Inflammation in mRCC: Target or Prognostic Factor?

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SIGNS OF INFLAMMATION

BIOCHEMICAL SIGNS

C-reactive protein

Erythrocyte sedimentation rate

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Erythrocyte sedimentation rate

Indirect signs

- **Trombocytosis**
- **Anemia**
- **Neutrophilia**

CLINICAL SIGNS

- **Fever**
- **Anorexia**
- **Weight loss**

NOT ROUTINELY ASSESSED CYTOKINES

- **IL6**
- **IL8**

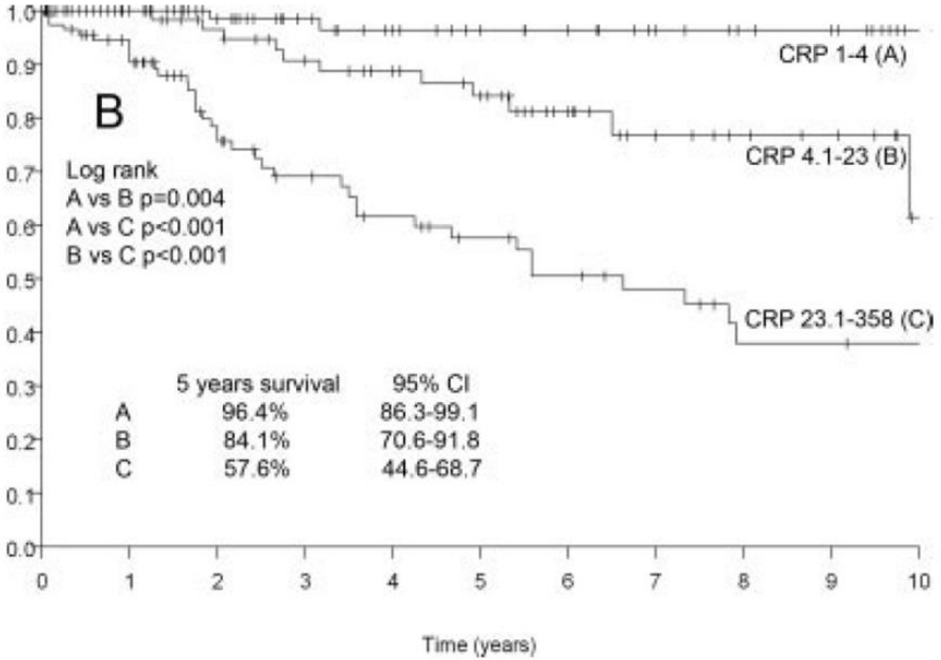
ON PATHOLOGY

- **Tumor infiltration by immunitary cells**

BASELINE **CRP** LEVELS IN THE POST-NEPHRECTOMY SETTING

An elevated CRP predicts poor survival in patients with localized RCC (1)(2)(3).

On 313 patients (CRP in mg/l):
RCC specific mortality



(1) Ito K et al. Impact of thrombocytosis and C-reactive protein elevation on the prognosis for patients with renal cell carcinoma. Int J Urol 2006 (13): 1365–70.
(2) Komai Y et al. Increased preoperative serum C-reactive protein level predicts a poor prognosis in patients with localized renal cell carcinoma. BJU Int. 2007 (99): 77–80.
(3) Karakiewicz PI et al. C-reactive protein is an informative predictor of renal cell carcinoma-specific mortality: a European study of 313 patients. Cancer 2007 (110): 1241–7.

BASELINE **CRP** LEVELS IN THE METASTATIC SETTING (**IMMUNOTHERAPY**)

n	Therapy	CRP	Impact	
425	Cytokines	≥ 11 mg/l	Worse OS	(1)
110	IL-2	> 8 mg/l	Most independent prognostic factor	(2)
181	Nephrectomy and medical treatment or medical treatment only, in most cases immunotherapy	> 67 mg/l	Remarkably poor prognosis despite treatment => QUID role of serum CRP in the decision whether to perform nephrectomy at the onset?	(3)

(1) Yasuda Y et al. Prognostic impact of pretreatment C-reactive protein for patients with metastatic renal cell carcinoma treated with tyrosine kinase inhibitors. Int J Clin Oncol. 2012 Aug 11.
(2) Casamassima A et al. C-reactive protein: a biomarker of survival in patients with metastatic renal cell carcinoma treated with subcutaneous interleukin-2 based immunotherapy. J Uro. 2005 (173): 52–5.
(3) Ito H et al. C-reactive protein in patients with advanced metastatic renal cell carcinoma: Usefulness in identifying patients most likely to benefit from initial nephrectomy. BMC Cancer 2012 (12): 337.

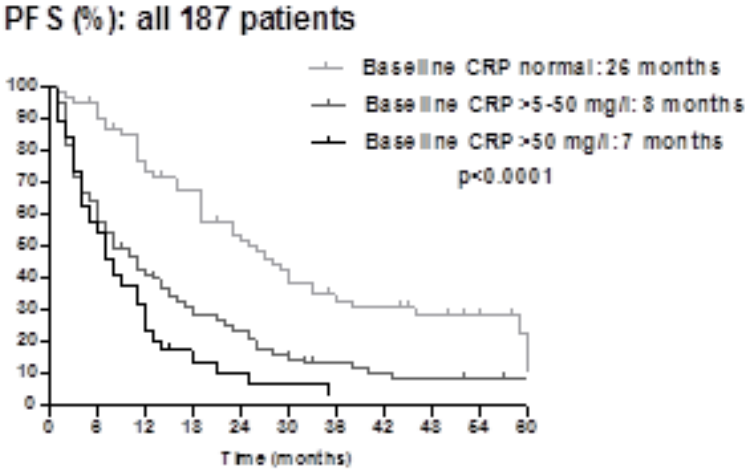
BASELINE **CRP** LEVELS IN THE METASTATIC SETTING (**ANTI-VEGFR-TKIs**)

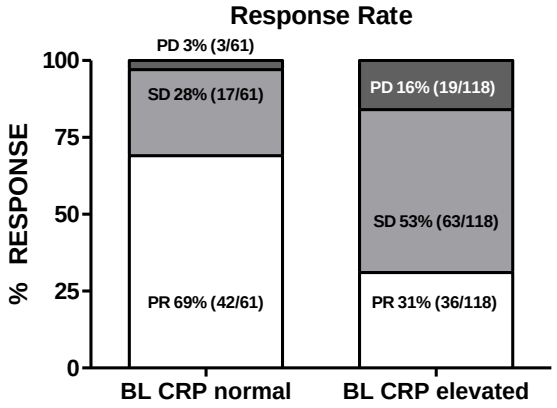
n	Therapy	CRP	Impact	
41	Sunitinib	> 3 mg/l	Shorter PFS (6.0 vs 19.0 months; p=0.036) Independent prognostic marker of OR (p=0.0163)	(1)
45	Sorafenib (after relaps on cytokines)	Elevated	A significantly poorer RR (p=0.031) In patients with normal baseline CRP levels: Hazard ratio for PFS was 2.24 (95%CI 1.01-5.00; p=0.046)	(2)
52	Sunitinib or sorafenib	> 8 mg/l	OS 15.9 months vs not reached (p=0.003)	(3)

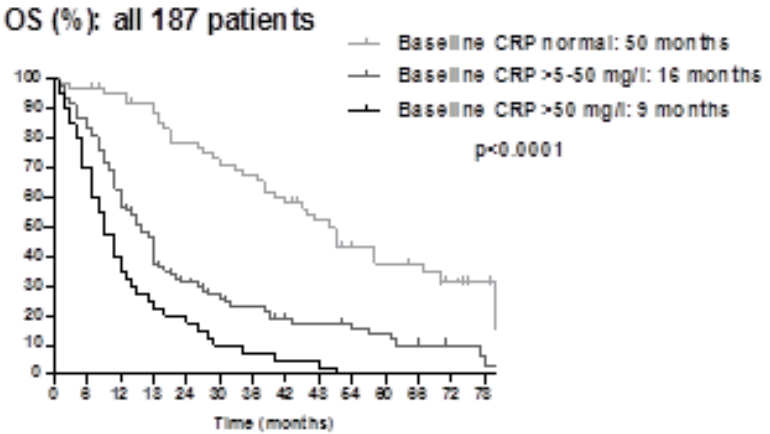
(1) Fujita T et al. C-reactive protein as a prognostic marker for advanced renal cell carcinoma treated with sunitinib. Int J Urol. 2012 Jun 6.
(2) Kusuda Y et al. Prognostic prediction in patients with metastatic renal cell carcinoma treated with sorafenib based on expression levels of potential molecular markers in radical nephrectomy specimens. Urol Oncol. 2011 Mar 9.
(3) Yasuda Y et al. Prognostic impact of pretreatment C-reactive protein for patients with metastatic renal cell carcinoma treated with tyrosine kinase inhibitors. Int J Clin Oncol. 2012 Aug 11.

BASELINE **CRP** LEVELS IN THE METASTATIC SETTING (**ANTI-VEGFR-TKIs**)

In 187 RCC patients treated with **sunitinib**







Beuselinck B et al. Manuscript in preparation

MAIN **PROMOTORS OF INFLAMMATION** IN RCC PRODUCED BY RCC CELLS

IL6

- mRCC: frequently associated with elevated IL6 levels
  - In vitro : some renal tumors can produce IL6.
- Higher IL6-levels
  - In patients with metastases compared to patients with tumors confined to the kidney.
  - Correlate with metastatic progression, poor prognosis, shorter survival post-nephrectomy.
  - Correlate with poor response to IL2 therapy.
  - In poorly differentiated tumors
- IL6 leads to production of CRP in the liver through the gp130 receptor

Ljungberg B et al. Serum interleukin-6 in relation to acute-phase reactants and survival in patients with renal cell carcinoma. Eur J Cancer. 1997 (33): 1794–1798.
Blay JY et al. Serum level of interleukin 6 as a prognosis factor in metastatic renal cell carcinoma. Cancer Res. 1992 (52): 3317-22.
Negrier S et al. Interleukin-6, interleukin-10, and vascular endothelial growth factor in metastatic renal cell carcinoma: prognostic value of interleukin-6--from the Groupe Francais d'Immunotherapie. J Clin Oncol. 2004 (22): 2371–2378.

MAIN **PROMOTORS OF INFLAMMATION** IN RCC PRODUCED BY RCC CELLS

IL8 (Neutrophil chemotactic factor)

1. Pro-inflammatory: induces chemotaxis in target cells (neutrophils and other granulocytes) causing them to migrate toward the site of infection.
2. A potent promoter of angiogenesis.

IL1

Tumor necrosis factor alpha

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Tumor necrosis factor alpha

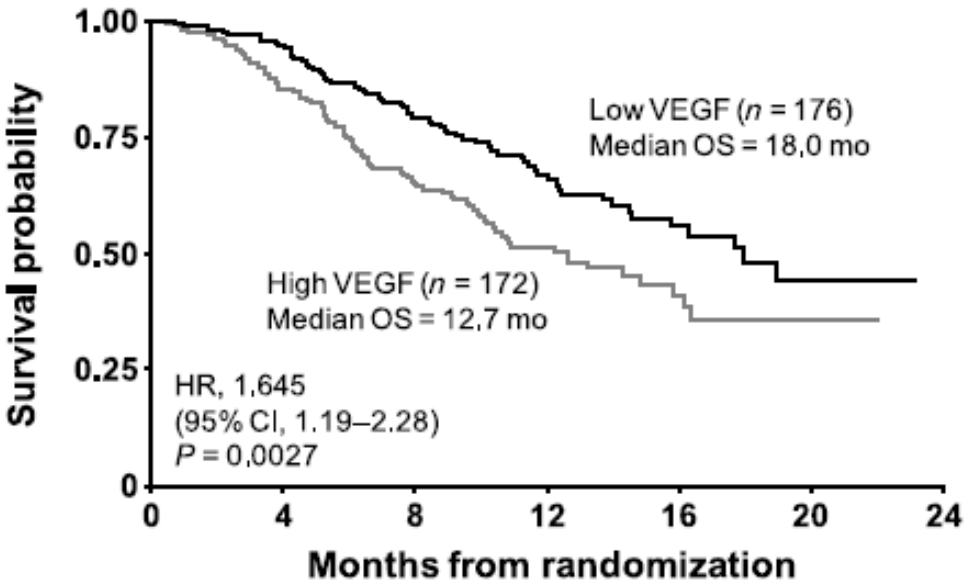
VEGF

- Important overexpression in RCC
- Leading to angiogenesis
- Chemotactic for macrophages and granulocytes and important for vascular permeability

PROGNOSTIC VALUE OF BASELINE **VEGF**-LEVELS IN THE METASTATIC SETTING

In 348 **placebo-treated** patients in the TARGET-trial:

Higher serum baseline VEGF levels linked to poorer OS.



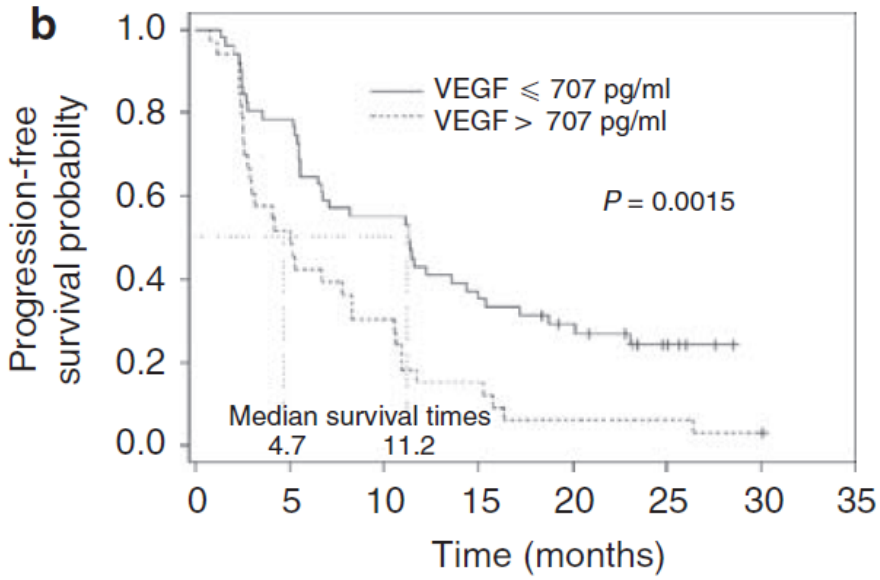
Peña C et al. Biomarkers predicting outcome in patients with advanced renal cell carcinoma: Results from sorafenib phase III Treatment Approaches in Renal Cancer Global Evaluation Trial. Clin Cancer Res. 2010 Oct 1;16(19):4853-63.

PROGNOSTIC VALUE OF BASELINE **VEGF**-LEVELS IN THE METASTATIC SETTING

Increased baseline serum VEGF associated with decreased survival in **sunitinib-treated** patients:

— VEGF-levels >707 pg/ml versus <707 pg/ml: median survival of 4.37 versus 11.2 months

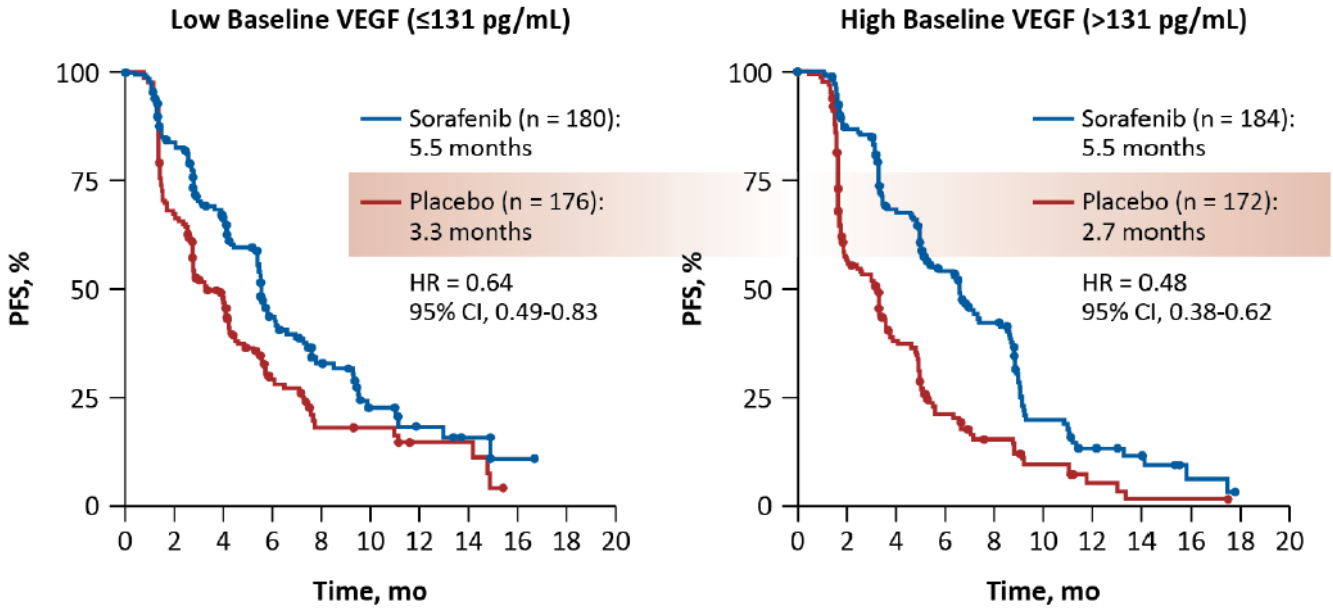
— Patients with higher baseline VEGF levels: higher probability of disease progression



Porta C et al. Predictive value of baseline serum vascular endothelial growth factor and neutrophil gelatinase-associated lipocalin in advanced kidney cancer patients receiving sunitinib. Kidney Int. 2010 May;77(9):809-15.

PROGNOSTIC VALUE OF BASELINE **VEGF**-LEVELS IN THE METASTATIC SETTING

- Placebo group: high baseline serum VEGF patients: shorter PFS than patients with low baseline VEGF.
- Reflecting an aggressive tumor.
- Thus indicating that high baseline VEGF-levels have a negative prognostic value.



Escudier B et al. Sorafenib for treatment of renal cell carcinoma: Final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. J Clin Oncol 2009; 27:3312.

PROGNOSTIC VALUE OF BASELINE **VEGF**-LEVELS IN THE METASTATIC SETTING

In **pazopanib** pivotal trial (versus **placebo**):

Higher serum VEGF levels: negative prognostic markers for OS in both treatment groups:

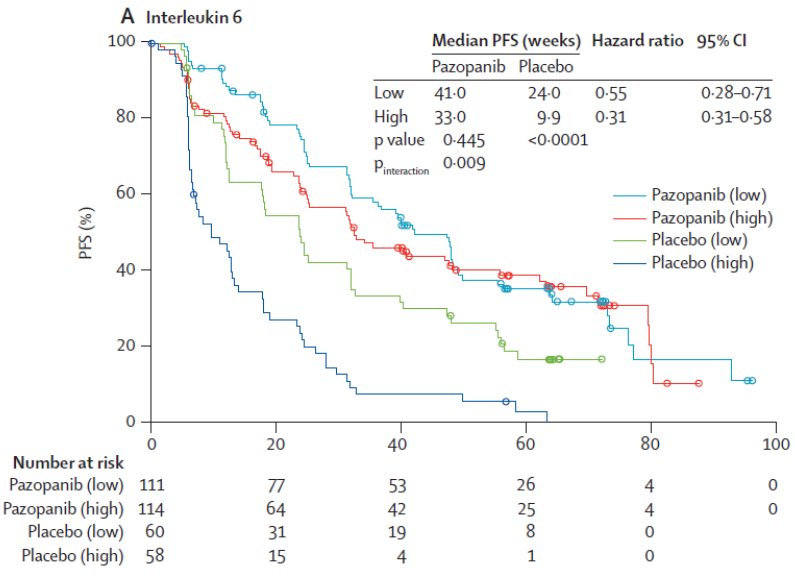
- In **pazopanib** treated patients: High VEGF-levels: 20.0 versus 25.5 months (p=0.04)
- In **placebo** treated patients: High VEGF-levels: 6.1 versus 23.5 months (p=0.001)

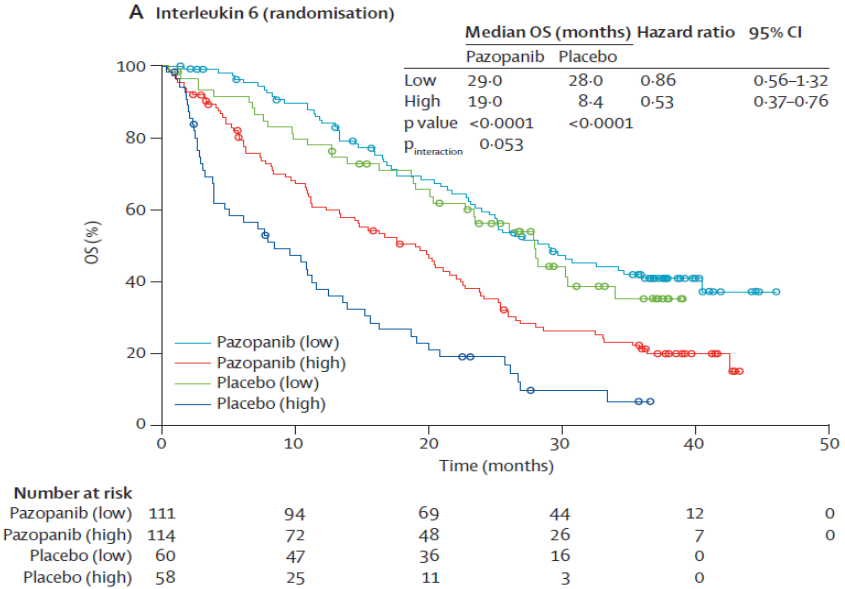
Tran HT et al. Prognostic or predictive plasma cytokines and angiogenic factors for patients treated with pazopanib for metastatic renal-cell cancer: a retrospective analysis of phase 2 and phase 3 trials. Lancet Oncol. 2012 Aug;13(8):827-37.

PROGNOSTIC VALUE OF BASELINE **IL6**-LEVELS IN THE METASTATIC SETTING

In the **pazopanib** pivotal trial: higher baseline IL6 levels: a negative prognostic markers for PFS and OS:

- In 118 placebo-treated patients: PFS 9.9 versus 24.0 weeks (p<0.0001).
- In 118 placebo-treated patients: OS 8.4 versus 28.0 months (p<0.0001).
- In 225 pazopanib-treated patients: OS 19.0 versus 29.0 months (p<0.0001).





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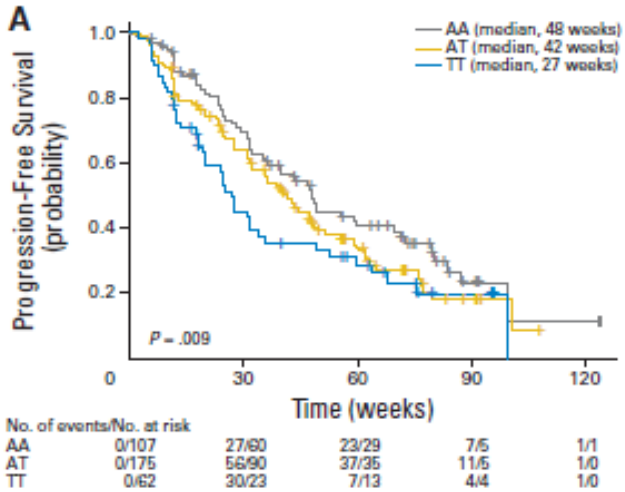
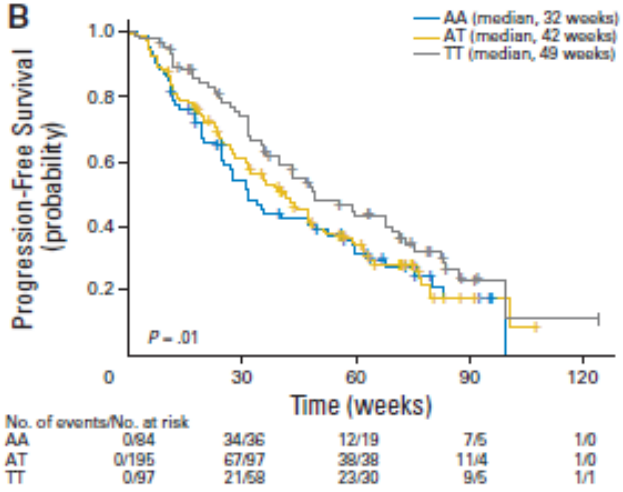
PROGNOSTIC VALUE OF BASELINE **IL8**-LEVELS IN THE METASTATIC SETTING

Polymorphisms in IL8 linked with higher IL8 expression => more alternative non-VEGF-dependent angiogenesis



PFS curves for IL8 2767A>T rs1126647
T-allele is linked to increased IL8 levels



PFS curves for IL8 -251T>A rs4073
A-allele is linked to increased IL8 levels

Xu Chun-Fang et al. Pazopanib Efficacy in Renal Cell Carcinoma: Evidence for Predictive Genetic Markers in Angiogenesis-Related and Exposure-Related Genes. J Clin Oncol 2011.

PROGNOSTIC VALUE OF BASELINE **IL8**-LEVELS IN THE METASTATIC SETTING

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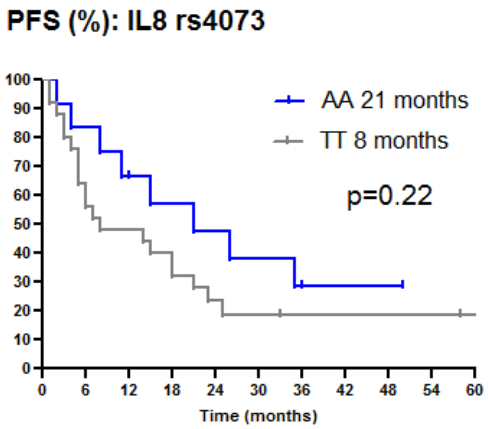

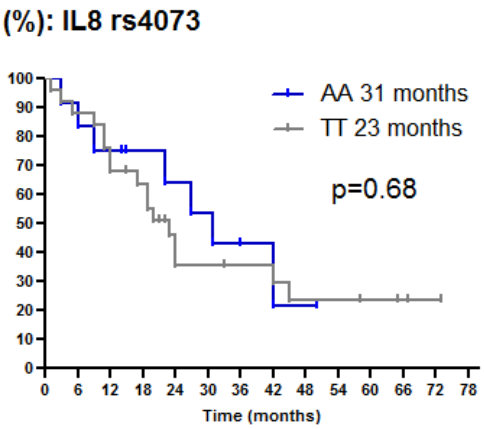

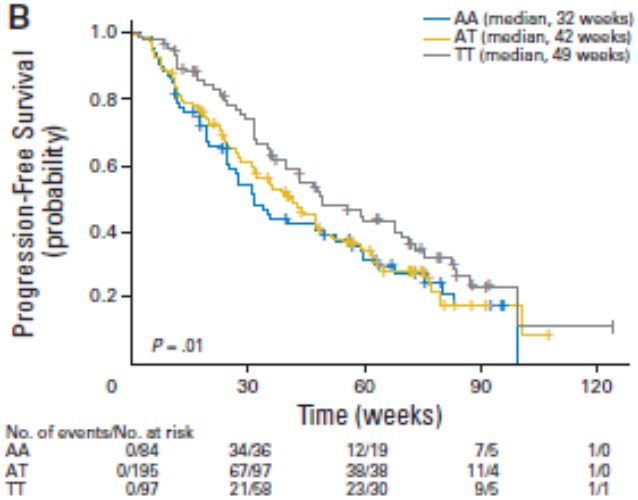

Beuselinck B et al. Single nucleotide polymorphisms associated with outcome in metastatic renal cell carcinoma treated with sunitinib. Br J Cancer. 2013 Mar 5;108(4):887-900.

WHY IS INFLAMMATION ASSOCIATED WITH POOR OUTCOME?

1. INFLAMMATION: a **consequence** of a more extended and more aggressive disease?

- Tumor cells secreting pro-inflammatory cytokines?
- Tumor causing an inflammatory reaction in the tumor micro-environment?

2. INFLAMMATION: a **driver** of the disease?

- Stimulating tumor growth?
- Promoting invasion (destruction of basal membrane)?
- Infiltrating immune cells promote carcinoma progression into metastatic disease
- Can induce EMT, which provides tumors with invasive, migratory and stem cell properties

3. INFLAMMATION: an inflammatory state leading to decreased treatment tolerance?

… ASSOCIATED WITH GOOD OUTCOME?

4. INFLAMMATION: a sign of an immune reaction against the tumor?

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TO TARGET!

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3. INFLAMMATION: an inflammatory state leading to decreased treatment tolerance?

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NOT TO TARGET!

4. INFLAMMATION: a sign of an immune reaction against the tumor?

TARGETING INFLAMMATION | BY TARGETING TNF | INFLIXIMAB = ANTI-TNF-MAB

2 sequential phase II studies of infliximab in immunotherapy-resistant or refractory RCC (1)

- Study 1: 16% (3/19) PR. Median duration of response 7.7 months
- Study 2: 61% (11/18) SD. Median duration of response 6.2 months
- Higher TNF-alpha levels => poor survival

Phase I/II trial of sorafenib and infliximab in advanced RCC (2)

- mPFS 6 months
- mOS 14 months
- The combination of sorafenib and infliximab does not warrant further evaluation in advanced RCC

(1) Harrison ML et al. Tumor necrosis factor alpha as a new target for renal cell carcinoma: two sequential phase II trials of infliximab at standard high dose. J Clin Oncol. 2007 (29) 4542-9.
(2) Larkin J et al. A phase I/II trial of sorafenib and inflixi;ab in advanced renal cell carcinoma. BJC 2010 (8): 1149-53.

TARGETING INFLAMMATION

BY TARGETING IL6

Siltuximab (CNTO 328)

- Chimeric murine-human monoclonal antibody that binds with high affinity and specificity to IL6
- Preclinical experience has shown that siltuximab inhibits the growth of human RCC tumors in nude mice

PHASE I/II STUDY

- Siltuximab continuous dosing in 68 mRCC patients
- Dosis ranging 1 mg/kg to 6 mg/kg

Rossi JF et al. A phase I/II study of siltuximab (CNTO 328), an anti-interleukin-6 monoclonal antibody, in metastatic renal cell cancer. Br J Cancer. 2010 Oct 12;103(8):1154-62.

TARGETING INFLAMMATION

BY TARGETING IL6

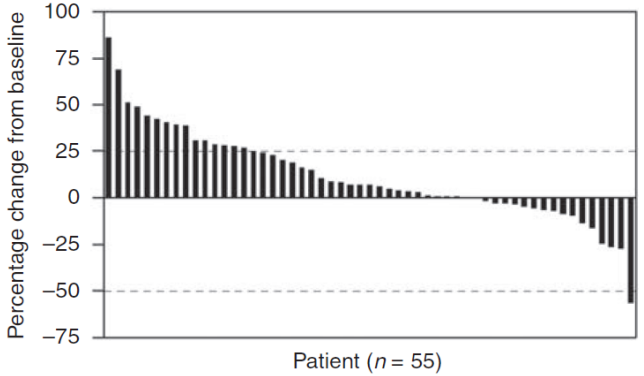
PHASE I/II STUDY Siltuximab (CNTO 328)

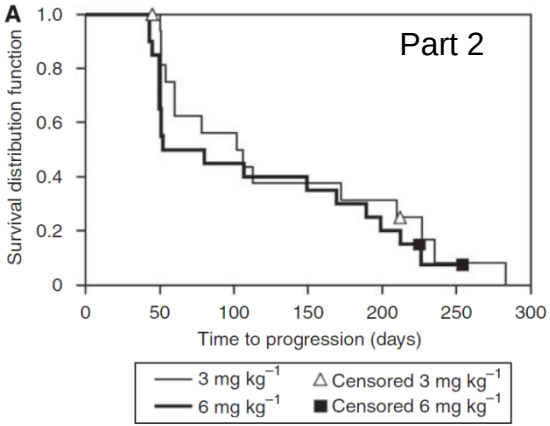
	PR	SD	PD	mTTP
Part 1	0/11	5/11	6/11	
Part 2	1/38	20/38	17/38	102 days
Part 3	0/20	13/20	7/20	80 days
TOTAL	1/69	38/69	30/69	

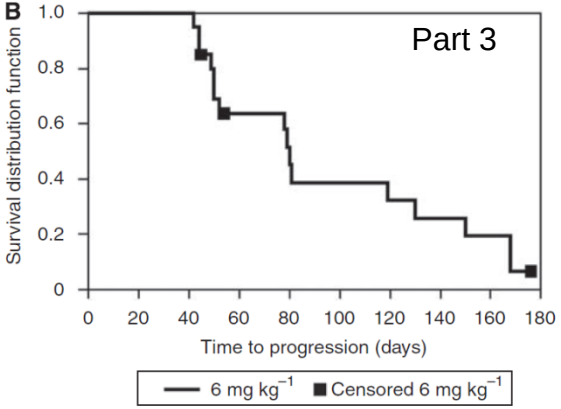
— The PR patient had neck and pancreatic metastases that had progressed despite HD IL2, IFN-alpha and 5-FU.

— He was progressive on day 283.

— CRP levels decreased from baseline 36 mg/l to below 10 mg/l and remained suppressed throughout the therapy.







Rossi JF et al. A phase I/II study of siltuximab (CNTO 328), an anti-interleukin-6 monoclonal antibody, in metastatic renal cell cancer. Br J Cancer. 2010 Oct 12;103(8):1154-62.

TARGETING INFLAMMATION

BY TARGETING IL8

COLON CARCINOMA

- Colon carcinoma cells rendered deficient in HIF transcription factors
- IL8: dominant role in the generation and maintenance of the tumour microcirculation
- Tumour angiogenesis blocked with a neutralising anti-IL8 antibody (1)

RENAL CELL CARCINOMA

- IL8-mediated angiogenesis: a key compensatory mechanism of resistance to sunitinib in murine models
- IL8 expression has been observed to be elevated in RCC tumors from patients refractory to sunitinib treatment
- Anti-IL8 antibody did not affect tumor growth in xenograft-bearing animals not yet exposed to a VEGF TKI, but after development of resistance to sunitinib, the combination of sunitinib and an anti-IL8 antibody effectively reduced tumor growth (2).

(1) Mizukami Y et al., Induction of interleukin-8 preserves the angiogenic response in HIF-1alpha-deficient colon cancer cells, Nat Med 11 (2005), pp. 992–997.
(2) Huang D et al. Interleukin-8 mediates resistance to antiangiogenic agent sunitinib in renal cell carcinoma. Cancer Res 70:1063-1071, 2010

TARGETING INFLAMMATION | BY TARGETING PGE2

CYCLOXYGENASE-2 (COX-2):

- Involved in prostaglandin E2 synthesis
- Associated with higher renal cell carcinoma stage
- COX-2 inhibition enhances IFN-α anti-tumor immune effects in pre-clinical models

PHASE II TRIAL: CELECOXIB AND IFN-A IN MRCC PATIENTS WITH MAXIMAL COX-2 EXPRESSION

- 17 cytokine-naive mRCC patients with tumors expressing ≥10% maximal COX-2 staining by IHC
- IFN-α 5 million units daily and celecoxib 400 mg orally twice daily

RESULTS

- 3 PR : objective response rate 18%
- TTP 5.6 months

=> Celecoxib plus IFN-α in RCC patients with maximally staining COX-2 tumors does not significantly enhance overall RR over IFN monotherapy.

Schwandt A et al. Clinical and immunomodulatory effects of celecoxib plus interferon-alpha in metastatic renal cell carcinoma patients with COX-2 tumor immunostaining. J Clin Immunol. 2011 Aug;31(4):690-8.

TARGETING INFLAMMATION

BY TARGETING VEGF

In 83 patients with clear cell mRCC treated with **sorafenib** (after cytokines)

Serum ESR tested before treatment and Q4W after first administration of sorafenib.

— Baseline ESR levels ranged from 3 to 154 mm/h

— 43 (41.0%) patients had an ESR level higher than 40 mm/h.

— Median PFS was 10.0 months (95% CI 7.6-12.4 months).

	mPFS
Decreased ESR	27 months
Stable ESR	12 months
Increased ESR	6 months

Independent predictors for PFS in multivariable Cox regression model analysis:

— Performance status

— Time from diagnoses to sorafenib treatment

— Number of metastatic organs

— ESR kinetics

ESR kinetics can be useful to monitor the treatment response and to predict PFS for mRCC patients treated with sorafenib as second-line therapy.

Zhang HL et al. Erythrocyte sedimentation rate kinetics as a marker of treatment response and predictor of prognosis in Chinese metastatic renal cell carcinoma patients treated with sorafenib. Int J Urol 2011 Jun;18(6):422-30.

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The most efficient anti-inflammatory therapy is most probably anti-VEGF-therapy!
Targeting an “UPSTREAM”-target, not a collateral event

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=> RATHER A PROGNOSTIC FACTOR

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