

Case #6—Advanced RCC: Choice of First-Line Systemic Therapy

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Clinical Case (1)

- **55-year-old female**
 - nonsmoker
 - primary care physician
 - persistent nonproductive cough and weight loss of 7 kg
- **CXR: Multiple (>15) bilateral pulmonary nodules consistent with metastases (≤ 3.0 cm)**
- **CT SCANS CHEST, ABD, PELVIS:**
 - Pulmonary nodules
 - No mediastinal lymph node
 - Left solid renal mass (7 cm)

Clinical Case (2)

- **PATHOLOGY:**
 - Transbronchial biopsy of a pulmonary nodule
 - Clear cell carcinoma
- **ECOG PS: 1**
- **LABS:**
 - Hgb 10.9 g/dL
 - Calcium, creatinine, and LDH: normal
- **BONE SCAN:**
 - Negative

Question 1

Which of the following therapeutic approaches would you recommend?

- **Left radical nephrectomy followed by systemic therapy**
- **Left partial (nephron-sparing) nephrectomy followed by systemic therapy**
- **Systemic therapy with a targeted agent. Consider nephrectomy later based on response to therapy and clinical course**

Comments

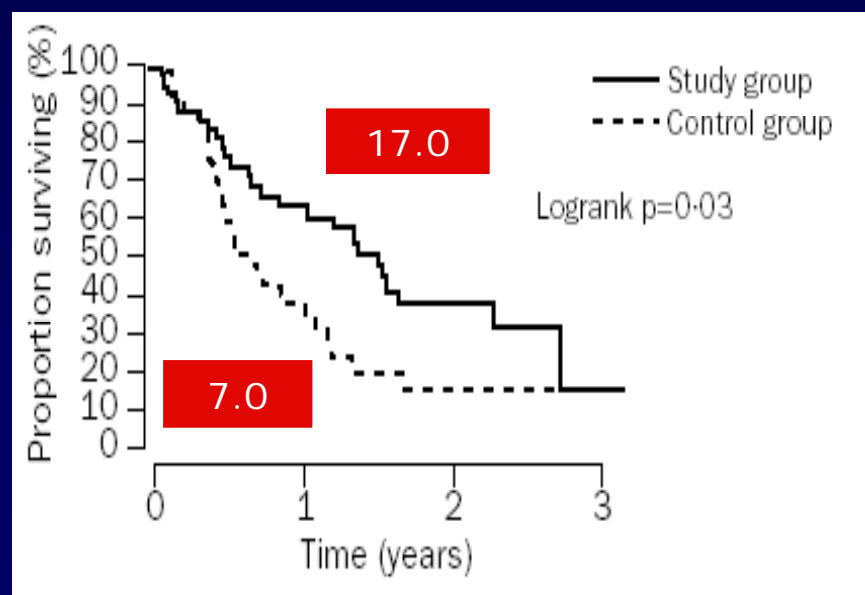
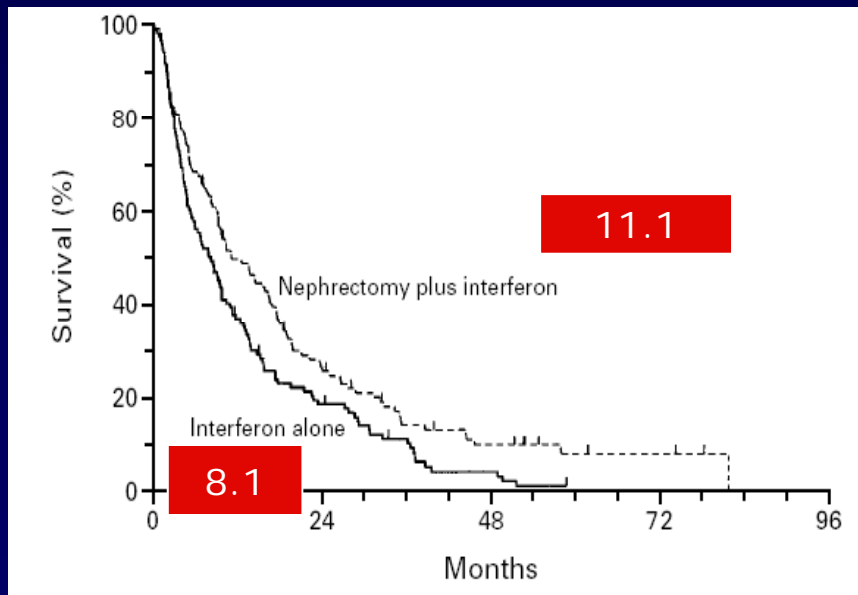
- **Left radical nephrectomy followed by systemic therapy**
- **Left partial (nephron-sparing) nephrectomy followed by systemic therapy**

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- **SURGERY IN THE CONTEXT OF MRCC ?**
- **LOCAL ISSUE (PARTIAL VS TOTAL) IN THE CONTEXT OF METASTATIC DISEASE ?**

Surgery in the Context of MRCC?

- Phase III trials SWOG/EORTC
- Surgery + IFN α vs IFN α
- Significant gain in OS for surgery

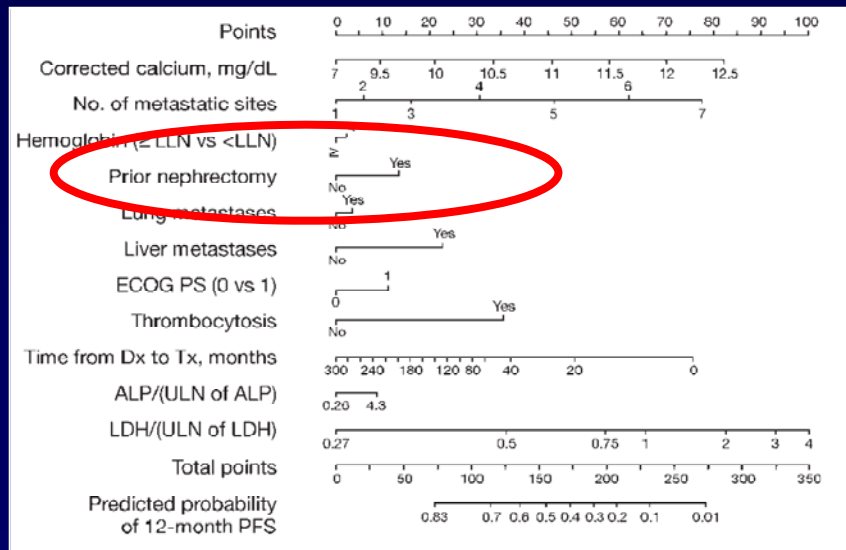


Surgery in the Context of MRCC?

- No data from prospective trials with antiangiogenic treatment
- Subgroup analysis in a post hoc situation: prior nephrectomy vs no

PFS ¹

OS ^{2,3}



NO IMPACT

1. Motzer RJ, et al. *Cancer*. 2008;113(7):1552-1558. 2. Heng DY, et al. *J Clin Oncol*. 2009;27(34):5794-5799. 3. Patil S, et al. *Ann Oncol*. July 25, 2010; [Epub ahead of print].

Surgery in the Context of MRCC

- To make a decision
- Outside definitive answer

**DO WE HAVE ANY REASON
TO CONSIDER ANY “EMERGENCY”
TO TREAT THE METASTATIC DISEASE?**

- PS1, only lung M+, Hb : 10.9 g/dL

**NO
FOLLOW THE STANDARD
DO A NEPHRECTOMY
OR JOIN A TRIAL “CARMENA”**

Radical vs Partial Nephrectomy

- **No data**
- **Choice of total or partial nephrectomy should be based on:**
 - **surgeon preference**
 - **skill level**

And

- **partial nephrectomy can maintain some renal function**
- **but depending on the site, a primary tumor this size (7 cm) may indicate radical nephrectomy**

Question 2

Which of the following first-line therapies would you recommend after nephrectomy?

- Sunitinib
- Bevacizumab + interferon (IFN) alpha
- Pazopanib
- Temsirolimus
- Clinical trial participation (COMPARZ, RECORD-2, RECORD-3, INTORACT, BeST)
- Immunotherapy

First-Line Options for RCC Treatment (Clear Cell Carcinoma)

| Population | Standard | Option |
|--|-----------------------------|----------------|
| <u>MSKCC risk:</u> Good or intermediate | Sunitinib | High-dose IL-2 |
| | Bevacizumab + IFN- α | Sorafenib |
| | Pazopanib | Clinical trial |
| <u>MSKCC risk :</u> Poor | Temsirolimus | Observation |
| | | Sunitinib |
| | | Clinical trial |

Escudier B, et al. *Ann Oncol*. 2009;20(Suppl 4):81-82.

de Reijke TM, et al. *Eur J Cancer*. 2009;45(5):765-773.

Ljungberg B, et al. *Guidelines on Renal Cell Carcinoma* [online]. 2009. Available online at:

http://www.uroweb.org/fileadmin/tx_eauguidelines/2009/Full/RCC.pdf. Accessed October 4, 2010.

National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: Renal cell carcinoma.

Available online at: http://www.nccn.org/professionals/physician_gls/PDF/kidney.pdf. Accessed October 4, 2010.

Classification of Patient's Case

- **MSKCC classification for clinical trials stratification.....not devoted to clinical practice**
 - **Time from Δ g-time to first Tt <1 year = 1**
 - **ECOG PS 1 (\geq KPS 80) = 0**
 - **Hgb <NLE = 1**
 - **Corrected Ca and LDH: NLE = 0**
- ⇒ INTERMEDIATE RISK POPULATION**

Phase III Trials in 1st-Line

| THERAPY | PFS | OS |
|-----------------------------|-------------------|--------------------|
| Sunitinib | 11 mo vs 5 mo | 26.4 mo vs 21.8 mo |
| Bevacizumab + IFN- α | 8.5 mo vs 5.2 mo | 18.3 mo vs 17.4 mo |
| | 10.2 mo vs 5.4 mo | 23.3 mo vs 21.3 mo |
| Pazopanib | 9.2 mo vs 4.2 mo | NA |

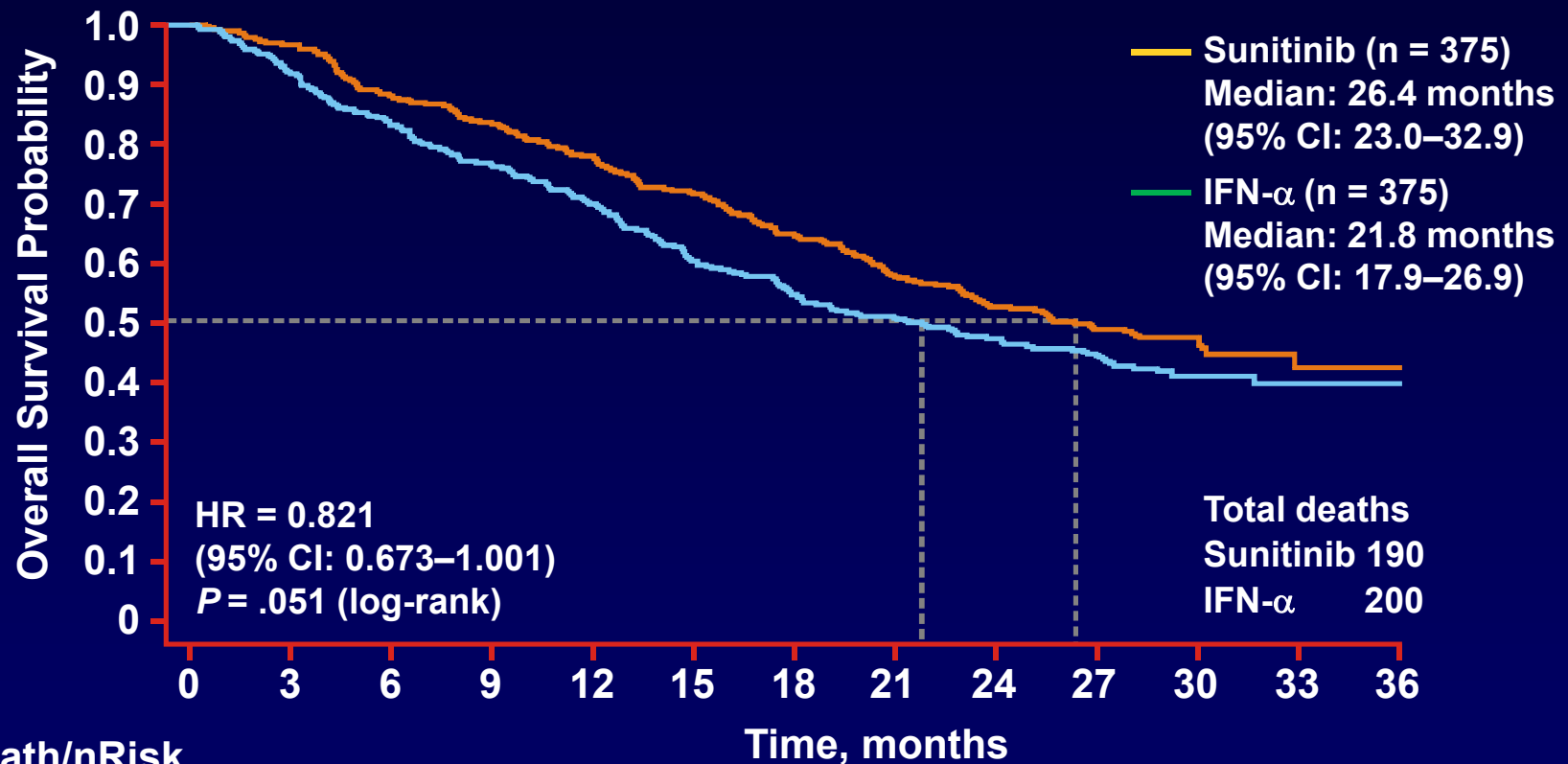
Rini BI, et al. *J Clin Oncol*. 2008;26(33):5422-5428. Escudier BJ, et al. *Lancet*. 2007;370(9605):2103-2111. Escudier, BJ et al. *J Clin Oncol*. 2009;27(15S): Abstract 5020. Rini BI, et al. *J Clin Oncol*. 2009;27(18S): Abstract LBA5019. Motzer RJ, et al. *J Clin Oncol*. 2009;27(22):3584-3590. Motzer RJ, et al. *N Engl J Med*. 2007;356(2):115-124. Sternberg CA, et al. *J Clin Oncol*. 2010;28(6):1061-1068.

Additional Information From Phase III

| THERAPY | ORR % | CR | PR |
|--------------------------------|-------|----|----|
| Sunitinib | 31 | 0 | 31 |
| Sunitinib | 47 | 3 | 44 |
| Bevacizumab + IFN- α | 31 | 1 | 30 |
| Bevacizumab + IFN- α | 25.5 | | |
| Pazopanib | 30 | | |

Rini BI, et al. *J Clin Oncol.* 2008;26(33):5422-5428. Escudier BJ, et al. *Lancet.* 2007;370(9605):2103-2111. Escudier, BJ et al. *J Clin Oncol.* 2009;27(15S): Abstract 5020. Rini BI, et al. *J Clin Oncol.* 2009;27(18S): Abstract LBA5019. Motzer RJ, et al. *J Clin Oncol.* 2009;27(22):3584-3590. Motzer RJ, et al. *N Engl J Med.* 2007;356(2):115-124. Sternberg CA, et al. *J Clin Oncol.* 2010;28(6):1061-1068.

Final Overall Survival



| nDeath/nRisk | 0 | 3 | 6 | 9 | 12 | 15 | 18 | 21 | 24 | 27 | 30 | 33 | 36 |
|--------------|-----|--------|--------|--------|--------|-------|-----|----|----|----|----|----|----|
| Sunitinib | 375 | 44/326 | 38/283 | 48/229 | 42/180 | 14/61 | 4/2 | | | | | | |
| IFN-α | 375 | 61/295 | 46/242 | 52/187 | 25/149 | 15/53 | 1/1 | | | | | | |

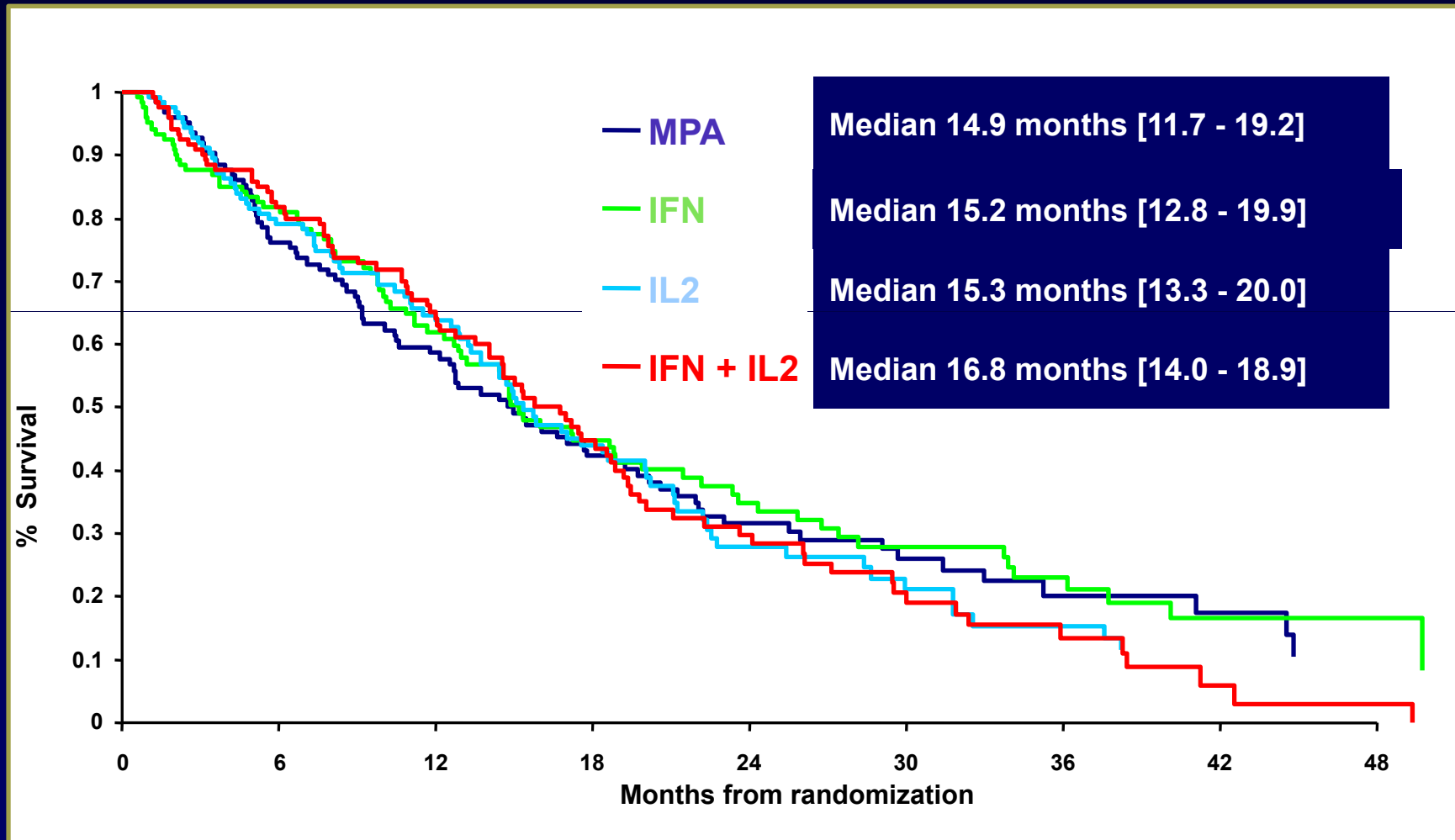
Which of the Following First-Line Therapies Would You Recommend After Nephrectomy?

- **Sunitinib**
- **Bevacizumab + interferon (IFN) alpha**
- **Pazopanib**
- **Temsirolimus**
- **Clinical trial participation (COMPARZ, RECORD-2, RECORD-3, INTORACT, BeST)**
- **Immunotherapy**

Temsirolimus

- **NO INDICATION DUE TO LACK OF DATA IN INTERMEDIATE-RISK POPULATION**
- **Intermediate-risk population in pivotal study: 24%**

Immunotherapy



Which of the Following First-Line Therapies Would You Recommend After Nephrectomy?

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Clinical Trials in 1st-Line

- **COMPARZ: pazopanib vs sunitinib**
- **RECORD 2: everolimus + bevacizumab vs interferon alpha + bevacizumab**
- **RECORD 3: everolimus followed by sunitinib vs sunitinib followed by everolimus**
- **INTORACT: temsirolimus + bevacizumab vs interferon alpha + bevacizumab**
- **BeST: temsirolimus + bevacizumab vs sorafenib + bevacizumab vs temsirolimus + sorafenib vs bevacizumab**

Conclusion Clinical Case

- **Perform nephrectomy**
- **Treat with antiangiogenics**
 - Sunitinib
 - Bevacizumab + interferon (IFN) alpha
 - Pazopanib
- **Or clinical trial**