Diagnosis and Intervention for Renal Cell Carcinoma (RCC)

This activity is provided by:

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Date
Saturday, September 9, 2017

Faculty
Laura S. Wood, RN, MSN, OCN
Renal Cancer Research Coordinator
Cleveland Clinic Taussig Cancer Institute
Cleveland, OH

Time
Lecture @ 10:30-AM

Location
JW Marriott Los Angeles
Los Angeles, CA

Target Audience
This educational activity is designed to meet the needs of oncology nursing professionals involved in care of patients with RCC.

Statement of Need
RCC is a disease whose treatment has been revolutionized over the past several years by the discovery of new targeted and immunologic therapy pathways, giving rise to new and effective treatments and emerging pathways for therapy. Given the pace at which research and clinical advances are occurring, there is a need for oncology nursing professionals to become better aware of appropriate diagnosis and staging as well as novel treatments and therapy algorithms that may improve the management of patients with RCC, their outcomes, and their survival and quality of life, and to be able to apply this knowledge to current and future patient care.

Learning Objectives/Learning Outcomes
Upon completion of this educational activity, learners should be better able to:
1. **Delineate** key guideline recommendations for diagnosis, staging, and treatment algorithms for patients with advanced renal cell carcinoma
2. **Distinguish** between targeted therapy and immunotherapy with respect to treatment options in advanced renal cell carcinoma
3. **Discuss** toxicity profile of systemic therapies approved for advanced renal cell carcinoma
4. **Describe** the role of nurses and advanced practitioners in managing treatment-related toxicities and maximizing clinical outcomes

Activity Agenda
1. Introduction (including pre-activity survey questions)
2. Diagnosis and surgical intervention for renal cell carcinoma (RCC)

A. Presentation and radiographic testing
B. Surgical options: radical & partial nephrectomy
C. Histological subtypes & staging of RCC

3. Systemic therapy for advanced RCC
   A. Front-line treatment
   B. Second-line treatment and beyond
4. Management of brain and bone metastasis
   A. Brain metastasis
   B. Bone metastasis
5. Case Studies
6. Conclusions (post-activity survey questions)
7. Question & answer session

To promote active learning and engage learners audience polling questions and discussion cases have been incorporated in the activity design.

Accreditation and Credit Statements

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American Academy of CME, Inc. designates this educational activity for 1.0 contact hour (1.0 pharmacotherapeutic contact hour).

Method of Participation

There are no fees for participating and receiving CE credit for this activity. In order to receive a CE certificate, learners must:

1) Review the CE information including the learning objectives and disclosure statements;
2) Attend the activity and document attendance;
3) Successfully complete and return the activity evaluation, your certificate will be made available

Please contact Paul Miniter, pminiter@academycme.org if you experience issues.

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Faculty

Laura S. Wood, RN, MSN, OCN
Renal Cancer Research Coordinator
Cleveland Clinic Taussig Cancer Institute
Cleveland, OH

Laura S. Wood discloses the following:
Promotional Speaker's Bureaus: Bristol Myers-Squibb, Pfizer, Exelixis, Novartis

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John JD Juchniewicz, MCIS, CHCP, Paul J. Miniter, MS, Natalie Kirkwood, RN, BSN, JD, Lead Nurse Planner, and Wendy Gloffke, PhD, American Academy of CME : No relevant financial relationships with any commercial interests.

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Faculty Biography

Laura Wood has 25 years of experience as an oncology nurse in a variety of clinical settings. She has been involved in the care of cancer patients participating in clinical trials since 1994, and is currently the Renal Cancer Clinical Research Coordinator in the Solid Tumor Oncology Program at the Cleveland Clinic Cancer Center in Cleveland, Ohio. She is the Cochair of the Kidney Cancer Association Nursing Advisory Board, coordinating and providing expertise in the development of education materials and web based information for patients and their loved ones.

Laura is active in the local and national Oncology Nursing Society and a member of the Clinical Trials and Biotherapy Special Interest Groups of the Oncology Nursing Society. A national and international lecturer on topics related to oncology nursing, and has authored many book chapters and journal articles on therapeutic approaches and nursing care in the management of cancer, with a focus in kidney cancer.

Laura was the recipient of the 2012 Oncology Nursing Society Clinical Lectureship Award, the 2005 Emma Barr Award for Clinical Excellence from the Cleveland Clinic Foundation, and the 2004 Oncology Nursing Society Excellence in Biotherapy Nursing Award.

Renal Cell Carcinoma

Laura S. Wood RN, MSN, OCN
Renal Cancer Research Coordinator
Cleveland Clinic Taussig Cancer Center

Objectives

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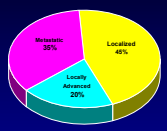
Renal Cell Carcinoma

- 63,900 new cases
- 14,400 deaths
- 2.5 % of all cancers



- Male : Female 3:2
- Median age ~ 64 yrs

Siegel RL et al. *CA Cancer J Clin.* 2017.

Renal Cell Carcinoma: Diagnosis

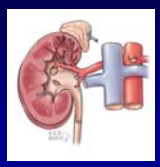
- Local symptoms
  - Hematuria
  - Flank pain
  - Palpable mass
- Systemic symptoms
  - Due to metastasis or paraneoplastic syndrome secondary to protein secretion
    - Hypercalcemia: parathyroid hormone-related protein
    - Hypertension: renin secretion
    - Erythrocytosis: erythropoietin secretion

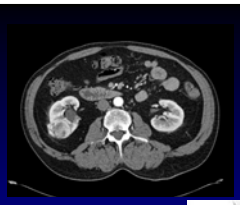
Case Study # 1

- 54 year old male, non-smoker
- Hypertensive 145/78 on amlodipine 10mg daily x 4 years
- Presents to PCP with right flank pain for 6 months and mild cough

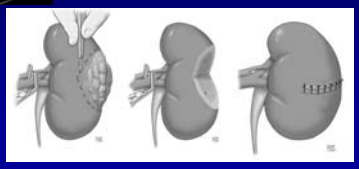
Surgical Intervention

- Radical nephrectomy
- Nephron-sparing surgery
  - Partial nephrectomy
- Open or laparoscopic procedure
- Probe ablation
  - Cryotherapy
  - Radio-frequency ablation (RFA)

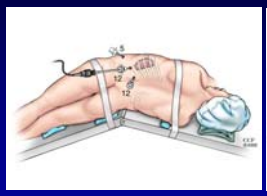




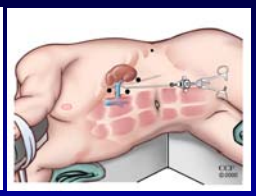
Partial Nephrectomy



Laparoscopic Surgery

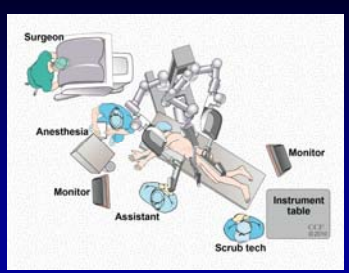


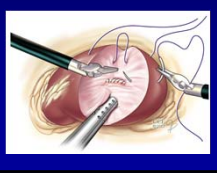
Retroperitoneal Approach



Transperitoneal Approach

Robotic Surgery

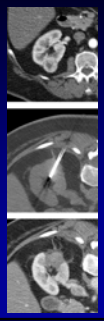




Indications for Ablative Procedure

- Small tumors
- Poor anesthesia risk
- Older patients with significant co-morbidity
- Compromised renal function
- Partial nephrectomy technically challenging
- Multiple tumors

Radiofrequency Ablation: RFA



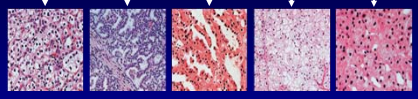
Cytoreductive Nephrectomy

- Improved survival in patients treated with cytokine therapy[1, 2]
- Phase II studies have demonstrated feasibility of surgery following targeted therapy[3,4,5,6,7]
- Phase III trials are ongoing
  - Who are the appropriate patients?
  - Which therapies provide the greatest benefit and least risk ?
  - What is the appropriate duration of neo-adjuvant therapy?

1. Flanigan et al. *NEJM*. 2001. 2. Mickisch et al. *Lancet*. 2001. 3. Margulis et al. *J Urol*. 2008. 4. Thomas et al. *J Urol*. 2009. 5. Jonasch et al. *JCO*. 2009. 6. Klink et al. *JCO*. 2012. 7. Rini et al, in press 2012.

Histological Classification of Human Renal Epithelial Neoplasms

RCC

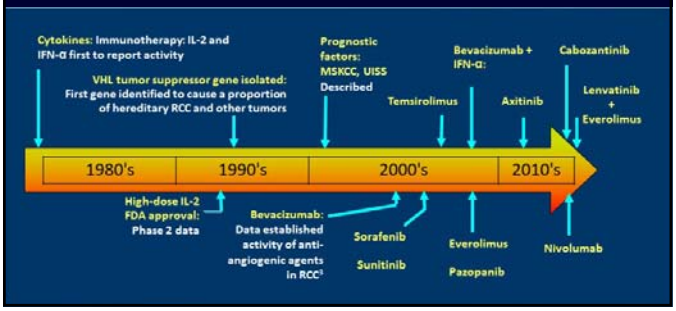


Type	Clear cell	Papillary type 1	Papillary type 2	Chromophobe	Oncocytoma
Incidence	75%	5%	10%	5%	5%
associated mutations	VHL	c-Met	FH	BHD	BHD

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

Linehan WM et al. *J Urol*. 2003.

The Last Decade in RCC Drug Development



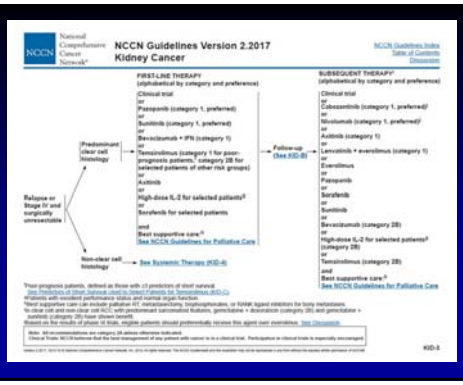
RCC Therapy in 2017

- **Immunotherapy**
  - IL-2
  - IFN-α
  - Nivolumab
- **VEGF Inhibitors**
  - Sunitinib
  - Sorafenib
  - Pazopanib
  - Bevacizumab + IFN-α
  - Axitinib
- **mTOR Inhibitors**
  - Temsirolimus
  - Everolimus
- **VEGF / cMET / AXL**
  - Cabozantinib
- **Combination**
  - Lenvatinib + Everolimus

NCCN Guidelines. Kidney Cancer. Version 2.2017.Available at https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf.

Role of the Nurse and Advance Practice Provider

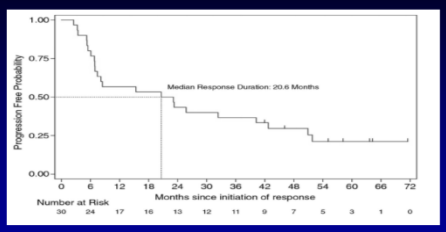
- Understand the available treatment options for RCC
- Provide appropriate patient education to maximize side effect management and Quality of Life
- Recognize that side effects are based on the drug's mechanism of action
- Focus on early assessment, intervention, and monitoring of adverse events


NCCN Guidelines Version 2.2017
Kidney Cancer

FIRST-LINE THERAPY
(alphabetical by category and preference)

SUBSEQUENT THERAPY[1]
(alphabetical by category and preference)

High-Dose Interleukin-2

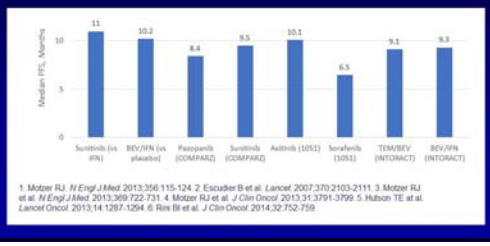


25% objective response rate; 11% durable remission rate (PFS ≥ 3 years)

McDermott et al. *Clin Can Res*. 2015

PFS in Phase 3 Front-Line Studies

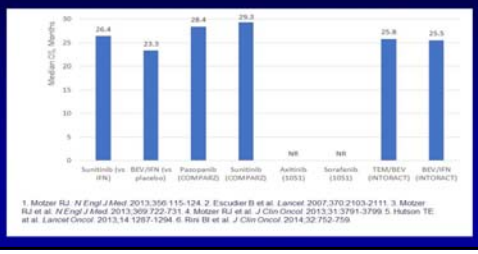
2007 2013 2014



1. Motzer RJ. *N Engl J Med* 2013;356:115-124. 2. Escudier B et al. *Lancet* 2007;370:2103-2111. 3. Motzer RJ et al. *N Engl J Med* 2013;369:722-731. 4. Motzer RJ et al. *J Clin Oncol* 2013;31:3791-3799. 5. Hutson TE et al. *Lancet Oncol* 2013;14:1287-1294. 6. Rini BI et al. *J Clin Oncol* 2014;32:752-759.

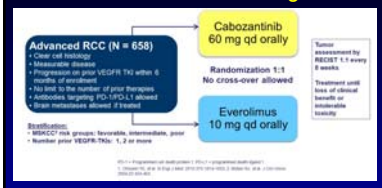
OS in Phase 3 Front-Line Studies

2007 2013 2014



1. Motzer RJ. *N Engl J Med* 2013;356:115-124. 2. Escudier B et al. *Lancet* 2007;370:2103-2111. 3. Motzer RJ et al. *N Engl J Med* 2013;369:722-731. 4. Motzer RJ et al. *J Clin Oncol* 2013;31:3791-3799. 5. Hutson TE et al. *Lancet Oncol* 2013;14:1287-1294. 6. Rini BI et al. *J Clin Oncol* 2014;32:752-759.

METEOR: Phase 3 Cabozantinib vs. Everolimus Following VEG-F Therapy

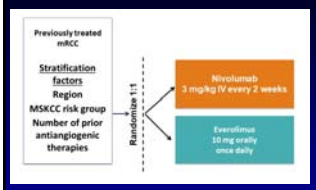


70% had only 1 prior VEGF

	Cabozantinib	Everolimus	
RR	17 %	3 %	p <0.0001
PFS	7.4 mo	3.9 mo	p=0.00026
OS	21.4 mo	16.5 mo	p <0.0001

Choueiri TK et al. *Lancet Oncol.* 2016

Phase 3 Nivolumab vs. Everolimus

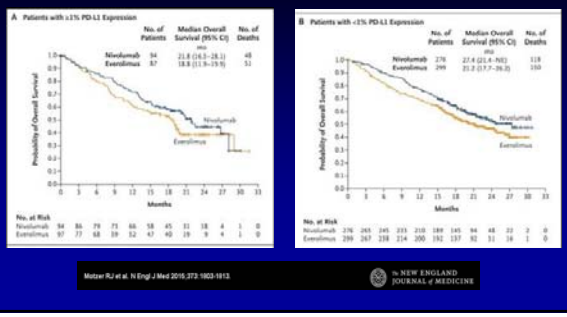


Phase 3 study 2nd-line + post-VEGF therapy in mRCC

	Nivolumab	Everolimus	
RR	25 %	5 %	p <0.001
PFS	4.6 mo	4.4 mo	p=0.011
OS	25.0 mo	19.6 mo	p=0.0018

Motzer RJ et al. *NEJM*. 2015

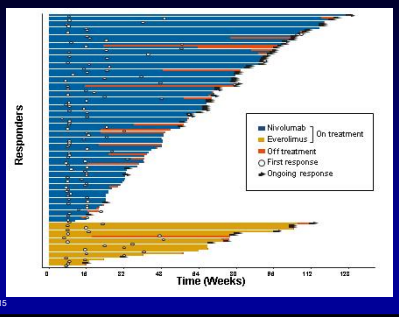
Nivolumab vs. Everolimus: Survival based on PD-L1 status



Motzer RJ et al. N Engl J Med 2015;373:1803-1813.

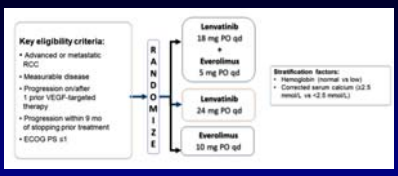
The NEW ENGLAND JOURNAL of MEDICINE

Continued Response Following Discontinuation



Motzer RJ et al. *NEJM*. 2015

Phase 2 Lenvatinib vs. Everolimus



	Lenvatinib + Everolimus	Lenvatinib	Everolimus
RR	43 %	27 %	6 %
PFS	12.8 mo	9.0 mo	5.6 mo
OS	25.5 mo	18.4 mo	17.5 mo

Motzer RJ et al. *Lancet*. 2015

Treatment of non-clear cell RCC

		Everolimus	Sunitinib
ASPEN[1]	PFS	5.6 mo	8.3 mo
	OS	13.2 mo	13.5 mo

		Everolimus	Sunitinib
ESPN[2]	PFS	4.1 mo	6.1 mo
	OS	10.5 mo	NR

1. Armstrong AJ et al. *Lancet Oncol*. 2016. 2. Tannir NM et al. Eur Urol. 2016.

Targeted Agents: Common Adverse Events

Adverse Event	Sorafenib & Axitinib	Sunitinib & Pazopanib	Cabozantinib	Lenvatinib	Bevacizumab	Everolimus	Temsirolimus
Fatigue	+	+	+	+	+	+	+
Hand-foot Syndrome	+	+	+	+			
Hypertension	+	+	+	+	+		
Diarrhea	+	+	+	+		+	+
Stomatitis	+	+	+	+		+	+
Myelosuppression		+	+			+	+
Pneumonitis						+	+
Infections						+	+
Hypersensitivity reaction					+		+
Proteinuria					+		
Metabolic syndrome						+	+

Nursing Management

- Patient education prior to initiation of therapy
- Written information and resources
- Awareness of “class effect” toxicities
- Pro-active approach to assessment and intervention
- Early and ongoing communication
- Intervene early and follow-up frequently

Dermatologic Side Effects

- Dry skin
- Rash
- Pruritis
- Hand-foot syndrome
  - Palmar-plantar erythrodysesthesia syndrome
  - Hand-foot skin reaction

The “3C” Approach to Manage MKI-HFSR

- Control calluses
  - Prophylactic removal of hyperkeratotic areas before & during treatment
  - Pumice stone, Ped Egg pedicure, podiatrist
- Comfort with cushions
  - Protect pressure-sensitive areas of hands & feet
    - Well-padded, well-fitting, soft shoes
    - Insole cushions or inserts
- Cover with creams
  - Frequent use of emolient creams
  - Keratolytic agents on callused areas of palms & soles

Wood L et al. *Community Oncology.* 2010.

Additional Side Effects

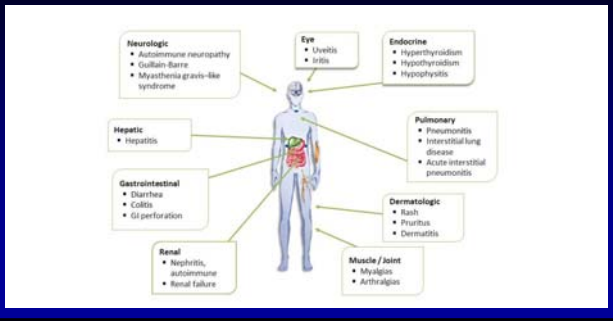
- Fatigue
- Diarrhea
- Nausea / Vomiting
- Mucositis
  - Clinical or Functional
- Anorexia
  - Other causes must be ruled out
- Hypertension

General Guidelines: Immunotherapy

- Early recognition of symptoms & frequent monitoring
- Establish correct diagnosis
  - Presentation can be subtle
  - Other causes must be ruled out
- irAEs can become severe & life threatening if diagnosis and appropriate treatment are delayed

Fecher LA et al. *The Oncologist*. 2013.

Immune-Related Adverse Events: irAEs



Case Study # 2

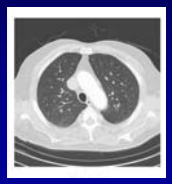
- 54 year male with metastatic renal cancer
- Treatment:
  - Sunitinib for 16 months
  - Nivolumab for 11 months
- Calls with increasing fatigue and DOE
  - Denies fever or chills
  - Nobody in family with URI symptoms
- Patient is worried his cancer is worse

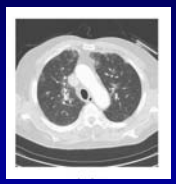
Options:

- Provide reassurance
  - He's getting CT scans in 2 weeks
  - Will assess disease before his next Nivolumab infusion
- See patient in the office in a few days if no improvement in symptoms
- Send to the ER

Nursing Management

- See in office today for evaluation
  - Resting & ambulatory pulse ox
  - CXR or CT scan





Nursing Management of immune-related irAEs

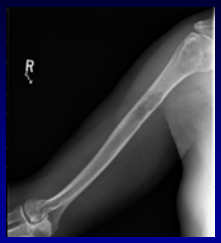
- Patient education
  - Review what irAEs are
- irAEs
  - Assessment
  - Management
  - Follow up
- Prednisone 1-2mg / kg and taper slowly
- Hold Nivolumab
  - Until symptoms resolved & Prednisone 10mg daily or below

mRCC: Brain and Bone metastasis

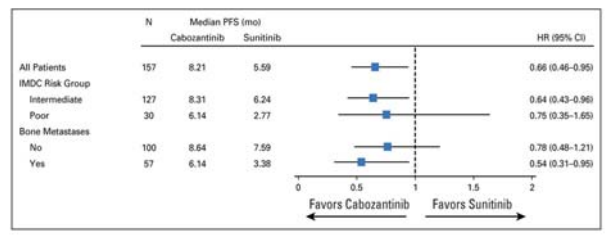
- Bone metastasis
  - Symptomatic
    - Limited ability to use NSAIDs due to CKD
    - Tylenol ineffective in treating bone pain
- Brain metastasis
  - Brain is a sanctuary site
  - Develop brain mets in spite of good systemic disease control
  - Interrupt systemic therapy, GK, then resume systemic therapy if patient had been responding to therapy

Case Study # 3

- 65 year old male
  - Axitinib 2nd-line therapy
- Pain right upper arm with movement



CABOSUN: Subgroup Analysis



Choueiri et al. 2017

Treatment of mRCC in 2017

1st-Line	2nd-Line
Clinical Trial	Clinical Trial
Sunitinib	Axitinib
Pazopanib	Cabozantinib
Bevacizumab/IFN	Nivolumab
Temsirolimus*	Lenvatinib/ Everolimus

* Poor risk

RCC: Role for Adjuvant Therapy ?

- ASSURE[1]: Sunitinib vs. Sorafenib vs. Placebo
  - Protocol amended to decrease starting doses of Sunitinib and Sorafenib due to toxicity
- PROTECT[2]: Pazopanib vs. Placebo
  - Protocol amended to decrease starting dose of Pazopanib due to toxicity
- S-TRAC[3]: Sunitinib vs. Placebo
  - Disease-Free-Survival 6.8 yrs vs. 5.6 yrs

1. Haas NB et al. *Lancet*. 2016. 3. Ravaud A et al. *NEJM*. 2016. Motzer RJ et al. *JCO*. 2017

Adjuvant Trials in RCC

Trial	Drug	DFS Benefit	OS Benefit	Patient Population
ASSURE	Sunitinib Sorafenib Placebo	No No	No No	Non clear cell included T2Gr3/4+ Starting dose lower
S-TRAC	Sunitinib Placebo	Yes (1.2 yrs) (HR 0.75)	No (immature, unpowered)	Clear cell T3+ Standard dose
PROTECT	Pazopanib Placebo	No	No	Clear cell T2Gr3/4+ Starting dose lower

- **Right dose of VEGFR TKI likely improves DFS in high risk resected RCC**
- **OS benefit still unclear**
- **Risk/benefit of 1 year DFS vs 1 year of toxicity needs to be considered**

1. Haas NB et al. *Lancet*. 2016. 3. Ravaud A et al. *NEJM*. 2016. Motzer RJ et al. JCO. 2017

Summary

- Significant improvement in treatment options for renal cancer
- Continued clinical trials to determine biomarkers that may facilitate most appropriate treatment selection
- Ongoing efforts to determine potential for adjuvant therapy in renal and urothelial cancers
- Clinical trial referral and enrollment is critical to improving treatment options and survival

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