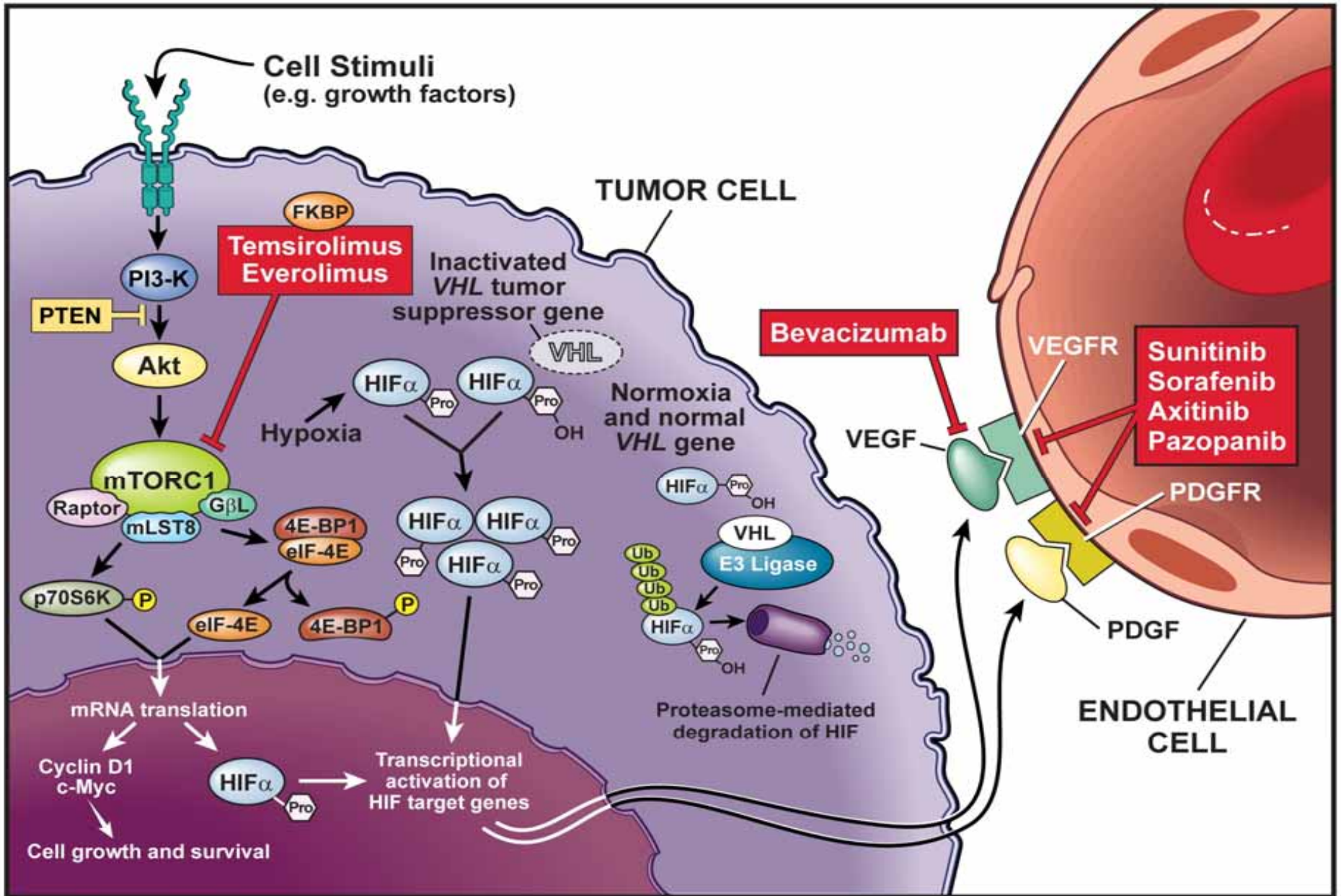


Sunitinib Immunomodulation in Metastatic RCC Patients

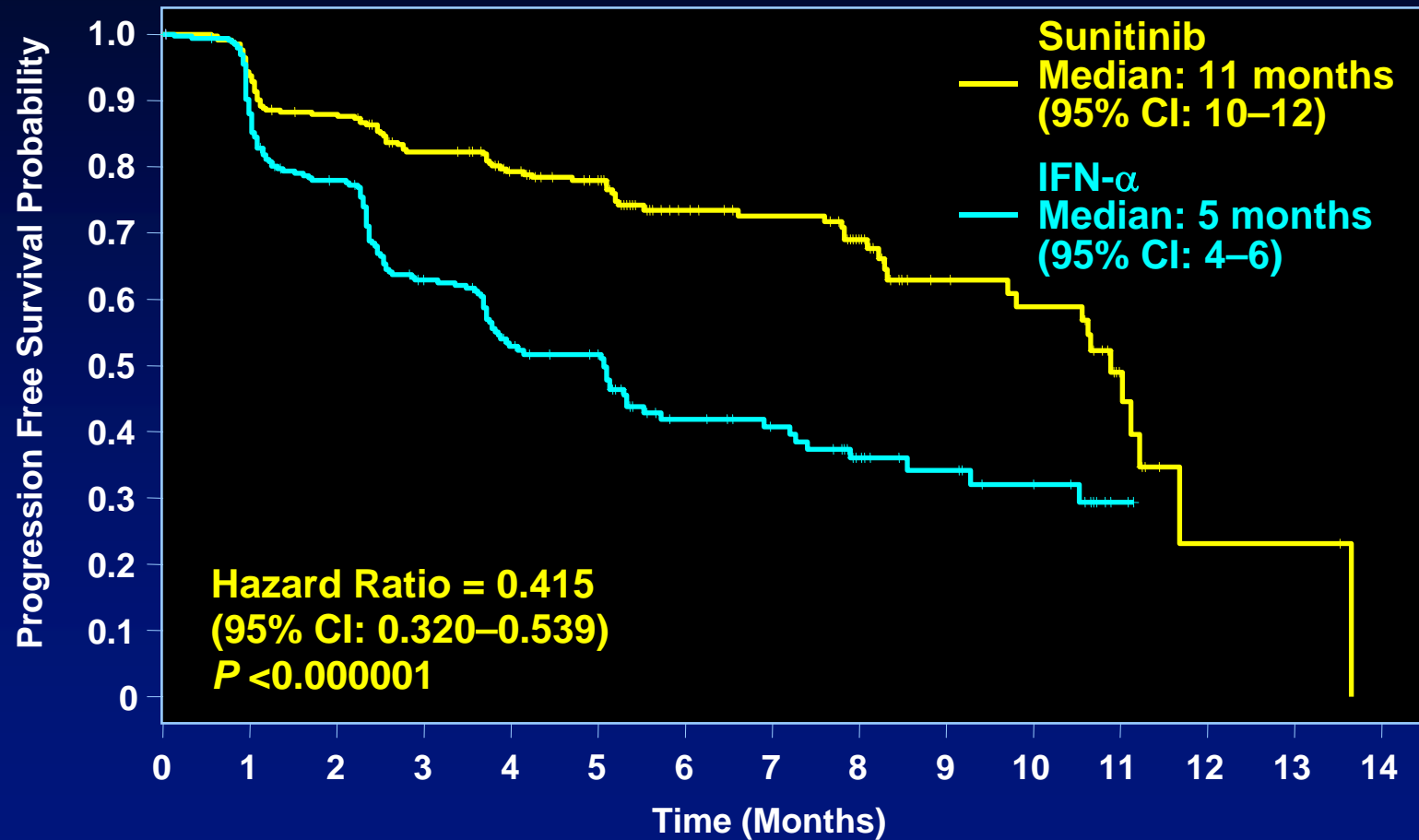
Brian I. Rini, M.D.

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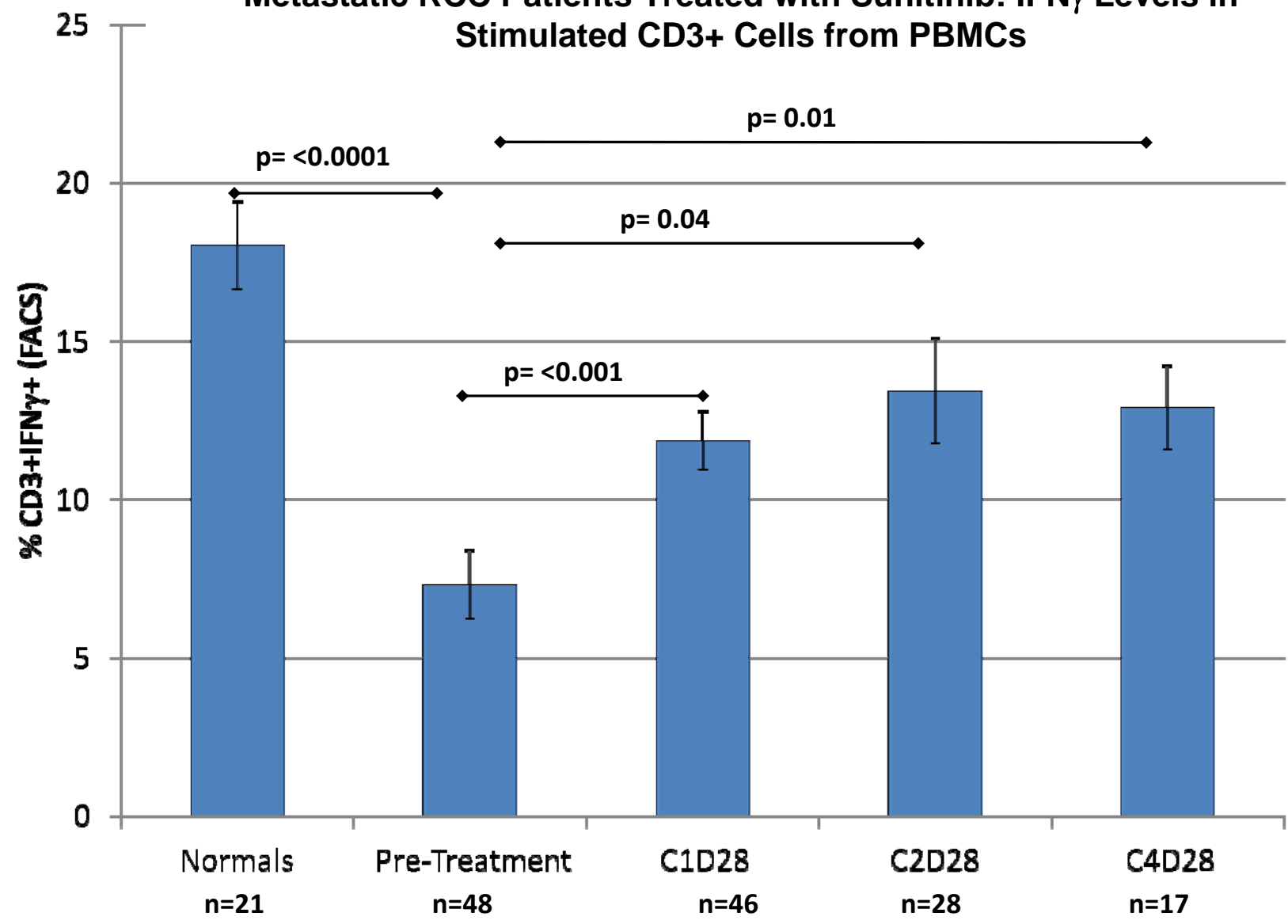




Sunitinib Progression-Free Survival

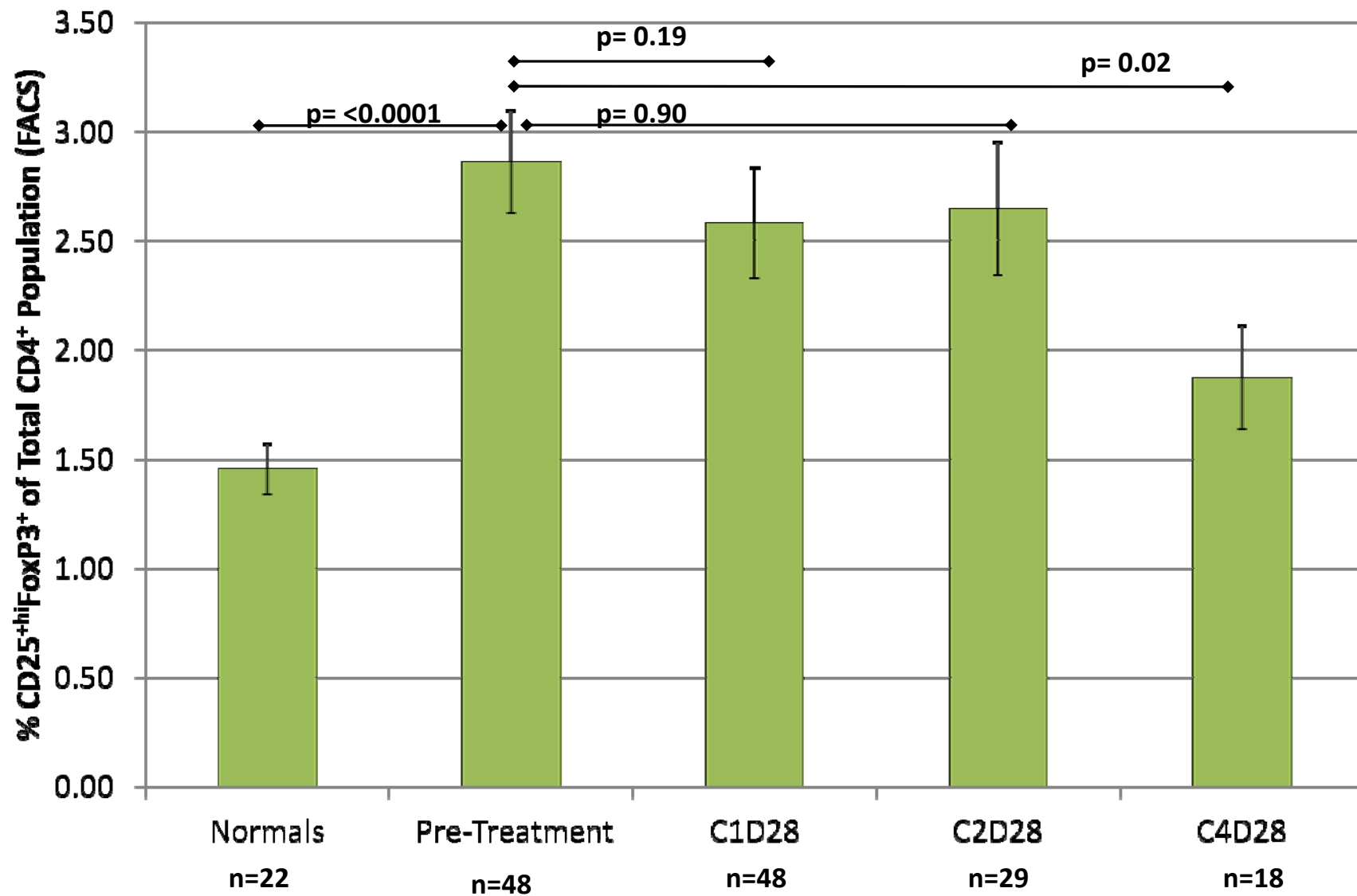


Metastatic RCC Patients Treated with Sunitinib: IFN γ Levels in Stimulated CD3+ Cells from PBMCs



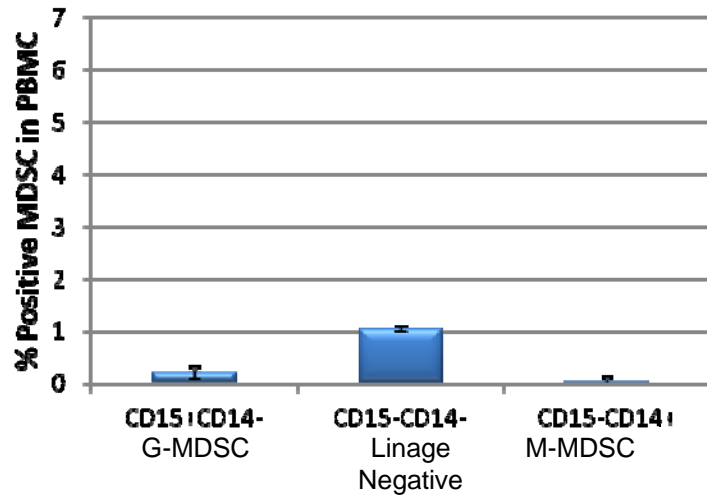
Sunitinib reverses type-1 immune suppression and decreases T-regulatory cells in renal cell carcinoma patients. Finke JH, Rini B, Ireland J, et al. Clin Cancer Res. 2008

Treg Levels in RCC Patients

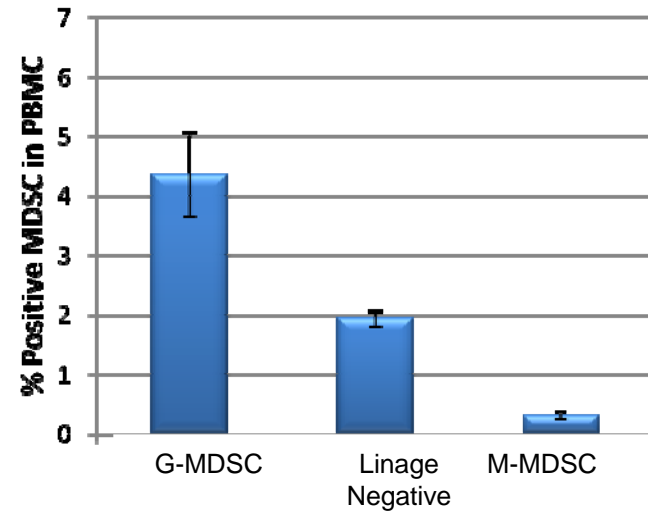


MDSC Subsets in RCC Patient Tumor and Peripheral Blood

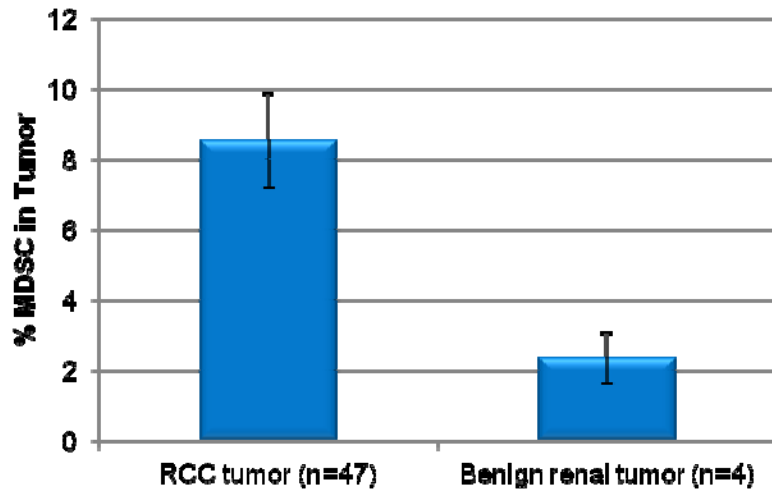
PBMC from Normals (n=20)



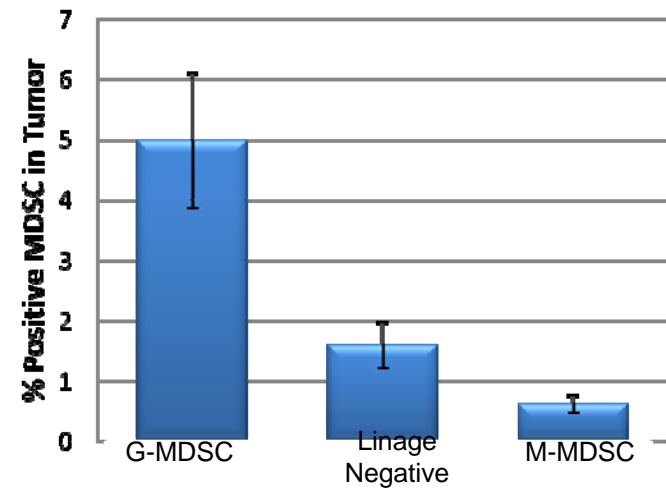
PBMC from RCC Patients (n=74)



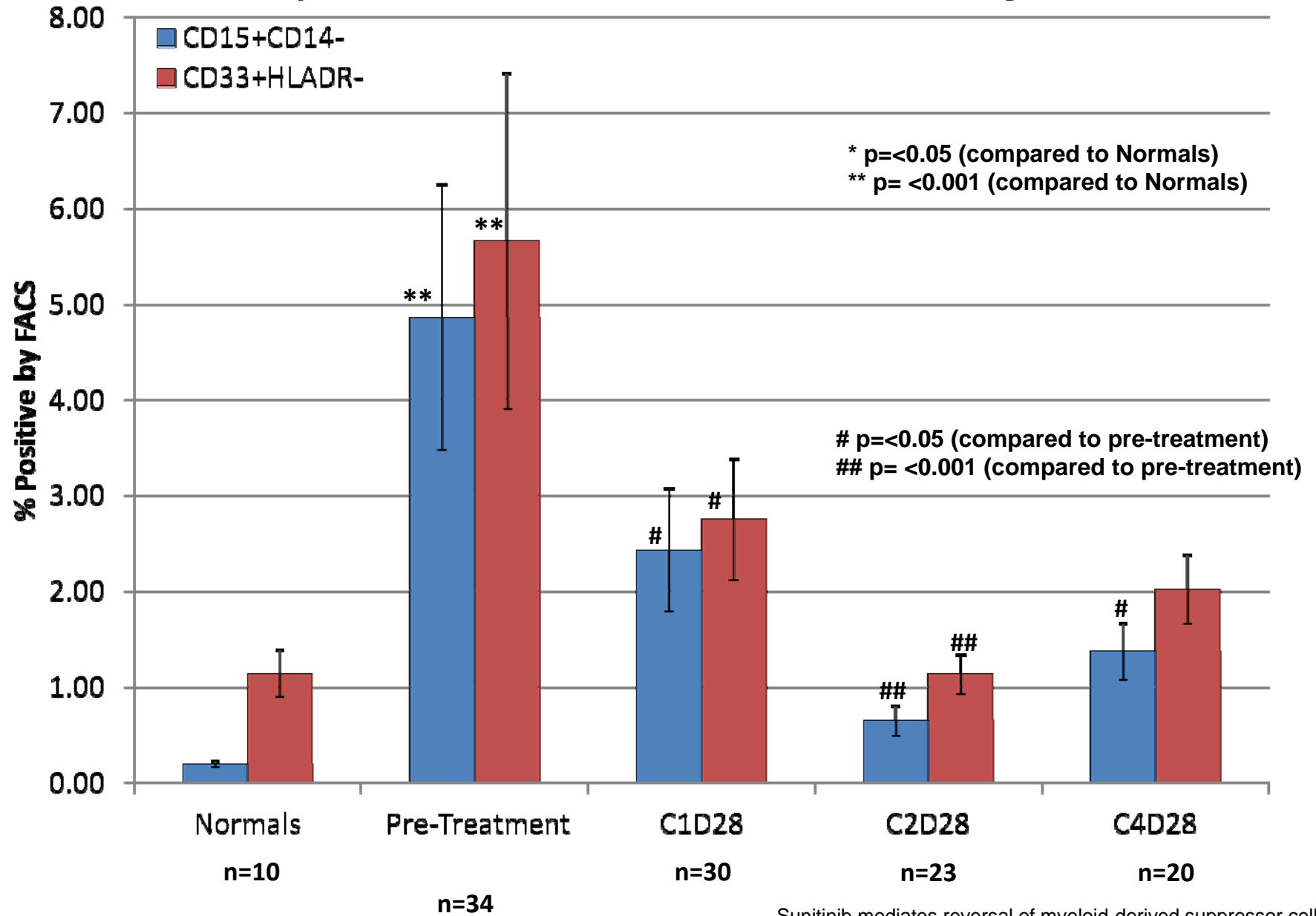
Renal Tumors



RCC Tumor (n=47)



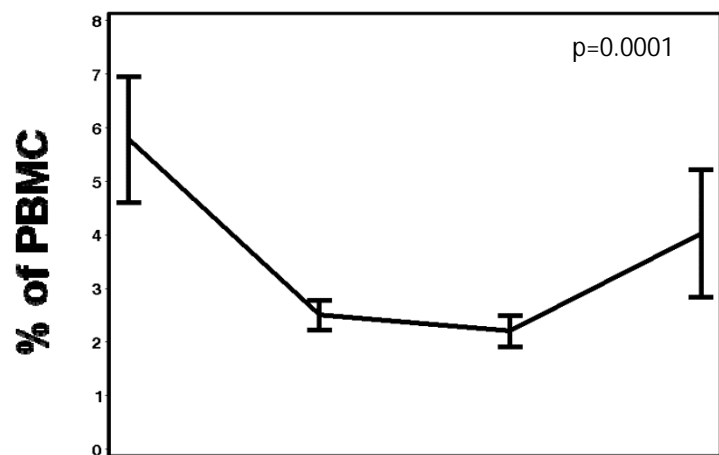
Peripheral Blood MDSCs in RCC Patients Receiving Sunitinib



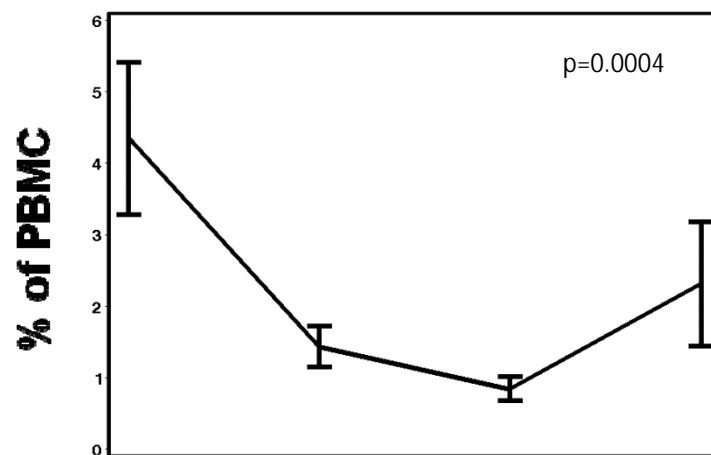
Sunitinib mediates reversal of myeloid-derived suppressor cell accumulation in renal cell carcinoma patients.
Ko JS et al. *Clin Cancer Res.* 2009

Changes in MDSC and MDSC Subpopulations Following 1, 2, and 4 Cycles of Sunitinib

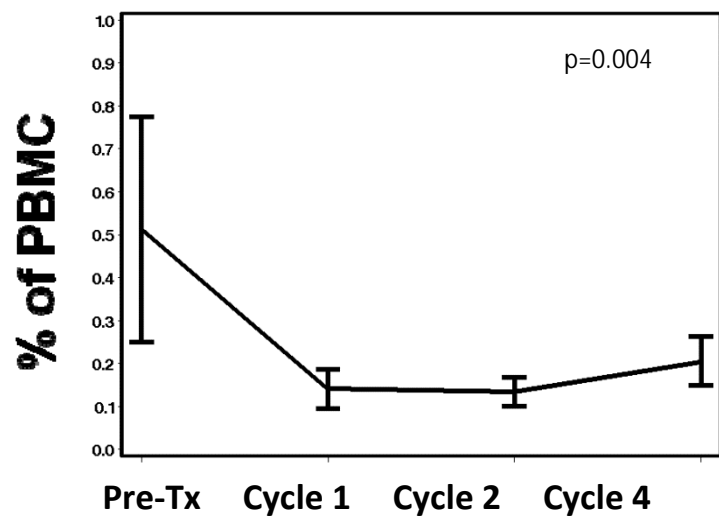
A. MDSC (Total Population) (n=24)



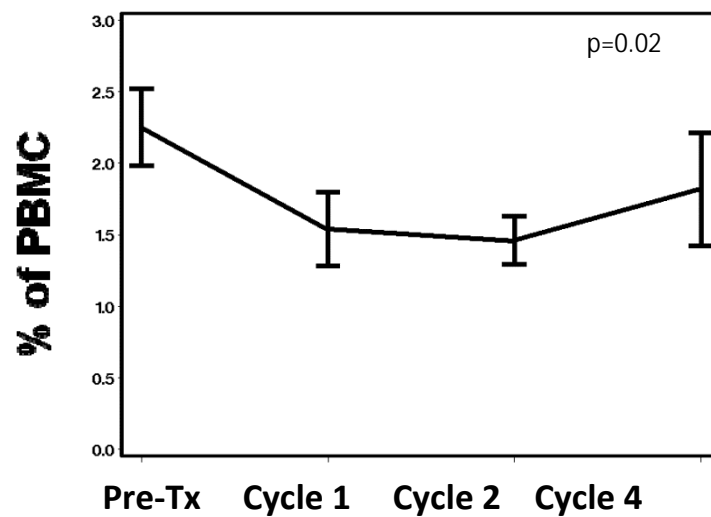
B. G-MDSC (n=25)



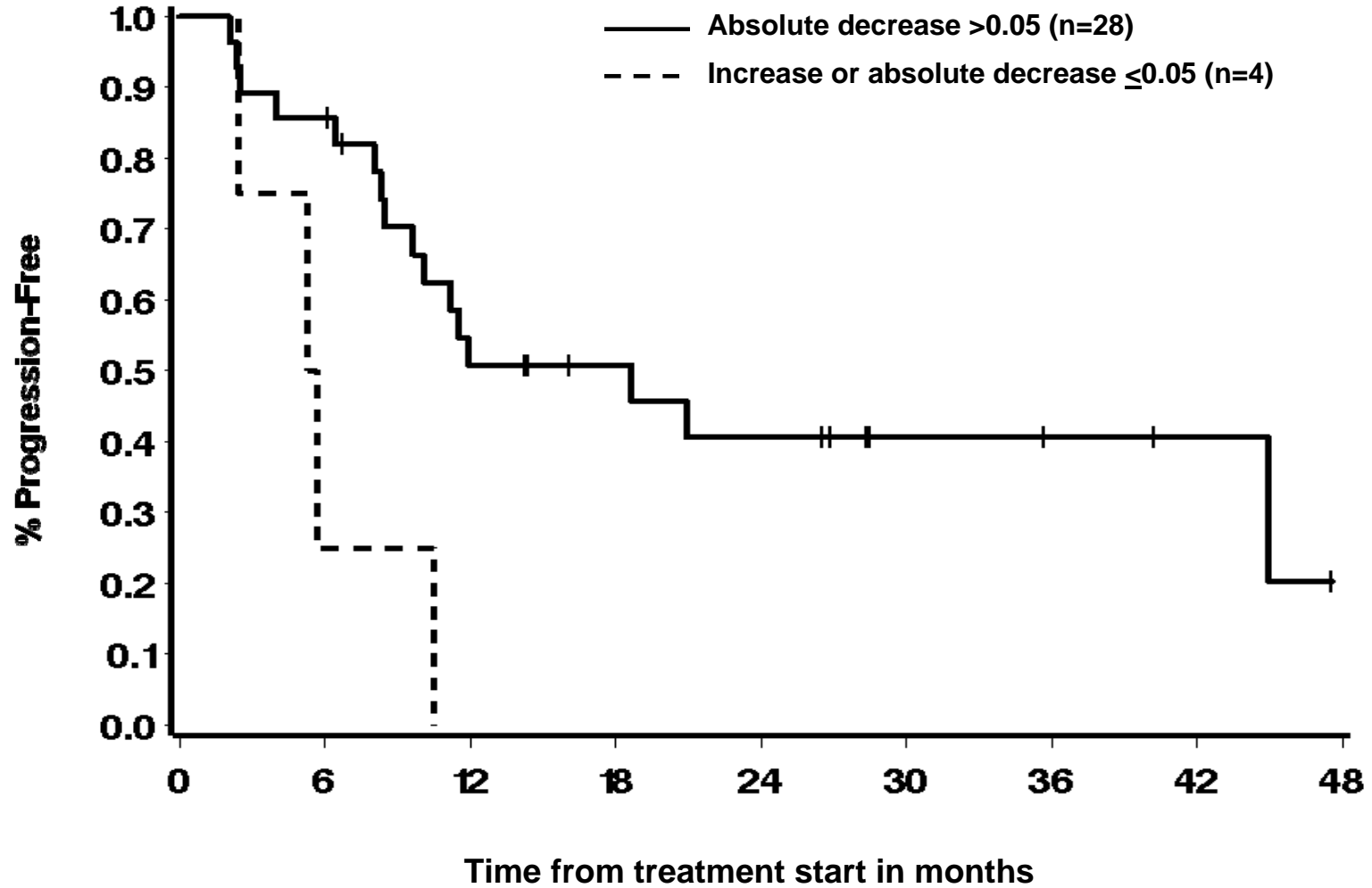
C. M-MDSC (n=15)



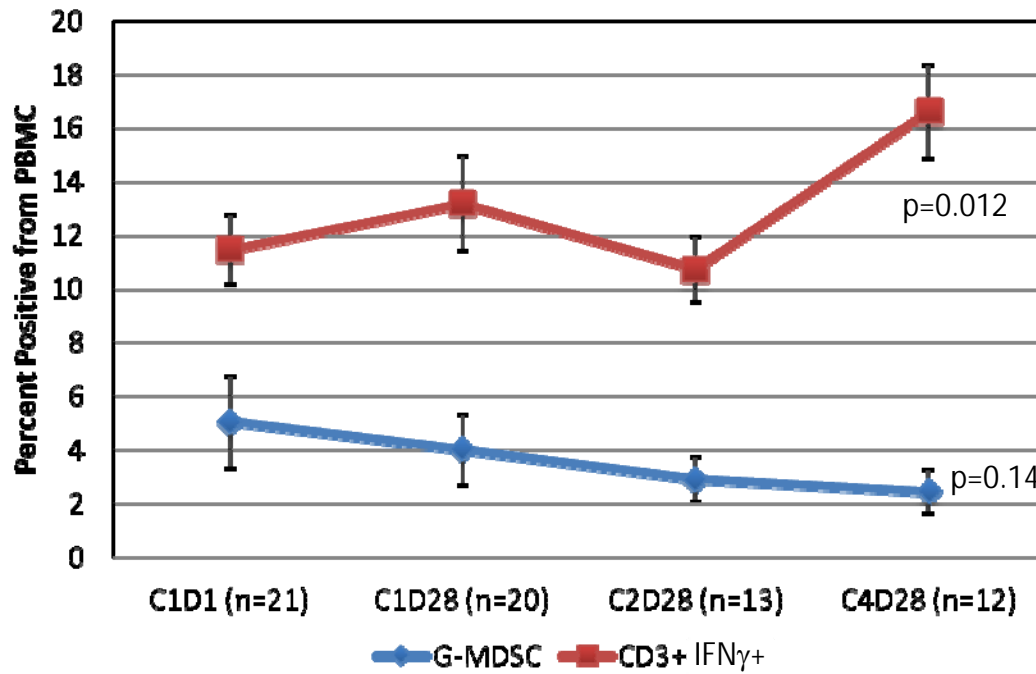
D. lin(-) MDSC (n=15)



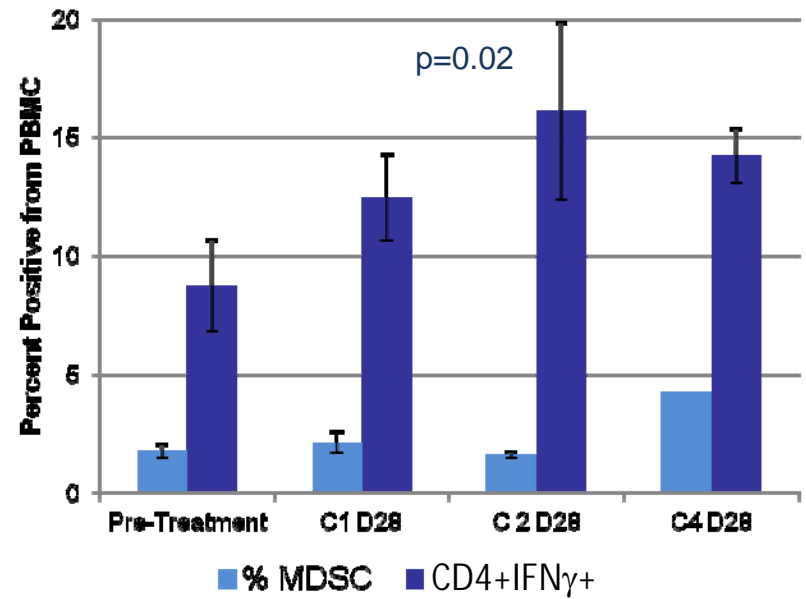
PFS according to absolute change in MDSC after 2 cycles of treatment



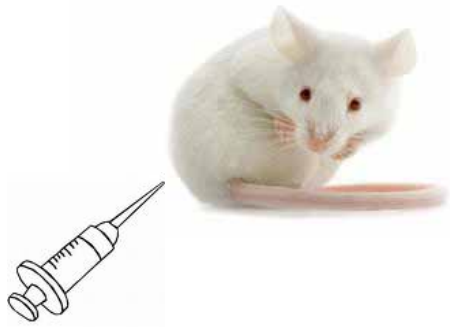
RCC Patients treated with Pazopanib



Temelrolimus (mTOR) Treated RCC Patients



Mouse tumor models to study sunitinib *in vivo*



1 million tumor cells
injected
subcutaneously

Day 0

sunitinib treatment
initiated 40mg/kg/day
i.p. at tumor diameter
~7mm

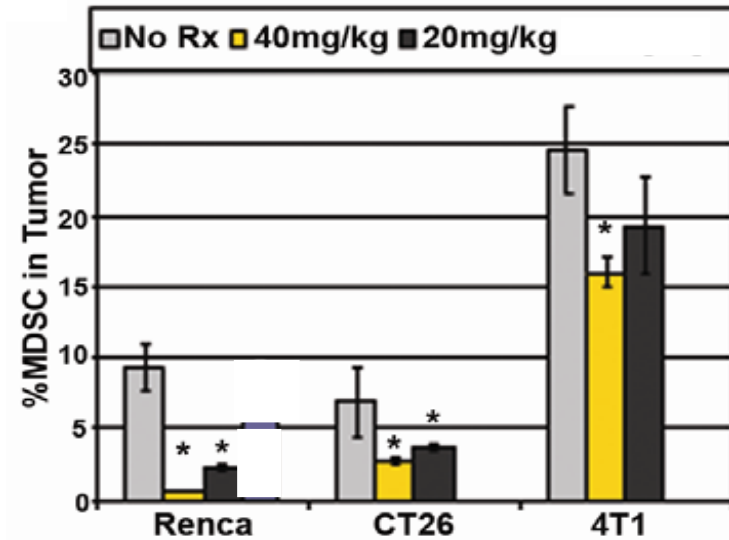
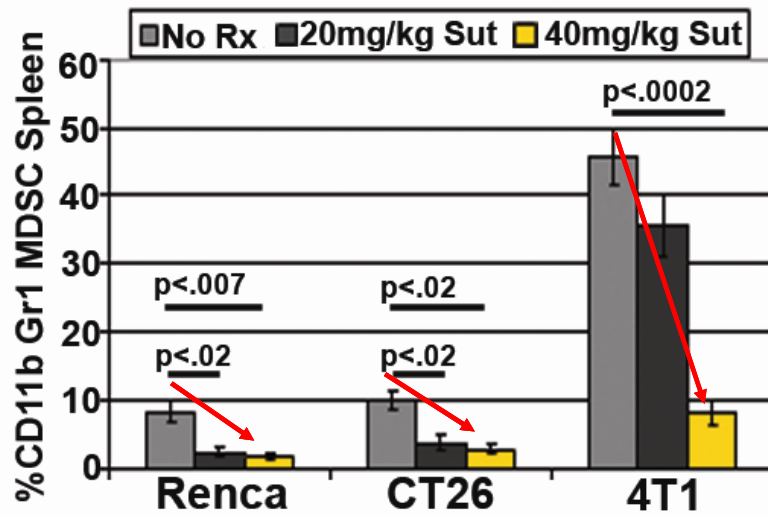
Day 9-16



mice sacrificed for
immunological
assays, etc.

Day 18-25

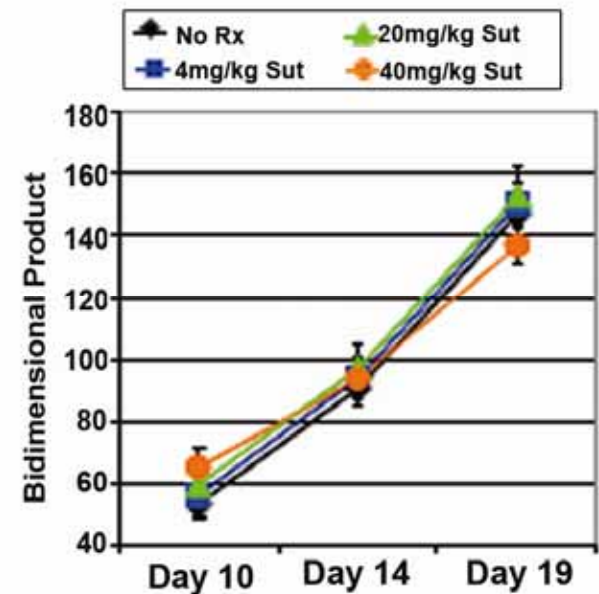
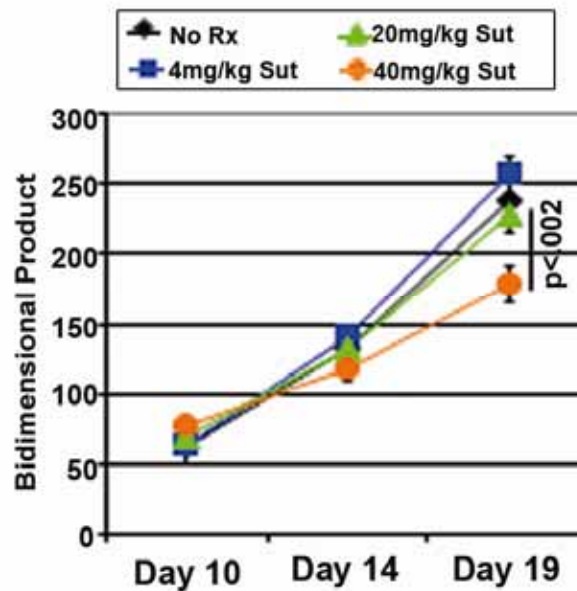
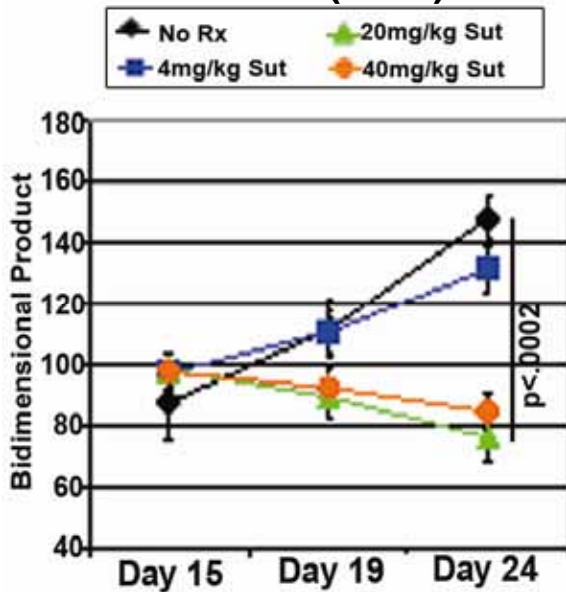
Sunitinib consistently decreases splenic MDSCs, but has a less consistent effect on intratumoral MDSCs. The effect on intratumoral MDSCs is predictive of its impact on tumor progression



Renca (RCC)

CT26 (Colon)

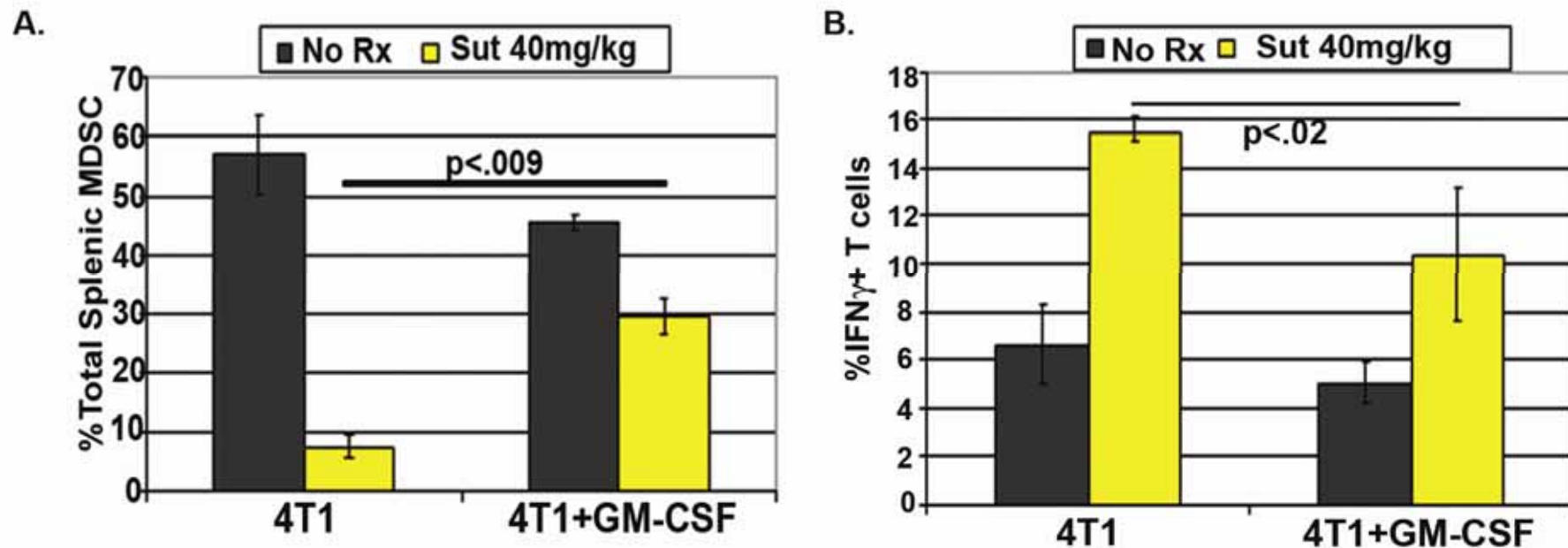
4T1 (Breast)



Direct and differential suppression of myeloid-derived suppressor cell subsets by sunitinib is compartmentally constrained. Rini B, Finke J et al. Cancer Res. 2010

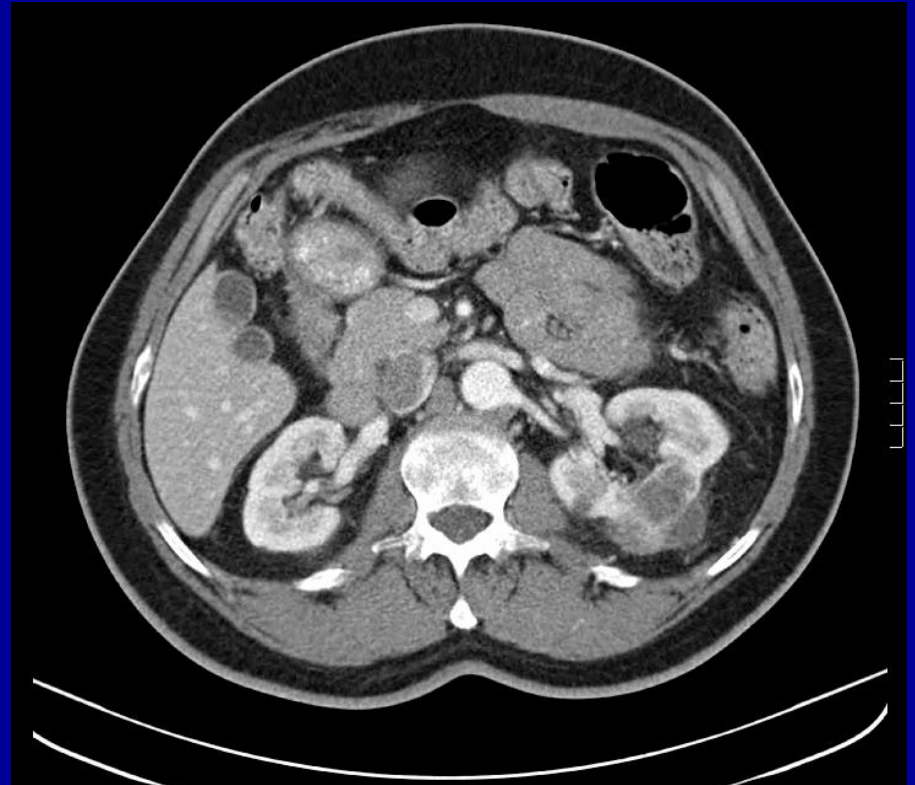
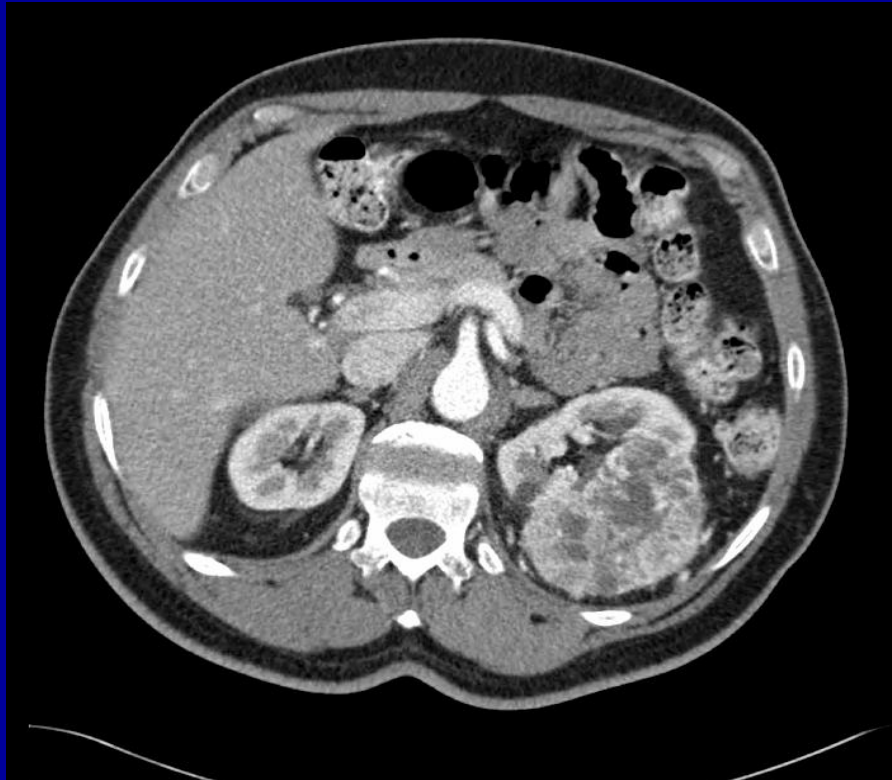
GM-CSF Renders Splenic MDSC Resistant to Sunitinib

In Vivo Administration of GM-CSF



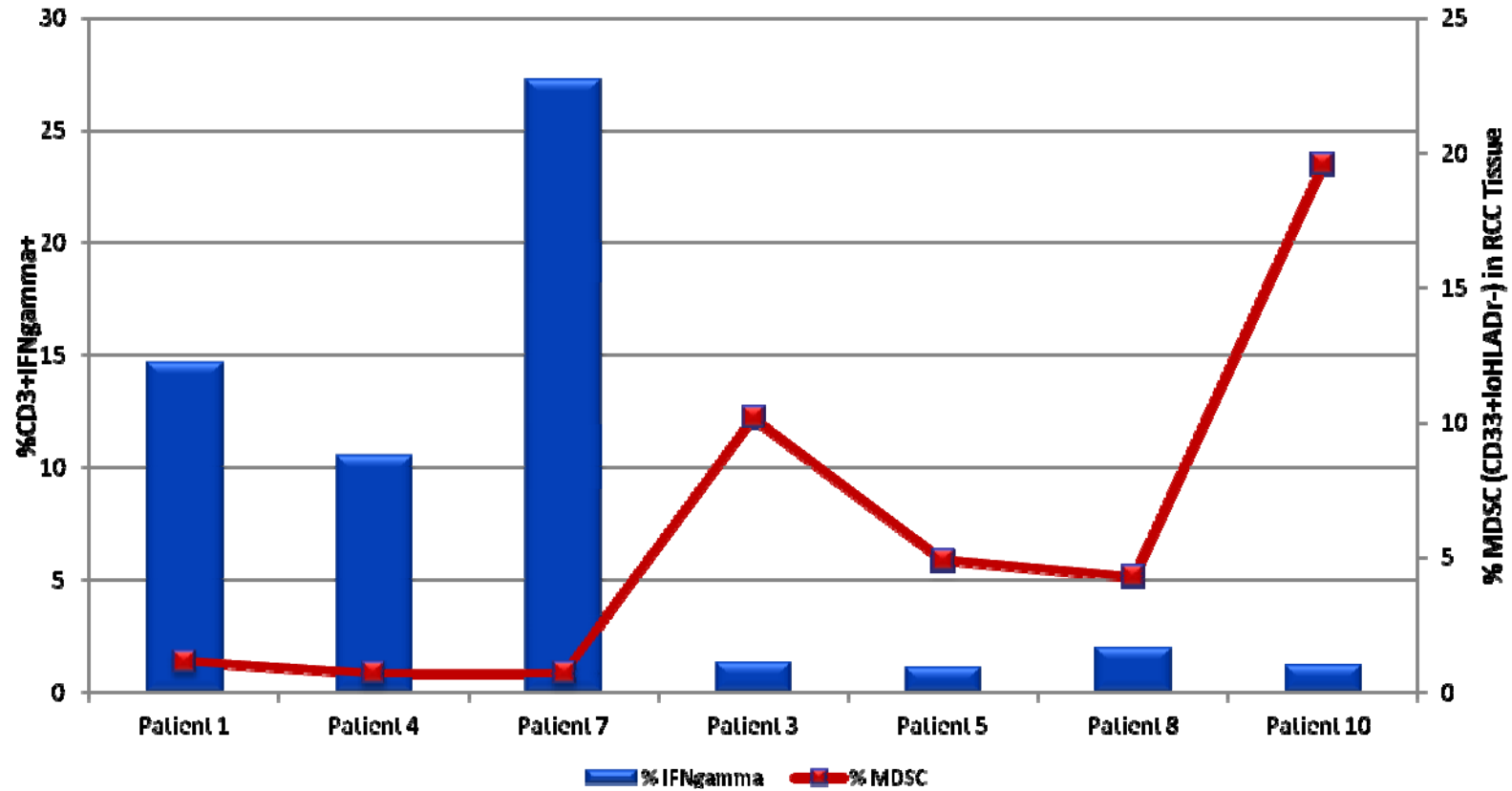
Recombinant murine GM-CSF was given (10 μ g/mouse/day) i.p. for 10 days beginning the day prior to sunitinib treatment.

Neoadjuvant sunitinib in RCC

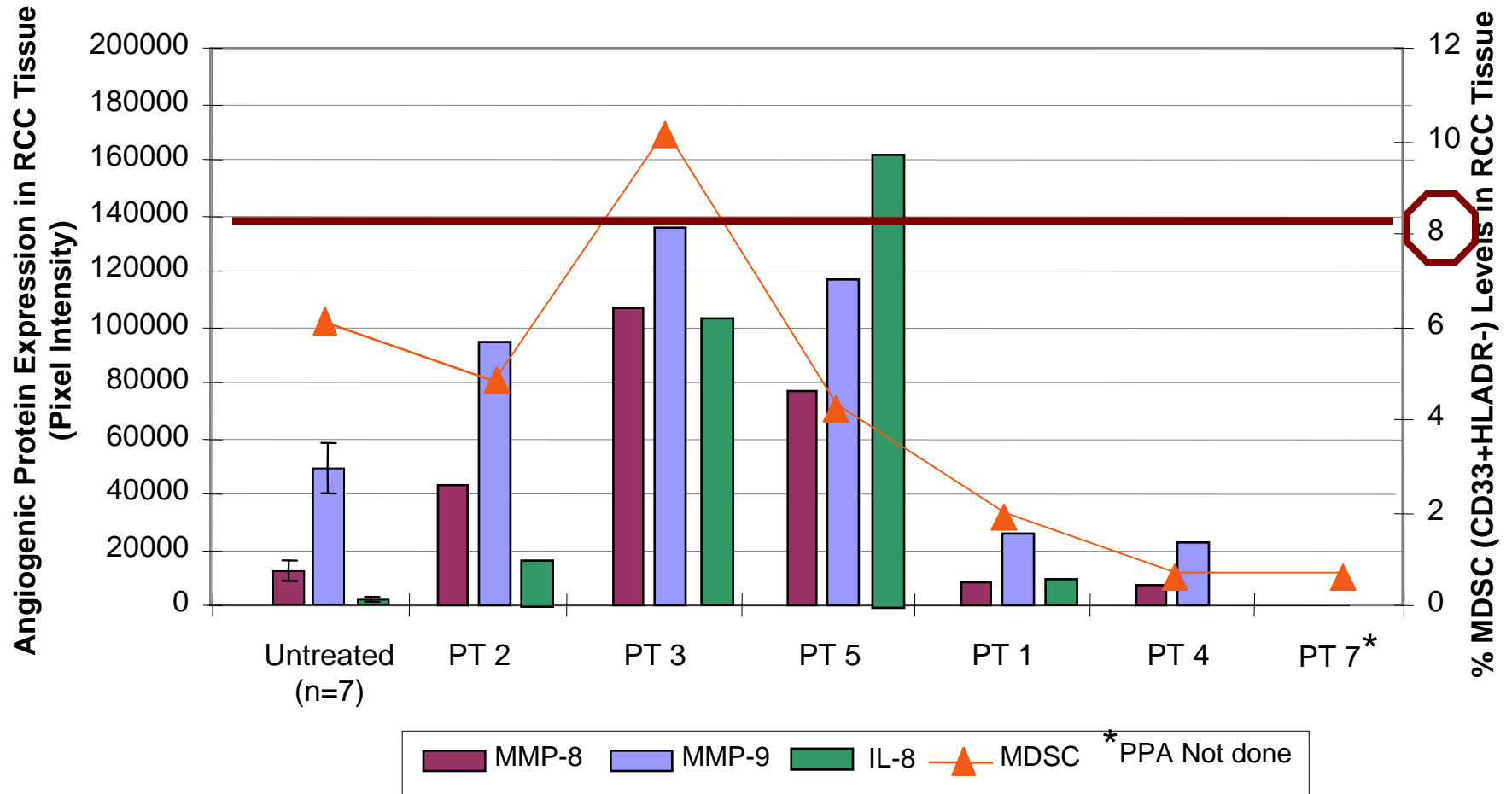


- Primary RCC baseline and after 2 cycles of sunitinib: tumor shrinkage enabled partial nephrectomy as the tumor has pulled away from the renal hilum.
- Viable RCC tumor cells were present in all post-sunitinib surgical specimens. No unexpected surgical morbidity was encountered.

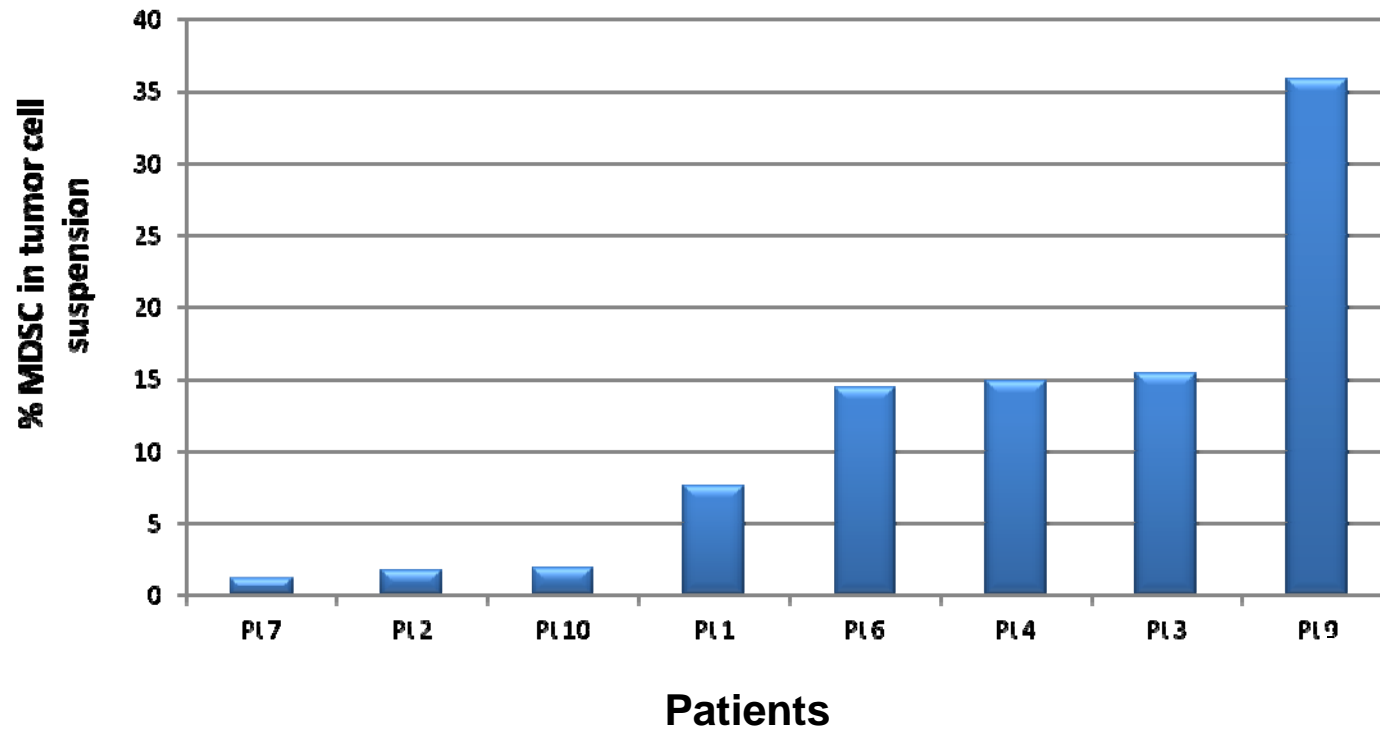
MDSC and T cells ability to produce IFN γ in RCC Tissue Post Sunitinib Treatment



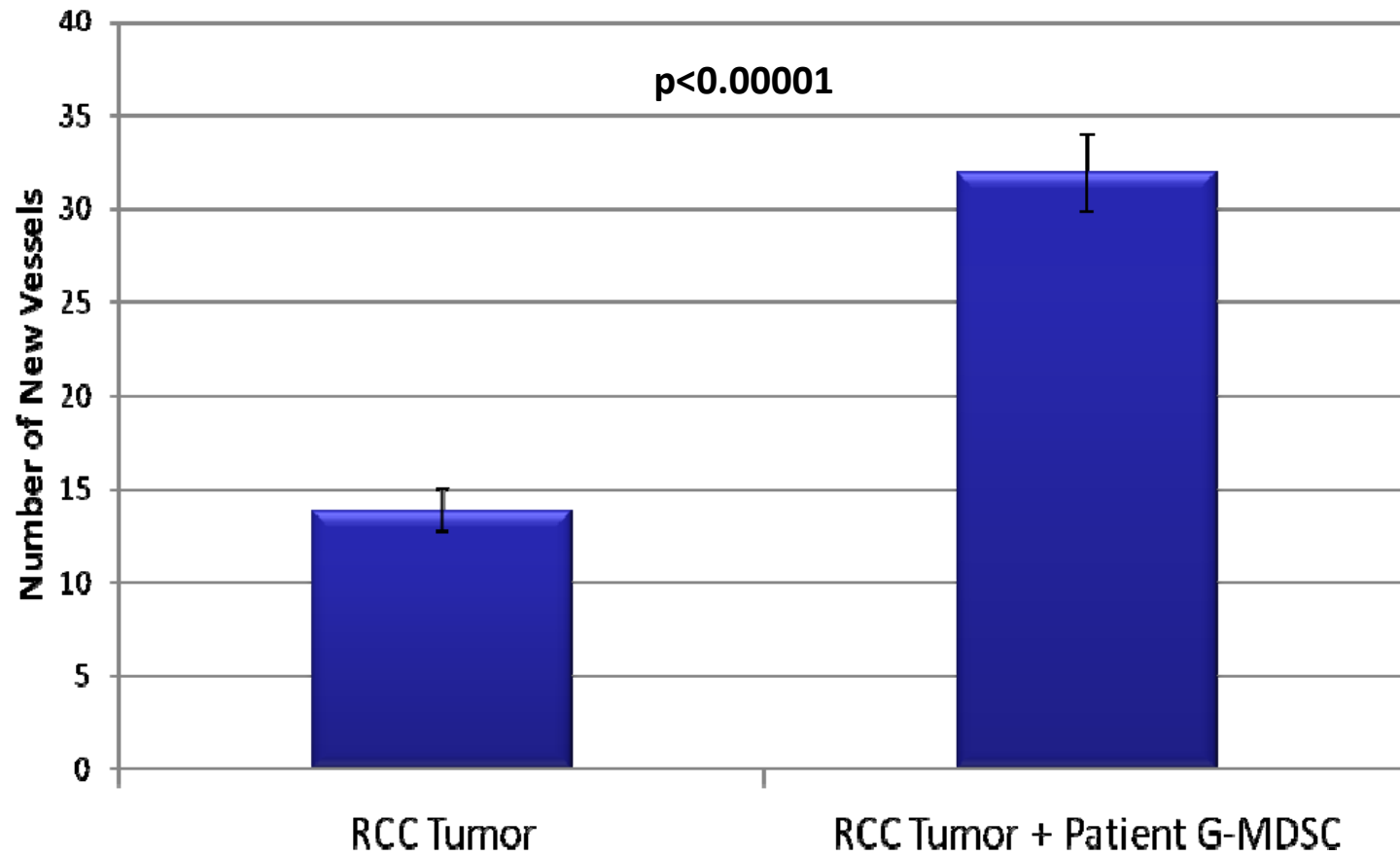
MDSC Persistence in RCC Tissue Post Neoadjuvant Sunitinib Treatment



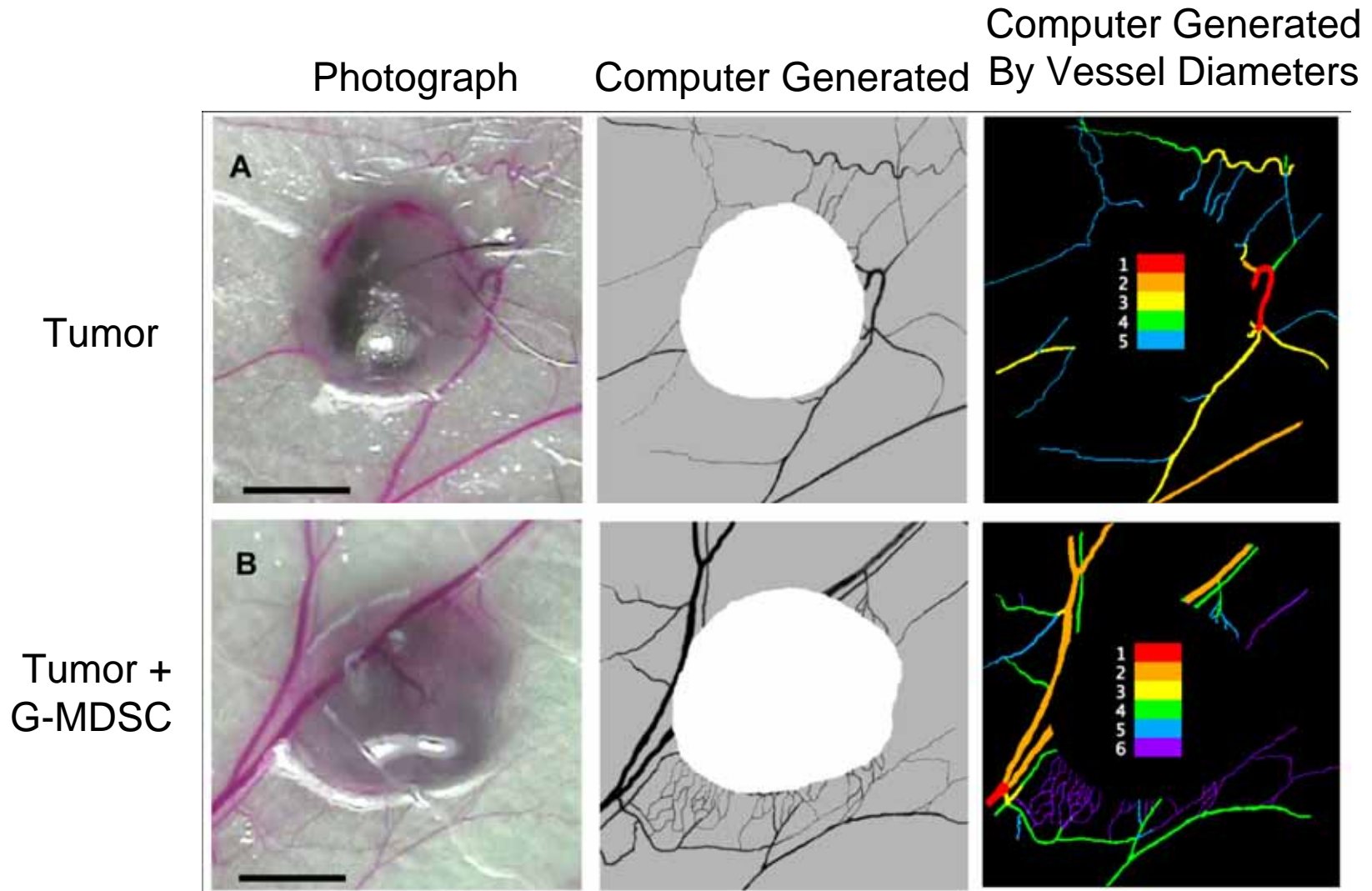
MDSC in post-treatment nephrectomy samples from neoadjuvant pazopanib clinical trial



Neoangiogenesis is induced by MDSC in a murine RCC xenograft model

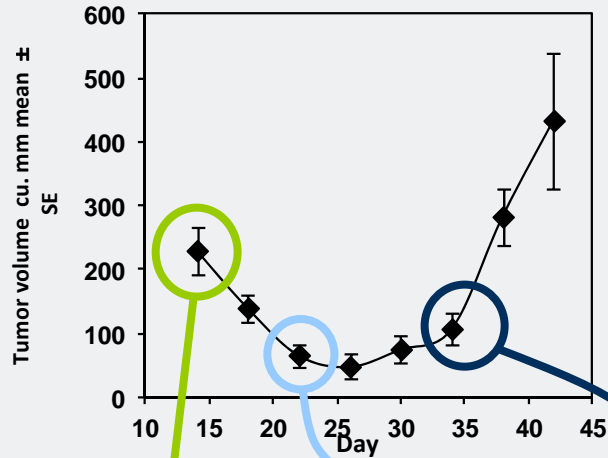


Nude Mouse Xenograft Model of Angiogenesis



VEGF therapy resistance is mediated by MEK and MDSC

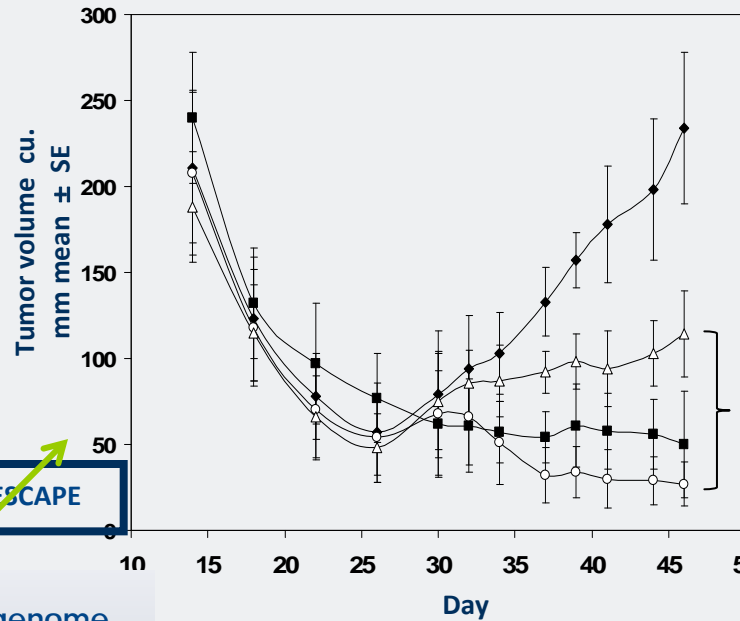
Human RCC tumor xenograft treated with sunitinib



PRE-SUNITINIB

SHRINKING

ESCAPE



sunitinib

sunitinib+
MEK inhibitor
added at
different
timepoints

Illumina whole genome expression of stroma-derived RNA revealed high expression of:

MDSC-associated genes including arginase, MMPs and IL-1 receptor

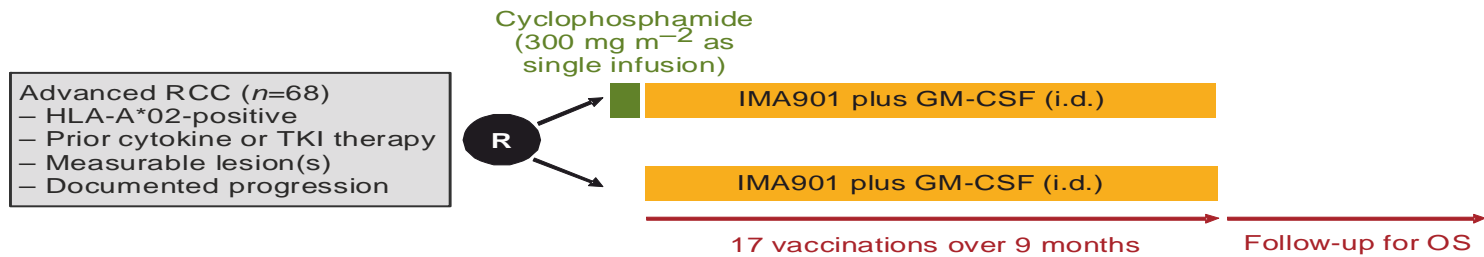
Illumina whole genome expression of tumor-derived RNA revealed high expression of:

CA9, IL8, HK2, MAPK7, MAPK3, ANGPT2, MAPKBP1, VEGFA

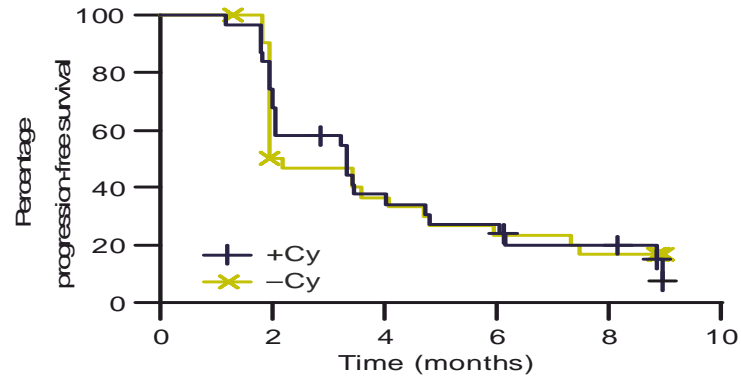
The next step is clinical development of combinations of sunitinib and MEK-targeted and/or MDSC-targeted therapy

Clinical Application of Sunitinib-induced Immunomodulation

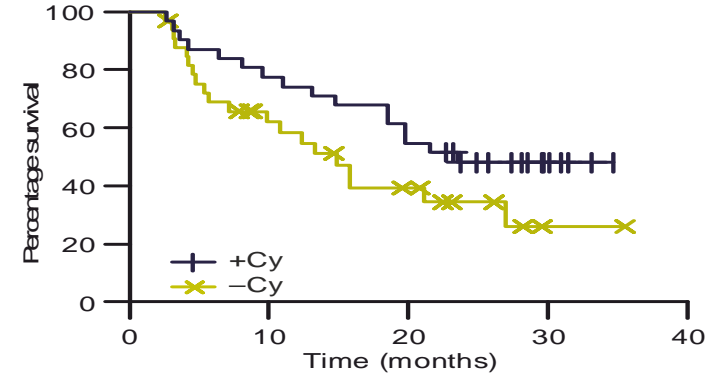
a



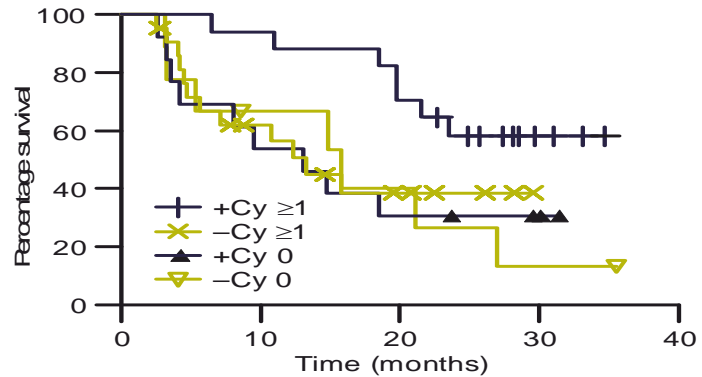
b



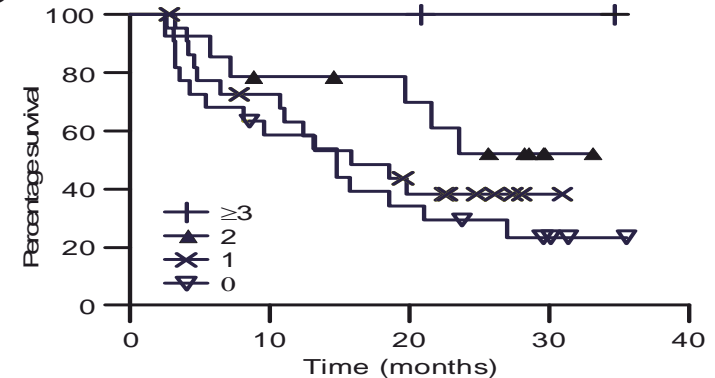
c



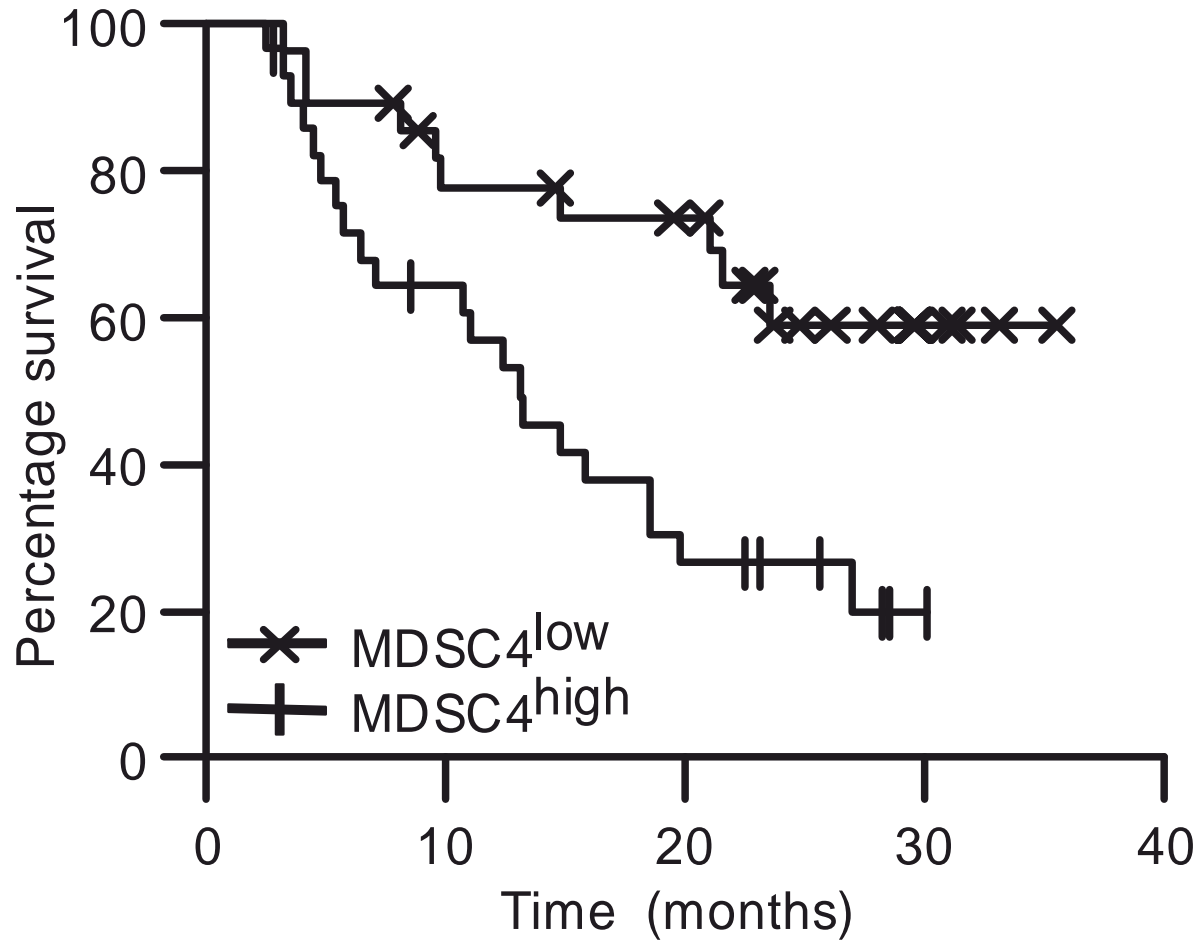
d



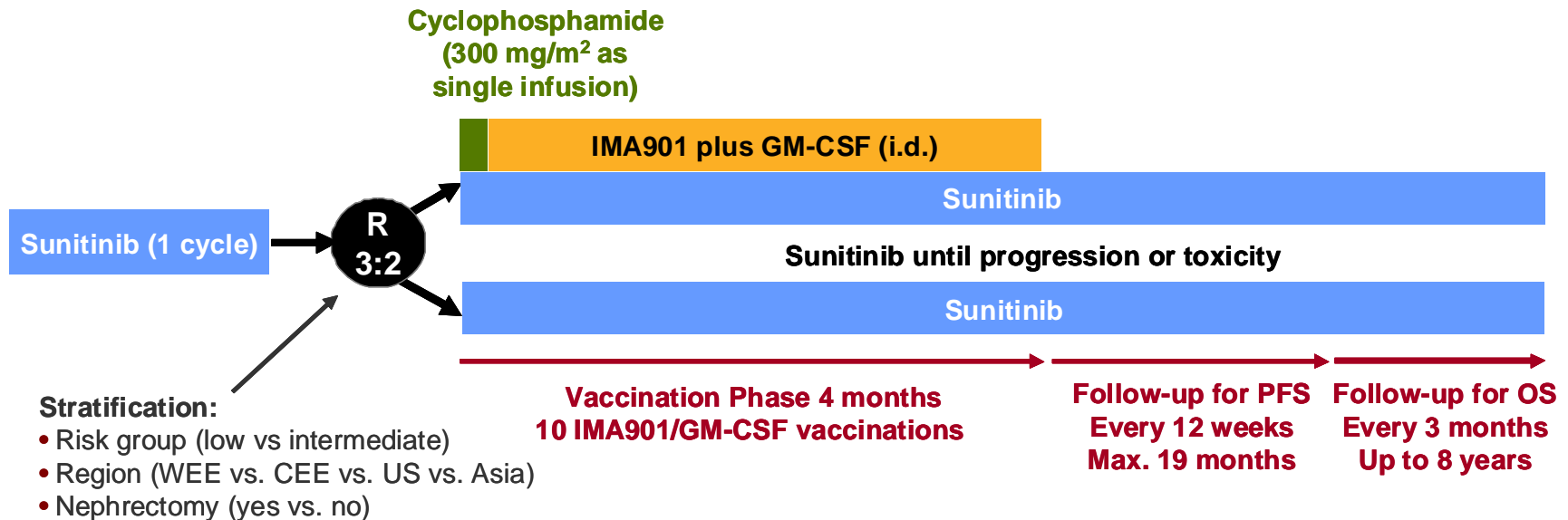
e



Baseline MDSC levels correlate with OS in patients treated with cyclophosphamide plus IMA091 Vaccine



IMA901 Renal Cell Cancer Phase 3 trial



N=330

- 1st line metastatic and/or locally advanced RCC
- HLA-A*02-positive
- Documented tumor lesions
- Favorable or intermediate risk (Heng et al., 2009)

*** IMA091 is a vaccine comprised of multiple, RCC tumor-associated peptides**

Primary endpoint

- Overall Survival

Secondary endpoints

- Overall Survival in biomarker-defined subgroup (pre-specified)
- Progression-free survival (PFS)
- Safety and tolerability
- Cellular immunomonitoring

Conclusions

- **Sunitinib therapy in metastatic RCC patients leads to declines in circulating Treg and MDSC and increases in IFN gamma-producing T cells.**
- **In vitro and in vivo work also demonstrates effects of sunitinib on immune cells and will provide insight into mechanism(s).**
- **Sunitinib leads to MDSC and other immune repertoire changes in RCC tumor tissue post treatment.**
- **Ongoing clinical trials in RCC are attempting to capitalize on the potential for sunitinib to augment anti-tumor immunity to enhance clinical benefit.**



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Immatics

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