome
  - Familial renal cancer
  - Hereditary renal oncocytoma

American Cancer Society. https://www.cancer.org/cancer/kidney-cancer

Memorial Sloan Kettering Cancer Center (MSKCC)/Motzer Prognostic Score

- Derived from clinical trials which treated mRCC patients with interferon

Risk Factors
Interval from diagnosis to treatment of < 1 year
Karnofsky performance status < 80%
Serum LDH > 1.5x ULN
Corrected serum Ca > ULN
Serum Hgb < LLN

» Favorable (low) risk: 0 risk factors
» Intermediate risk: 1-2 risk factors
» Poor (high) risk: ≥ 3 risk factors

Motzer RJ et al. *J Clin Oncol*. 2002;20(1):289-96.
National Comprehensive Cancer Network. Kidney Cancer (Version 2.2019).

International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) Criteria

- Derived from clinical trials which treated mRCC patients with tyrosine kinase inhibitors

Risk Factors
Interval from diagnosis to treatment of < 1 year
Karnofsky performance status < 80%
Corrected serum Ca > ULN
Serum Hgb < LLN
Neutrophils > ULN
Platelets > ULN

» Favorable risk: 0 risk factors
» Intermediate risk: 1-2 risk factors
» Poor risk: ≥ 3 risk factors

Heng DY et al. J Clin Oncol. 2009;27(34):5794-9.
National Comprehensive Cancer Network. Kidney Cancer (Version 2.2019).

Treatment: Adjuvant

Treatment Overview: Stages I-III

Stage I	Stage II	Stage III
Partial nephrectomy Radical nephrectomy Active surveillance Ablation	Partial nephrectomy Radical nephrectomy	Radical nephrectomy Partial nephrectomy
Surveillance	Clinical trial or Surveillance	High risk^ clear cell: clinical trial (preferred), surveillance, or sunitinib*

^ High risk: tumor stage III, regional lymph node mets, or both
* Category 2B

National Comprehensive Cancer Network. Kidney Cancer (Version 2.2019).

ASSURE (ECOG-ACRIN E2805)

- Phase III, double-blind, randomized, placebo-controlled

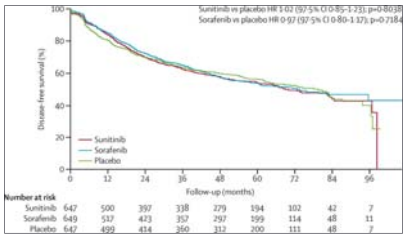
1943 high-risk patients
- Treatment naïve
- ECOG PS 0-1
- Adequate organ function

Sunitinib | Sorafenib | Placebo

Haas NB et al. Lancet. 2016;387(10032):2008-16.

ASSURE (ECOG-ACRIN E2805)

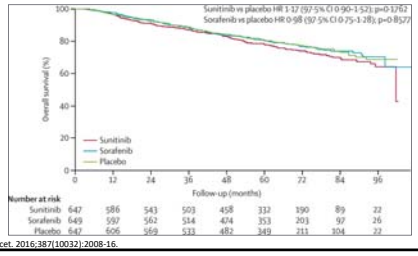
- Disease free survival (DFS): 5.8 years sunitinib vs 6.1 years sorafenib vs 6.6 years placebo



Haas NB et al. Lancet. 2016;387(10032):2008-16.

ASSURE (ECOG-ACRIN E2805)

- 5-year overall survival (OS): 77.9% sunitinib vs 80.5% sorafenib vs 80.3% placebo



Haas NB et al. Lancet. 2016;387(10032):2008-16.

S-TRAC

- Phase III, double-blind, randomized, placebo-controlled

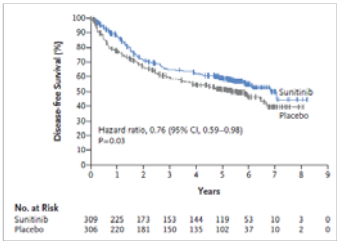
615 high-risk patients
- Clear cell
- Treatment naïve
- ECOG PS 0-2

Sunitinib | Placebo

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

S-TRAC

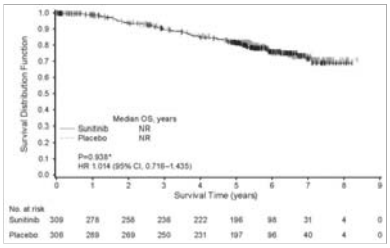
- DFS: 6.8 years vs 5.6 years (p=0.03)



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

S-TRAC

- Median OS: NR vs NR (HR 1.01, p=0.94)



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

PROTECT

- Phase III, double-blind, randomized, placebo-controlled

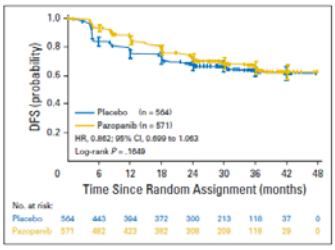
1538 high-risk patients
- Predominant clear cell
- Karnofsky PS ≥ 80%
- Adequate organ function

Pazopanib | Placebo

Motzer RJ et al. J Clin Oncol. 2017;35(35):3916-3923.

PROTECT

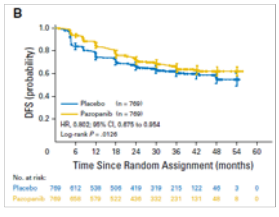
- 4-year DFS_{600}: 61% vs 61% (p=0.1649)



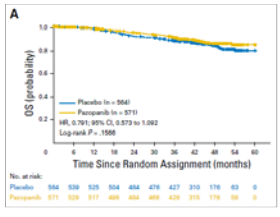
Motzer RJ et al. J Clin Oncol. 2017;35(35):3916-3923.

PROTECT

- 4-year DFS_{800}

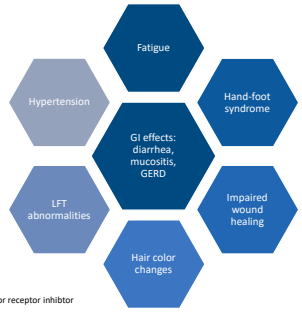


- 4-year OS_{600}



Motzer RJ et al. J Clin Oncol. 2017;35(35):3916-3923.

Time Out: VEGFRi Toxicity



VEGFRi: vascular endothelial growth factor receptor inhibtor

Schmidinger M. EJC Suppl. 2013;11(2):172-91.

Ongoing Research

EVEREST: Phase III double-blind study of 1545 high-risk patients randomized to everolimus vs placebo x 1 year

KEYNOTE-564: Phase III double-blind study of patients randomized to pembrolizumab vs placebo x 1 year

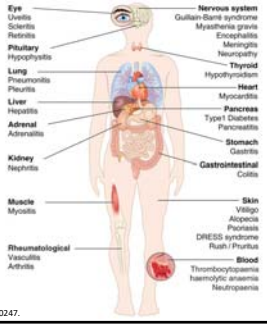
IMmotion010: Phase III double-blind study of patients randomized to atezolizumab vs placebo x 1 year

PROSPER: Phase III randomized study of perioperative nivolumab vs observation x 10 months

CheckMate 914: Phase III double-blind study of patients randomized to ipilimumab/nivolumab vs placebo x 1 year

ClinicalTrials.gov: NCT01120249, NCT03024996, NCT03142334, NCT03055013, NCT03138512.

Time Out: Immunotherapy Toxicity



Varricchi G et al. ESMO Open. 2017;2(4):e000247.

Treatment: Metastatic

Treatment Overview: Stage IV

Potentially surgically resectable primary w/ solitary metastatic site	Potentially surgically resectable primary w/ multiple metastatic sites	Surgically unresectable
Nephrectomy/ metastastectomy Ablation	Cytoreductive nephrectomy	Tissue sampling

First-line systemic therapy

National Comprehensive Cancer Network. Kidney Cancer (Version 2.2019).

NCCN Guidelines (2017): First-Line Treatment Options

FIRST LINE THERAPY
Clinical trial
Pazopanib* (preferred)
Sunitinib* (preferred)
Bevacizumab + interferon alfa-2b*
Temsirolimus (*poor risk, **other risk groups)
Axitinib
High-dose IL-2 (selected patients)
Active surveillance (if asymptomatic)
Best supportive care

* Category 1
** Category 2B

National Comprehensive Cancer Network. Kidney Cancer (Version 2.2017).

2017 NCCN Category 1 (Preferred) 1st Line Agents

Study	Purpose	Study Design	PFS	ORR	Comments
Motzer et al. (Phase III)	1st line sunitinib	750 pt randomized to sunitinib vs IFN-α	11 mo vs 5 mo (p<0.001)	31% vs 6% (p<0.001)	Establishes sunitinib as new 1st line
Sternberg et al. (Phase III)	1st line pazopanib	435 pt randomized to pazopanib vs placebo	9.2 mo vs 4.2 mo (p<0.001)	30% vs 3% (p<0.001)	PFS benefit seen for tx naïve and prior cytokine tx
COMPARZ (Phase III)	1st line pazopanib vs sunitinib	1110 pt randomized to pazopanib vs sunitinib	8.4 mo vs 9.5 mo (HR 1.05) **NON-INFERIOR**	31% vs 25% (p=0.03)	SE profile favors pazopanib, no difference in OS Establishes pazopanib as another 1st line option

Motzer RJ et al. N Engl J Med 2007;356(2):115-124
Sternberg et al. J Clin Oncol. 2010;28(6): 1061-1068.
Motzer RJ et al. N Engl J Med 2013;369(8):722-731

NCCN Guidelines (2018): First-Line Treatment Options

Risk Category	Preferred regimens	Other recommended regimens	Useful under certain circumstances
Favorable	Pazopanib* Sunitinib*	Ipilimumab/nivolumab Cabozantinib**	Active surveillance Axitinib** Bevacizumab/interferon alfa-2b* High-dose IL-2
Intermediate/ Poor	Ipilimumab/nivolumab* Cabozantinib	Pazopanib* Sunitinib*	Axitinib** Bevacizumab/interferon alfa-2b* High-dose IL-2 Temsirolimus*

* Category 1
** Category 2B

National Comprehensive Cancer Network. Kidney Cancer (Version 2.2019).

CheckMate 214

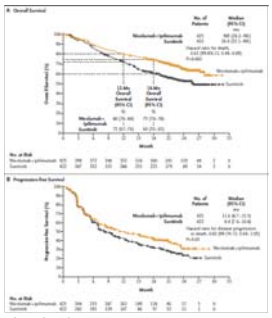
- Phase III, randomized, open-label

1096 patients (all risk groups)
- Clear cell
- Treatment naïve
- Karnofsky PS ≥ 70%

Ipilimumab/ Nivolumab | Sunitinib

Motzer et al. N Engl J Med 2018; 378:1277-1290.

CheckMate 214



Intermediate/Poor Risk

Endpoint	Result
18-month OS	75% vs 60% (p<0.001)
Median PFS	11.6 mo vs 8.4 mo (p=0.03)
ORR	42% vs 27% (p<0.001)
CR	9% vs 1%

Motzer et al. N Engl J Med 2018; 378:1277-1290.

CheckMate 214

Favorable Risk

Endpoint	Result
18-month OS	88% vs 93% (p=0.27)
Median PFS	15.3 mo vs 25.1 mo (p<0.001)
ORR	29% vs 52% (p<0.001)
CR	11% vs 6%

PD-L1 status

- 26% in the ipilimumab/ nivolumab group and 29% in the sunitinib group had ≥1% PD-L1 expression
  - ORR (≥1% PD-L1 exp): 58% vs 22% (p<0.001)
  - ORR (<1% PD-L1 exp): 37% vs 28% (p=0.05)

Motzer et al. N Engl J Med 2018; 378:1277-1290.

CABOSUN

- Phase II, randomized, open-label

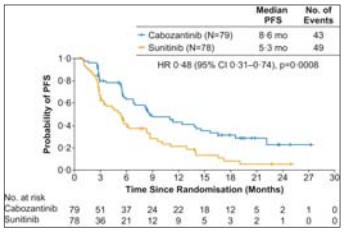
157 int/poor risk patients
- Clear cell
- Treatment naïve
- ECOG 0-2

Cabozantinib | Sunitinib

Choueiri TK et al. J Clin Oncol. 2017;35(6):591-597.

CABOSUN

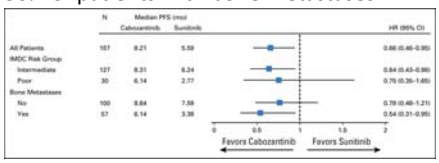
- Updated PFS: 8.6 mo vs 5.3 mo (p=0.0008)



Choueiri TK et al. J Clin Oncol. 2017;35(6):591-597.
Choueiri TK et al. Eur J Cancer. 2018;94:115-125.

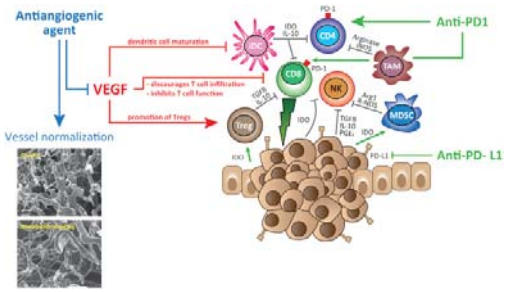
CABOSUN

- Updated OS: 26.6 mo vs 21.2 mo
- ORR: 33% vs 12%
- 36% of patients with bone metastases



Choueiri TK et al. J Clin Oncol. 2017;35(6):591-597.
Choueiri TK et al. Eur J Cancer. 2018;94:115-125.

Time Out: Combined Immunotherapy + VEGFRi



Manegold C et al. J Thorac Oncol. 2017;12(2):194-207.

IMmotion 151

- Phase III, open-label, randomized study

915 patients (all risk groups)
- Clear cell or sarcomatoid
- Treatment-naïve
- Karnofsky PS ≥ 70%

Atezolizumab/ Bevacizumab

Sunitinib

Motzer RJ et al. J Clin Oncol 36, 2018 (suppl 6: 578-578.)

IMmotion 151

- Co-primary endpoints
  - PFS for PD-L1+: 11.2 mo vs 7.7 mo (p=0.0217)
    - Consistent amongst all risk groups
  - OS for ITT population: data immature
- Secondary endpoints
  - PFS for ITT population: 11.2 mo vs 8.4 mo (p=0.0219)
  - ORR for PD-L1+: 43% vs 35%
  - ORR for ITT population: 37% vs 33%

Motzer RJ et al. J Clin Oncol 36, 2018 (suppl 6: 578-578.)

JAVELIN Renal 100

- Phase 1b, open-label, dose-finding study
  - Inclusion:
    - Clear-cell component
    - Treatment naïve
    - ECOG ≤1
    - Resected primary tumor
  - Avelumab 10 mg/kg q2 weeks + axitinib 5 mg BID
  - Initial report of 55 patients (all risk groups)

Choueiri TK et al. Lancet Oncol. 2018;19(4):451–460.

JAVELIN Renal 100

- Dose-limiting toxicities in the first 4 weeks of treatment
  - One grade 3 proteinuria

	All grades	Grade 3	Grade 4	Grade 5
All events	53 (96%)	26 (47%)	5 (9%)	1 (2%)
Diarrhoea	32 (58%)	2 (4%)	0	0
Dysphonia	26 (47%)	0	0	0
Hypertension	26 (47%)	16 (29%)	0	0
Fatigue	25 (46%)	2 (4%)	0	0
PPE syndrome	17 (31%)	4 (7%)	0	0
ALT increased	16 (29%)	4 (7%)	0	0
Rash	16 (29%)	1 (2%)	0	0
AST increased	14 (26%)	1 (2%)	0	0
Hypothyroidism	14 (26%)	0	0	0
Amylase increased	13 (24%)	3 (6%)	1 (2%)	0
Decreased appetite	13 (24%)	1 (2%)	0	0
Mucosal inflammation	13 (24%)	1 (2%)	0	0
Infusion-related reaction*	11 (20%)	1 (2%)	0	0
Lipase increased	11 (20%)	1 (2%)	3 (6%)	0
Nausea	11 (20%)	1 (2%)	0	0

- ORR: 58% - 3 CR (6%), 29 PR (53%)
- ORR by PD-L1 expression:

	Objective Response	Odds Ratio
1% Cutoff		
≥1%	66%	3.38
<1%	36%	
5% Cutoff		
≥5%	68%	2.11
<5%	50%	

Choueiri TK et al. Lancet Oncol. 2018;19(4):451–460.

KEYNOTE-427

- Single-arm, open-label, 2-cohort, phase II study
  - 2 cohorts:
    - ccRCC (cohort A)
    - Non-ccRCC (B)
  - Inclusion:
    - Clear cell
    - Treatment-naïve
    - Karnofsky PS ≥70%
  - 107 patients received pembrolizumab 200 mg IV q3 weeks
- Results
  - 37.3% favorable risk, 47.3% intermediate risk, and 15.5% poor risk per IMDC
  - ORR: 33.6% (1 CR and 35 PR)
    - Favorable: 27.5%
    - Intermediate/poor risk: 37.3%
  - Grade 3-5 AE: 18.2%
    - Grade 5 pneumonitis, n=1

McDermott DF et al. J Clin Oncol 36, 2018 (suppl; abstr 4500).

Pembrolizumab + Axitinib

- Phase 1b, non-randomized, open-label, dose-finding
  - Inclusion: predominant clear-cell, treatment-naïve, ECOG 0-1
- Results:

Response	n=52
Best overall response	
Complete response	4 (8%)
Partial response	34 (65%)
Stable disease	8 (15%)
Progressive disease	3 (6%)
Indeterminate	3 (6%)
Objective responses	38 (73%)

Atkins MB et al. Lancet Oncol 2018;19:405-15.

Pembrolizumab + Axitinib

	Grade 1-2	Grade 3
Any adverse event	18 (35%)	33 (63%)*
Fatigue	33 (63%)	5 (10%)
Diarrhoea	32 (62%)	5 (10%)
Hypertension	14 (27%)	12 (23%)
Dysphonia	24 (46%)	0
Increased alanine aminotransferase concentration	15 (29%)	4 (8%)
Decreased appetite	18 (35%)	1 (2%)
Hypothyroidism	19 (37%)	0
Nausea	18 (35%)	1 (2%)
Palmar-plantar erythrodysaesthesia	17 (33%)	2 (4%)
Increased aspartate aminotransferase concentration	14 (27%)	2 (4%)
Weight decreased	12 (23%)	2 (4%)
Proteinuria	12 (23%)	1 (2%)
Arthralgia	12 (23%)	0
Dysgeusia	12 (23%)	0
Abdominal pain	11 (21%)	0
Oral pain	10 (19%)	1 (2%)
Dry skin	10 (19%)	0

Atkins MB et al. Lancet Oncol 2018;19:405-15.

BTCRC-GU14-003

- Phase Ib/II, non-randomized, open-label study of pembrolizumab + bevacizumab
- Inclusion:
  - Clear cell
  - Failure of at least one systemic therapy (phase Ib) or treatment naïve (phase II)
- Phase II results (n=48)
  - ORR: 60.9 % (0 CR, 28 PR)
  - Median PFS: 17 months (95% CI = 11.3, 24.8)
  - Grade 4 AE:
    - Hyponatremia (n=1)
    - Hyperglycemia (n=1)
  - Grade 5 AE
    - Heart failure (n=1)

Dudek AZ et al. J Clin Oncol 36, 2018 (suppl; abstr 4558).
ClinicalTrials.gov: NCT02348008.

Additional Combinations

- CheckMate 9ER
  - Phase 3, open-label study of nivolumab + cabozantinib or ipilimumab/nivolumab + cabozantinib vs sunitinib in previously untreated patients
- Pembrolizumab + lenvatinib
  - Phase Ib/II, open-label study in patients with ≤2 prior therapies (both 1st and 2nd line)
  - RCC n=30
  - Primary endpoint – ORR: 66.7%
  - 73% required lenvatinib dose reduction

Choueiri TK et al. J Clin Oncol 36, 2018 (suppl; abstr TPS4598).
Lee CH et al. J Clin Oncol 36, 2018 (suppl; abstr 4560).
ClinicalTrials.gov: NCT02501096, NCT03141177.

One more twist… CARMENA

- Randomized, phase III, non-inferiority trial
  - Inclusion:
    - Clear-cell histology
    - mRCC amenable to cytoreductive nephrectomy (CN)
    - Eligible for sunitinib
    - Absence of brain mets
  - 450 patients with intermediate/poor risk mRCC randomized to CN followed by sunitinib (started within 6 wk of surgery) vs sunitinib
- Results:
  - Overall survival
    - Intermediate risk: 19 mo vs 23.4 mo (HR 0.92)
    - Poor risk: 10.2 mo vs 13.3 mo (HR 0.85)
  - No difference in ORR (35.9% vs 35.9%) or PFS (7.2 mo vs 8.3 mo)
  - **Sunitinib alone is not inferior to CN followed by sunitinib**

Méjean A et al. N Engl J Med. 2018; 379:417-427.

NCCN Guideline: 1st Line Treatment Updates

- 2018 Updates
  - Add ipilimumab/nivolumab, cabozantinib
  - Add risk stratification
  - Separate into preferred/other treatment options
- New research which could impact future updates
  - Atezolizumab/bevacizumab
  - Avelumab/axitinib
  - Pembrolizumab
  - Pembrolizumab/axitinib
  - Pembrolizumab/bevacizumab
  - Nivolumab/cabozantinib
  - Pembrolizumab/lenvatinib

How do we choose 1st line?

- Risk stratify
  - Favorable
    - Sunitinib
    - Pazopanib
    - **Atezolizumab/bevacizumab?**
    - **Avelumab/axitinib?**
    - **Pembrolizumab?**
    - **Pembrolizumab + bevacizumab or lenvatinib?**
- Risk stratify
  - Intermediate/Poor
    - Ipilimumab/nivolumab
    - Cabozantinib
    - Pazopanib or sunitinib
    - **Atezolizumab/bevacizumab?**
    - **Avelumab/axitinib?**
    - **Pembrolizumab?**
    - **Pembrolizumab + bevacizumab or lenvatinib?**
  - Poor
    - Temsirolimus

How do we choose 1st line?

- Performance status
  - Good: may tolerate combination immunotherapy/TKI or TKI alone
  - Poor: likely to tolerate immunotherapy better
- Disease burden
  - Aggressive: TKI
  - Indolent: immunotherapy
- Strength of data
- PD-L1+
  - Ipiimumab/nivolumab
  - Avelumab/axitinib
  - Atezolizumab/bevacizumab

NCCN Guidelines (2017): Subsequent Treatment Options

SUBSEQUENT THERAPY

Clinical trial

Cabozantinib* (preferred)

Nivolumab* (preferred)

Axitinib*

Lenvatinib + everolimus*

Everolimus

Pazopanib

Sorafenib

Sunitinib

Bevacizumab**

High-dose IL-2** (selected patients)

Temsirolimus**

Best supportive care

* Category 1
** Category 2B

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NCCN Guidelines (2018): Subsequent Treatment Options

Preferred regimens	Other recommended regimens	Useful under certain circumstances
Cabozantinib* Nivolumab* Ipilimumab/nivolumab	Axitinib* Lenvatinib/everolimus* Everolimus Pazopanib Sunitinib	Bevacizumab** Sorafenib** High-dose IL-2** Temsirolimus**

* Category 1
** Category 2B

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Subsequent Therapy: Category 1 Options

Study	Purpose	Study Design	Primary Endpoint	ORR	Comments
METEOR (Phase III)	2nd line cabozantinib	658 pt randomized to cabozantinib vs everolimus	PFS: 7.4 mo vs 3.8 mo (p<0.001)	21% vs 5% (p<0.001)	Dose reduction required in 60% vs 25%
CheckMate 025 (Phase III)	2nd line nivolumab	821 pt randomized to nivolumab vs everolimus	OS: 25 mo vs 19.6 mo (p=0.002) *1st OS benefit 2nd line*	25% vs 5% (p<0.002)	QOL significantly greater with nivolumab
AXIS (Phase III)	2nd line axitinib	723 pt randomized to axitinib vs sorafenib	PFS: 6.7 mo vs 4.7 mo (p<0.001)	19% vs 9% (p=0.0001)	Only 37% of pt able to increase axitinib dose
Motzer et al. (Phase II)	2nd line lenvatinib/ everolimus	153 pt randomized to lenvatinib + everolimus vs everolimus vs lenvatinib	PFS: 14.6 mo vs 5.5 mo (p=0.0005) vs 7.4 mo (p=0.12)	43% vs 6% (p<0.0001) vs 27% (p=0.1)	71% of combo and 62% of lenvatinib alone required dose reduction

Choueiri EK et al. N Engl J Med 2015;373(19):1814-1823.
Motzer et al. N Engl J Med 2015;373(19):1803-1813.
Rini BI. Lancet 2011; 378(9807):1931-1939.
Motzer et al. Lancet Oncol 2015; 16(15):1473-1482.

NCCN Guideline: Subsequent Treatment Updates

- 2018 Updates
  - Add ipilimumab/nivolumab
  - Separate into preferred/other treatment options
- Possible future updates
  - Pembrolizumab/lenvatinib?

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Novel 2nd Line or Greater Combinations

- ECHO-202/KEYNOTE-037
  - Phase I/II open-label study of pembrolizumab + epacadostat in 33 patients with prior VEGFi but no prior immunotherapy
  - ORR = 47% if 1 prior tx; ORR = 0% ≥2 prior tx
- Cabozantinib + glutaminase inhibitor
- Nivolumab + ibrutinib
- Vorolanib, everolimus, or combination

Lara P et al. J Clin Oncol. 2017: 35(15 suppl), 4515.
ClinicalTrials.gov: NCT02178722, NCT03428217, NCT02899078, NCT03095040.

How do we choose 2nd or later line?

- Patient specific factors
  - Performance status
  - Volume of disease/location of metastases
- Continue to sequence therapies
  - Optimal order not known
  - If we use immunotherapy upfront can we re-challenge in a later line?
- Patient preference

Conclusion

- Treatment landscape of RCC has completely changed
  - Updates for both adjuvant therapy and therapy for metastatic disease
- Additional changes on the horizon
  - Immunotherapy/VEGFi combinations
  - Novel combinations
- Outstanding questions
  - How do we sequence?
  - Can we re-challenge with immunotherapy?

I Kid(ney) You Not: Updates on Renal Cell Carcinoma

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