

It's not a four legged animal  
anymore

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## Disclosure

- No disclosures

Four legged animal which use the tips of their toes, usually hoofed, to sustain their whole body weight while moving.

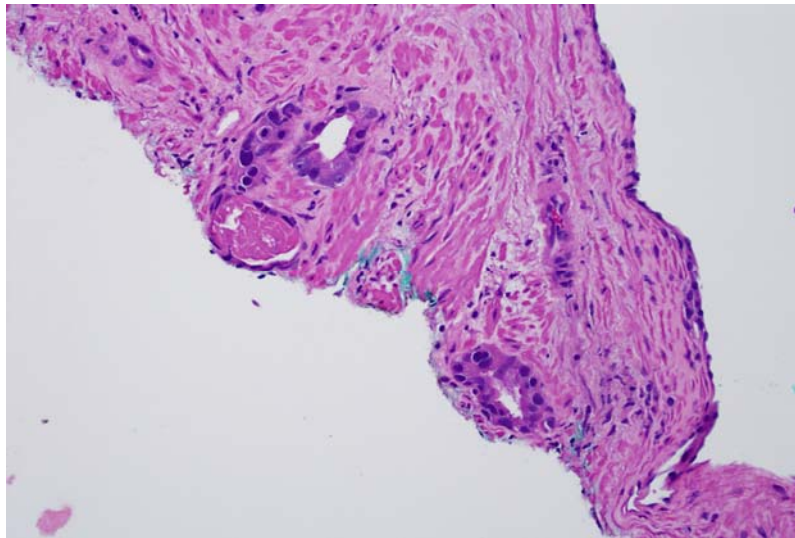


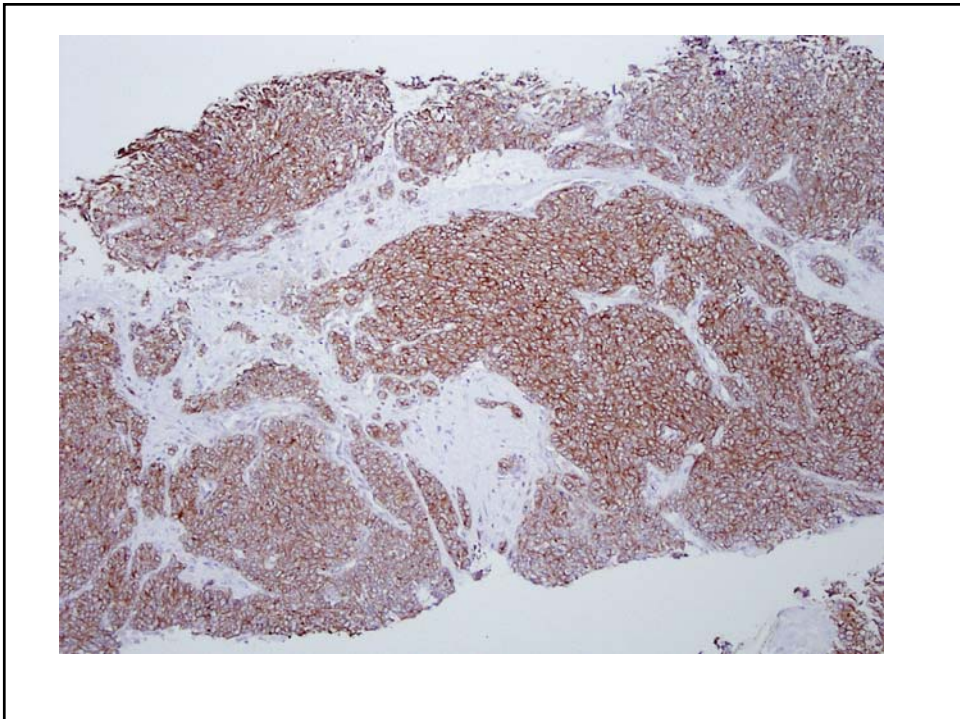
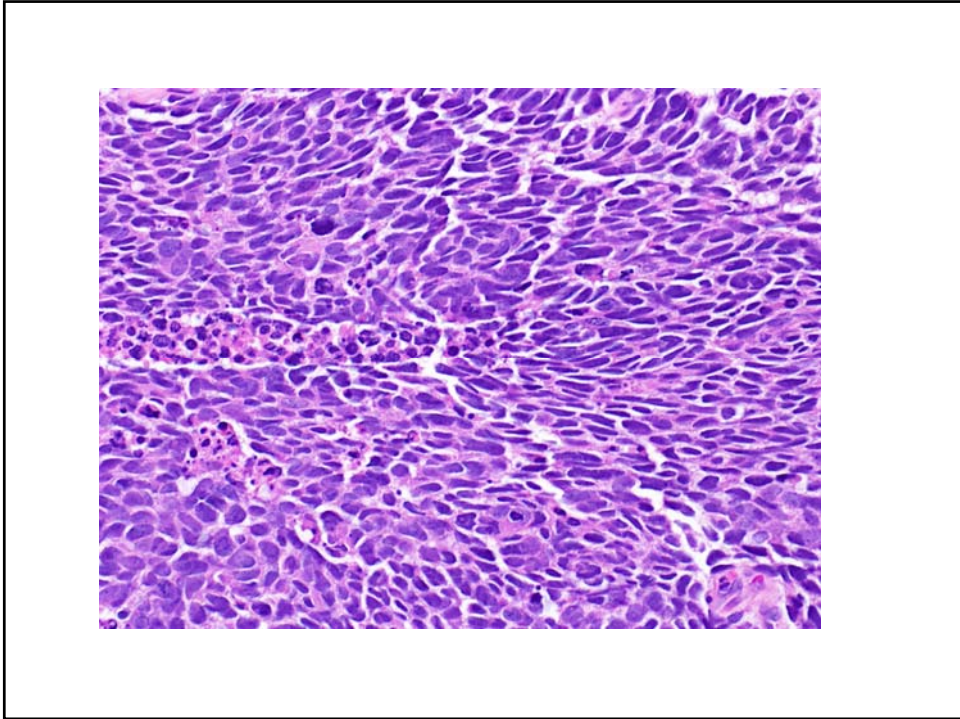
## Goals

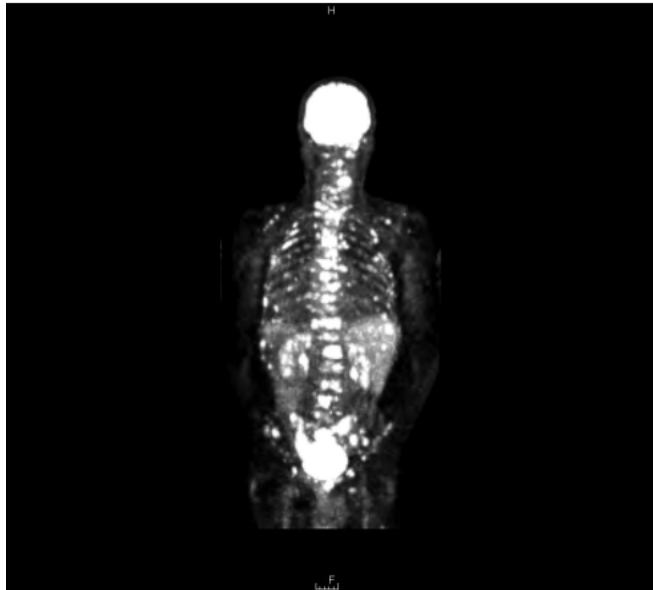
- What translates in the terms of clinical outcomes after histopathological and molecular diagnosis.
- Pathological information specifically being looked at by clinical researchers.

## Prostate cancer-Clinical case

- 78 year old presented to PCP with urinary complaints and PSA of 2.69
- Prostate exam showed a nodule
- Urologist performed a biopsy shows



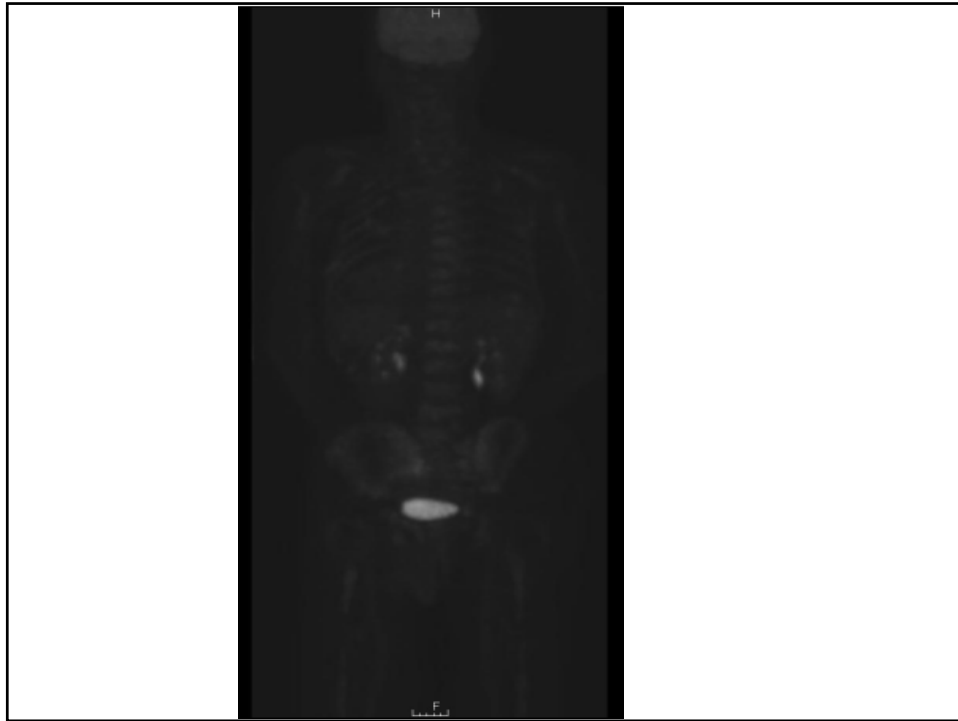




Fine needle Aspiration of bone and liver confirmed as small cell carcinoma.

## Treatment

- Patient received 6 cycles of carboplatin and etoposide. And scan shows



## Prostate cancer

- **Small cell prostate cancer and neuroendocrine differentiation:** - Peculiarities
  1. Androgen receptor negative- Does not respond to androgen deprivation.
  2. Will not respond to androgen withdrawal- Similarly prostate adenocarcinoma respond to withdrawal of androgen deprivation
  3. Respond to platinum and etoposide combination.- Adenocarcinoma response
  4. Rapidly progressive and fatal

Results of a phase II study with doxorubicin, etoposide, and cisplatin in patients with fully characterized small-cell carcinoma of the prostate. Papandreou CN1, J Clin Oncol. 2002 Jul 15;20(14):3072-80.

## What clinicians looking for

- What percentage of tissue has small cell component
- If tumor has neuroendocrine differentiation- is it high grade or low grade
- Clinical practice – Patient with biopsy of primary cancer shows mixed histology we request biopsy evaluation of metastatic site to evaluate which component is present in the metastasis

## Clinical trials in Prostate Adenocarcinoma

- Trials targeting androgen receptor or its pathway -Patients with small cell or high grade neuroendocrine differentiation are excluded.
- Trials targeting PSMA - It may be important to differentiate between Gleason 10 and small cell carcinoma. PSMA is negative on these patients.
- Trials targeting novel therapy for adenocarcinoma in neoadjuvant setting will also rule out small cell or Sarcomatoid variants.

## How many hooves



## Kidney cancer- Non Clear cell

- Non Clear cell carcinoma- Papillary, Sarcomatoid variant, Collecting duct
- Poor response to immunotherapy.
- Underrepresented in clinical trial with VEGF and mTOR inhibitor.
- No clear therapy. And usually portends poor survival and outcomes
- Pathway appears to play a role, more so in type 1 papillary renal cell carcinoma.

(Upton, Parker et al. 2005)C-met  
(Motzer, Bacik et al. 2002)



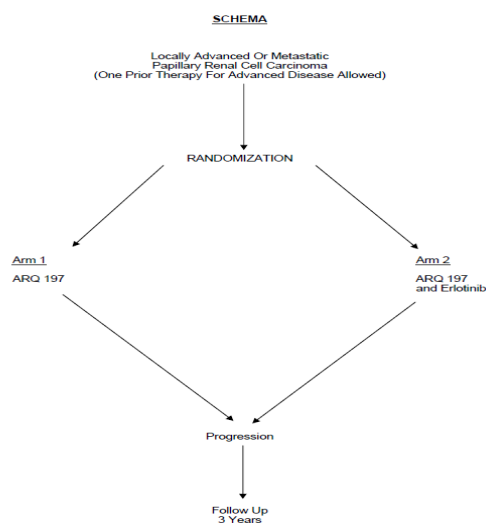
## Papillary Carcinoma

- c-Met pathway plays a role in tumor-genesis more so in type 1. ①
- Epidermal growth factor and c-Met signal pathway cross talk . EGFR activation may lead to constitutive c-Met phosphorylation. ②
- Clinical trials are ongoing looking at both targets in this subset of tumors.

1.(Schmidt, Junker et al. 1999)

2.(Jo, Stolz et al. 2000)

**S1107**, "Parallel (Randomized) Phase II Evaluation of ARQ 197 and ARQ197 in Combination with Erlotinib in Papillary Renal Cell Carcinoma."



## Eligibility Criteria

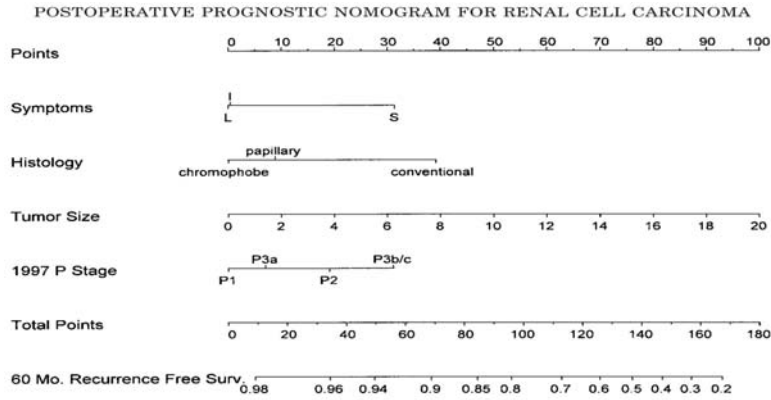
- Patients must have histologically or cytologically confirmed papillary histology renal cell carcinoma which is metastatic, or locally advanced and unresectable.
- Mixed histologies will be allowed provided that they contain  $\geq 50\%$  of the papillary component

## Adjuvant treatment in kidney cancer

- Adjuvant immuno-chemotherapy fail to demonstrate any benefit in high risk disease after nephrectomy.①
- Immunotherapy alone showed worse outcomes in adjuvant settings.②
- 1.(Atzpodien, Schmitt et al. 2005)
- 2. (Clark, Atkins et al. 2003)

## Adjuvant therapy clinical trials

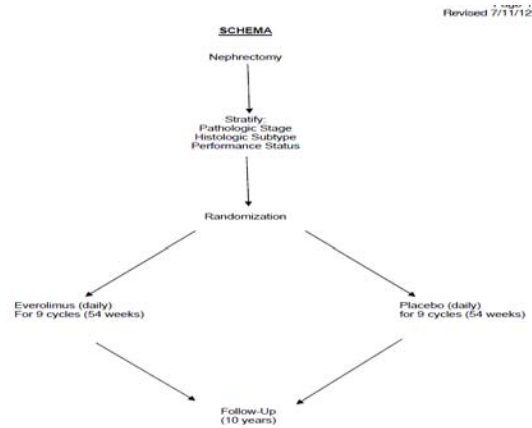
- Nomograms exist which can predict recurrence of kidney cancer upto 12 years post nephrectomy. ①



1.(Kattan, Reuter et al. 2001)

## Ongoing clinical trials

- S0931**, “EVEREST: EVERolimus for Renal Cancer Ensuing Surgical Therapy, A Phase III Study.



NOTE: Procedure for optional unblinding of treatment at recurrence outlined in Section 7.5.

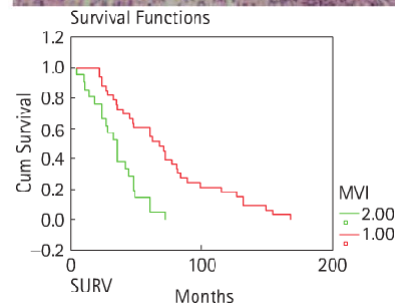
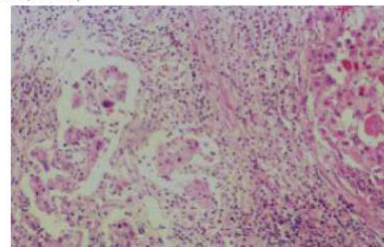
## Inclusion criteria

- **Intermediate High Risk Group**
- pT1b G3-4, N0 (or pNX where clinically N0), M0 (>4cm)
- pT2a-b G1-2, N0 (or pNX where clinically N0), M0
- pT2 a-b G3-4, N0 (or pNX where clinically N0), M0
- pT3a G1-2, N0 (or pNX where clinically N0), M0
- Microvascular invasion of the renal vein of pT1a-pT3a (as long as pT3a is Grade 1-2) N0 (or pNX where clinically N0) M0
- where clinically N0) M0
- **Very High Risk Group**
- pT3a G3-4, N0 (or pNX where clinically N0), M0
- pT3b-c G any, N0 (or pNX where clinically N0), M0
- pT4 G any, N0 (or pNX where clinically N0), M0
- pT any G any, N+ (fully resected), M0
- Microvascular invasion of the renal vein with above other characteristics

## Relation of microvessel density with microvascular invasion, metastasis and prognosis in renal cell carcinoma

Esin Yildiz, Semih Ayan\*, Fahrettin Goze, Gokhan Gokce\* and Emin Y. Gultekin\*,  
Departments of Pathology and \*Urology, Cumhuriyet University, Sivas, Turkey

- Presence of MVI appears to be a marker for identifying patients with an adverse prognosis.



## Exclusion criteria

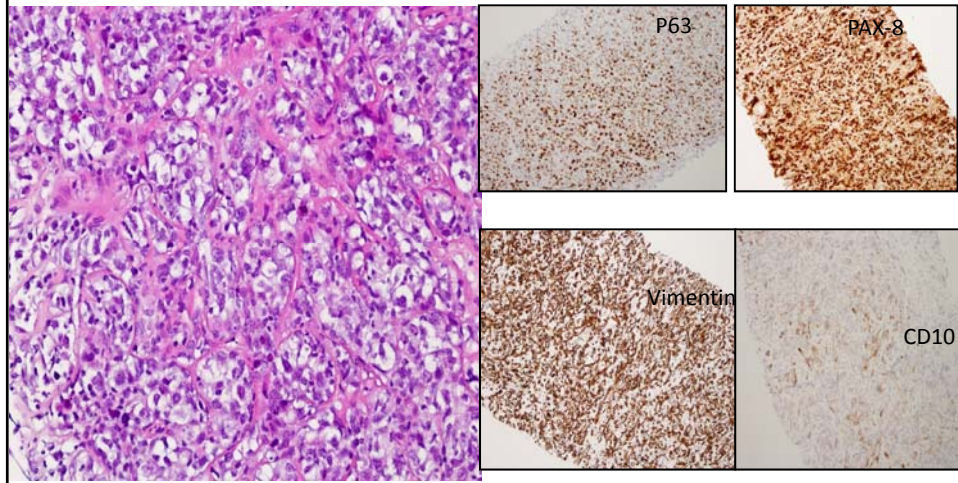
- Collecting duct or medullary carcinomas
- Positive renal vein margins are eligible unless there is invasion of the renal vein **wall** at the margin (provided no other margins are positive).

## Size and the skin color



# High grade undifferentiated tumors

- Rule out lymphoma and germ cell tumors



## The New England Journal of Medicine

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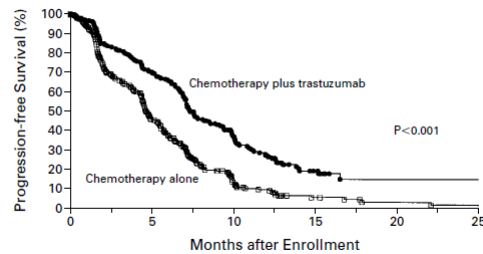
VOLUME 344

MARCH 15, 2001

NUMBER 11



### USE OF CHEMOTHERAPY PLUS A MONOCLONAL ANTIBODY AGAINST HER2 FOR METASTATIC BREAST CANCER THAT OVEREXPRESSES HER2



(Slamon, Leyland-Jones et al. 2001)

## Her-2 positive breast cancer

- 20 percent of breast cancers overexpress human epidermal growth factor receptor 2 (HER2),
- Transmembrane glycoprotein epidermal growth factor receptor (EGFR) with tyrosine kinase activity.
- Historically, overexpression of this receptor was associated with an increased risk of disease recurrence and an overall worse prognosis

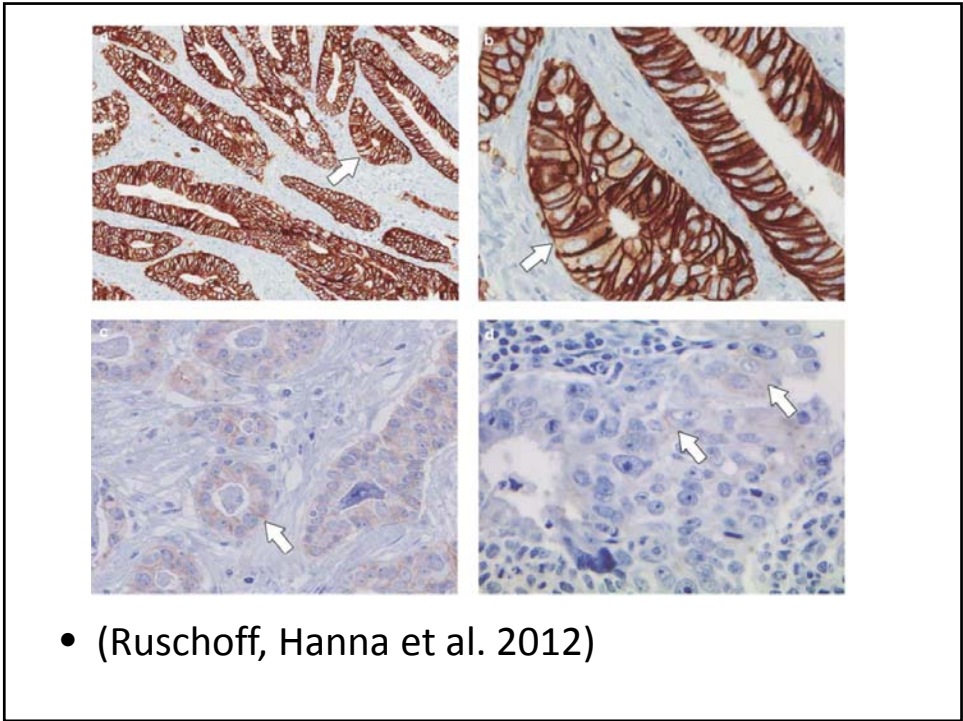
## IHC criteria by ASCO/CAP guidelines

- IHC3+ if there is complete and intense circumferential membrane staining within >10 percent of tumor cells.
- IHC2+ if (1) there is incomplete and/or weak/moderate circumferential membrane staining within >10 percent of tumor cells, or (2) complete and intense circumferential membrane staining within <10 percent of tumor cells. All IHC 2+ tumors are reported as HER2 equivocal

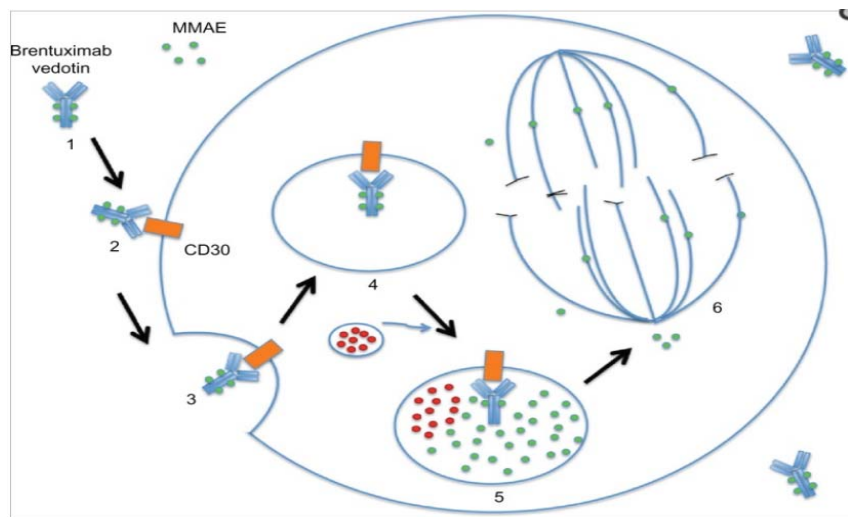
Wolff, A. C., et al. (2013). "Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update." *J Clin Oncol* 31(31): 3997-4013.



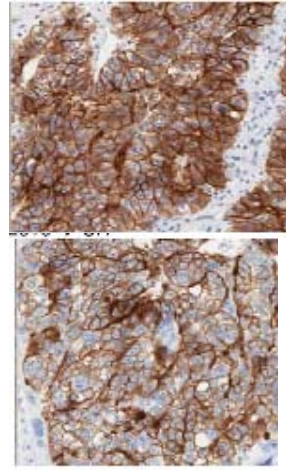




### CD30 positive Hodgkin or Testicular cancer



- Patients with advanced testicular cancer not responding platinum based first line and second line therapy



Antitumor activity of brentuximab vedotin in CD30 positive refractory germ cell tumors.  
Costantine Albany MD Abstract 327 ASCO GU2013

## Large cell Ca of the lung is not enough

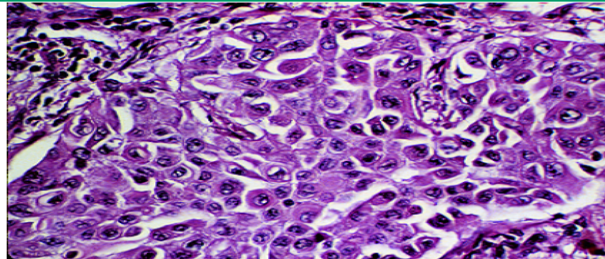
**Source of Specimen(s):**  
800ml of opaque tan right thoracentesis fluid

Pathologist:  
QUIJUIS, BERNADETTE  
BELITSOS, JAMES MD

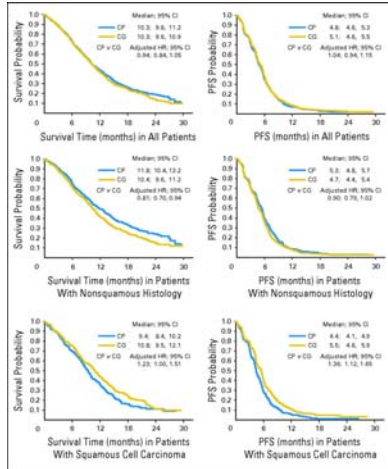
**Final Diagnosis:**  
RIGHT THORACENTESIS FLUID CYTOSPIN AND CELL BLOCK SECTIONS:  
POSITIVE FOR LARGE CELL MALIGNANCY.

CPG/mk 01/31/14  
T bi; M emb sec, 3 sl

*C. B.*  
**Large cell undifferentiated carcinoma of the lung**



**Kaplan-Meier overall survival and progression-free survival (PFS) curves for the entire population, patients with nonsquamous histology (adenocarcinoma plus large cell), and patients with squamous histology.**



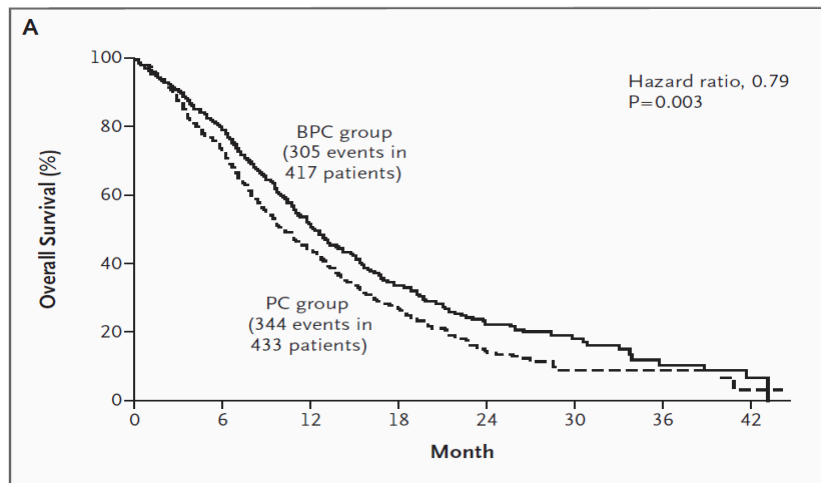
Scagliotti G V et al. JCO 2008;26:3543-3551

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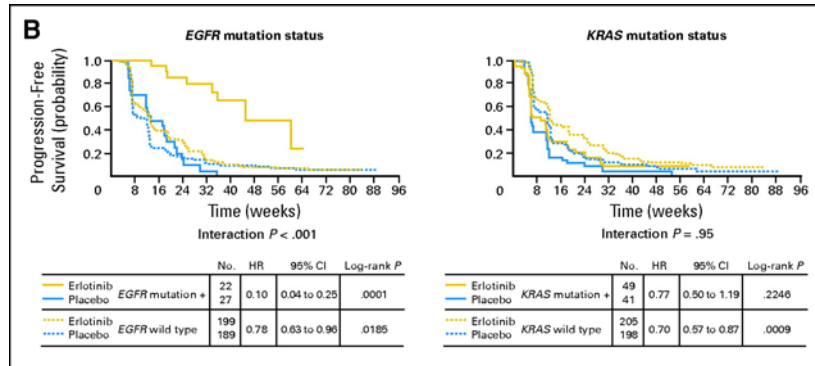


**Paclitaxel–Carboplatin Alone or with Bevacizumab for Non–Small-Cell Lung Cancer**

Alan Sandler, M.D., Robert Gray, Ph.D., Michael C. Perry, M.D., Julie Brahmer, M.D.,



(A) Kaplan-Meier estimates of progression-free survival according to biomarker status and treatment arm.



Brugger W et al. JCO 2011;29:4113-4120

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JOURNAL OF CLINICAL ONCOLOGY ASCO

Cumulative five-year disease-specific survival rates for GISTs classified as risk level I through

Risk Level	Tumor Size	Mitotic rate	DFS at 5 years
I	≤ 5 cm	<5/50HPF	100 %
II	<5 cm 5-10 cm	6-10/50 HPF <5/50 HPF	96%
III	<5 cm 5-10cm >10 cm	>10 / 50 HPF 6-10/50 HPF <5/50 HPF	67%
IV	>5cm	>10/ 50 HPF	25%

## Lymph nodes in resected specimen

(B) COLON, DISTAL MARGIN, EXCISION:

1. INVASIVE ADENOCARCINOMA (1.4 CM) MODERATELY DIFFERENTIATED.
2. INVASION TO LEVEL OF SUBMUCOSA (T1).
3. LYMPHOVASCULAR AND PERINEURAL INVASION NOT DEFINITELY IDENTIFIED.
4. SIX LYMPH NODES NEGATIVE FOR CARCINOMA (0/6)
5. RESECTION MARGINS NEGATIVE FOR CARCINOMA.
6. PATHOLOGIC STAGE: pT1 N0.

- As per NCCN minimal number of lymph nodes reported in the path specimen should be 12 , otherwise further analysis of specimen should be performed

Histopathology

Histopathology 2012, 61, 511-542. DOI: 10.1111/j.1365-2598.2012.04357.x

REVIEW

Techniques to increase lymph node harvest from gastrointestinal cancer specimens: a systematic review and meta-analysis

## Microsatellite instability

- High levels of DNA microsatellite instability (MSI-H), defined as instability in  $\geq 30$  percent of microsatellite loci. (Thibodeau, Bren et al. 1993)
- Clinical relevance in making treatment decisions
- Better prognosis
- Adjuvant 5-FU-based chemotherapy is less beneficial

Ribic, C. M., et al. (2003). "Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer." *N Engl J Med* **349**(3): 247-257.

Four legged animal with no hooved feet and an odd number of toes on each foot, as well as mobile upper lips and a similar tooth structure and can carry humans for pleasure



Thank you