Advances in the Treatment of Renal Cell Carcinoma

Learning Objectives

Upon completion, participants should be able to:

• Identify patients with metastatic renal cell carcinoma who may benefit from cytoreductive nephrectomy
• Discuss the impact of adjuvant sorafenib on outcomes in oligometastatic renal cell carcinoma patients
Highlights From ASCO 2018

Tian Zhang, MD

Cytoreductive Nephrectomy

- Independent predictor of survival in MSKCC and IMDC prognostic models

**MSKCC Model**

- Risk factors are:
  - No prior nephrectomy
  - KPS < 80
  - Low HGB
  - High LDH

- 0 risk factors (164 patients, 30 alive)
- 1 or 2 risk factors (348 patients, 23 alive)
- 3, 4, or 5 risk factors (144 patients, 1 alive)

**IMDC Model**

- Nephrectomy
- No nephrectomy
- But only for patients with 1, 2, or 3 IMDC risk factors
CARMENA

• Prospective, multicenter, open-label, randomized, phase 3 noninferiority study

- Confirmed metastatic ccRCC / biopsy
- ECOG PS 0-1
- Eligible for nephrectomy
- Brain metastases absent/controlled by treatment
- No prior systemic therapy for RCC

Primary endpoint: OS
Secondary endpoints: PFS, ORR, clinical benefit, safety

Arm A: Nephrectomy + Sunitinib
3-6 Wks
Nephrectomy
50 mg QD 4 wks on / 2 wks off

Arm B: Sunitinib
50 mg QD 4 wks on / 2 wks off

40 patients in Arm A did not receive sunitinib
38 patients in Arm B received secondary nephrectomy

Median follow-up was 50.9 months (range 0.0-86.6)
40 patients in Arm A did not receive sunitinib
38 patients in Arm B received secondary nephrectomy

**CARMENA: Patient Characteristics and OS**


HR (95% CI) = 0.89 (0.71-1.10)
Noninferiority study ≤ 1.20

Media
CARMENA: Nephrectomy for Which mRCC Patients?

- Patients who may benefit from nephrectomy are those with a small metastatic burden (< 10%-15% of total tumor burden) with large primary and excellent PS
- Systemic therapies should be attempted before nephrectomy in patients with more metastatic burden or worse PS


Immunotherapy in mRCC: KEYNOTE-427

Keynote-427: (NCT02853344)

- Pembrolizumab* shows promising antitumor activity as monotherapy in first-line ccRCC across IMDC risk groups
- Forms basis for adjuvant studies and combination studies in metastatic setting

Confirmed ORR by Blinded Independent Central Review

<table>
<thead>
<tr>
<th>Response</th>
<th>n</th>
<th>%</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>ORR</td>
<td>42</td>
<td>38.2</td>
<td>29.1-47.9</td>
</tr>
<tr>
<td>DCR (CR + PR + SD ≥ 6 mo)</td>
<td>65</td>
<td>59.1</td>
<td>49.3-68.4</td>
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Best overall response

<table>
<thead>
<tr>
<th>Response</th>
<th>n</th>
<th>%</th>
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<tbody>
<tr>
<td>CR</td>
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<tr>
<td>PR</td>
<td>39</td>
<td>35.5</td>
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<tr>
<td>SD</td>
<td>35</td>
<td>31.8</td>
</tr>
<tr>
<td>PD</td>
<td>31</td>
<td>26.2</td>
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</table>

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Immunotherapy in mRCC

<table>
<thead>
<tr>
<th>Immunotherapy</th>
<th>Phase</th>
<th>N</th>
<th>IMDC Poor</th>
<th>ORR</th>
<th>CR</th>
<th>ORR (PD-L1+)</th>
<th>mPFS</th>
<th>Trt Disc Due to AEs</th>
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<tbody>
<tr>
<td>Nivolumab</td>
<td>1b</td>
<td>24</td>
<td>NA</td>
<td>13%</td>
<td>8%</td>
<td>NA</td>
<td>6 m</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>(CA209-009)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Atezolizumab*</td>
<td>2</td>
<td>103</td>
<td>8%</td>
<td>25%</td>
<td>11%</td>
<td>28%</td>
<td>6.1 m</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>(IMmotion150)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pembrolizumab*</td>
<td>2</td>
<td>110</td>
<td>15.5%</td>
<td>38%</td>
<td>2.7%</td>
<td>50%</td>
<td>8.7 m</td>
<td>10.9%</td>
</tr>
<tr>
<td></td>
<td>(KEYNOTE-427)</td>
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<tr>
<td>Nivo+Ipi (ITT)</td>
<td>3</td>
<td>550</td>
<td>17%</td>
<td>39%</td>
<td>9.8%</td>
<td>53%</td>
<td>12.4 m</td>
<td>22%</td>
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<tr>
<td></td>
<td>(Checkmate 214)</td>
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- Pembrolizumab monotherapy better tolerated with fewer treatment discontinuations but lower CR rates
  - 10.9% of patients discontinued pembrolizumab due to AE

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Biomarkers to Predict Immunotherapy Response

- Systemic therapies are improving, and better biomarkers are needed to identify patients who would benefit as well as those who are resistant to immunotherapies
- Promising biomarkers from ASCO 2018 include:
  - Tumor infiltrating T cells
  - Insertion-and-deletion (indel) burden
  - Gut microbiome

**Biomarker: Tumor-Infiltrating T Cells**

- Infiltrating CD8+ T cells correspond with immunotherapy response
- T cells increase on treatment
- IFN-γ signaling higher in responders

![Graphs showing Pretreatment: IHC Cell Proportion: CD8 and Increased CD8 After Treatment for All.](image1)


**Biomarker: Indels**

- Indels correspond with OS
- T cells and macrophages in the tumor microenvironment correspond with response to immunotherapy

![Graphs showing Exonic Frameshift Indel Count and Immune Infiltrate, ESTIMATE score.](image2)

Biomarker: Gut Microbiome

- Fecal microbiota diversity does not differ between responders and nonresponders
- *Akkermansia muciniphila* and *Bacteroides* species are more abundant in responders to immunotherapy


Conclusion

- CARMENA showed importance of careful selection of patients for cytoreductive nephrectomy
  - Large primary tumors, low metastatic burden, excellent PS
- In Keynote-427, pembrolizumab* monotherapy well tolerated and has disease activity for mRCC
  - Basis for ongoing adjuvant and combination trials
- Better biomarkers are needed to predict for immunotherapy sensitivity and resistance
  - Promising biomarkers from ASCO: tumor-infiltrating CD8+ T cells, indel burden, and gut microbiome

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Oligometastases

- Distinct clinical state
- Metastases limited in number and/or destination organ
- More indolent biology earlier in the metastatic cascade

"An attractive consequence of the presence of a clinically significant oligometastatic state is that some patients so affected should be amenable to a curative therapeutic strategy."

Ablative Radiation for the Treatment of Oligometastatic RCC

- SBRT can control oligometastases, including “radioresistant” tumors
- 18 patients with RCC and limited metastases were treated using SBRT
- At 2 years’ follow-up, LeC was 91.4%, OS 85%
  - Patients who underwent treatment for all metastatic sites had a 2-year LeC of 100%
- SBRT treatment was well tolerated
  - Most common toxicity was fatigue (61.1%)
- Freedom from any post-SBRT therapy was 64.2% at 1 year

Identifying Oligometastatic Patients Who May Benefit From Ablative Radiation

- Analysis of 361 exclusively extracranial oligometastatic patients treated with HIGRT
- RPA used to stratify patients into 5 classes
- OS and PFS were well stratified based on RPA class
- Patients with BKP or long disease-free intervals have promising overall outcomes

<table>
<thead>
<tr>
<th>Class</th>
<th>3-Year OS</th>
<th>3-Year PFS*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: All BKP patients</td>
<td>75% (95% CI, 66%-85%)</td>
<td>44% (95% CI, 32%-57%)</td>
</tr>
<tr>
<td>2: Patients with non-BKP diseases and a disease-free interval of ≥ 75 months</td>
<td>85% (95% CI, 67%-100%)</td>
<td>17% (95% CI, 13%-23%)</td>
</tr>
<tr>
<td>3: Patients with non-BKP diseases, disease-free interval of &lt; 75 months, and ≤ 2 metastases</td>
<td>55% (95% CI, 48%-64%)</td>
<td></td>
</tr>
<tr>
<td>4: Patients with non-BKP diseases, disease-free interval of &lt; 75 months, ≥ 3 metastases, and age &lt; 62 years</td>
<td>38% (95% CI, 24%-60%)</td>
<td></td>
</tr>
<tr>
<td>5: All remaining patients</td>
<td>13% (95% CI, 5%-38%)</td>
<td></td>
</tr>
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</table>

Molecular Subtyping of Colorectal Liver Metastases

- 134 patients with liver metastases from colorectal cancer
  - Molecular analysis of limited de novo liver metastases
- Patients were uniformly treated with perioperative chemotherapy, definitive treatment of primary cancer, and partial hepatectomy for resection of liver metastases
- 113-gene signature validated in independent MSKCC dataset

Integration of Intrinsic Molecular Subtypes and Clinical Risk Stratification

- Molecular subtypes of CRCLM significantly improve clinical risk stratification for identifying patients with favorable prognoses after hepatic resection of limited de novo CRCLM
STOMP Study: Phase 2 RCT

- **Primary endpoint**
  - Time to ADT

- **Stratification**
  - PSA DT
  - Location of metastases

- **Reason to start ADT**
  - Symptoms
  - Local progression
  - Polymetastatic progression

---

**Enrollment**

- Assessed for eligibility (N = 208)
- Randomized (N = 62)
- 0 lost to follow-up

**Allocation**

- Allocated to surveillance arm (n = 31)
  - 26 received allocated intervention
  - 5 received MDT as per protocol
- Allocated to MDT (n = 31)
  - 31 received allocated intervention
  - 31 were analyzed in the primary analysis
  - 26 were analyzed per protocol

- Excluded (N = 146)
  - Not meeting inclusion criteria (n = 77)
  - Declined to participate (n = 69)

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**STOMP Study: Biochemical Progression**

- **Best PSA Response, %**

  - **Surveillance**
  - **MDT**

- **Biochemical RFS**

  - **Surveillance**
  - **MDT**

  - HR, 0.53; 95% CI, 0.30-0.94; P = .03

  - ADT-free survival longer with MDT than with surveillance alone (P = .03)
RESORT: Study Design

Key Eligibility Criteria
- Histologic diagnosis of predominantly ccRCC
- Maximum 3 metastatic lesions (independently of the site)
- Absence of radiological residual lesions following surgical removal of metastatic disease
- Histologically proven disease-free margins of resected surgical specimen
- No more than 3 months from radical resection of metastases
- ECOG PS of 0-2

Randomized 1:1
Stratification according to:
- Time from nephrectomy (> or < 12 months)
- Site of disease (lung vs other)
- Number of lesions (single vs multiple)

Primary endpoint: RFS
Secondary endpoints: OS, safety profile
Exploratory endpoints: Translational analyses on blood and tumor samples

Sorafenib*

Observation for 52 weeks

RESORT: Sorafenib and mRFS

- Adjuvant sorafenib not associated with improved outcomes

![Graph showing mRFS in the Two Treatment Arms]

<table>
<thead>
<tr>
<th></th>
<th>N. of Pts</th>
<th>N. of Events</th>
<th>Median (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm = OBS</td>
<td>36</td>
<td>12</td>
<td>35.0</td>
</tr>
<tr>
<td>Arm = Sorafenib</td>
<td>32</td>
<td>14</td>
<td>29.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>12-Month RFS (% 95% CI)</th>
<th>24-Month RFS (% 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm = OBS</td>
<td>74 (59-91)</td>
<td>59 (42-82)</td>
</tr>
<tr>
<td>Arm = Sorafenib</td>
<td>62 (46-84)</td>
<td>52 (35-76)</td>
</tr>
</tbody>
</table>

*Starting dose: Sorafenib 400 mg once a day for 3 weeks. After 21 days the dose should be increased to the standard dose (400 mg bid) if the patient has not experienced greater than grade I skin toxicity or greater than grade II of any other toxicity.

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Conclusion

• Increased understanding of the molecular underpinnings of oligometastatic disease
• Favorable outcomes in patients with oligometastatic prostate and kidney cancer
• Improved biochemical RFS in the treatment of oligometastatic prostate cancer
• Adjuvant sorafenib is not associated with improved outcomes for oligometastatic RCC patients

Contact Information

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Renal Cell Carcinoma: Abbreviations and Acronyms

ADT = androgen deprivation therapy
AE = adverse event
ATB = antibiotics
BKP = breast, kidney, or prostate cancers
ccRCC = clear cell renal cell carcinoma
CR = complete response
CRCLM = colorectal cancer liver metastases
DCB = durable clinical benefit
DCR = disease control rate
DOR = duration of response
DT = doubling time
ECOG = Eastern Cooperative Oncology Group
EOMES = eomesodermin
EMT = epithelial-mesenchymal transition
HGB = hemoglobin
HIGRT = hypofractionated image-guided radiotherapy
IFN = interferon gamma
IHC = immunohistochemistry
indel = insertion-and-deletion
ITT = intention to treat
IMDC = International Metastatic Renal Cell Carcinoma Database Consortium
KPS = Karnofsky Performance Score
LDH = lactate dehydrogenase
LeC = lesion control
MDT = metastasis-directed therapy
mPFS = median progression-free survival
mRCC = metastatic renal cell carcinoma
mRFS = median recurrence-free survival
MSI = microsatellite instability
MSKCC = Memorial Sloan Kettering Cancer Center
NA = not available
NR = nonresponder
OBS = observation
ORR = objective response rate
OS = overall survival
PD = progressive disease
PD1 = programmed death 1
PD-L1 = programmed death-ligand 1
PFS = progression-free survival
PR = partial response
PS = Performance Status
PSA = prostate-specific antigen
R = responder
RCC = renal cell carcinoma
RCT = randomized controlled trial
RFS = recurrence-free survival
RPA = recursive partitioning
SBRT = stereotactic body radiotherapy
SD = stable disease
SNF = similarity network fusion
TKI = tyrosine kinase inhibitor