

**INTERNATIONAL
GENITOURINARY
ONCOLOGY
CONGRESS**



**A.C. Camargo
Cancer Center**

Clinical Biomarker in Kidney Cancer

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Disclosures

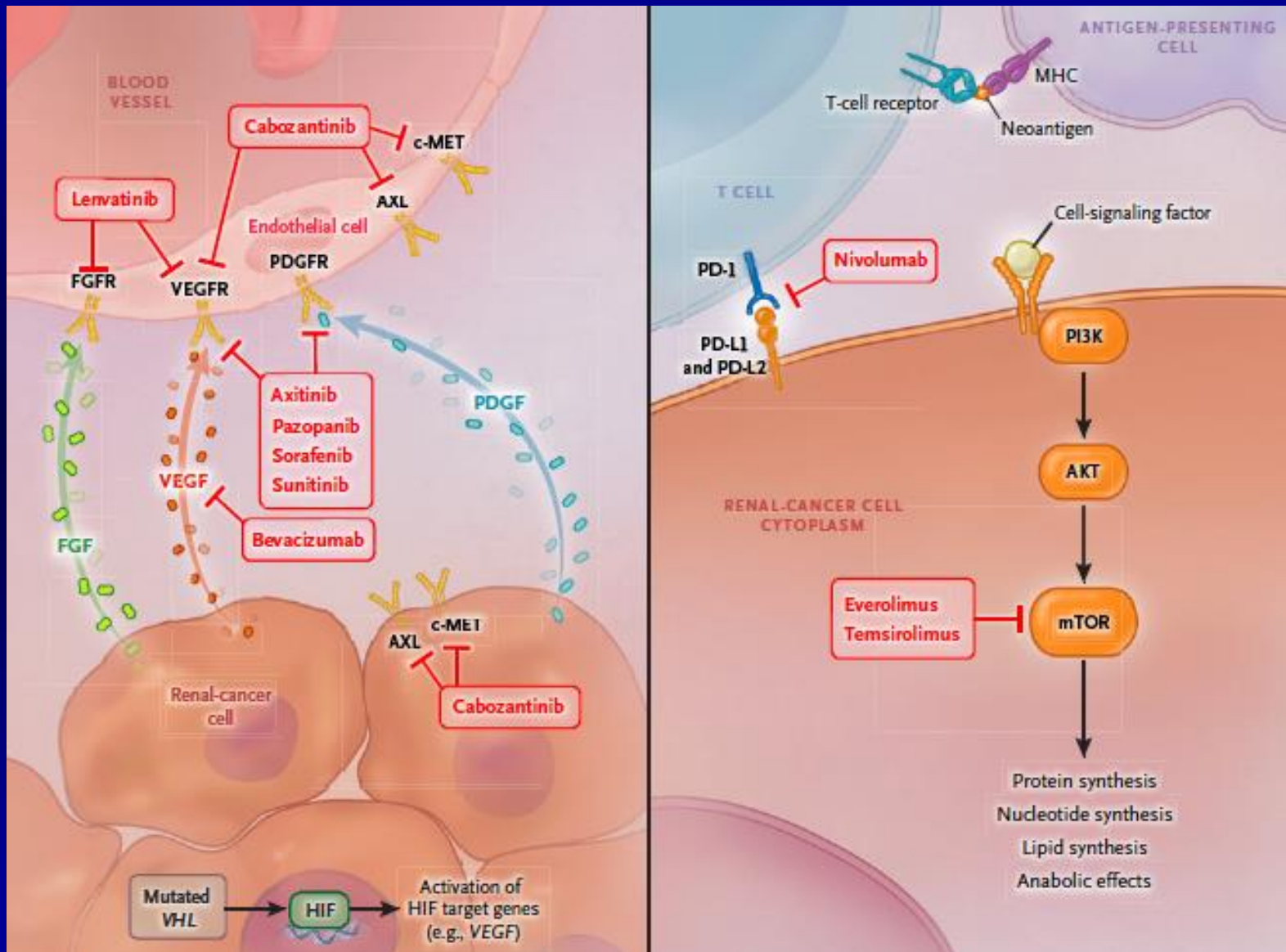
**I am on the Speaker's Bureau with Pfizer
and Bayer**

Clinical trials of BMS and Pfizer

Kidney Cancer

- 70% new cases in developed countries
- US: 63,000 new cases/year and 14,000 deaths in 2017
- Clear cell renal carcinoma (70%) , papillary (10–15%), chromophobe (5%), collecting duct (< 1%)

Metastatic Renal Cell Carcinoma (mRCC)



Metastatic Renal Cell Carcinoma (mRCC)

- Treatment selection is based on clinical data (IMDC prognostic model), patient comorbidities and toxicity profiles
- Length of response and benefit of survival varies between the patients
- Biomarkers : identify patients most likely to respond to treatment

Biomarkers

Biological

Protein expression

on tumour cell membrane or secretion of tumour markers in serum, e.g. Cytokine and angiogenic factors, PDL1 expression

Genetic

Changes in DNA or mRNA

of the *tumour* (dynamic) or *patient* (static)
e.g. Single nucleotide polymorphisms in angiogenesis genes

Epigenetic

Changes in chromosome structure

that lead to altered gene expression, e.g. DNA methylation and histone modification¹⁶

Clinical

Changes in clinical features

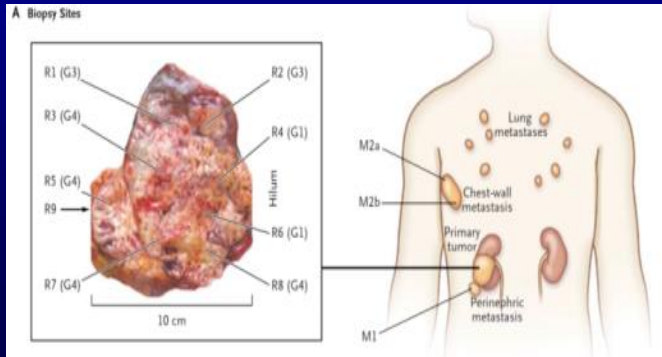
associated with a switch in tumour response, e.g. Hypertension

Personalized Medicine

- **Breast cancer:** HER2+ patients (trastuzumab, Pertuzumab, TDM1, lapatinib, neratinib)
- **Metastatic melanoma:** BRAF_{V600E} (BRAF-inhibitors)
- **NSCLC:** EGFR + (gefitinib, erlotinib, afatinib, osimertinib)
EGFR T790M
ALK+ (crizotinib)
- **Colon cancer:** wild wt (cetuximab, panitumumab)
- **MMR-deficient tumors:** anti-PDL1
- **BRCA mutated :** PARP-inhibitors

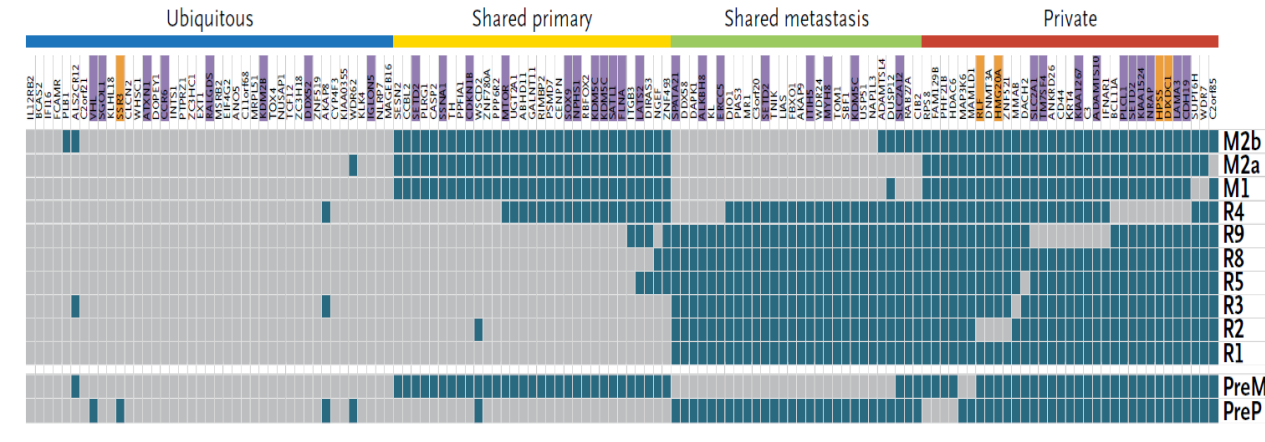
Renal Cell Carcinoma ?

Intratumor Heterogeneity



Challenge in biomarker development

B Regional Distribution of Mutations

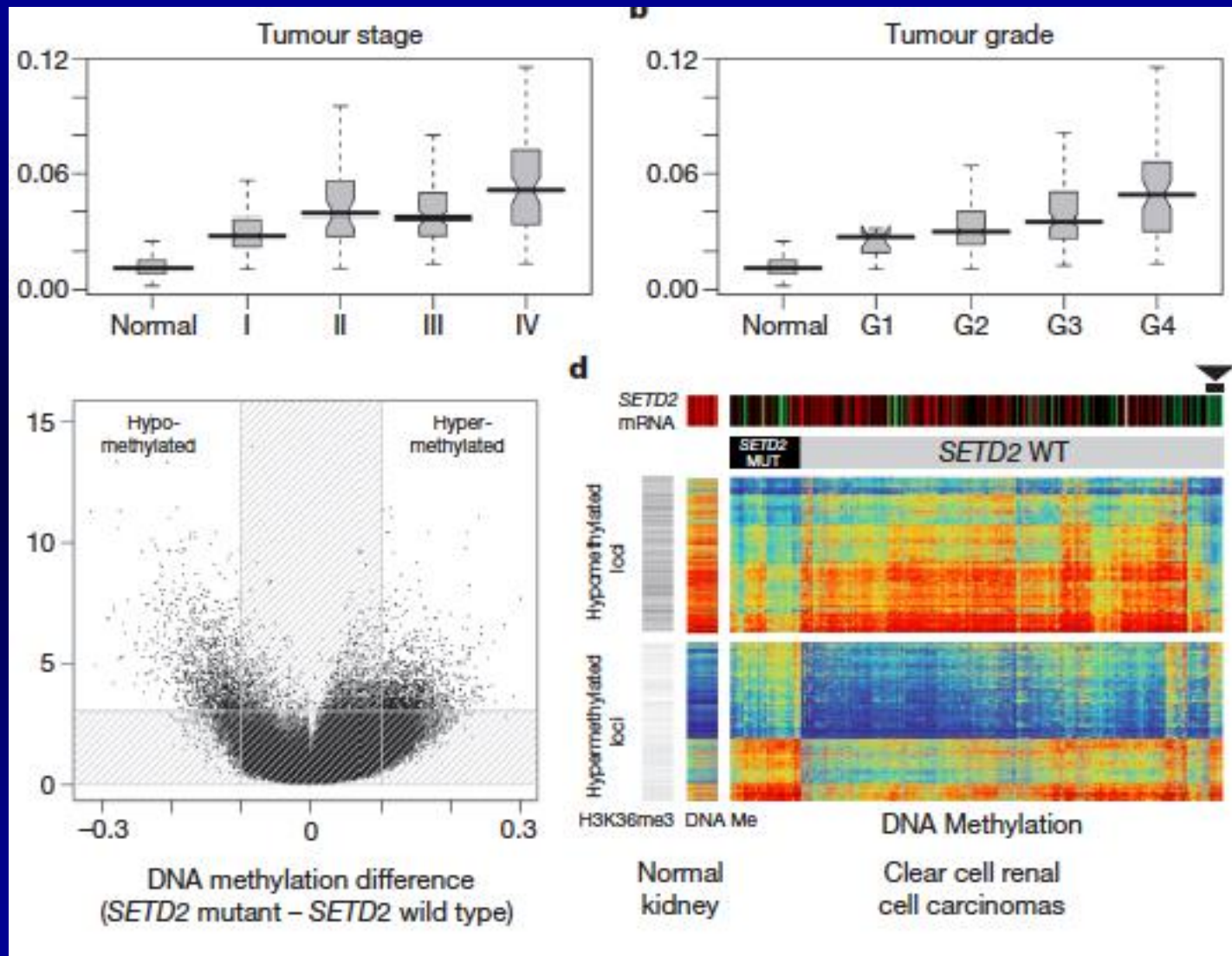


65% of mutations are heterogeneous and were not present in every biopsy

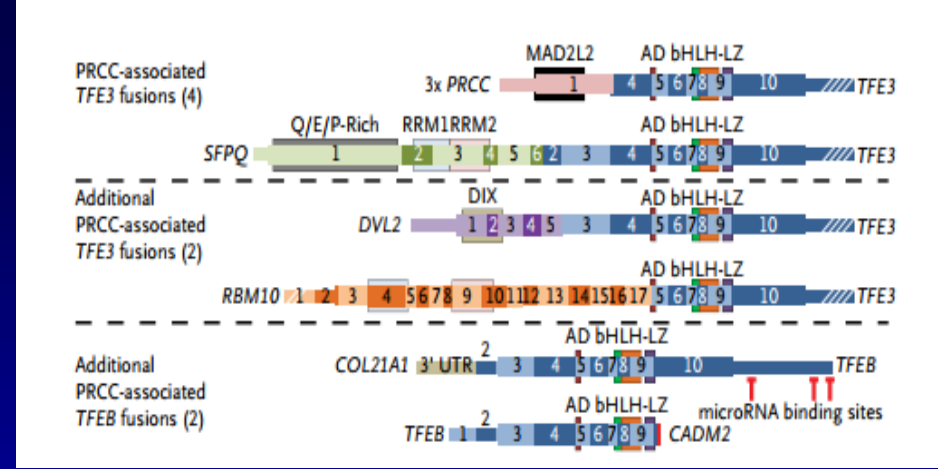
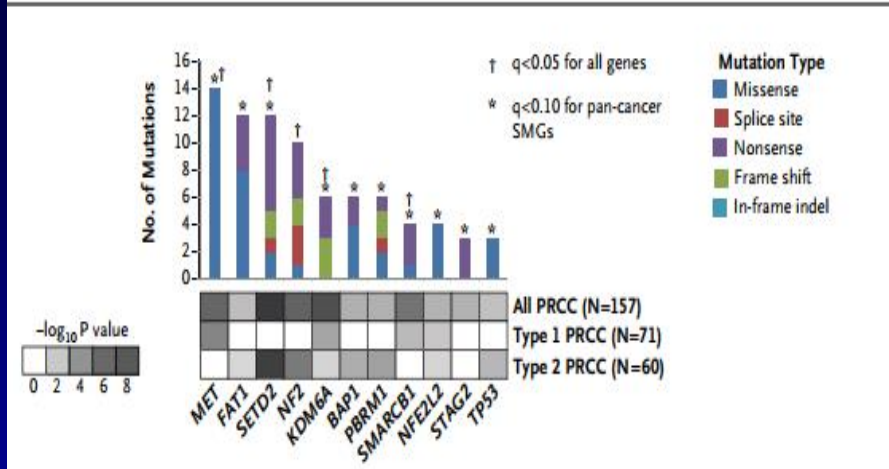
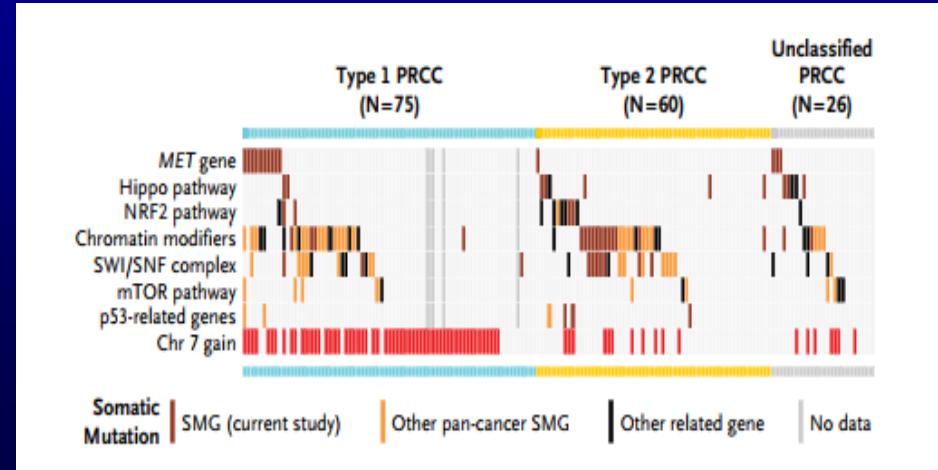
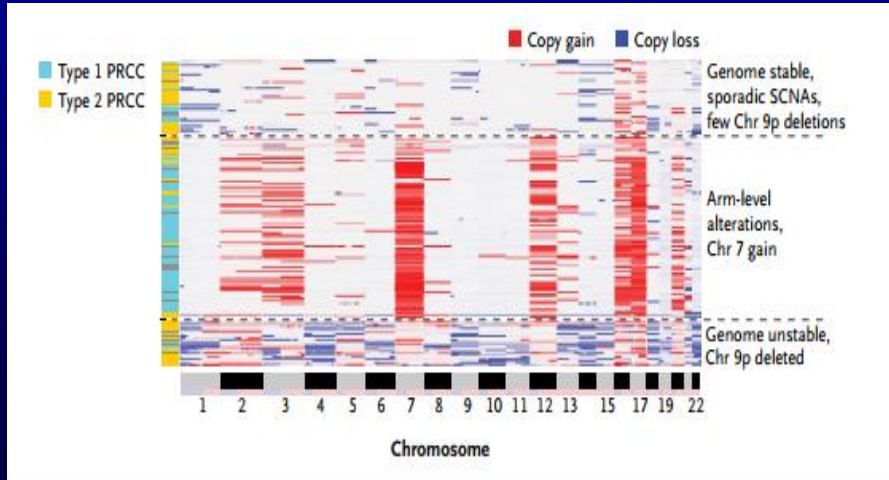
Biomarkers in mRCC

- Predict clinical outcomes and help clinical management decisions
- Potential candidates for novel prognostic and predictive biomarkers :
 - circulating biomarkers , microRNA profiles, protein expression, PDL1 expression tumor, gene expression profiling, T-cell receptor sequencing

Clear Cell Renal Carcinoma



Papillary Renal-Cell Carcinoma



Prognostic Biomarkers

- Chromatin remodeling genes are the most frequently mutated genes in RCC after VHL (PBRM1 ~33%, SETD2 12%, BAP1 ~10%, KDM5C ~7%)
- *PBRM1*, *SETD2*, *BAP1* and *KDM5C* are associated with tumors of advanced stage and *BAP1* with higher grade tumors ¹
- Mutations in *BAP1* and/or *SETD2* : shorter survival ²

Biological Biomarkers

- 292 pts treated with sunitinib- EFFECT trial
- Lower baseline Ang-2 ($p=0.019$), higher MMP-2 ($p=0.0327$) and lower HIF α tumor expression ($p=0.0341$) were related to better outcomes ¹
- No significance for VEGF-A and VEGFR3 SNPs ¹
- Based on ROC analysis neither has sensitivity and specificity for clinical patient selection pre-treatment ²

1. Motzer RJ et al. *Cancer Chemother Pharmacol.*;74(4):739-50

2. English PA et al. *Future Oncol.* 2016 ;12(2):175-82

Biomarker-Based Phase II Trial of Savolitinib in Patients With Advanced Papillary Renal Cell Cancer

Toni K. Choueiri, Elizabeth Plimack, Hendrik-Tobias Arkenau, Eric Jonasch, Daniel Y.C. Heng, Thomas Powles, Melanie M. Frigault, Edwin A. Clark, Amir A. Handzel, Humphrey Gardner, Shethah Morgan, Laurence Albiges, and Sumanta Kumar Pal

- 119 papillary RCC Savolitinib (MET TK)
- MET -MET driven : chromosome 7 copy gain, focal MET or HGF gene amplification, or MET kinase domain mutation
- MET status - predictive of response to Savolitinib

PD-L1 expression as biomarker

- Pretreatment with nivolumab - higher levels of tumor PD-L1 expression → reduced rate of survival¹
- Pretreatment with VEGF-targeted agents : PD-L1 expression related to outcomes²
- High level of PD-L1 and IMDC score: select patients for immune checkpoints inhibitors in 1st line? ³

1. MotzerRJ et al. N Engl J Med 2015;373:1803-13

2. Choueiri TK et al. Clin Cancer Res 2015;21:1071-7

3. Escudier B et al. ESMO 2017 .Abstract LBA5.

Clinical Biomarkers

- Hypertension ^{1,2,3}
- Hypothyroidism
- Hand–foot syndrome ³
- IMDC score ⁴
- Neutrophil/Lymphocyte ratio (NLR) ⁵

1. Rini, BI et al. *J Natl Cancer Inst* 2011;103:763-773

2. Donskov F et al. *J Cancer* 2015;113(11):1571-80

3. Rautiola J et al. *BJU Int.* 2016 ;117(1):110-7

4. Heng D et al..*J Clin Oncol.* 2009;27: 5794-5799

5. Templeton AJ et al. *Eur Urol* 2016;70:358–364

Clinical Biomarkers

- Neutropenia and hypertension → longer PFS and OS
- Hand-foot syndrome → longer OS
- On-treatment biomarkers → independent of baseline prognostic factors, including IMDC criteria

Hypertension (HTN)

- Retrospective analysis of 544 mRCC pts
- Sunitinib-induced HTN : higher ORR and longer PFS and OS

Rini, BI et al. *J Natl Cancer Inst* 2011;103:763-773

Hypothyroidism

- AC Camargo Cancer Center: 50 pts treated with sunitinib
1st line: 40% hypothyroidism
- Hypothyroidism : higher RR ($p < 0.001$)

Pinto , FAI et al. *J Clin Oncol* 2012 30:5_suppl, 466-466

Neutrophil/Lymphocyte Ratio (NLR)

- Higher NLR at baseline was associated with shorter OS and PFS

Templeton AJ et al. *Eur Urol* 2016;70:358–364

- AC Camargo Cancer Center: 816 pts mRCC treated (2007-2016)
- 116 pts
- $\text{NLR} \leq 4$: longer OS and curative intent metastasectomy

Fares AF et al. *J Clin Oncol* 2017;35:5_suppl.e16051

Conclusion

- Currently there no predictive markers in RCC to aid treatment selection- PD-L1 expression and gene profile
- Many potential biomarkers in RCC have been identified but most do not meet the criteria of high sensitivity and specificity
- Clinical biomarkers including HA, NLR, hypothyroidism help to confirm the benefit but not aid in therapy selection