The NCCN Value Initiative:
Using NCCN Evidence Blocks™
in Clinical Decisions

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NCCN Guidelines Program

- 49 multidisciplinary panels with 26-30 experts per panel
- It is estimated that Guidelines Panel Members contributed more than 26,000 hours in 2015
- 62 NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) updated continuously
- Cover continuum and all modalities of cancer care
- Available free of charge on the Internet
- Accepted as standard for clinical care and policy in oncology in United States
- Basis for insurance coverage policy and quality evaluation
- 6.7 million copies downloaded in 2015 to 180 countries

NCCN Categories of Evidence and Consensus

- **Category 1:** Based upon high-level evidence, there is uniform NCCN consensus (≥85%) that the intervention is appropriate.
- **Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus (≥85%) that the intervention is appropriate.
- **Category 2B:** Based upon lower-level evidence, there is NCCN consensus (50-85%) that the intervention is appropriate.
- **Category 3:** Based upon any level of evidence, there is major NCCN disagreement (at least 3 institutions on each side) that the intervention is appropriate.

*All recommendations are category 2A unless otherwise noted.*
Stakeholder Requests

- Information on why a Panel has made a recommendation on the algorithm itself
- Need to provide information about “cost” even if not used to make recommendations
- Growing concept and awareness of “value” in making choices

Principles of “Value”

- Value has many definitions
- The patient perception of value is most important
- Value varies greatly from patient to patient
- Providing information that allows the patient to “create the value formula” in shared decision making is optimal
Operational Assumptions

• NCCN Panel Members are disease sub specialists who know their disease sites well
• Panel members integrate recommendations into an ongoing standard of care
• They consider efficacy, safety, quality of evidence and consistency of evidence routinely in making recommendations
• Providing insight into these evaluations will be helpful to clinicians and patients

NCCN Evidence Blocks™

• Use consistent methodology and display to inform decision-making
• Measures
  – Efficacy
  – Safety
  – Quality of Evidence
  – Consistency of Evidence
  – Affordability
• More shading is better
## Efficacy of Regimens Scale

<table>
<thead>
<tr>
<th>Score</th>
<th>Summary</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Highly effective</td>
<td>Often provides long-term survival advantage or curative potential</td>
</tr>
<tr>
<td>4</td>
<td>Very effective</td>
<td>Sometimes provides long-term survival advantage or curative potential</td>
</tr>
<tr>
<td>3</td>
<td>Moderately effective</td>
<td>Modest, no, or unknown impact on survival but often provides control of disease</td>
</tr>
<tr>
<td>2</td>
<td>Minimally effective</td>
<td>Modest, no, or unknown impact on survival and sometimes provides control of disease</td>
</tr>
<tr>
<td>1</td>
<td>Palliative only</td>
<td>Symptomatic benefit only</td>
</tr>
</tbody>
</table>

## Safety of Regimen Scale

<table>
<thead>
<tr>
<th>Score</th>
<th>Summary</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Usually no meaningful toxicity</td>
<td>Uncommon or minimal side effects. No interference with activities of daily living.</td>
</tr>
<tr>
<td>4</td>
<td>Occasionally toxic</td>
<td>Rare significant toxicities or low-grade toxicities only. Little interference with activities of daily living.</td>
</tr>
<tr>
<td>3</td>
<td>Mildly toxic</td>
<td>Experience of mild toxicity. Interference with activities of daily living is common.</td>
</tr>
<tr>
<td>2</td>
<td>Moderately toxic</td>
<td>Significant toxicities often occur; life threatening toxicity is uncommon. Interference with activities of daily living is common.</td>
</tr>
<tr>
<td>1</td>
<td>Highly toxic</td>
<td>Usually severe, significant toxicities or life threatening/fatal toxicity often observed. Interference with activities of daily living is usual and/or severe.</td>
</tr>
</tbody>
</table>

**Note:** For significant chronic or long-term toxicities, score decreased by 1.
# Data Quality/Quantity of Regimens Scale

<table>
<thead>
<tr>
<th>Score</th>
<th>Summary</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>High quality</td>
<td>Multiple well-designed randomized trials and/or meta-analyses</td>
</tr>
<tr>
<td>4</td>
<td>Good quality</td>
<td>Several well-designed randomized trials</td>
</tr>
<tr>
<td>3</td>
<td>Average quality</td>
<td>Low quality randomized trials or well-designed non-randomized trials</td>
</tr>
<tr>
<td>2</td>
<td>Low quality</td>
<td>Case reports or clinical experience only</td>
</tr>
<tr>
<td>1</td>
<td>Poor quality</td>
<td>Little or no evidence</td>
</tr>
</tbody>
</table>

# Data Consistency of Regimens Scale

<table>
<thead>
<tr>
<th>Score</th>
<th>Summary</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Highly consistent</td>
<td>Multiple trials with similar outcomes</td>
</tr>
<tr>
<td>4</td>
<td>Mainly consistent</td>
<td>Multiple trials with some variability in outcome</td>
</tr>
<tr>
<td>3</td>
<td>May be consistent</td>
<td>Few trials or only trials with few patients; lower quality trials whether randomized trials or not</td>
</tr>
<tr>
<td>2</td>
<td>Inconsistent</td>
<td>Meaningful differences in direction of outcome between quality trials</td>
</tr>
<tr>
<td>1</td>
<td>Anecdotal evidence only</td>
<td>Evidence in humans based upon anecdotal experience</td>
</tr>
</tbody>
</table>
Affordability of Regimens Scale

<table>
<thead>
<tr>
<th>Score</th>
<th>Summary/Definition</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Very inexpensive</td>
<td>Affordability refers to overall cost of an intervention including drug cost,</td>
</tr>
<tr>
<td>4</td>
<td>Inexpensive</td>
<td>required supportive care, infusions, toxicity monitoring, management of</td>
</tr>
<tr>
<td>3</td>
<td>Moderately expensive</td>
<td>toxicity, probability of care being delivered in the hospital.</td>
</tr>
<tr>
<td>2</td>
<td>Expensive</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Very expensive</td>
<td></td>
</tr>
</tbody>
</table>

Generation of NCCN Evidence Blocks™

- Location of systemic therapy recommendation are identified on the Guideline
- A survey instrument is developed including the 5 measures for each systemic recommendation
- Individual panel members complete the survey for each regimen across all 5 measures
- Responses are collated and an average score for each regimen and each measure is generated
- The results are translated into a graphical Evidence Block
- Evidence Block is placed in the Guideline algorithm
- NCCN Category of Evidence and Consensus is also maintained
Efficacy Score of 3 = modest, no, or unknown impact on survival, but often provides control of disease.

Safety Score of 2 = Significant toxicities often occur, life threatening/fatal toxicity is uncommon. Interference with activities of daily living is usual.
Quality and Quantity of Data score of 5 = Multiple well-designed randomized trials and/or meta-analyses.

Consistency of Evidence score of 4 = Multiple trials with some variability in outcome.
Affordability score of 4 = Inexpensive.
ENOCRINE THERAPY FOR RECURRENT OR STAGE IV DISEASE

Premenopausal patients with hormone-receptor positive disease should have ovarian ablation/suppression and follow postmenopausal guidelines.

<table>
<thead>
<tr>
<th>Postmenopausal Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-steroidal aromatase inhibitor (anastrozole)</td>
</tr>
<tr>
<td>Non-steroidal aromatase inhibitor (letrozole)</td>
</tr>
<tr>
<td>Steroidal aromatase inactivator ( exemestane)</td>
</tr>
<tr>
<td>Exemestane + everolimus</td>
</tr>
<tr>
<td>Palbociclib + letrozole</td>
</tr>
<tr>
<td>Palbociclib + fulvestran (category 1)</td>
</tr>
<tr>
<td>Fulvestran</td>
</tr>
<tr>
<td>Tamoxifen</td>
</tr>
<tr>
<td>Toremifene</td>
</tr>
<tr>
<td>Megestrol acetate</td>
</tr>
<tr>
<td>Fluoxymesterone</td>
</tr>
<tr>
<td>Ethinyl estradiol</td>
</tr>
</tbody>
</table>

A combination of exemestane with everolimus can be considered for patients who meet the eligibility criteria for BOLERO-2 (progressed within 12 mo or on non- steroidal AI, or any time on tamoxifen).

Palbociclib in combination with letrozole may be considered as a treatment option for first-line therapy for postmenopausal patients with hormone-receptor positive, HER2-negative metastatic breast cancer.

1For postmenopausal women or for premenopausal women receiving ovarian suppression with an LHRH agonist, with hormone-receptor positive and HER2-negative metastatic breast cancer.

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ENDOCRINE THERAPY FOR RECURRENT OR STAGE IV DISEASE

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Note: For more information regarding the categories and definitions used to the NCCN evidence blocks, see page 843.

All recommendations are category 2A unless otherwise indicated.

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NCCN Guidelines with NCCN Evidence Blocks™ Currently Available

- Breast Cancer
- Chronic Myelogenous Leukemia (CML)
- Colon Cancer
- Kidney Cancer
- Melanoma
- Multiple Myeloma
- Diffuse Large B-Cell Lymphoma
- Non-Small Cell Lung Cancer (NSCLC)
- Prostate Cancer
- Rectal Cancer

ASCO’s Value Framework

- Compares new treatment with existing treatment as compared in randomized clinical trials
- Different methodologies for advanced disease and adjuvant setting
- Three Parameters: Benefit, Toxicity, Cost
- What it is: Standardized information for doctors and patients
- What it is not: A ranking system that can compare any two drugs to one another
ASCO’s Value Framework

- Single score for each regimen
- “Net health benefit” score derived from efficacy and toxicity
  - Favors overall survival benefit over other outcomes
- Compares only clinical trial results
  - Head to head comparisons
  - Difficult to assess the range of interventions
- Cost a separate calculation
  - Drug acquisition cost only

Net Health Benefit

- The added benefit patients may receive from a new cancer drug compared with a standard of care
- Maximum: 130 points (advanced) and 100 points (adjuvant)
Memorial Sloan Kettering Cancer Center
Drug Abacus

Estimates value-based cost of 51 oncology agents approved since 2001 based on
• Anticipated outcomes of the treatment,
  – Efficacy
  – Toxicity
• Economic variables
  – Development cost
  – Rarity multiplier
  – Novelty
  – Population size

Institute for Clinical and Economic Review (ICER)

• Developed by: Payors, industry, ASCO, patient group
• Provides model for evaluating effectiveness and value for use by technology assessment groups
• “Value based price benchmark”
• Criteria:
  – Comparative effectiveness
  – Incremental cost
  – Benefits/disadvantages
  – Expected uptake (level of use)
NCCN Evidence Blocks™ Summary

- NCCN Evidence Blocks™ provide information, not a conclusion
- Transparent data presentation
- This allows an efficient comparison across multiple options
- Respects the individual patient, physician, or other stakeholder value system(s)
- A basis for framing decisions and value considerations.

Treatment Algorithms in Metastatic Renal Cell Carcinoma

Eric Jonasch, MD
Professor, GU Medical Oncology
UT MD Anderson Cancer Center
Treatment for Renal Cell Carcinoma

A → B → C?

Histological Classification of Human Renal Epithelial Neoplasms

RCC

<table>
<thead>
<tr>
<th>Type</th>
<th>Incidence (%)</th>
<th>Associated mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear cell</td>
<td>75%</td>
<td>VHL</td>
</tr>
<tr>
<td>Papillary type 1</td>
<td>5%</td>
<td>c-Met</td>
</tr>
<tr>
<td>Papillary type 2</td>
<td>10%</td>
<td>FH</td>
</tr>
<tr>
<td>Chromophobe</td>
<td>5%</td>
<td>Folliculin</td>
</tr>
</tbody>
</table>

VHL=von Hippel-Lindau; FH=fumarate hydratase; BHD=Birt-Hogg-Dubé.
### VHL Gene and Gene Product

- Located on 3p25
- 213 amino acid protein

<table>
<thead>
<tr>
<th>Type I VHL</th>
<th>Type II VHL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sporadic VHL</td>
<td>(Missense Mutations)</td>
</tr>
<tr>
<td>(Deletion/Truncation)</td>
<td></td>
</tr>
<tr>
<td>( \beta )</td>
<td>( \alpha )</td>
</tr>
</tbody>
</table>

#### Binds:
- Fibronectin
- PKC
- Collagen I and IV

#### Associates with:
- TRiC (for folding)
- Endoplasmic reticulum
- Primary cilium

PKC = protein kinase C; TRiC = tail-less complex polypeptide 1 (TCP-1) ring complex.

### VHL Mutation Replicates the Hypoxic State

Transcription of:
- VEGF
- Other angiogenic factors

VEGF = vascular endothelial growth factor; HIF = hypoxia-inducible factor.
Treatment by Stage

• Stage 1, 2, 3:
  – Nephrectomy
  – Investigational Question: Adjuvant Therapy?
  – No role for targeted agents or IFN in this setting outside of a clinical trial.

• Stage 4:
  – Cytoreductive nephrectomy for patients with performance status 0 or 1, and resectable primary.
  – Avoid doing nephrectomy on patients with high disease burden.
  – Systemic therapy as per guidelines.
INITIAL WORKUP

Suspicious mass →

- H&P
- CBC, comprehensive metabolic panel
- Urinalysis
- Abdominal/pelvic CT or abdominal MRI with or without contrast depending on renal insufficiency
- Chest imaging
- Bone scan, if clinically indicated
- Brain MRI, if clinically indicated
- If urothelial carcinoma suspected (eg, central mass), consider urine cytology, ureteroscopy
- Consider needle biopsy, if clinically indicated

KID-1

STAGE | PRIMARY TREATMENT | FOLLOW-UP (category 2B)
--- | --- | ---
Stage I (pT1a) | Partial nephrectomy (preferred) or Radical nephrectomy (if partial not feasible or central location) or Active surveillance in selected patients or Ablative techniques for non-surgical candidates | Follow-up (See KID-B) → Relapse See First-Line Therapy (KID-3)
Stage I (pT1b) | Partial nephrectomy or Radical nephrectomy | 
Stage II, III | Radical nephrectomy | 
Stage IV | See KID-2 | 

KID-1

MSKCC Risk Factor Model in mRCC

Risk factors associated with worse prognosis
- KPS <80
- Low serum hemoglobin (13 g/dL/11.5 g/dL: M/F)
- High corrected calcium (10 mg/dL)
- High lactate dehydrogenase (300 U/L)
- No nephrectomy or < 1 yr from Dx to Treatment

Proportion Surviving

Years from Start of IFN-α
**Heng Criteria for Prognosis in TKI Treated Patients**

1. KPS< 80
2. Diagnosis to treatment less than 1 year
3. Anemia
4. Hypercalcemia
5. Thrombocytosis
6. Leukocytosis

Heng et al J Clin Oncol 2009

**Overall Survival**

- Favorable: 0 factors (mOS 37 mos)
- Intermediate: 1-2 factors (mOS 27 mos)
- Poor: 3-6 factors (mOS 8.8 mos)

Median follow-up 26 months, n=645

Heng et al J Clin Oncol 2009
Antiangiogenic Agents:

1. Sunitinib
2. Pazopanib
3. Bevacizumab + IFN
4. Sorafenib
5. Axitinib
6. Cabozantinib

Mammalian Target of Rapamycin Inhibitors (mTORi)

1. Temsirolimus
2. Everolimus
Immunomodulatory Agents

1. Nivolumab
2. Interleukin 2

Key Questions

1. Is there a “best” frontline TKI?
2. Is there an “ideal” sequence after frontline treatment failure?
3. What is the role of mTOR inhibitors for RCC in 2016 and beyond?
Frontline Treatment

Kidney Cancer
NCCN Evidence Blocks™

Efficacy of Regimen/Agent
1 Highly effective: Often provides long-term survival advantage or has curative potential
2 Very effective: Sometimes provides long-term survival advantage or has curative potential
3 Moderately effective: Moderate, no, or unknown impact on survival but often provides control of disease
4 Minimally effective: Modest, no, or unknown impact on survival and sometimes provides control of disease
5 Palliative: Provides symptomatic benefit only

Quality of Evidence
6 High quality: Multiple well-designed randomized trials and/or meta-analyses
5 Good quality: Several well-designed randomized trials
4 Average quality: Low quality randomized trials or well-designed non-randomized trials
3 Low quality: Case reports or clinical experience only
2 Poor quality: Little or no evidence
1 Consistency of Evidence
6 Highly consistent: Multiple trials with similar outcomes
5 Mostly consistent: Multiple trials with some variability in outcome
4 May be consistent: Few trials or only trials with few patients; lower quality trials whether randomized or not
3 Inconsistent: Meaningful differences in direction of outcome between quality trials
2 Anecdotal evidence: Evidence in humans based upon anecdotal experience
1

Affordability of Regimen/Agent (Includes drug cost, supportive care, infusions, toxicity monitoring, management of toxicity)
6 Very expensive
5 Inexpensive
4 Moderately expensive
3 Expensive
2 Very expensive
1

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Phase 3 Trial of Sunitinib vs IFN-α in Patients With Untreated Metastatic RCC

Motzer et al. NEJM 2007

Phase 3 Trial of Sunitinib vs IFN-α in Patients With Untreated Metastatic RCC

Sunitinib
Median: 11.0 mo
(95% CI 10.7-13.4)

HR = 0.538
(95% CI 0.439-0.658)

P < .000001

IFN-α
Median: 5.1 mo
(95% CI 3.9-6.6)

Phase III Study of Pazopanib Versus Placebo in Untreated and Pretreated Patients

Overall study population
Treatment naïve subpopulation

Comparz Study

**Key Eligibility Criteria**
- Advanced/metastatic RCC
- Clear-cell histology
- No prior systemic therapy
- Measurable disease (RECIST 1.0)
- KPS ≥ 70
- Adequate organ function

**Stratification Factors**
- KPS 70/80 vs 90/100
- Prior nephrectomy
- Baseline LDH >1.5 vs ≤1.5×ULN

**Randomized 1:1**

**Pazopanib**
- 800 mg qd continuous dosing
- Dose reductions to 600 mg or 400 mg

**Sunitinib**
- 50 mg qd
- 4 wk on/2 wk off
- Dose reductions to 37.5 mg or 25 mg

**Primary Endpoint: Progression-free Survival (independent review)**

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Median PFS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pazopanib</td>
<td>557</td>
<td>8.4 mo (8.3, 10.9)</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>553</td>
<td>9.5 mo (8.3, 11.1)</td>
</tr>
</tbody>
</table>

HR (95% CI) = 1.047 (0.898, 1.220)

Motzer et al NEJM 2014
## Interim Analysis of Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Median OS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pazopanib</strong></td>
<td>557</td>
<td>28.4 mos (26.2, 35.6)</td>
</tr>
<tr>
<td><strong>Sunitinib</strong></td>
<td>553</td>
<td>29.3 mos (25.3, 32.5)</td>
</tr>
</tbody>
</table>

HR (95% CI) = 0.908 (0.762, 1.082)
P-value = 0.275

---

## Treatment Duration and Dose Adjustments

<table>
<thead>
<tr>
<th></th>
<th>Pazopanib (n = 554)</th>
<th>Sunitinib (n = 548)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median duration of treatment (months, range)</td>
<td>8.0 (0–40)</td>
<td>7.6 (0–38)</td>
</tr>
<tr>
<td>Dose reductions, %</td>
<td>44</td>
<td>51</td>
</tr>
<tr>
<td>Discontinuations due to AEs¹, %</td>
<td>24</td>
<td>19</td>
</tr>
</tbody>
</table>

¹. Most common reason: pazopanib arm (liver event, 6%); sunitinib arm (cytopenia, 3%)

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Motzer et al NEJM 2014
Phase 3 Study of Temsirolimus and IFN in Advanced RCC: Study Design

Eligibility Criteria
- Histologically confirmed, measurable (RECIST) advanced (stage IV or recurrent) RCC
- No prior systemic therapy
- Karnofsky PS ≥ 60
- Fasting serum cholesterol ≤ 350 mg/dL, triglycerides ≤ 400 mg/dL
- Minimum of 3 poor-risk features required*

Randomization
(N=626)  (n=207) IFN escalating to 18 MU SC 3 times weekly
(N=209) Temsirolimus 25 mg IV weekly
(N=210) Temsirolimus 15 mg IV weekly + IFN 6 MU SC weekly 3 times weekly

Primary end point: OS

*Risk Factors
- LDH > 1.5 × ULN
- Hgb < LLN
- Corrected calcium > 10 mg/dL
- Time from diagnosis to first treatment < 1 y
- Karnofsky PS 60-70
- Multiple organ sites of metastasis

RECIST = Response Evaluation Criteria in Solid Tumors; LDH = lactate dehydrogenase; Hgb = hemoglobin.
Key Differences Compared to Most Frontline Studies

- All intermediate/poor risk patients
- One third did not have nephrectomy
- Twenty percent had non-clear cell RCC

Phase 3 Study of Temsirolimus and IFN in Advanced RCC: OS by Treatment Arm

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>n</th>
<th>Median OS, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN</td>
<td>207</td>
<td>7.3</td>
</tr>
<tr>
<td>Temsirolimus</td>
<td>209</td>
<td>9.9</td>
</tr>
<tr>
<td>Temsirolimus + IFN</td>
<td>210</td>
<td>8.4</td>
</tr>
</tbody>
</table>

Phase 3 Study of Temsirolimus and IFN in Advanced RCC: OS by Treatment Arm

Absence of prospective TKI to temsirolimus comparisons in poor risk population impairs our ability to move on from temsirolimus


Second Line Treatment
SUBSEQUENT THERAPY

Predominant clear cell histology

Clinical trial or Targeted therapy:
- After tyrosine kinase inhibitor therapy
  - Axitinib (category 1)
  - Everolimus (category 1)
  - Cabozantinib (category 1)
  - Nivolumab (category 1)
- Sorafenib
- Sunitinib
- Pazopanib
- Temsirolimus (category 2B)
- Bevacizumab (category 2B)

- After cytokine therapy
  - Axitinib (category 1)
  - Sorafenib (category 1)
  - Sunitinib (category 1)
  - Pazopanib (category 1)
- Temsirolimus
- Bevacizumab

or Cytokine therapy:
- High-dose IL-2 for selected patients (category 2B)

and Best supportive care:
See NCCN Guidelines for Palliative Care

KID-3
Everolimus vs. Placebo Phase 3 Trial: Key Data from RECORD-1

Motzer et al. Lancet 2008

- Median PFS: Everolimus 14.7 mos vs. Placebo 5.6 mos
- Log rank P = 0.001
- Stratified HR 0.665 (95% CI 0.544–0.812)

Axitinib Phase III Randomized Study
PFS Assessment

Rini et al. Lancet 2011

- mPFS: Axitinib 6.7 mos vs. Sorafenib 4.7 mos
- Log-rank P < 0.0001
- Stratified HR 0.665 (95% CI 0.544–0.812)
Cabozantinib

- Oral small molecule inhibitor of tyrosine kinases including MET, VEGF receptors, and AXL\(^1\)

- MET/AXL signaling increased in chronically VEGF treated RCC, and was associated with EMT\(^2\)

- AXL signaling is prometastatic\(^3\)

\(^1\) Yakes FM et al., Mol Cancer Ther, 2011
\(^2\) Zhou and Jonasch Oncogene 2015
\(^3\) Rankin and Giaccia PNAS 2015

Study Design

Advanced RCC (N=650)
- Clear cell histology
- Measurable disease
- Progression on prior VEGFR TKI within 6 months of enrollment
- No limit to the number of prior therapies
- Antibodies targeting PD-1/PD-L1 allowed
- Brain metastases allowed if treated

Stratification:
- MSKCC\(^1\) risk groups: favorable, intermediate, poor
- Number prior VEGFR-TKIs: 1, 2 or more

Randomization 1:1
- No cross-over allowed
- Treatment until loss of clinical benefit or intolerable toxicity

Cabozantinib 60 mg qd orally

Everolimus 10 mg qd orally

Choueiri and Motzer NEJM 2015

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Progression-Free Survival
Independent Central Radiology Review

<table>
<thead>
<tr>
<th></th>
<th>No. at Risk</th>
<th>Median PFS</th>
<th>No. of Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabozantinib</td>
<td>187</td>
<td>7.4 (5.6-9.1)</td>
<td>121</td>
</tr>
<tr>
<td>Everolimus</td>
<td>188</td>
<td>3.8 (3.7-5.4)</td>
<td>126</td>
</tr>
</tbody>
</table>

Hazard ratio, 0.58 (95% CI 0.45-0.75, P<0.001)

Choueiri and Motzer NEJM 2015

Sunitinib as Only Prior VEGFR TKI
Post-hoc PFS Subset Analysis

<table>
<thead>
<tr>
<th></th>
<th>No. at Risk</th>
<th>Median PFS</th>
<th>No. of Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabozantinib</td>
<td>76</td>
<td>9.1 (5.6-11.2)</td>
<td>45</td>
</tr>
<tr>
<td>Everolimus</td>
<td>77</td>
<td>3.7 (1.9-4.2)</td>
<td>58</td>
</tr>
</tbody>
</table>

Hazard ratio, 0.41 (95% CI 0.28-0.61)

Choueiri and Motzer NEJM 2015
Kaplan-Meier Estimates of Overall Survival
Interim Analysis (49% Information Fraction)

Overall Survival (%)
No. at Risk
Cabozantinib 330 317 294 189 101 32 6 1 0
Everolimus 328 306 260 156 88 24 5 1 0

Hazard ratio, 0.67 (95% CI 0.51-0.89, P=0.005)
(Medians cannot yet be estimated due to frequent early censoring)

The interim boundary to reach significance (P=0.0019) was not reached
Survival follow up is continuing to the planned final analysis

Choueiri and Motzer NEJM 2015
## Significant Toxicities

<table>
<thead>
<tr>
<th>Preferred Term, %</th>
<th>Cabozantinib (N=331)</th>
<th></th>
<th>Everolimus (N=322)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3/4</td>
<td>All Grades</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td><strong>Any adverse event</strong>*</td>
<td>100</td>
<td>68</td>
<td>&gt;99</td>
<td>58</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>74</td>
<td>11</td>
<td>27</td>
<td>2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>56</td>
<td>9</td>
<td>46</td>
<td>7</td>
</tr>
<tr>
<td>Nausea</td>
<td>50</td>
<td>4</td>
<td>28</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>46</td>
<td>2</td>
<td>34</td>
<td>&lt;1</td>
</tr>
<tr>
<td>PPE syndrome</td>
<td>42</td>
<td>8</td>
<td>6</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>37</td>
<td>15</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>32</td>
<td>2</td>
<td>14</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>31</td>
<td>2</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>25</td>
<td>&lt;1</td>
<td>19</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Anemia</td>
<td>17</td>
<td>5</td>
<td>38</td>
<td>16</td>
</tr>
<tr>
<td>Cough</td>
<td>18</td>
<td>&lt;1</td>
<td>33</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>19</td>
<td>3</td>
<td>28</td>
<td>4</td>
</tr>
<tr>
<td>Rash</td>
<td>15</td>
<td>&lt;1</td>
<td>28</td>
<td>&lt;1</td>
</tr>
<tr>
<td><strong>Events of interest</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycaemia</td>
<td>5</td>
<td>&lt;1</td>
<td>19</td>
<td>5</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>0</td>
<td>0</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>GI Perforation</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Fistula</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Events reported in at least 25% of patients in either study group; PPE, palmar-plantar erythrodysesthesia

Choueiri and Motzer NEJM 2015

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**ORIGINAL ARTICLE**

### Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma

**Trial Schema**

- **821 pts mRCC w. clear cell**
- **Prior antiangiogenic therapy**

- **Nivolumab 3mg/kg IV Q2 weeks**
- **Everolimus 10mg PO Daily**

- **Overall Survival**
- **Response Rate**
- **Progression Free Survival**

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**Objective Response Rate**

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab N=410</th>
<th>Everolimus N=411</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective Response Rate</strong></td>
<td>103 (25) <strong>P&lt;0.001</strong></td>
<td>22 (5)</td>
</tr>
<tr>
<td><strong>Odds ratio (95% CI)</strong></td>
<td>5.98 (3.68-9.72)</td>
<td></td>
</tr>
<tr>
<td><strong>Best Overall Response</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>4 (1)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>PR</td>
<td>99 (24)</td>
<td>20 (5)</td>
</tr>
<tr>
<td>SD</td>
<td>143 (35)</td>
<td>227 (55)</td>
</tr>
<tr>
<td>PD</td>
<td>23 (6)</td>
<td>114 (28)</td>
</tr>
<tr>
<td>Not evaluated</td>
<td></td>
<td>48 (12)</td>
</tr>
<tr>
<td><strong>Median time to response, months (range)</strong></td>
<td>3.5 (1.4-24.8)</td>
<td>3.7 (1.5-11.2)</td>
</tr>
<tr>
<td><strong>Median duration of response, months (range)</strong></td>
<td>12.0 (0-27.6)</td>
<td>12.0 (0-22.2)</td>
</tr>
<tr>
<td><strong>Median Duration of Treatment, months (range)</strong></td>
<td>5.5 (&lt;1 to 29.6)</td>
<td>3.7 (0.2 to 25.7)</td>
</tr>
</tbody>
</table>

Motzer and Sharma *NEJM* 2015

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Progression Free Survival

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Overall Survival

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**PD-L1 expression and OS**

*Table 2. Treatment-Related Adverse Events Reported in 10% or More of Treated Patients in Either Group.*

<table>
<thead>
<tr>
<th>Event</th>
<th>Nivolumab Group (N = 616)</th>
<th>Everolimus Group (N = 397)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3 or 4</td>
</tr>
<tr>
<td>number of patients (percent)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All events</td>
<td>312 (79)</td>
<td>76 (19)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>134 (33)</td>
<td>10 (2)</td>
</tr>
<tr>
<td>Nausea</td>
<td>57 (14)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>57 (14)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>50 (12)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>48 (12)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Rash</td>
<td>41 (10)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Cough</td>
<td>36 (9)</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>32 (8)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>30 (7)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>17 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>16 (4)</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>11 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>11 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>9 (2)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>8 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>5 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>3 (1)</td>
<td>0</td>
</tr>
</tbody>
</table>

Motzer and Sharma NEJM 2015
Key question is whether we can predict who will benefit from either.
Emerging data suggest degree of immune infiltrate (“hot tumors”) may be associated with nivolumab response.
Where does this leave mTOR inhibitors? Response possibly associated with PI3K pathway mutations.

Non Clear Cell RCC
Summary

- Treatment for RCC is rapidly evolving, with new agents being approved for different disease states.

- Evidence Blocks permit succinct interpretation of data which can generate a dialogue between patients and the treatment team.

- Ongoing refinement of the Evidence Blocks in the context of new evidence will increase the power of this tool in summarizing treatment options for patients with RCC.