Making Optimal Therapeutic Decisions in Patients with Advanced Renal Cell Carcinoma – An Interactive Webcast!

Presented by:
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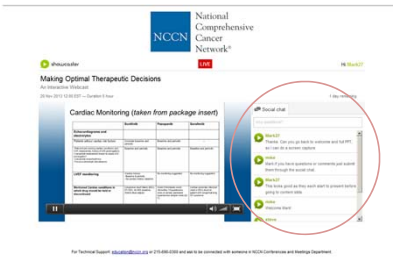
This activity is supported by an educational grant from Pfizer.

Opening Remarks

- To submit a question - there will be a chat window next to the video window, just click to enter a name for ID purposes, then submit. Please use this feature for any clinical questions and logistical concerns you have regarding the session. This is the only online method of communicating questions or concerns. Should you need additional assistance please e-mail education@nccn.org or call 215-690-0300 and ask to be connected with someone in the NCCN Conferences and Meetings Department.



Opening Remarks

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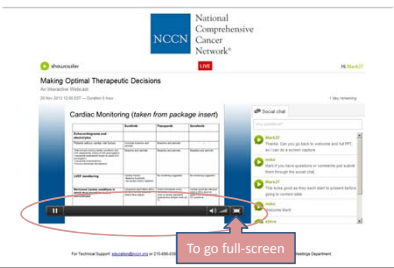

Accreditation Information

- Credit will be provided to physicians, nurses, and pharmacists (1.25 contact hours) through completion of an evaluation and post-test. All registered participants will receive an e-mail from our CE and Grants Department within 3-5 business days with instructions on how to access this evaluation and post-test at http://education.nccn.org/node/34303. Certificates will be generated automatically upon successful completion of this step. Should you not receive an e-mail within 5 days, please contact us at education@nccn.org.
- If you participated with a group of peers, a list of everyone who attended in your group must be submitted within two weeks of the activity in order for the participants to be eligible to receive credit. This list is in addition to individual registration. Attendee lists will not be accepted after two weeks post-activity. Lists can be sent to education@nccn.org and should contain full contact information for each participant, including first and last name, credentials, mailing address, phone number, and e-mail address.
- If you have not individually registered, please register at: http://www.cvent.com/d/w4qkbp

Accreditation Information

- It is required by the ACCME that all educational activities are designed to change participant ***competence, performance, or patient outcomes.***
- To meet this requirement, NCCN asks that all participants complete the outcomes measures described below:
  - The post-test and evaluation as indicated in e-mail you will receive within 3-5 business days of the conclusion of this activity. This is required to receive credits or your certificate of completion. You must be registered in advance to receive credits or certificate. Certificates will be generated automatically upon successful completion of this step.
  - The follow-up post test (to be sent 30 days after the activity has ended to demonstrate an increase in participant competence)
  - The follow-up survey (to be sent 60 days after the activity has ended to demonstrate an increase in participant performance)
- NCCN greatly appreciates your compliance with completing the aforementioned post-test and surveys. All of these measures will be available by logging into your account at http://education.nccn.org. Reminder e-mails will be sent to the participants via e-mail. If you have any questions or concerns, please e-mail education@nccn.org.

Accreditation Information

Intended Audience:

This webcast is designed to meet the educational needs of medical oncologists, surgical oncologists, radiation oncologists, endocrinologists, nurses, pharmacists, and other healthcare professionals who manage patients with thyroid cancer.

Learning Objectives:

Following this program, participants should be able to:

- Apply the existing and emerging clinical research data to make evidence-based selection of first-line therapy for treatment of advanced renal cell cancer
- Select optimal subsequent lines of treatment to improve outcomes of patients with advanced RCC
- Describe the toxicities of targeted therapies used in treatment of renal cell cancer and outline the strategies used to effectively manage them

Accreditation Information

Physicians
The National Comprehensive Cancer Network (NCCN) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

NCCN designates this live activity for a maximum of *1.25 AMA PRA Category 1 Credit(s)™*.

Physicians should only claim credit commensurate with the extent of their participation in the activity.

Nurses
This activity is approved for 1.25 contact hours.

National Comprehensive Cancer Network is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

Accreditation as a provider refers to recognition of educational activities only; accredited status does not imply endorsement by NCCN or ANCC of any commercial products discussed/displayed in conjunction with the educational activity.

Kristina M. Gregory, RN, MSN, OCN, is our nurse planner for this educational activity.

Accreditation Information

Pharmacists
Pharmacy Educational Objective
After completing these activities, the participant should be able to:
Provide accurate and appropriate counsel as part of the treatment team.

Accreditation Statement
National Comprehensive Cancer Network is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Credit Designation
National Comprehensive Cancer Network designates each of these continuing education activities for 1.25 contact hour(s) (0.125 CEUs) of continuing education credit in states that recognize ACPE accredited providers.

Type of Activity
Knowledge

UAN: 0836-0000-13-120-L01-P

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All faculty and activity planners participating in NCCN continuing education activities are expected to disclose any conflict(s) of interest related to the content of their presentation(s) as defined by the ACCME's, ANCC's, and ACPE's Standards for Commercial Support. All faculty presentations have been reviewed for adherence to the ACCME's Criterion 7: The provider develops activities/educational interventions independent of commercial interests (SCS 1, 2, and 6) by experts on the topics.

The presenters of this webcast have disclosed the following relevant financial relationships:

Toni K. Choueiri, MD
Aveo: Scientific Advisor
Bayer HealthCare: Scientific Advisor
Genentech, Inc.: Scientific Advisor
GlaxoSmithKline: Grant/Research Support, Scientific Advisor
Novartis Pharmaceuticals Corporation: Scientific Advisor
Pfizer Inc.: Grant/Research Support, Scientific Advisor

Laurie Appleby, MS, APRN
Pfizer Inc.: Scientific Advisor

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Robert W. Carlson, MD
Genentech, Inc.: Grant/Research Support
sanofi-aventis US: Grant/Research Support

Ann Gianola
Actelion Pharmaceuticals US, Inc: Grant/Research Support

Deborah Moonan, RN, BSN
AstraZeneca: Stockholder/Former Employee

Valesta Tejan-Kamara
AstraZeneca: Former Employee

The NCCN scientists listed below, who have reviewed content, have no financial relationships to disclose:
Mary A. Dwyer, MS, CGC; Rashmi Kumar, PhD

While NCCN is pleased to respond to as many questions as possible during this webcast, NCCN will not be able to respond to your individual questions of a clinical nature after the webcast has concluded. We are also not able to offer recommendations on patient care regarding specific cases.

Faculty Biographies

Toni K. Choueiri, MD, is a genitourinary medical oncologist at Dana-Farber Cancer Institute and Brigham and Women's Hospital, both in Boston, Massachusetts where he is the leader of the Kidney Cancer Center and the Co-director of the multidisciplinary Kidney Cancer Clinic. He serves on the NCCN Kidney/Testicular Cancer Panel and on the Medical Advisory Board of the Kidney Cancer Association and has a joint appointment at Harvard Medical School as an Assistant Professor of Medicine.

Dr. Choueiri received his medical degree from Universite Saint Joseph-Faculte de Medecine. He subsequently completed his residency in Internal Medicine and his fellowship in Hematology/Medical Oncology at Cleveland Clinic Foundation.

Dr. Choueiri is interested in developing novel therapies in kidney cancer and in the discovery of prognostic and predictive markers in this disease. His work is funded by the American Society of Clinical Oncology and the National Cancer Institute.

Laurie H. Appleby, MS, APRN, is a Nurse Practitioner, Lank Center for Genitourinary Oncology, at Dana-Farber Cancer Institute.

Ms. Appleby earned her Bachelor of Science in Nursing degree from Northeastern University and her Master of Science in Primary Care Nursing from Simmons College in Boston. She is a certified Advanced Practice Registered Nurse.

Ms. Appleby is a member of the Kidney Cancer Association's Nurse Advisory Board as well as other notable professional organizations including the Oncology Nursing Society and the Massachusetts Nursing Association. Ms. Appleby is a sought after lecturer and has been invited to present on a variety of topics by many prominent organizations.

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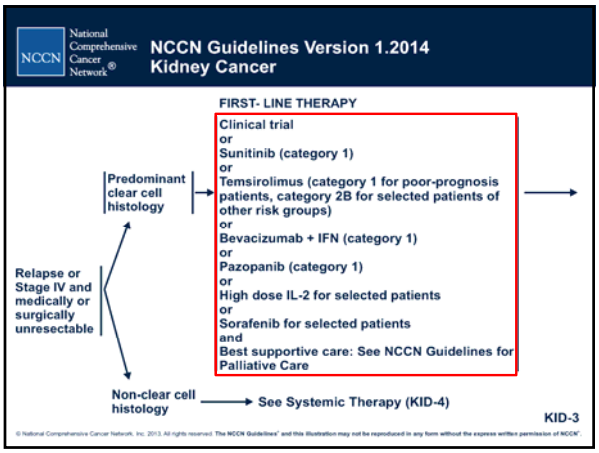
Case Study #1

The Patient

- Ms. Stevens is a 65 year old woman, former smoker, diagnosed with clear cell type mRCC two years ago, after presenting with hematuria.
  Renal u/s at that time, revealed 6.5 cm L renal mass.
- **Radical Nephrectomy: stage III ccRCC, Grade 3/4**
- 2013
  CAP CT: new bilateral pulmonary nodules
  Biopsy: (+) ccRCC
- PMH:
  - CAD, s/p stent placement 2009
  - HTN, on Atenolol 50mg and HCTZ qd



Targeted Agents for Advanced RCC

Level I evidence

Agent	Target	Efficacy in Randomized Phase III Trials			
		Comparison	No.	ORR	PFS (mos)
-1st line:					
Bevacizumab	VEGF	IFN-α +/- bevacizumab	649	31% vs 13%	**10.2 vs 5.4**
		IFN-α +/- bevacizumab	732	26% vs 13%	**8.5 vs 5.2**
Sunitinib	VEGF-R	Sunitinib vs IFN-α	750	37% vs 9%	**11.1 vs 5**
Sorafenib	VEGF-R	Sorafenib vs Placebo[4]	903	10% vs 2%	**5.5 vs 2.8**
Pazopanib	VEGF-R	Pazopanib vs Placebo	435	30% vs 3%	**11.1 vs 2.8/9.2 vs.4.2 (untreated/treated)**
Temsirolimus	mTOR	Tems vs IFN-α vs. combo	626	9% vs 7% vs 11%	3.7 vs 1.9
-Refractory: to 1st line					
Everolimus	mTOR	Everolimus vs Placebo	416	2% vs 0%	**4.9 vs 1.8**
Axitinib	VEGF-R	Axitinib vs Sorafenib	723	19% vs 9%	**6.7 vs 4.7**

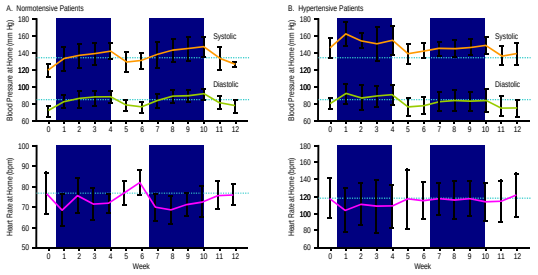
Patient continued..

- Started on therapy with Sunitinib (50 mg x 28 days on with 14 days off).
- Has come to the clinic for second opinion and to discuss treatment options.

Physician/Patient Appointment Video

Initial Visit

Home Blood-Pressure Monitoring in Patients Receiving Sunitinib



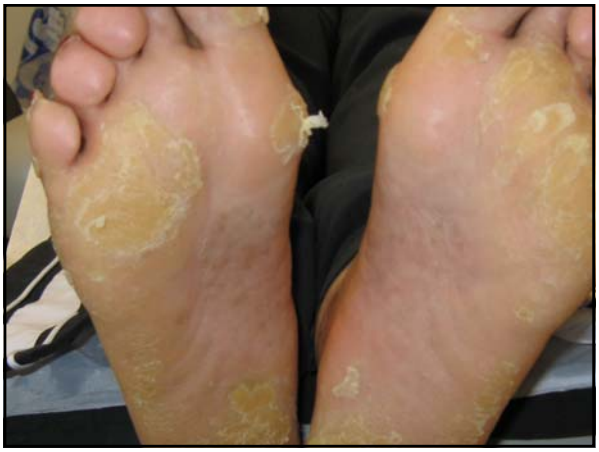
Azizi et al. *NEJM* 2008

Cardiac Monitoring (*taken from package insert*)

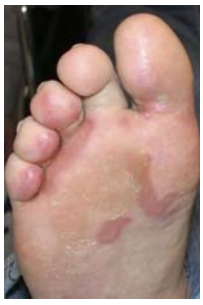
	Sunitinib	Pazopanib	Sorafenib
Echocardiograms and electrolytes			
Patients without cardiac risk factors	Consider baseline and periodic	Baseline and periodic	-
-Relevant pre-existing cardiac conditions (incl. CHF, bradycardia, history of QTc prolongation) -Concurrent medications known to cause QTc prolongation* -Concurrent antiarrhythmics -Previous electrolyte disturbances	Baseline and periodic	Baseline and periodic	Baseline and periodic
LVEF monitoring	-Cardiac history: Baseline & periodic - No cardiac history: baseline	No monitoring suggested	No monitoring suggested
Mentioned Cardiac conditions in which drug should be held or discontinued	Congestive heart failure (D/C); EF<50% &>20% baseline (hold & dose adjust)	Avoid if thrombotic event <6months; If hypertensive crisis or severe, persistent hypertension despite meds (D/C)	Cardiac ischemia/ infarction (hold or D/C); Avoid in patient with congenital long QT syndrome

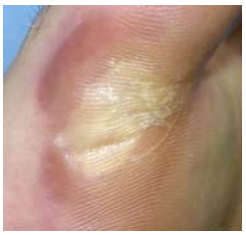
Drugs known to cause QTc prolongation (not a complete list)

- **Alpha 1-blocker:** alfuzosin
- **Antianginals:** bepridil, ranolazine
- **Antiarrhythmics:** amiodarone, disopyramide, dofetilide, dronedarone, flecainide, ibutilide, procainamide, quinidine, sotalol
- **Antibiotics:** azithromycin, ciprofloxacin, clarithromycin, erythromycin, gatifloxacin, levofloxacin, moxifloxacin, ofloxacin, sulfamethoxazole/trimethoprim, telithromycin)
- **Antidepressants:** amitriptyline, citalopram, clomipramine, doxepin, escitalopram, fluoxetine, imipramine, nortriptyline, paroxetine, sertraline, trazodone, venlafaxine
- **Antiemetics:** dolasetron, granisetron, ondansetron
- **Antihistamines:** astemizole, diphenhydramine
- **Antifungals**: fluconazole, itraconazole, ketoconazole, voriconazole
- **Antimuscarinics:** solifenacin
- **Antipsychotics/mania:** chlorpromazine, clozapine, haloperidol, lithium, mesoridazine, pimozide, quetiapine, risperidone, thioridazine, ziprasidone
- **Dopaminergic:** amantadine
- **Opiates:** methadone
- **Antineoplastics:** arsenic trioxide, eribulin, lapatinib, nilotinib, tacrolimus, tamoxifen, vandetanib



Hand Foot Skin Reaction (HFSR)





Physician/Patient Appointment Video

First staging CTs visit

Physician/Patient Appointment Video

At 5 months visit

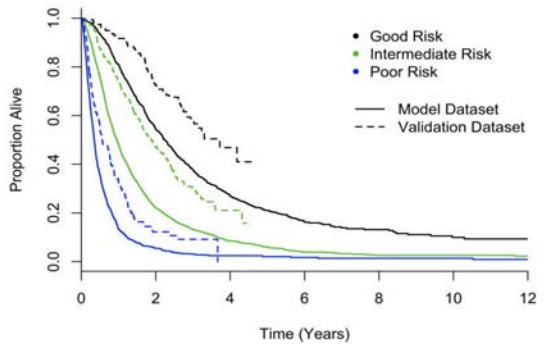
Physician/Patient Appointment Video

6 weeks later

Physician/Patient Appointment Video

After 10 months of sunitinib

Overall Survival, pre vs. post targeted therapy: shifting the survival curves!



Xie, Heng and Choueiri, International Metastatic RCC Database Consortium (Personal communication)

No Approved Combinations with Targeted Agents (yet)

Combo	Outcome	Conclusion
Sunitinib + IFN (Phase II)	12% PR, PFS: 11.9 m Moderate toxicity	Full dose of Sunitinib not possible
Bev+ IL-2 (Phase II)	9% PR, PFS: 3.1 m Moderate toxicity	No benefit over each agent alone
Sorafenib + IFN (Phase II)	Trial 1: 19% PR, PFS: 7 m Trial 2: 33% PR, PFS 10 m	No benefit over each agent alone
Sunitinib + Temsirolimus (Phase I)	Severe short-term toxicities	Too toxic to proceed
Sunitinib+ Bevacizumab (phase I)	Severe long-term toxicities	Too toxic to proceed
Bev +/- Erlotinib (Randomized phase II)	PFS Bev Alone: 8.5 m PFS Combo: 9.9 m (**p=0.5**)	No advantage of adding an EGFR inhibitor
Bev +temsirolimus *vs.* Bev + IFN (Randomized phase III)	PFS: 9.1 vs. 9.3 months	No advantage for Bev+ Tem over Bev+ IFN

Targeted Agents for Advanced RCC

Level I evidence

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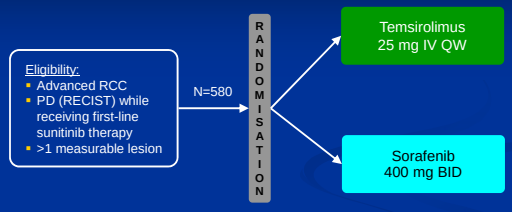
Only prior sunitinib: mTOR inhibitor (everolimus) or VEGF TKI (axitinib) ?

	RECORD-1 (everolimus) *(N=43,13% of all pts)*	AXIS (axitinib) *(N=194, 26% of all pts)*
Response Rate	1-2%	11%
PFS (months)	4.6[1]	4.8
FKSI scores (disease-related symptoms)	Minimal impact vs. placebo[2]	Similar to sorafenib[3]
Discontinuation due to AEs[4]	14%	9%

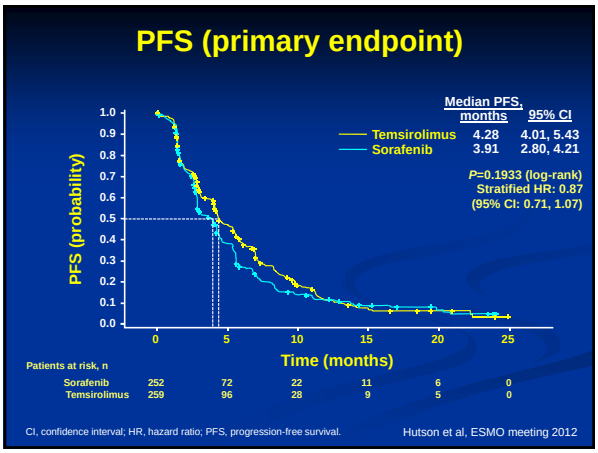
1. Calvo, et al. *EJC* 2012
2. Beaumont et al, *Oncologist* 2011
3. Cella et al, *ASCO meeting* 2011
4. Updated Package Inserts for everolimus and axitinib (accessed May 13, 2012)

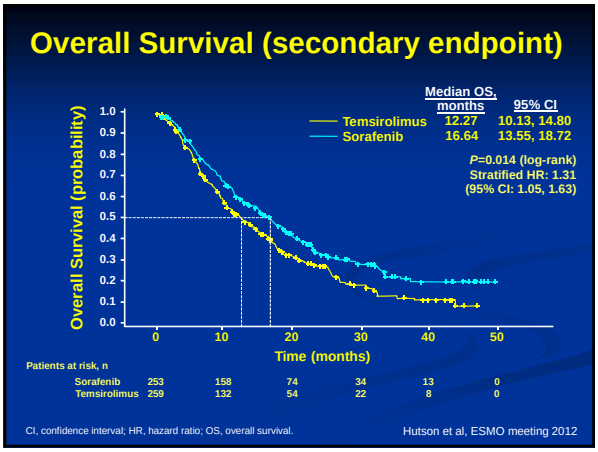
INTORSECT (404): Second-line Treatment with Temsirolimus Versus Sorafenib



- Primary endpoints: PFS, safety and tolerability

Hutson et al, ESMO meeting 2012





Everolimus side effects

- **Everolimus may cause serious side effects including:**
  - pneumonitis (an inflammation of the lungs)
  - Infection
  - high blood sugar levels
  - high lipids
- **The most common side effects of everolimus include**:
  - mouth sores
  - fatigue
  - cough
  - diarrhea
  - rash
  - itching

Physician/Patient Appointment Video

Visit 3 weeks after

Physician/Patient Appointment Video

After 8 weeks

Pneumonitis management

- Hold therapy?
- Steroids?
- Re-challenge?
- R/O infection?
- Parameters to consider:
  - Symptoms, fever, pOx, exam, CT findings, stability of target lesions.

Physician/Patient Appointment Video

After 7 months

Metastatic RCC: Potential Predictive Biomarkers of Efficacy (not for routine use!)

	Cytokines[1-4]	VEGF-Targeted[5-10]	mTOR inh.[11-15]
Biomarker	CAIX (IL-2) CAIX SNPs STAT-3 SNPs (IFN)	VHL CAIX HIF1 and HIF2 SNPs in VEGF pathway Cytokine and Angiogenic Factors (CAFs)	pS6, pAKT PTEN LDH serum levels Cholesterol levels mTOR/PI3K SNPs

1. Atkins, et al. Clin Cancer Res, 2006. **2**. de Martino, et al. J Urol, 2009. **3**. McDermott, et al. ASCO 2010. **4**. Ito, et al. JCO, 2007. **5**. Choueiri et al, J Urol, 2008. **6**. Qu et al, Urol Oncol. 2012. **7**. Patel et al, ASCO 2008. **8**. Schutz , et al. ASCO 2012. **9**. Pena, et al. Clin Cancer Res., 2010. **10**. Tran et al, Lancet Oncol 2012. **11.** Cho et al, Clin GU Cancer, 2007. **12**. Figlin, et al. Cancer 2009. **13.** Armstrong et al, JCO, 2012. **14.** Lee et al, Clin Cancer Res 2012. **15**. Pomerantz et al, ASCO 2012.

Sonpavde and Choueiri. Br. J. Cancer, 2012

Axitinib

Ms. Stevens has been started on therapy with axitinib 5mg bid.

- Side effects
  - Diarrhea
  - Fatigue
  - Dysphonia
  - HFSR
  - bleeding

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- If you have not individually registered, please register at: http://www.cvent.com/d/w4qkbp
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