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

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National Comprehensive Cancer Network®

NCCN.org – For Clinicians | **NCCN.org/patients** – For Patients

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NCCN Evidence Blocks™

Robert W. Carlson, MD

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”

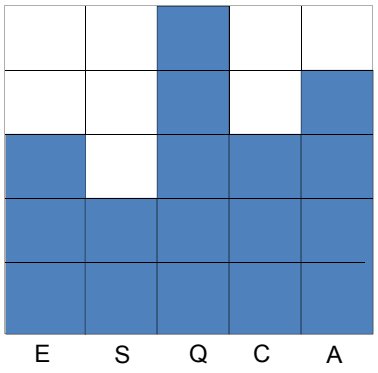
- Value has many definitions
- The patient perception of value is most important
- Value varies greatly from patient to patient
- Providing information that allows the patient to “create the value formula” in shared decision making is optimal

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

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

Safety of Regimen Scale

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

Note: For significant chronic or long-term toxicities, score decreased by 1

Data Quality/Quantity of Regimens Scale

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

Data Consistency of Regimens Scale

Score	Summary	Definition
5	Highly consistent	Multiple trials with similar outcomes
4	Mainly consistent	Multiple trials with some variability in outcome
3	May be consistent	Few trials or only trials with few patients; lower quality trials whether randomized trials or not
2	Inconsistent	Meaningful differences in direction of outcome between quality trials
1	Anecdotal evidence only	Evidence in humans based upon anecdotal experience

Affordability of Regimens Scale

Score	Summary/Definition
5	Very inexpensive
4	Inexpensive
3	Moderately expensive
2	Expensive
1	Very expensive

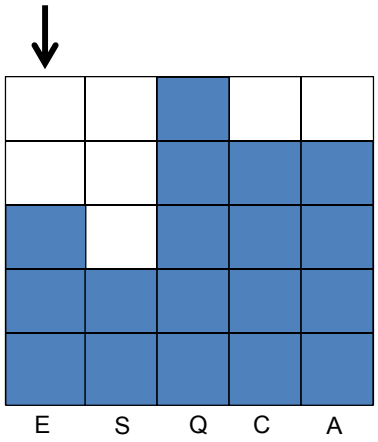
Affordability refers to overall cost of an intervention including drug cost, required supportive care, infusions, toxicity monitoring, management of toxicity, probability of care being delivered in the hospital.

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

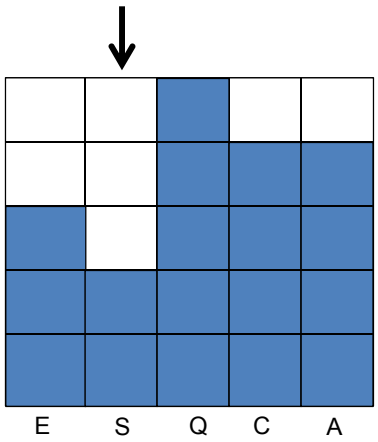
NCCN Evidence Blocks™

Efficacy Score of 3 = modest, no, or unknown impact on survival, but often provides control of disease.



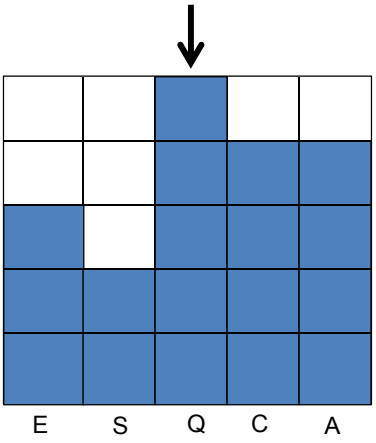
NCCN Evidence Blocks™

Safety Score of 2 = Significant toxicities often occur, life threatening/fatal toxicity is uncommon. Interference with activities of daily living is usual.



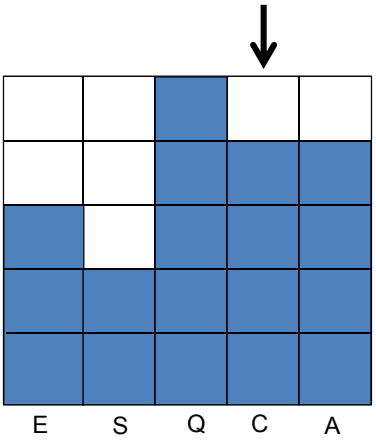
NCCN Evidence Blocks™

Quality and Quantity of Data score of 5 = Multiple well-designed randomized trials and/or meta-analyses.



NCCN Evidence Blocks™

Consistency of Evidence score of 4 = Multiple trials with some variability in outcome.



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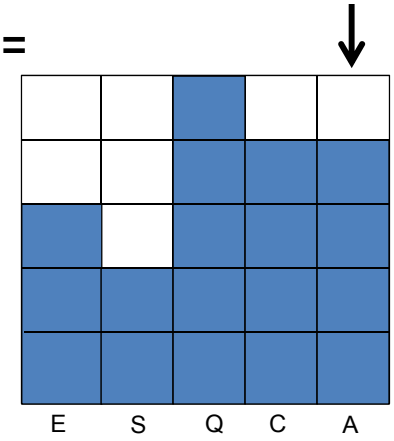
NCCN Evidence Blocks™

Affordability score of 4 =
Inexpensive.



National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Breast Cancer

NCCN Evidence Blocks™

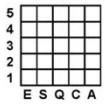
Version 1.2016
NCCN.org

NCCN Evidence Blocks™

National Comprehensive Cancer Network®

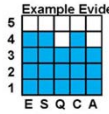
NCCN Guidelines Version 1.2016
Breast Cancer
NCCN Evidence Blocks™

NCCN EVIDENCE BLOCKS CATEGORIES AND DEFINITIONS



E = Efficacy of Regimen/Agent
S = Safety of Regimen/Agent
Q = Quality of Evidence
C = Consistency of Evidence
A = Affordability of Regimen/Agent

Example Evidence Block



E = 4
S = 4
Q = 3
C = 4
A = 3

Efficacy of Regimen/Agent

5	**Highly effective:** Often provides long-term survival advantage or has curative potential
4	**Very effective:** Sometimes provides long-term survival advantage or has curative potential
3	**Moderately effective:** Modest, no, or unknown impact on survival but often provides control of disease
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Affordability of Regimen/Agent (includes drug cost, supportive care, infusions, toxicity monitoring, management of toxicity)

5	Very inexpensive
4	Inexpensive
3	Moderately expensive
2	Expensive
1	Very expensive

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NCCN Guidelines Version 1.2016
Invasive Breast Cancer
NCCN Evidence Blocks™

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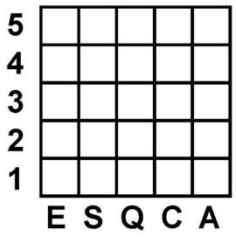
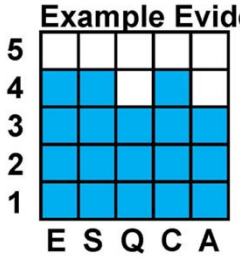
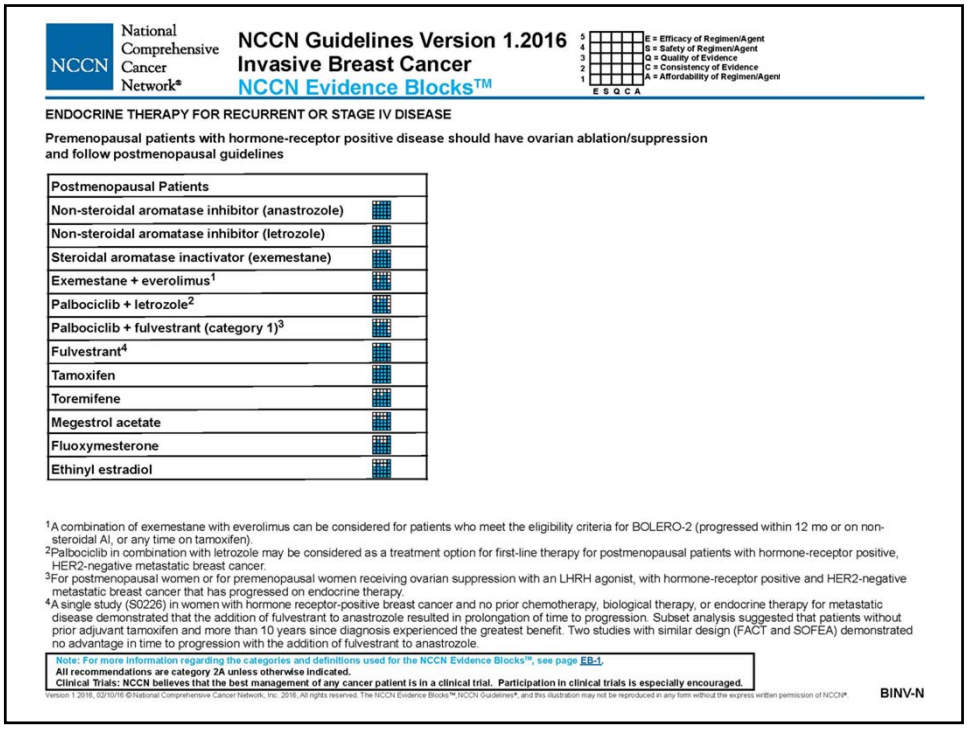


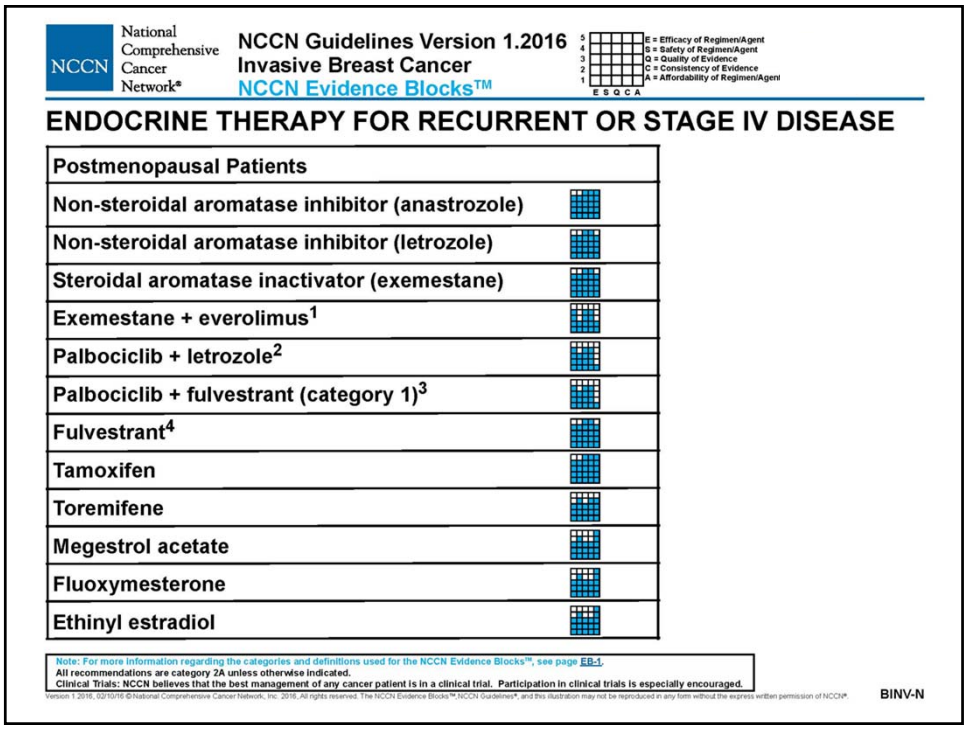
Example Evidence Block



E = 4
S = 4
Q = 3
C = 4
A = 3

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.





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

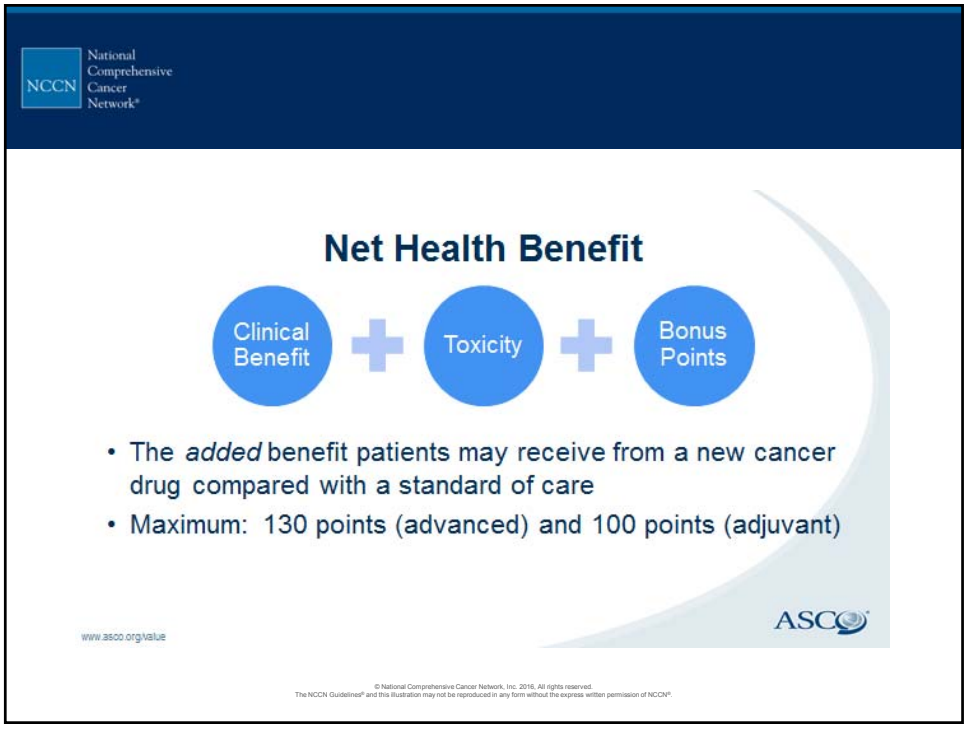
ASCO's Value Framework

- 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

www.asco.org/value

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



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
  - Novelty
  - Rarity multiplier
  - 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

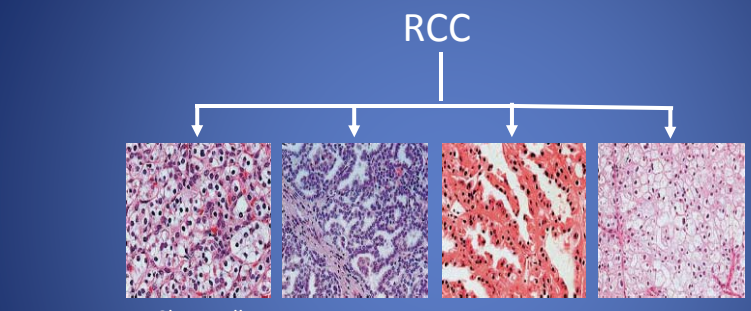
- NCCN Evidence Blocks™ provide information, not a conclusion
- Transparent data presentation
- This allows an efficient comparison across multiple options
- Respects the individual patient, physician, or other stakeholder value system(s)
- A basis for framing decisions and value considerations.

Treatment Algorithms in Metastatic Renal Cell Carcinoma

Eric Jonasch, MD
Professor, GU Medical Oncology
UT MD Anderson Cancer Center

Treatment for Renal Cell Carcinoma

Histological Classification of Human Renal Epithelial Neoplasms



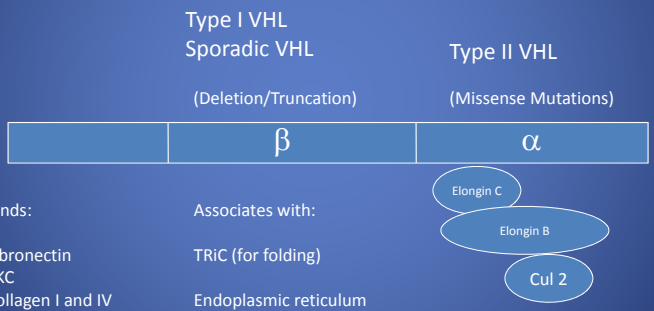
Type	Clear cell	Papillary type 1	Papillary type 2	Chromophobe
Incidence (%)	*75%*	*5%*	*10%*	*5%*
Associated mutations	*VHL*	*c-Met*	*FH*	*Folliculin*

VHL=von Hippel-Lindau; FH=fumarate hydratase; BHD=Birt-Hogg-Dubé.

Modified from Linehan WM et al. *J Urol.* 2003;170:2163-2172.

VHL Gene and Gene Product

- Located on 3p25
- 213 amino acid protein



Binds:

Fibronectin
PKC
Collagen I and IV

Associates with:

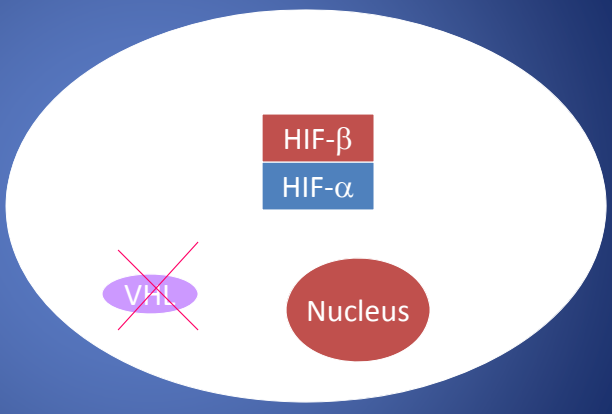
TRiC (for folding)

Endoplasmic reticulum

Primary cilium

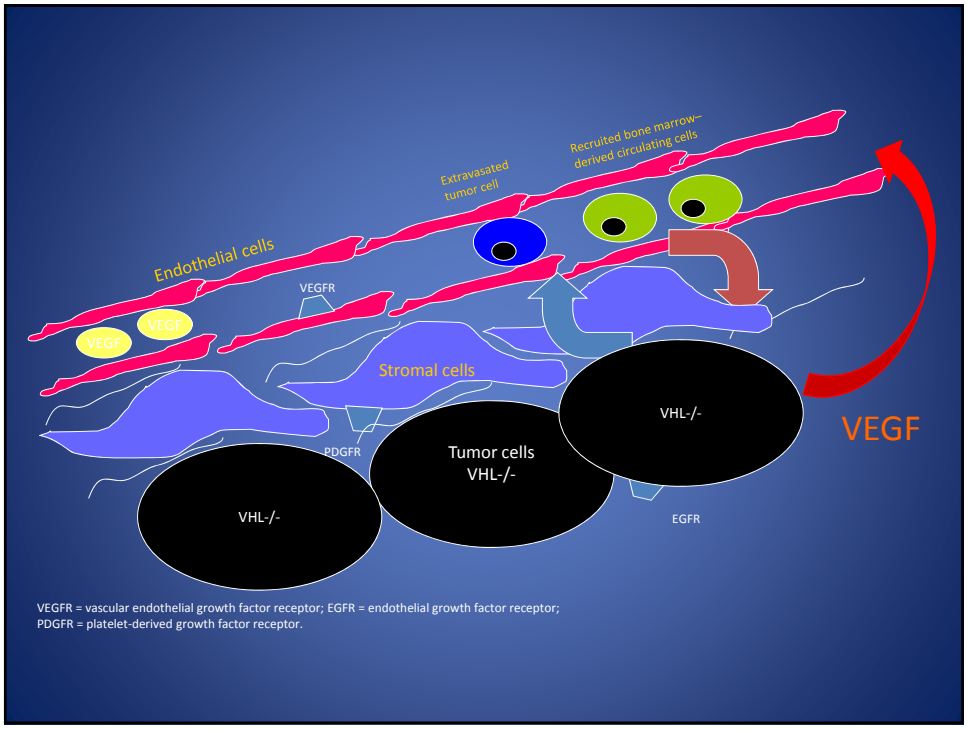
PKC = protein kinase C; TRiC = tail-less complex polypeptide 1 (TCP-1) ring complex.

VHL Mutation Replicates the Hypoxic State



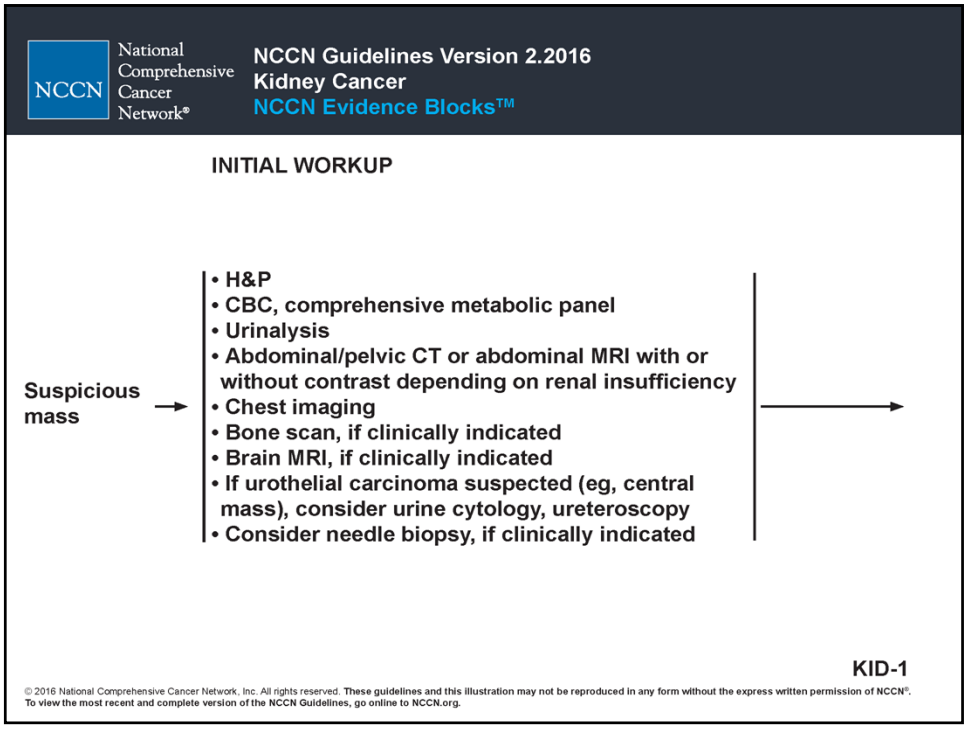
Transcription of:
VEGF
Other angiogenic factors

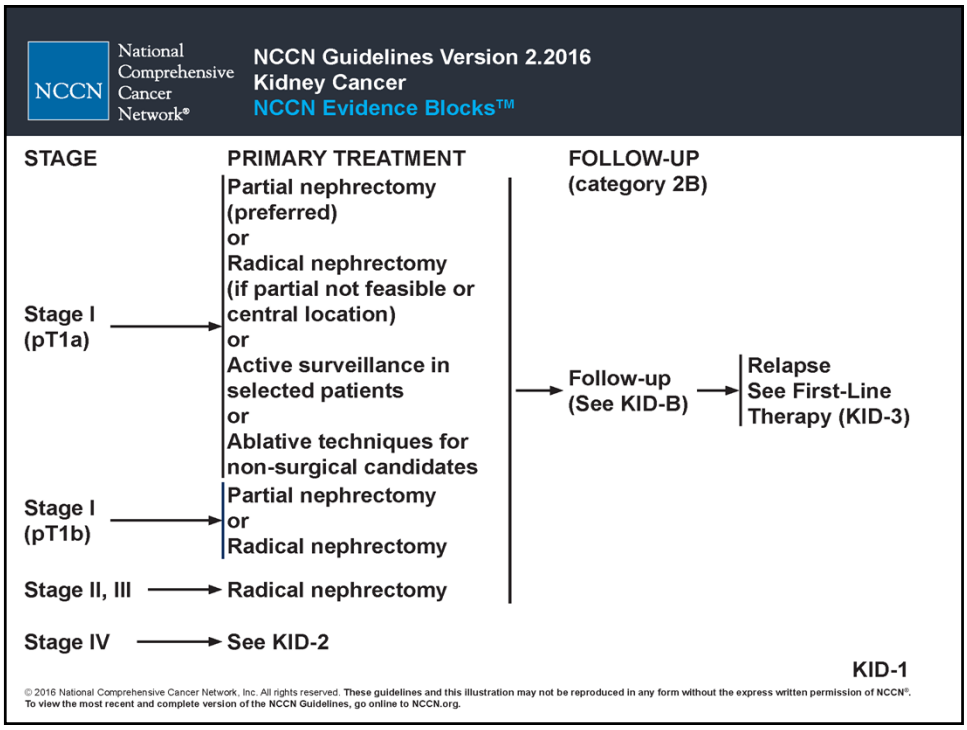
VEGF = vascular endothelial growth factor; HIF = hypoxia-inducible factor.

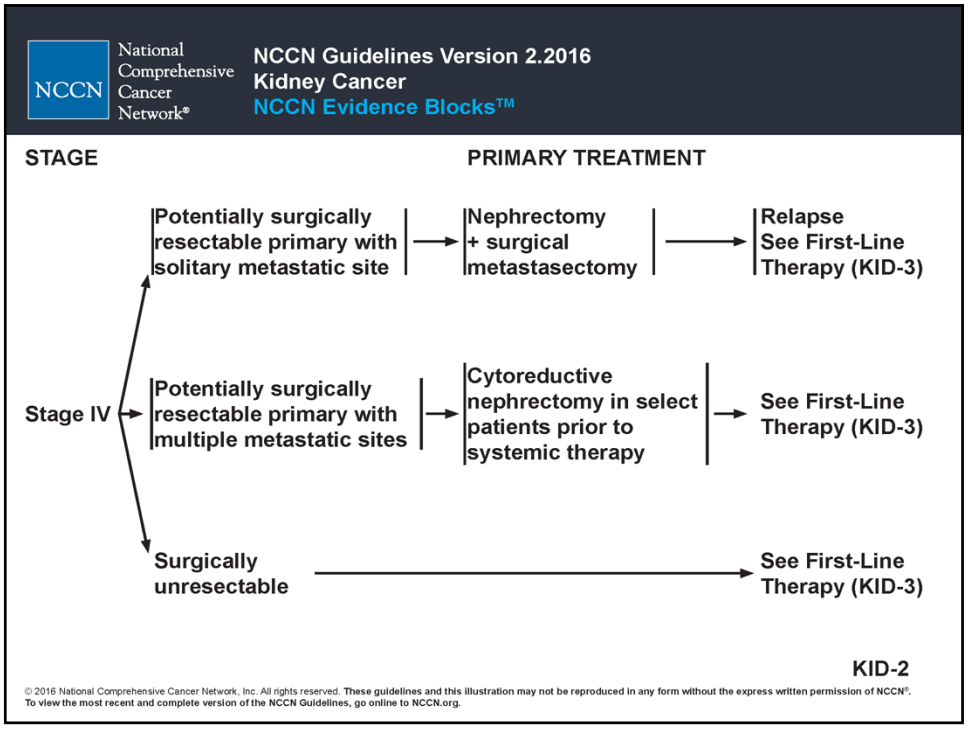


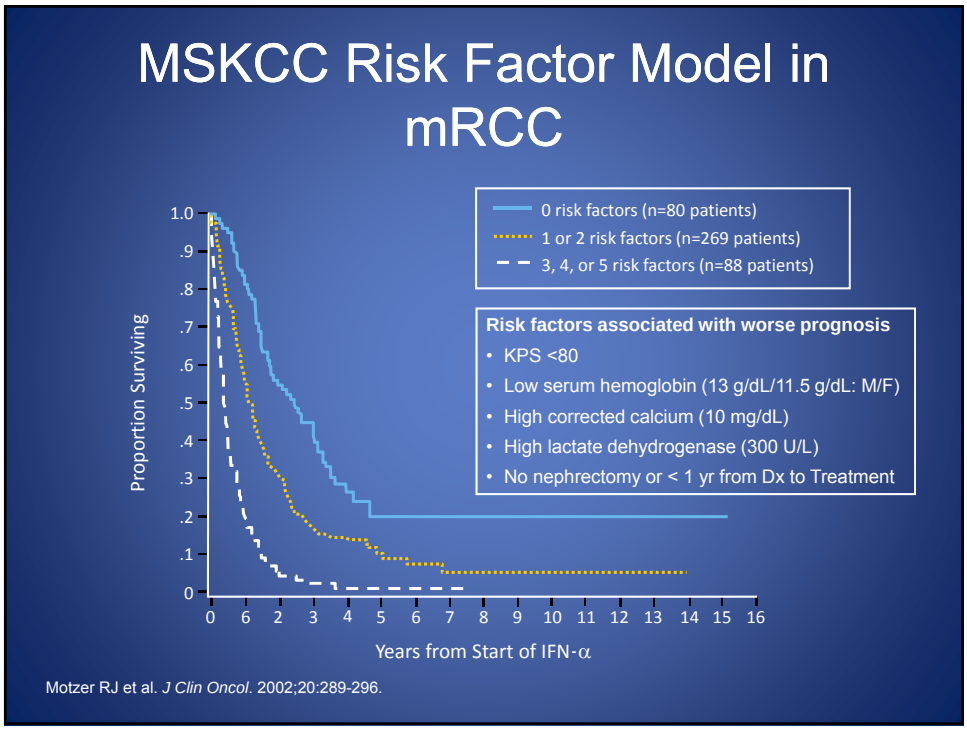
Treatment by Stage

- 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.





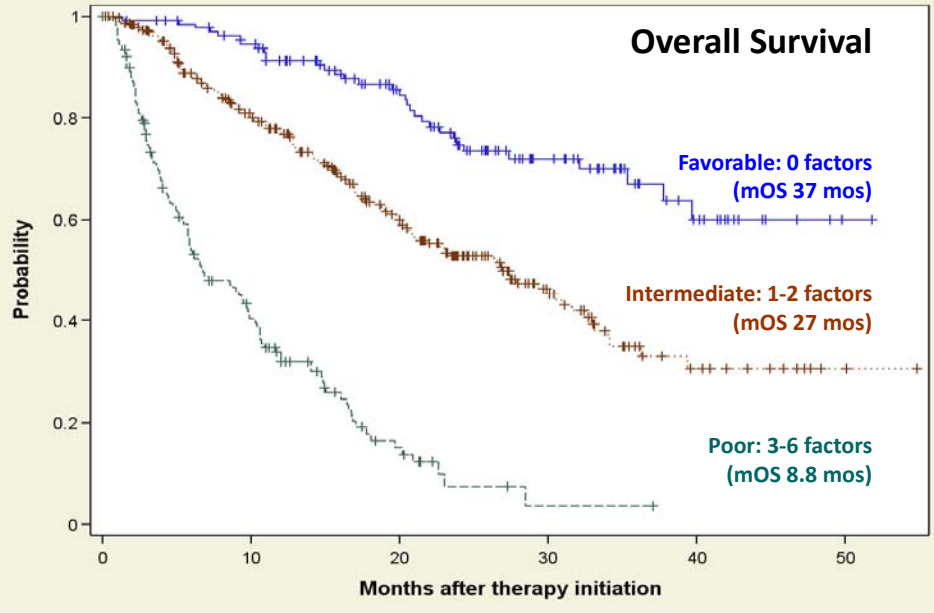




Heng Criteria for Prognosis in TKI Treated Patients

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



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

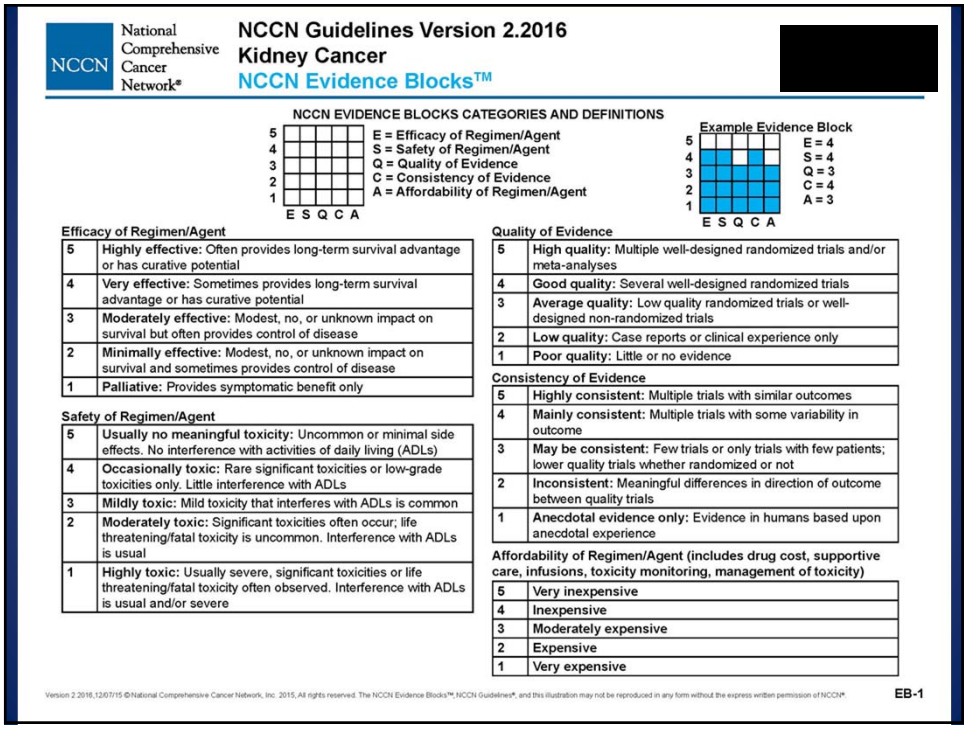
Immunomodulatory Agents

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



National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2016
Kidney Cancer
NCCN Evidence Blocks™

[redacted]

NCCN EVIDENCE BLOCKS CATEGORIES AND DEFINITIONS

E = Efficacy of Regimen/Agent
S = Safety of Regimen/Agent
Q = Quality of Evidence
C = Consistency of Evidence
A = Affordability of Regimen/Agent

E S Q C A

Example Evidence Block

E = 4
S = 4
Q = 3
C = 4
A = 3

E S Q C A

Efficacy of Regimen/Agent

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Affordability of Regimen/Agent (includes drug cost, supportive care, infusions, toxicity monitoring, management of toxicity)

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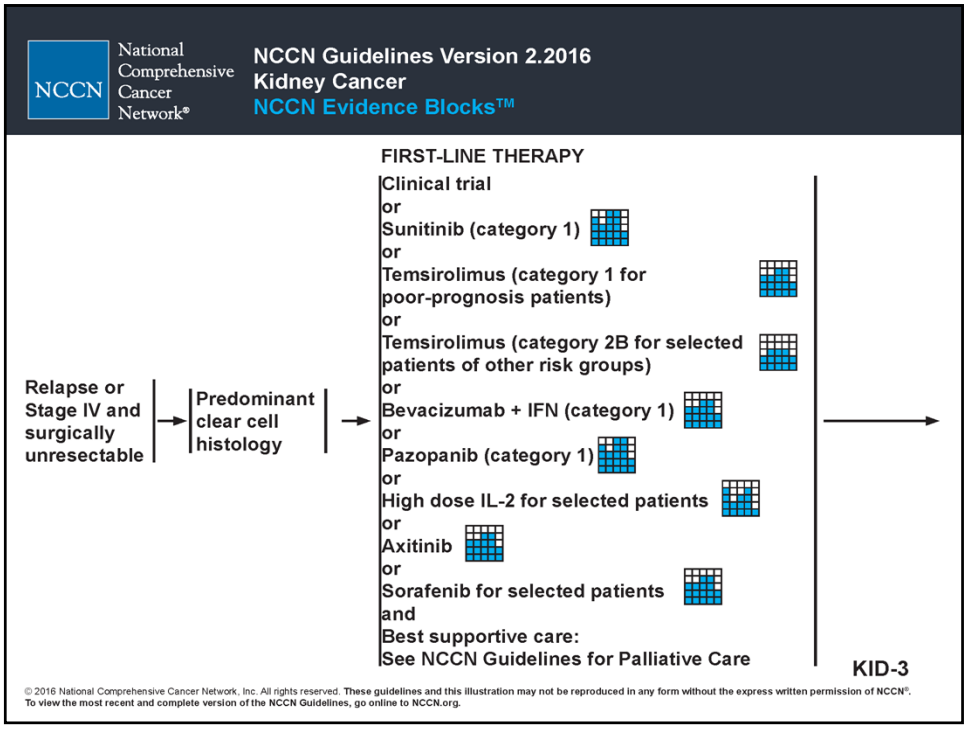
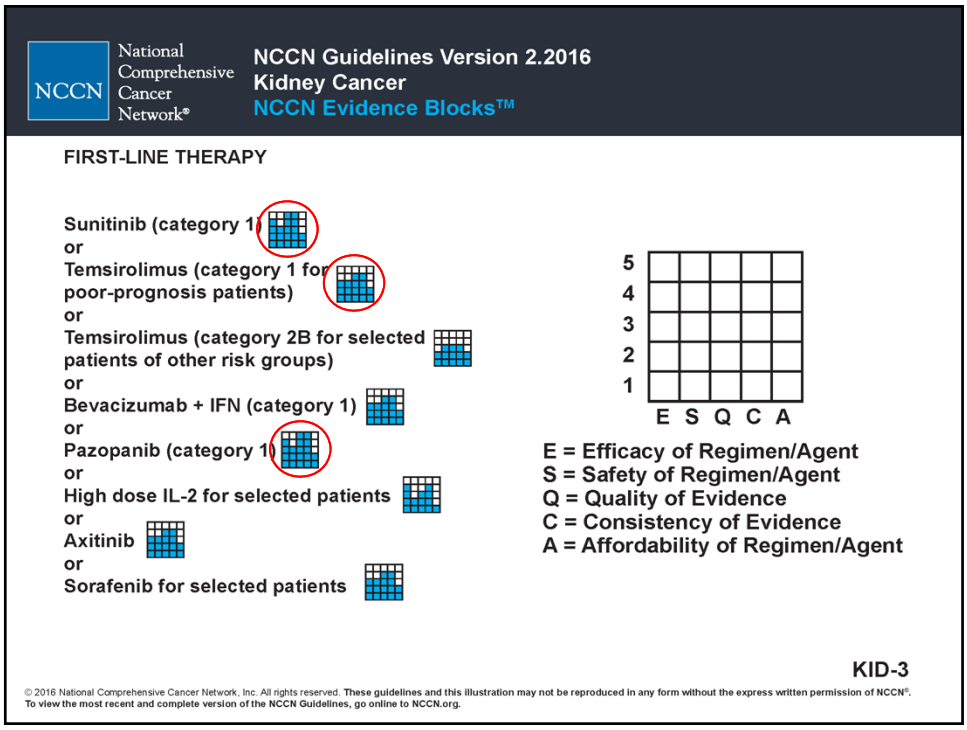
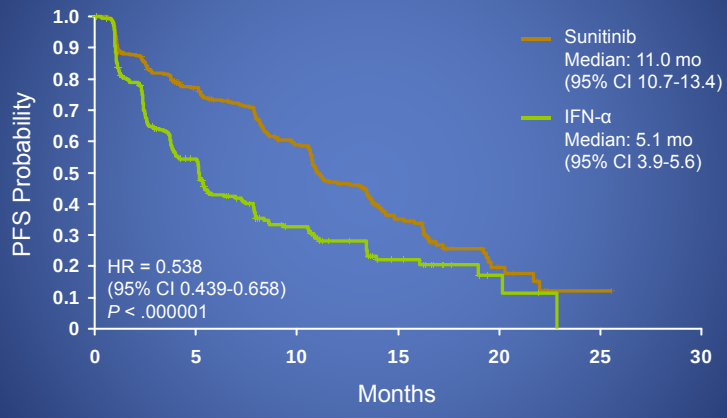
EB-1



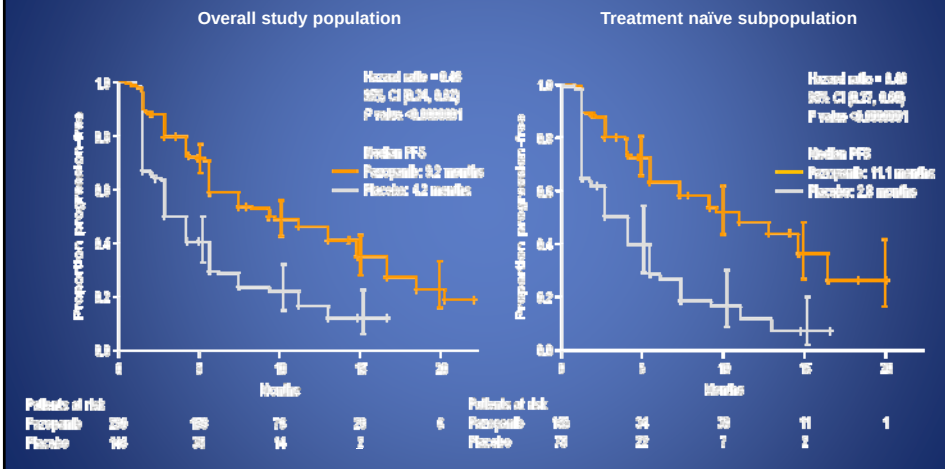


Phase 3 Trial of Sunitinib vs IFN-α in Patients With Untreated Metastatic RCC

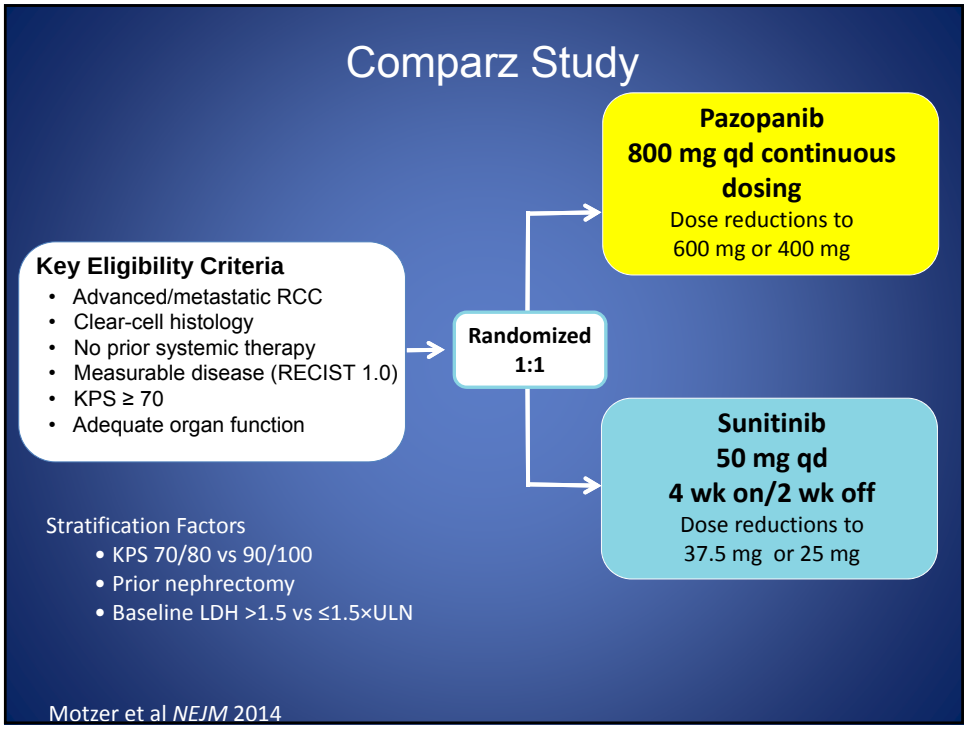


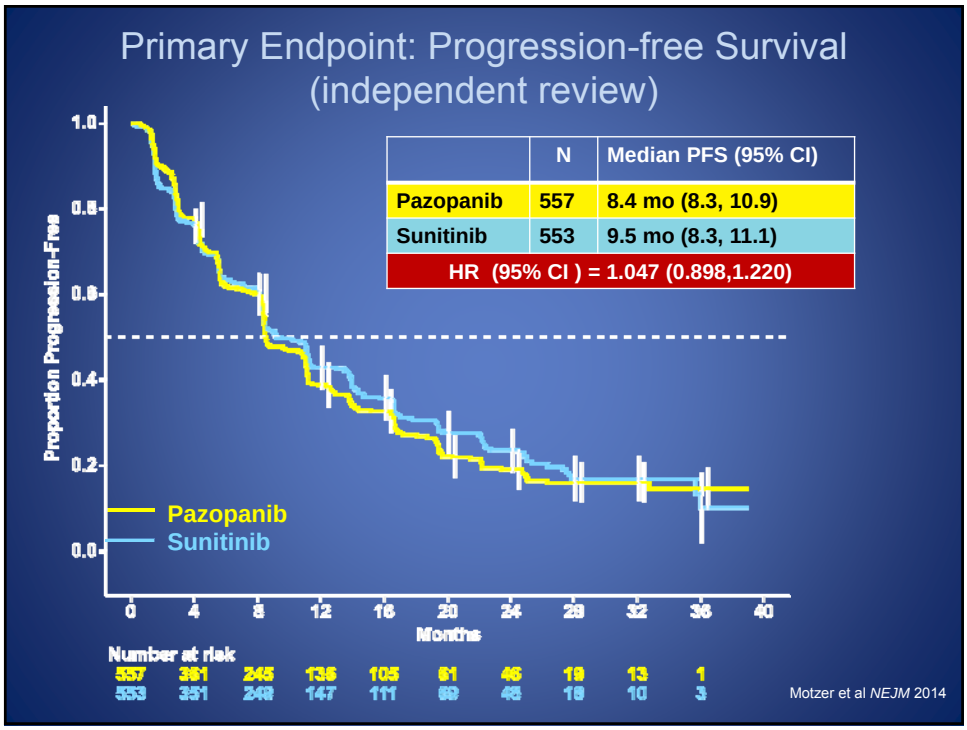
Motzer *et al* NEJM 2007

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

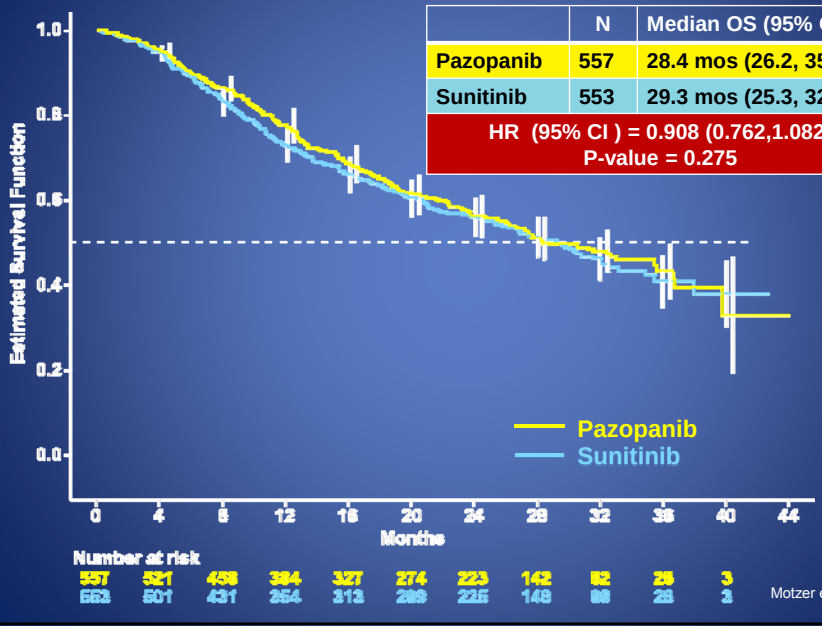


Sternberg CN, et al. *J Clin Oncol*. 2010;28:1061–1068.





Interim Analysis of Overall Survival



	N	Median OS (95% CI)
Pazopanib	557	28.4 mos (26.2, 35.6)
Sunitinib	553	29.3 mos (25.3, 32.5)
HR (95% CI) = 0.908 (0.762,1.082) P-value = 0.275		

Motzer et al *NEJM* 2014

Treatment Duration and Dose Adjustments

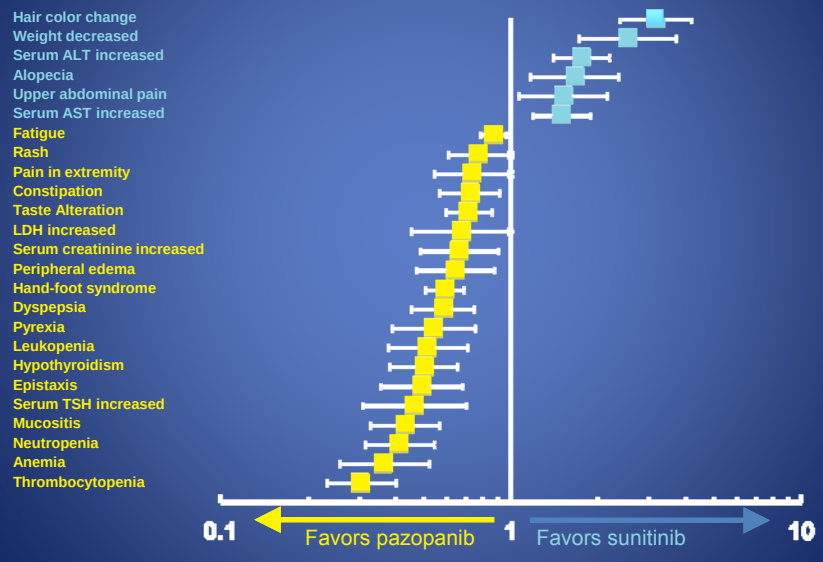
	Pazopanib (n = 554)	Sunitinib (n = 548)
Median duration of treatment (months, range)	8.0 (0−40)	7.6 (0−38)
Dose reductions, %	44	51
Discontinuations due to AEs[1], %	24	19

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

Motzer et al *NEJM* 2014

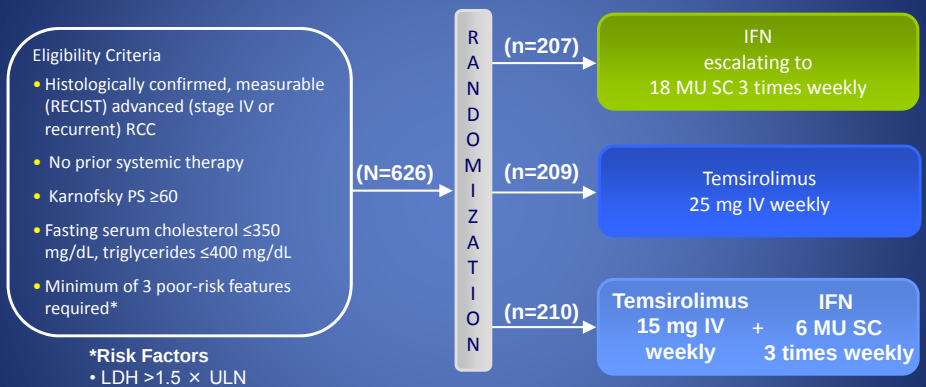
Relative Risk in Adverse Events

AE occurrence ≥10% in either arm; 95% CI for RR does not cross 1



Motzer et al *NEJM* 2014

Phase 3 Study of Temsirolimus and IFN in Advanced RCC: Study Design



***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

Primary end point: OS

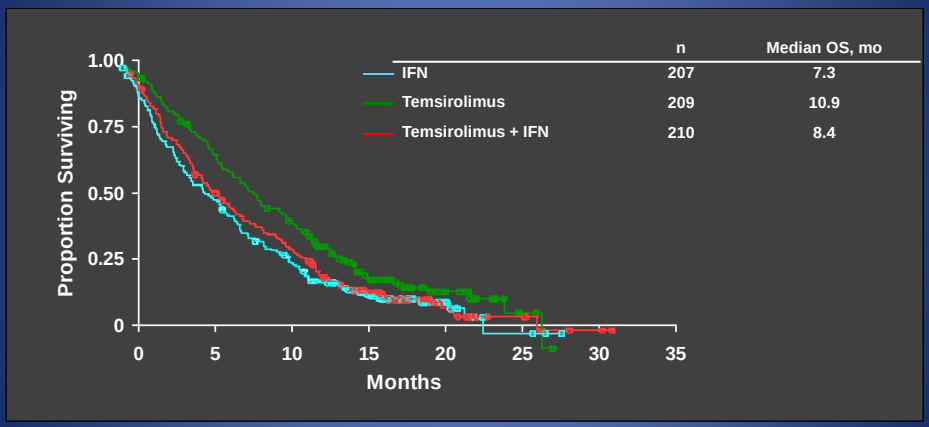
RECIST = Response Evaluation Criteria in Solid Tumors; LDH = lactate dehydrogenase; Hgb = hemoglobin.

Hudes G et al. *N Engl J Med*. 2007;356:2271-2281.

Key Differences Compared to Most Frontline Studies

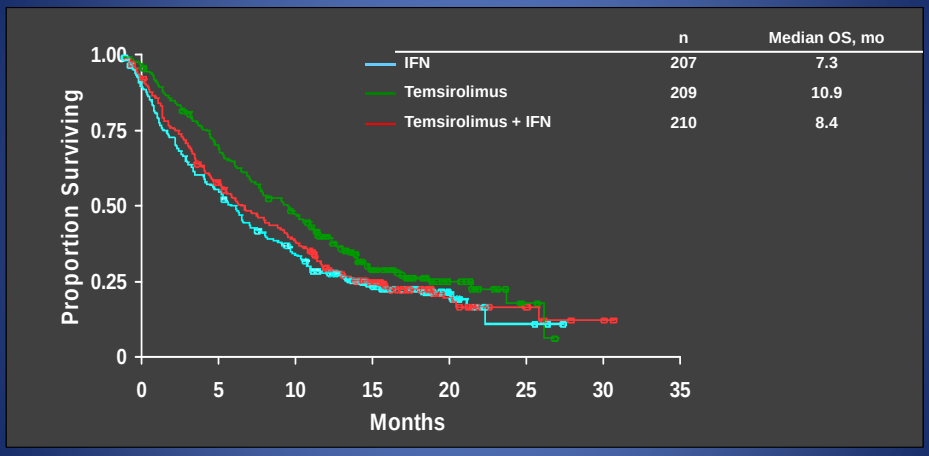
- All intermediate/poor risk patients
- One third did not have nephrectomy
- Twenty percent had non-clear cell RCC

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



Hudes G et al. *N Engl J Med*. 2007;356:2271-2281.

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

Hudes G et al. *N Engl J Med*. 2007;356:2271-2281.

Second Line Treatment

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Kidney Cancer
NCCN Evidence Blocks™

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

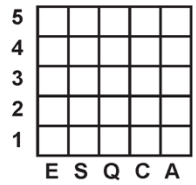
KID-3

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2016
Kidney Cancer
NCCN Evidence Blocks™

SUBSEQUENT 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)



E = Efficacy of Regimen/Agent
S = Safety of Regimen/Agent
Q = Quality of Evidence
C = Consistency of Evidence
A = Affordability of Regimen/Agent

KID-3

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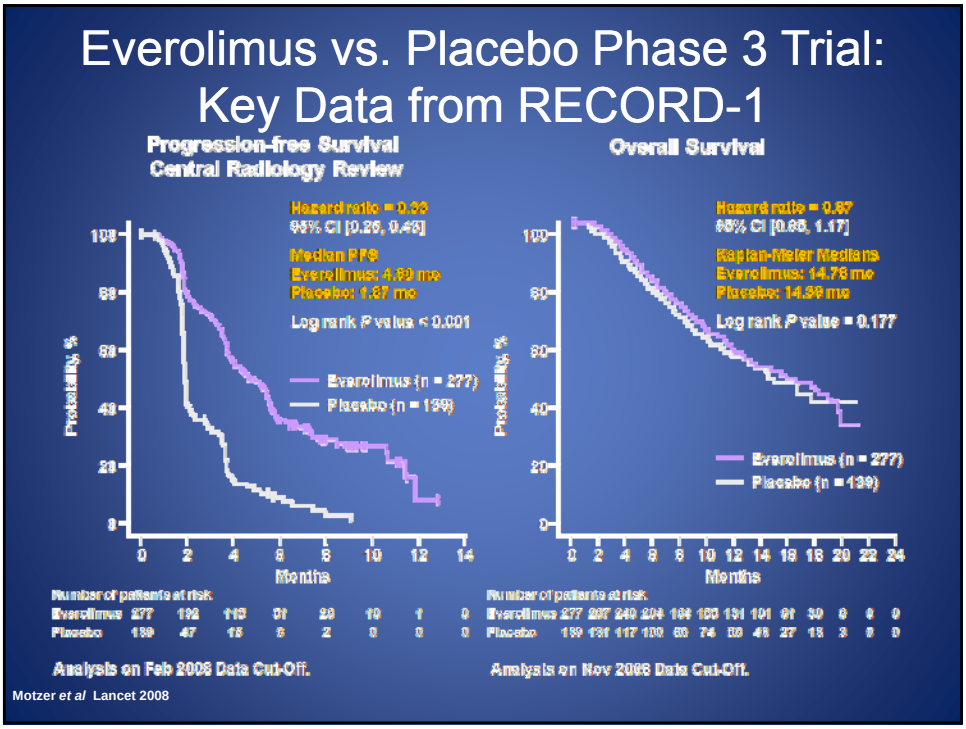
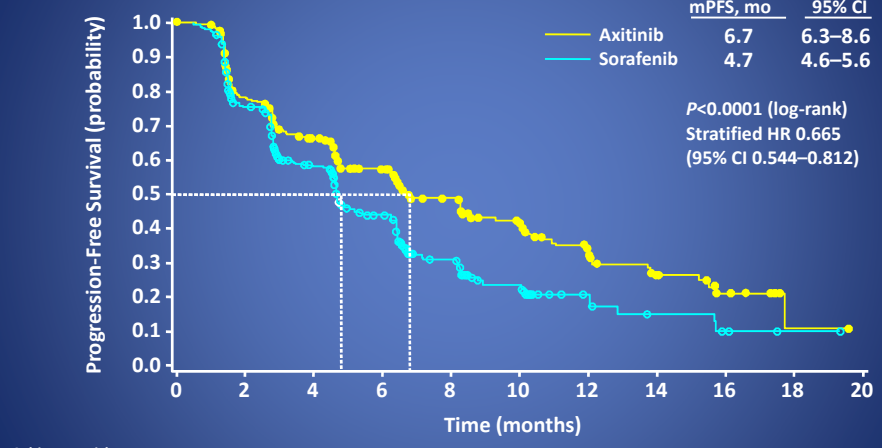
Everolimus vs. Placebo Phase 3 Trial: Key Data from RECORD-1



Motzer *et al* Lancet 2008

Axitinib Phase III Randomized Study PFS Assessment



Subjects at risk, n

Axitinib	361	256	202	145	96	64	38	20	10	1	0
Sorafenib	362	224	157	100	51	28	12	6	3	1	0

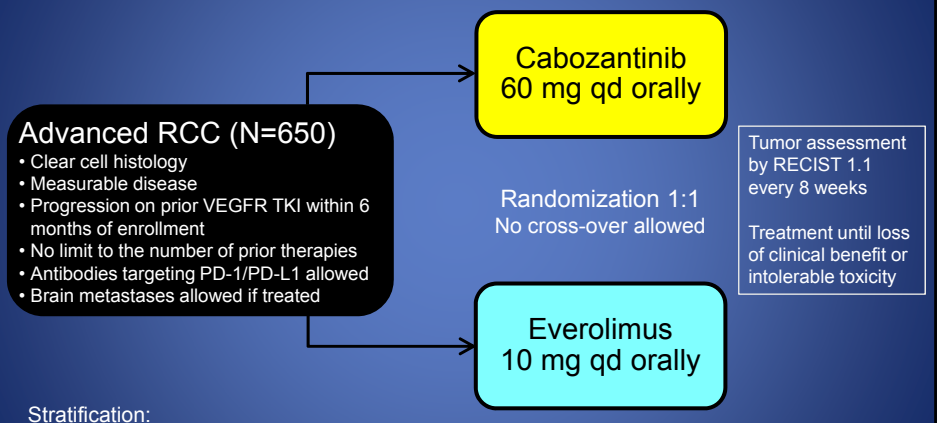
Rini *et al* Lancet 2011

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

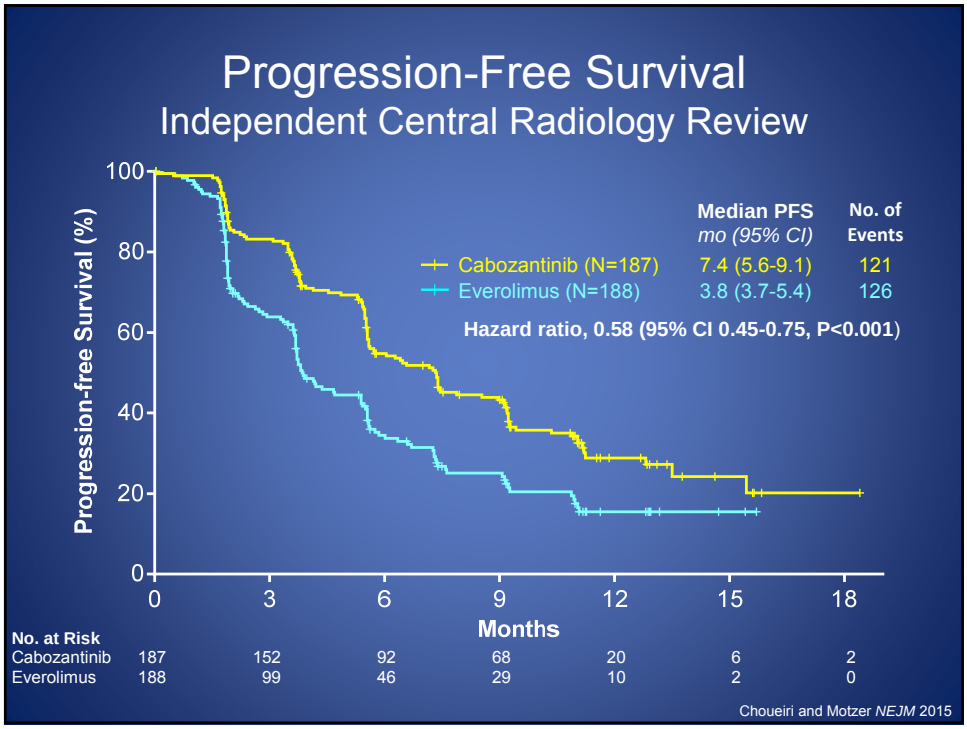
Study Design

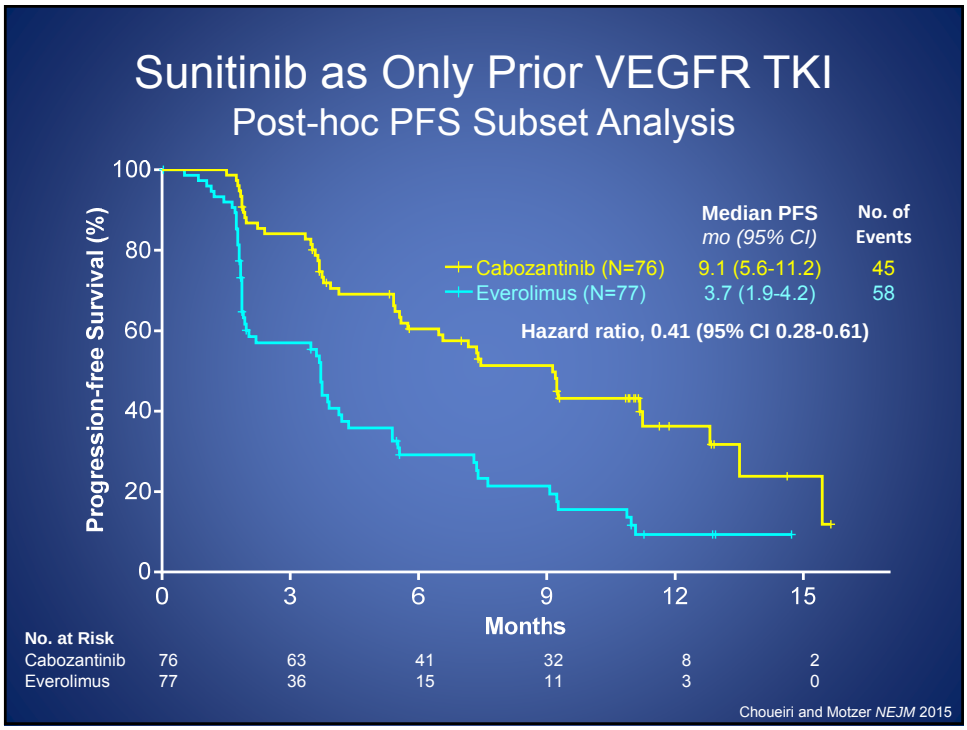


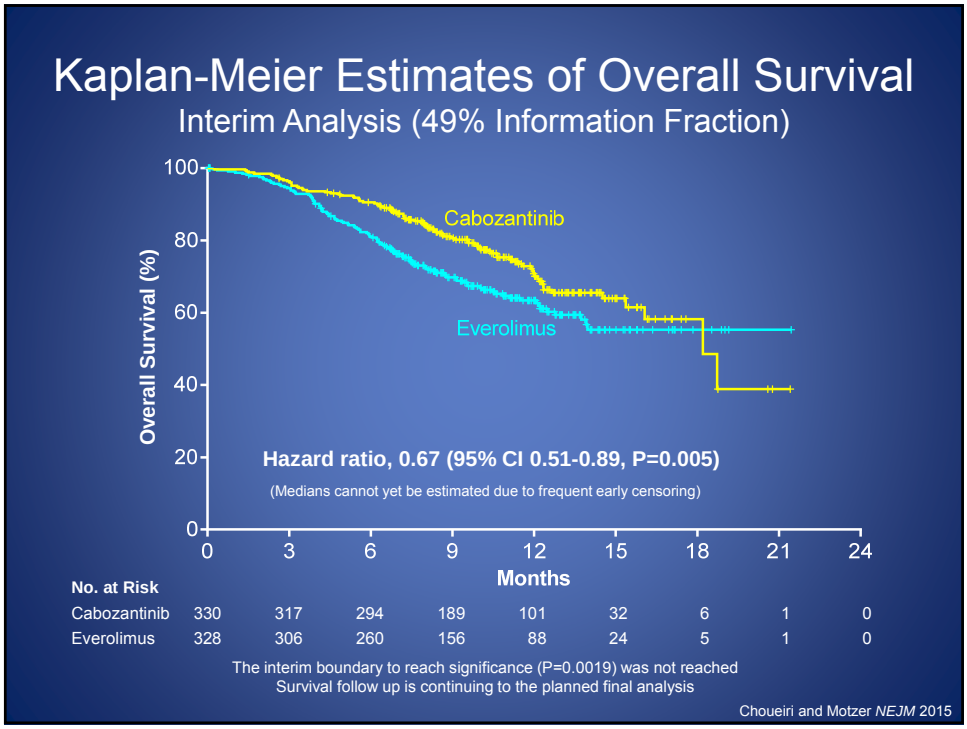
Stratification:

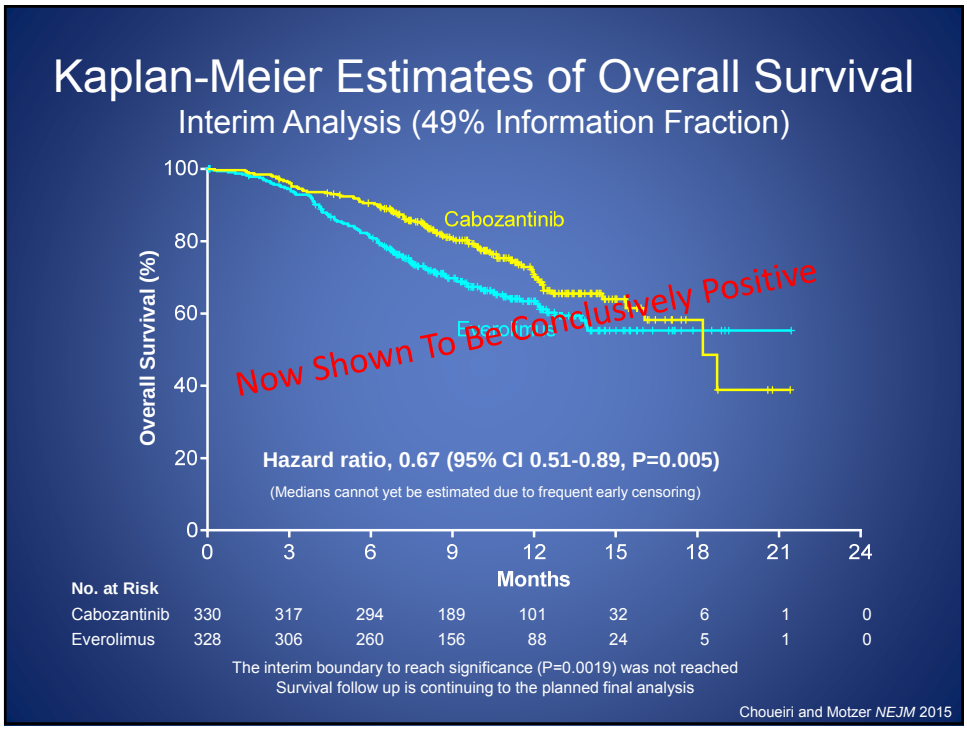
- MSKCC[1] risk groups: favorable, intermediate, poor
- Number prior VEGFR-TKIs: 1, 2 or more

Choueiri and Motzer *NEJM* 2015









Significant Toxicities

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

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

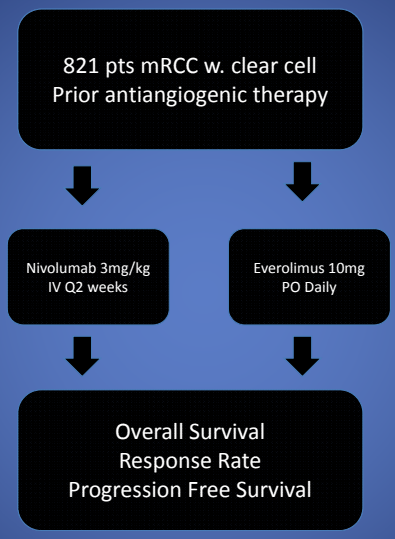
Choueiri and Motzer *NEJM* 2015

ORIGINAL ARTICLE

Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma

R.J. Motzer, B. Escudier, D.F. McDermott, S. George, H.J. Hammers, S. Srinivas, S.S. Tykodi, J.A. Sosman, G. Procopio, E.R. Plimack, D. Castellano, T.K. Choueiri, H. Gurney, F. Donskov, P. Bono, J. Wagstaff, T.C. Gauler, T. Ueda, Y. Tomita, F.A. Schutz, C. Kollmannsberger, J. Larkin, A. Ravaud, J.S. Simon, L.-A. Xu, I.M. Waxman, and P. Sharma, for the CheckMate 025 Investigators*

Trial Schema



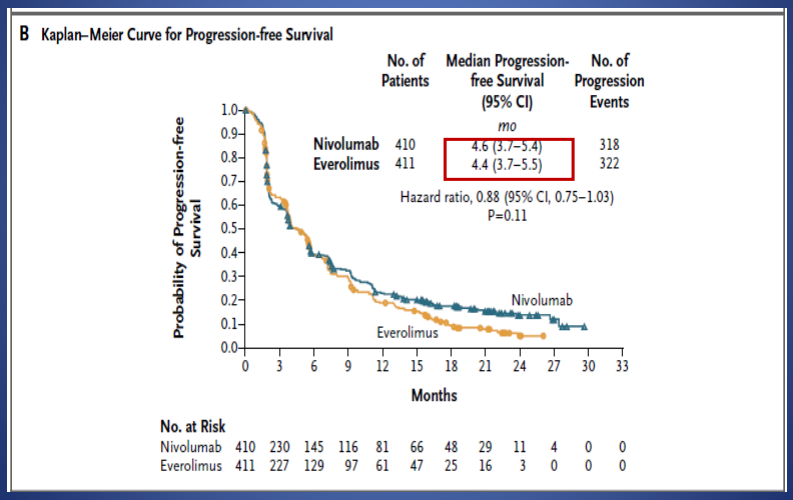
Motzer and Sharma *NEJM* 2015

Objective Response Rate

	Nivolumab N=410	Everolimus N=411
Objective Response Rate n (%)	**103 (25)** **P<0.001**	22 (5)
Odds ratio (95% CI)	5.98 (3.68-9.72)	
Best Overall Response		
CR	4 (1)	2 (<1)
PR	**99 (24)**	20 (5)
SD	141 (34)	227 (55)
PD	143 (35)	114 (28)
Not evaluated	23 (6)	48 (12)
Median time to response, months (range)	**3.5 (1.4-24.8)**	3.7 (1.5-11.2)
Median duration of response, months (range)	12.0 (0-27.6)	12.0 (0-22.2)
Median Duration of Treatment, months (range)	5.5 (<1 to 29.6)	3.7 (0.2 to 25.7)

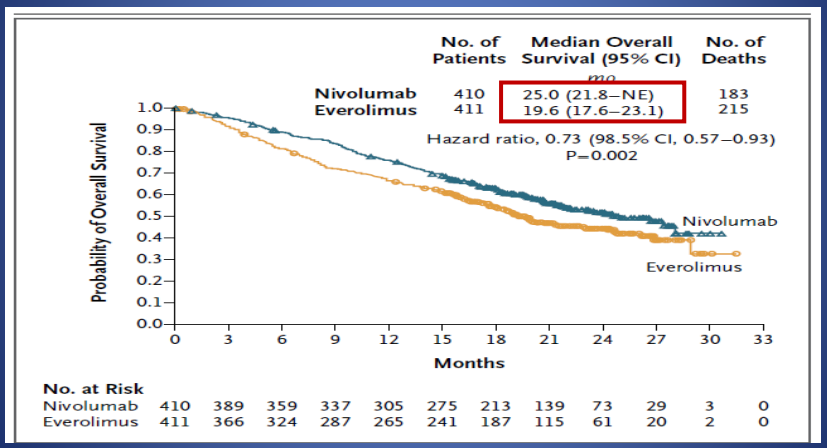
Motzer and Sharma *NEJM* 2015

Progression Free Survival



Motzer and Sharma *NEJM* 2015

Overall Survival



** Pre-specified HR (for death) of 0.76 was met & exceeded

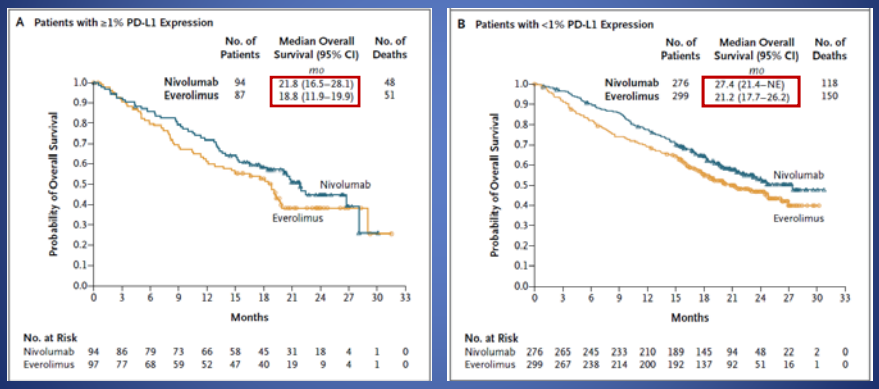
Motzer and Sharma *NEJM* 2015

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

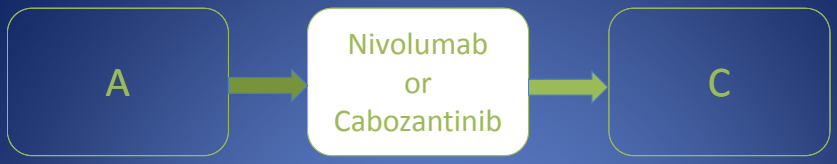
Event	Nivolumab Group (N=406)		Everolimus Group (N=397)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
All events	319 (79)	76 (19)	349 (88)	145 (37)
Fatigue	134 (33)	10 (2)	134 (34)	11 (3)
Nausea	57 (14)	1 (<1)	66 (17)	3 (1)
Pruritus	57 (14)	0	39 (10)	0
Diarrhea	50 (12)	5 (1)	84 (21)	5 (1)
Decreased appetite	48 (12)	2 (<1)	82 (21)	4 (1)
Rash	41 (10)	2 (<1)	79 (20)	3 (1)
Cough	36 (9)	0	77 (19)	0
Anemia	32 (8)	7 (2)	94 (24)	31 (8)
Dyspnea	30 (7)	3 (1)	51 (13)	2 (1)
Peripheral edema	17 (4)	0	56 (14)	2 (1)
Pneumonitis	16 (4)	6 (1)	58 (15)	11 (3)
Mucosal inflammation	11 (3)	0	75 (19)	12 (3)
Dysgeusia	11 (3)	0	51 (13)	0
Hyperglycemia	9 (2)	5 (1)	46 (12)	15 (4)
Stomatitis	8 (2)	0	117 (29)	17 (4)
Hypertriglyceridemia	5 (1)	0	64 (16)	20 (5)
Epistaxis	3 (1)	0	41 (10)	0

Motzer and Sharma *NEJM* 2015

PD-L1 expression and OS

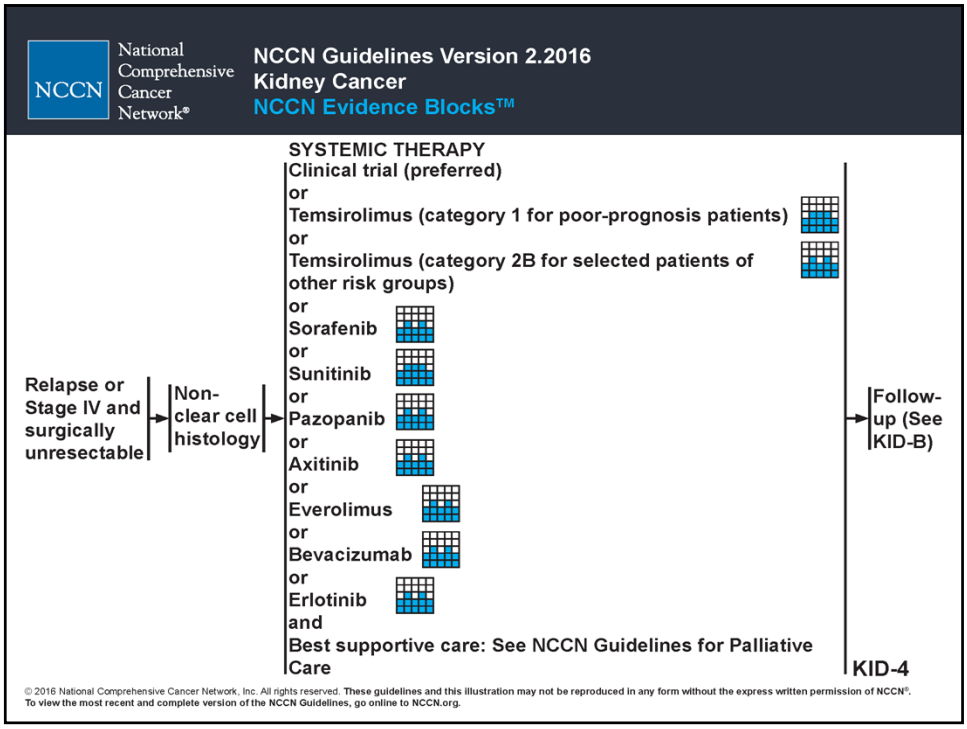


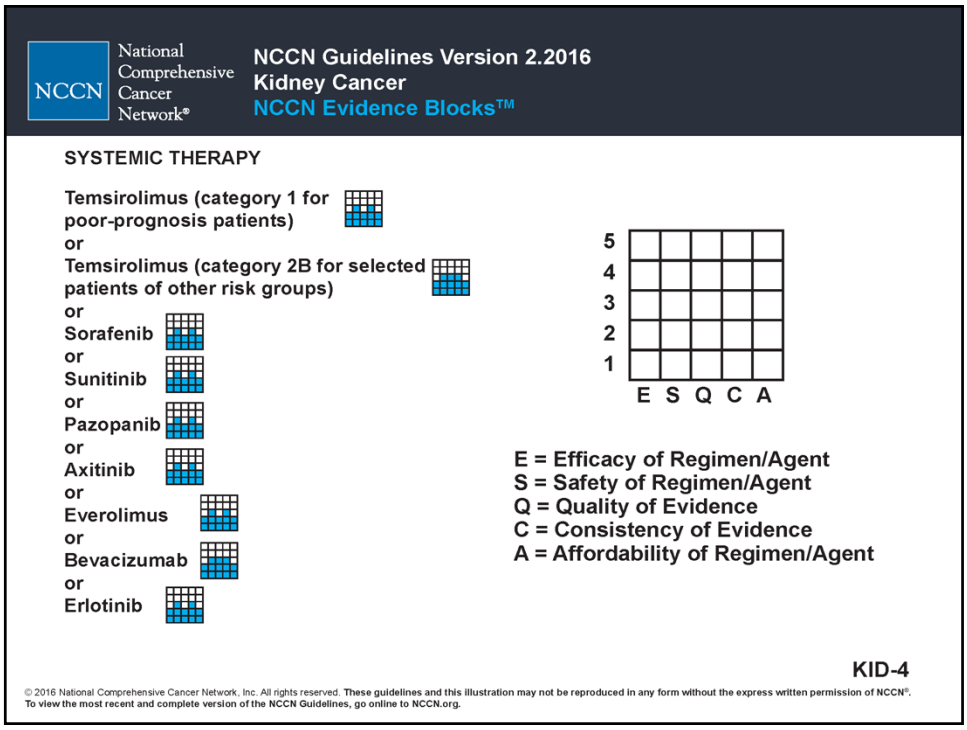
Motzer and Sharma *NEJM* 2015



- 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 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.