



Werkgroep Immunotherapie Nederland
voor Oncologie

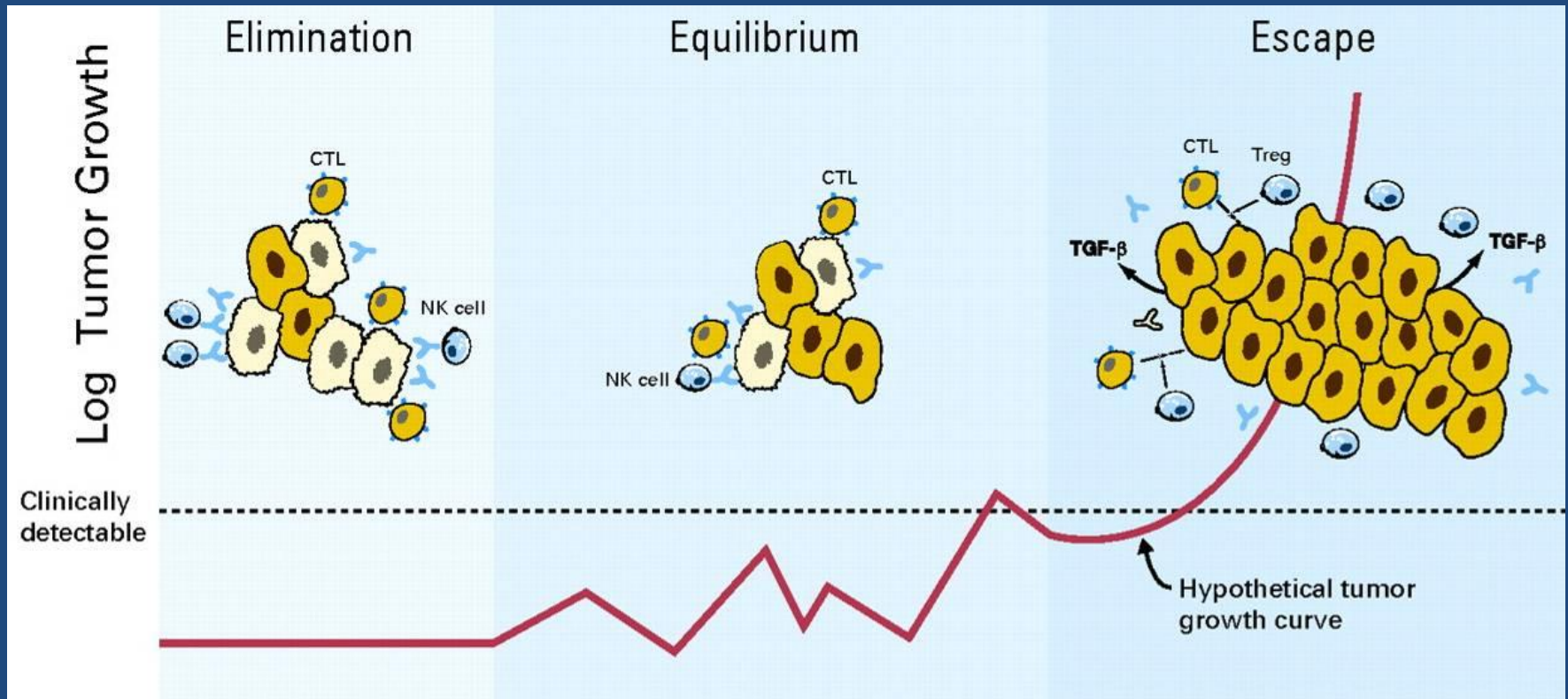
Immunotherapie bij Niercelcarcinoom Pro

Fons van den Eertwegh
Department of Medical Oncology

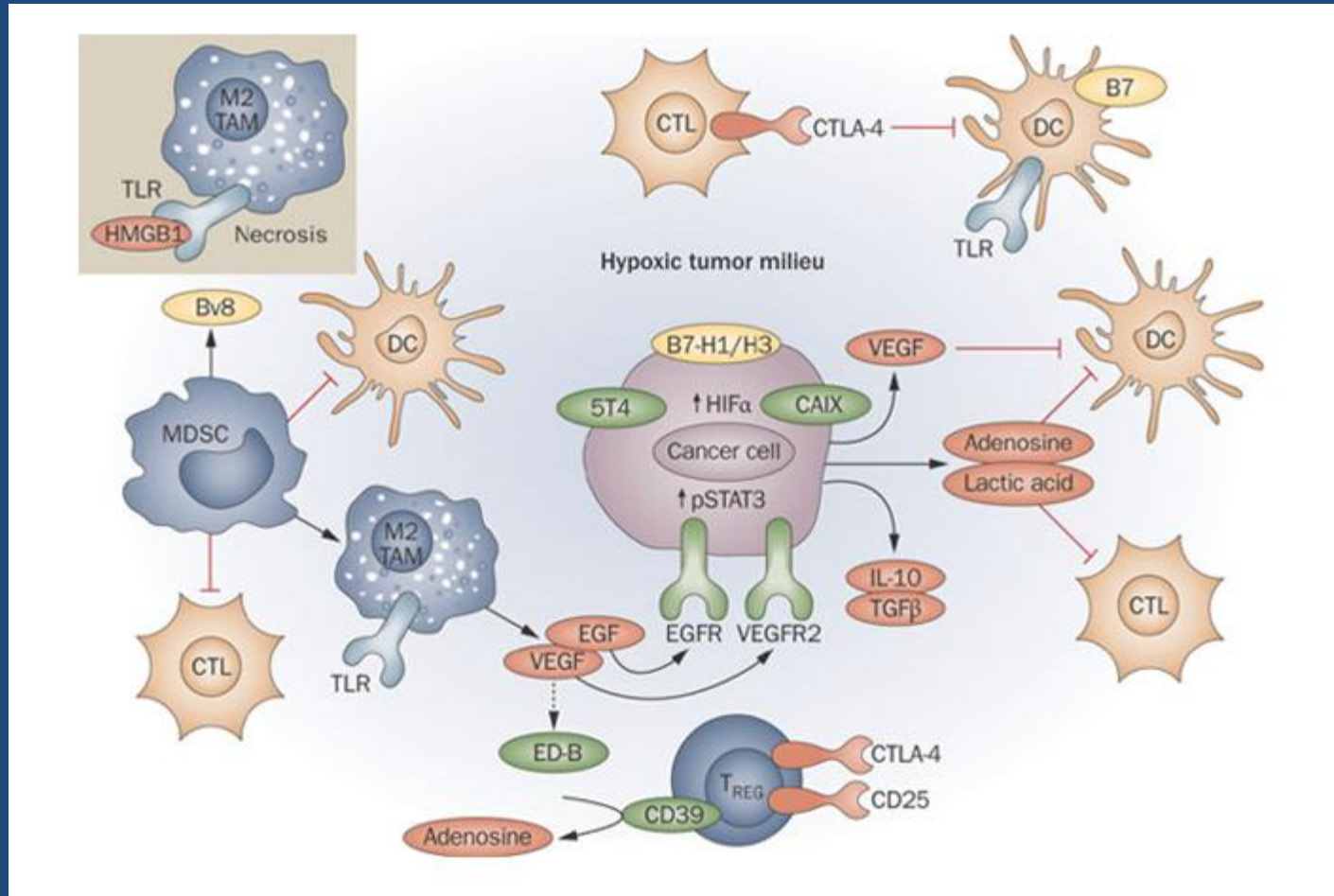
Immune system and renal cell carcinoma

- Complete remission after nephrectomy (< 1%, 4% only lung)
- Long term stabilization after nephrectomy
- Immune cells and suppressive factors in primary/metastases
- Tumor responses after immunotherapy
 - IL-2 and IFN- α
 - allogeneic transplantation
 - vaccination
 - ipilimumab

Tumor immunity immunoediting



Immunomodulatory factors in human tumor biology



Immunotherapy

- Non-specific:
 - Immunostimulating drugs (e.g. IFN- α , IL-2)
 - Allogeneic bone marrow transplantation
 - Regulatory antibodies (CTLA-4, PD1, CD40, etc.)
- Specific:
 - Vaccination
 - Tumor-specific T-cells

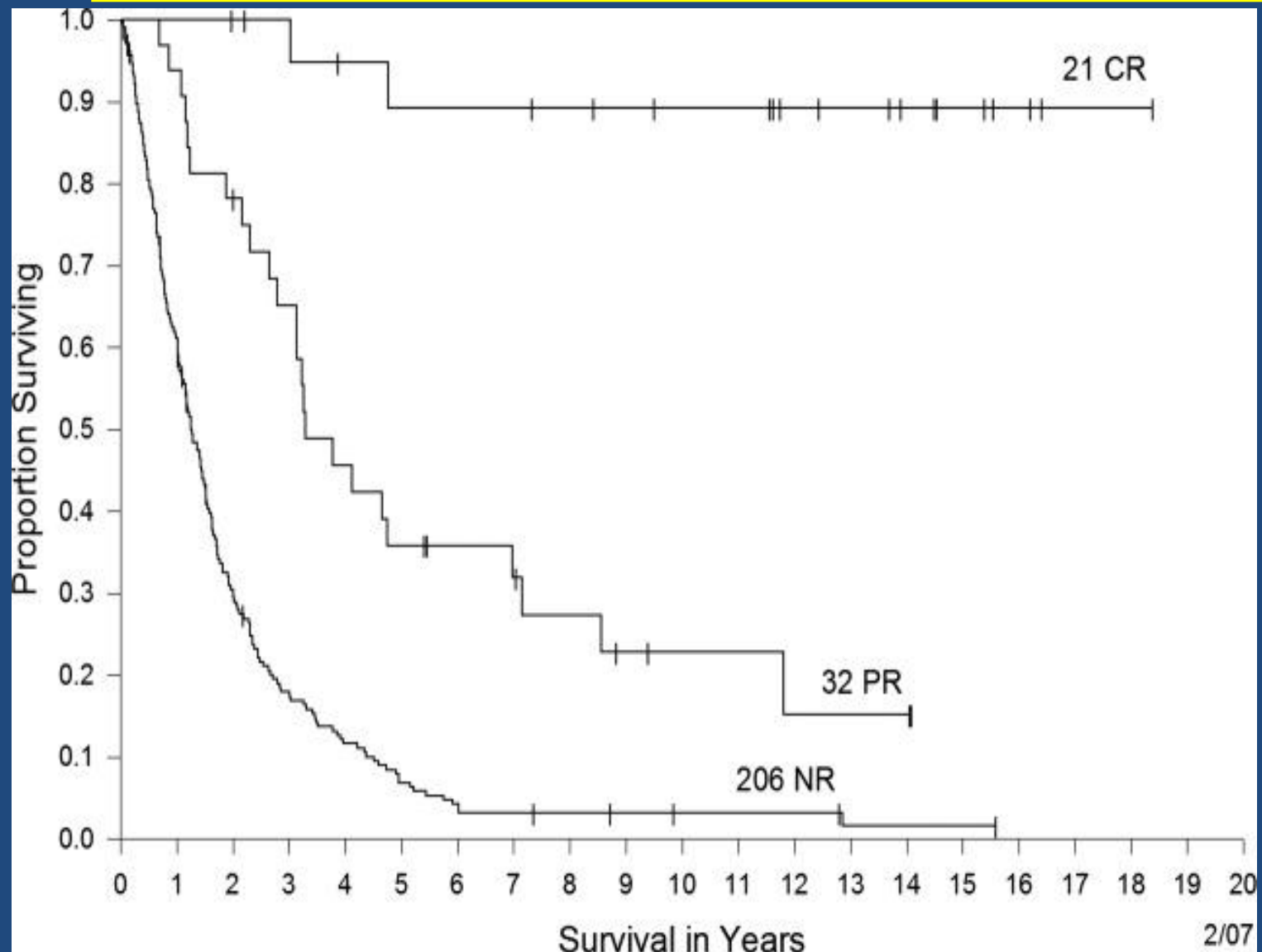
Interleukin 2

- Stimulates proliferation of T cells and natural killer cells
- Enhances cytotoxic activity of T cells and natural killer cells (LAK cells)

Phase II trials of IL-2 in metastatic Renal Cell Carcinoma

Study	No. Assessable Patients	rHuIL-2 Regimen (Dose x 10 ⁶ IU)	Percent		CR + PR
			No.CR	No.PR	
Rosenberg	38	0.1/kg IV q 8hr, 2-wk cycle	4	3	18
Negrier et al	32	18/m ² , d1-5 and 12-16 3-wk intervals	2	4	19
Bukowski et al	41	60/m ² IV, TIW	1	4	12
Geertsen et al	30	18/m ² IV, d1-5 1-wk intervals	2	4	20
Von der Maase et al	51	18/m ² IV, d1-5 and 12-15 3-wk rest	2	6	16
Lissoni et al	48	6 SC, qd	1	13	29
Rosenberg et al	149	0.72/kg IV bolus, q 8hr 2 Tx cycles, maximum 15 doses	10	20	20
Buter et al	46	18 SC, qd d 1-5 then dose reduction 4 or 6 wks consecutive	2	7	20

Metastatic renal cell carcinoma high dose interleukine 2 (n= 259)



Side effects of Interleukin 2

- Increases capillary permeability
 - fluid retention, interstitial edema, ARDS
- hypotension
- influenza-like symptoms
- renal insufficiency, oliguria
- CNS toxicity
- skin rashes

Interferon- α

- inhibits cell division
- activates macrophages and monocytes
- increases NK cell activity
- activates cytotoxic T-lymphocytes
- increases HLA-class I expression

Interferon- α in Metastatic RCC randomized study

Multicenter randomised trial:

174 patients: interferon-alpha s.c. (three doses 5 MU, 5 MU, 10 MU for the first week, then 10 MU three times per week for a further 11 weeks)

176 patients: 12 weeks, once daily 300 mg medroxyprogesterone acetate

Medical Research Council Renal Cancer
Collaborators

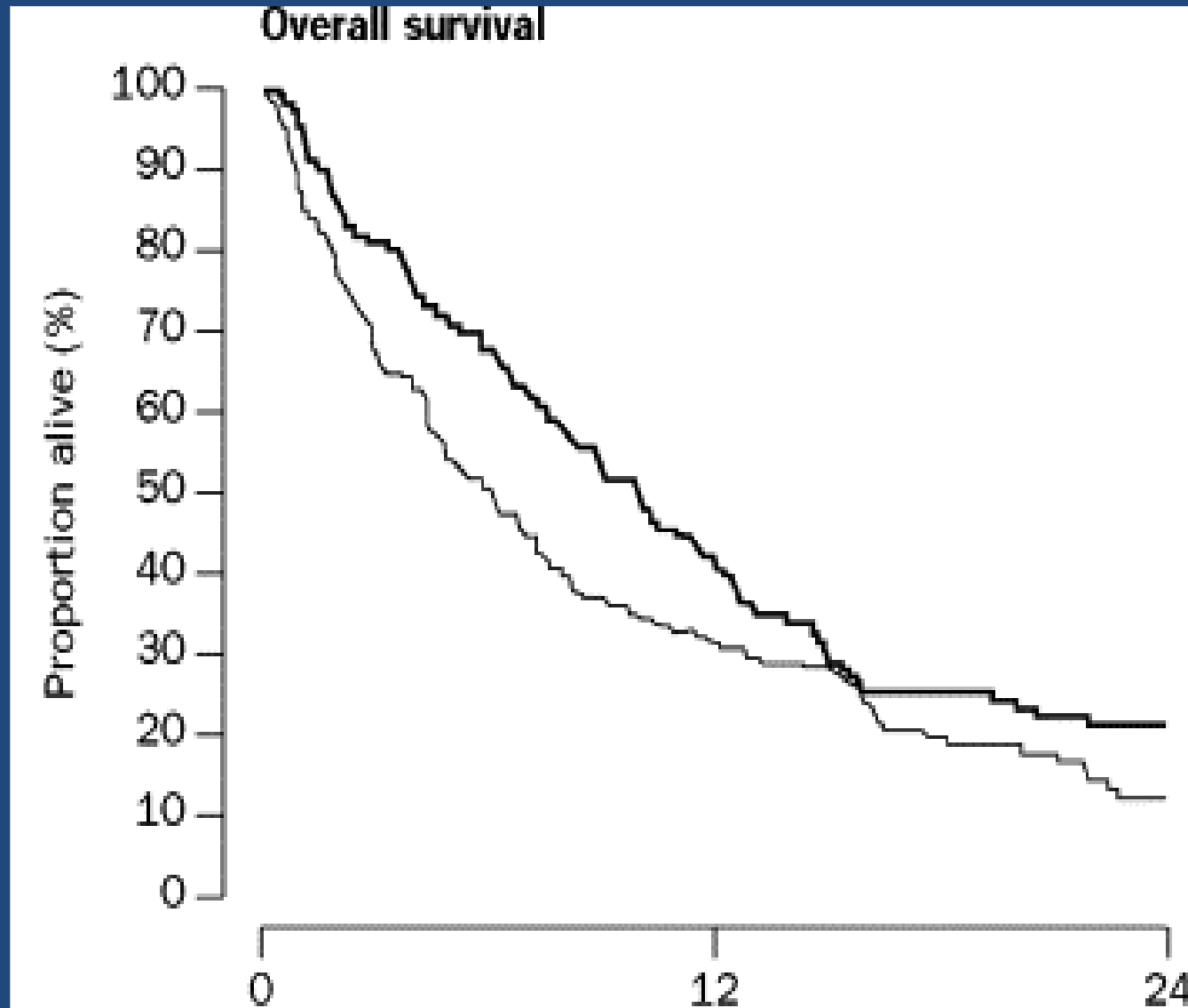
Lancet 1999: 253:14-17

Results MRC trial IFN-alpha in metastatic RCC

- 14% responses (CR 2%; PR 12%)
- 28% reduction in the risk of death in the IFN-alpha group
- IFN-alpha gave a 12% improvement in 1 year survival (31% versus 43%)
- IFN-alpha gave an improvement in median survival of 2.5 months (6 versus 8.5 months)
- IFN-alpha had significant more side effects

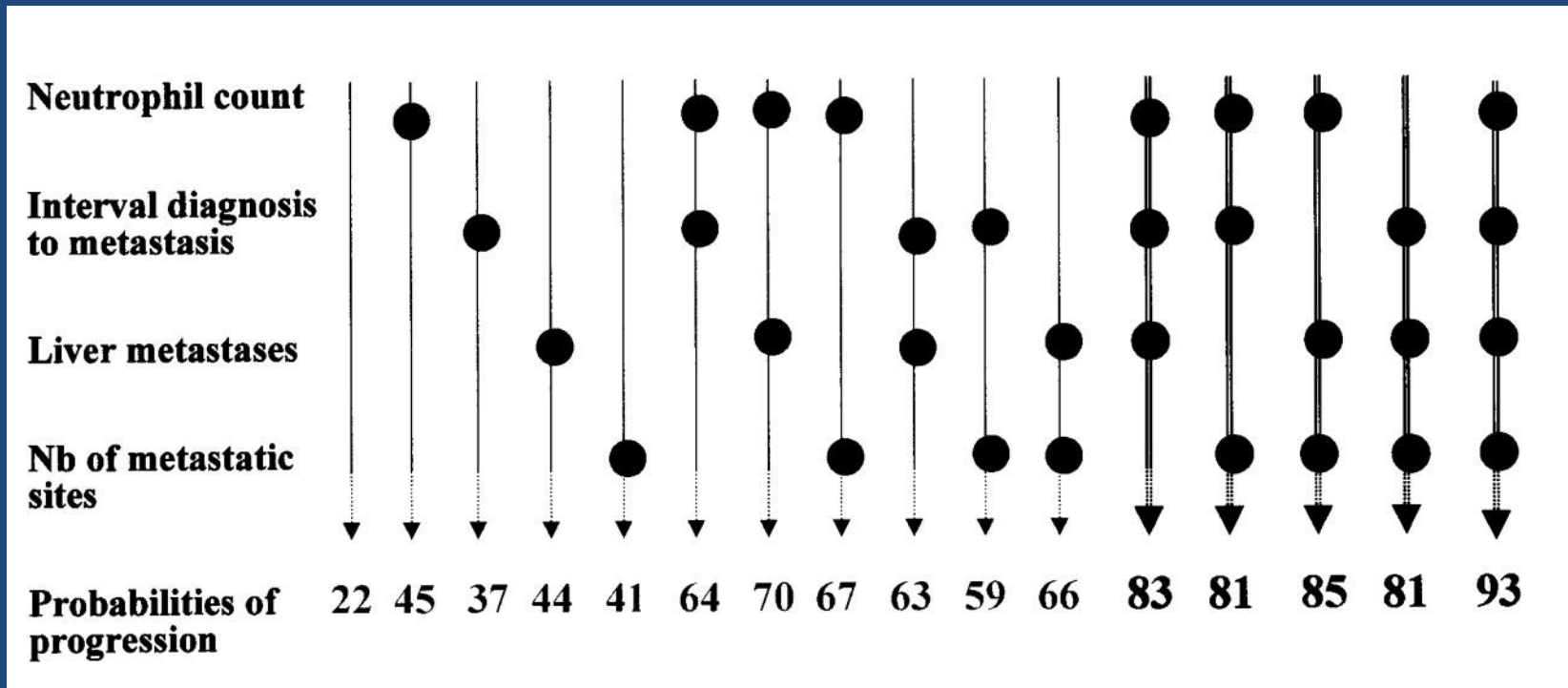
Metastatic renal cell carcinoma

Interferon-alpha improves survival



Cytokine treatment for RCC

predictive factors for rapid progression



Immunotherapy in favorable group

Table 3. Response rates according to treatment arm

	IFN- α + i.v. IL-2 (<i>n</i> = 80)	IFN- α + s.c. IL-2 (<i>n</i> = 75)	Total (<i>n</i> = 155)
Response at week 12, <i>n</i> (%)*			
Missing value	2	0	2
Nonevaluable patients	5 (3.8)	3 (4.0)	8 (5.2)
Complete response	3 (3.8)	1 (1.3)	4 (2.6)
Partial response	11 (14.1)	15 (20.0)	26 (17.0)
Disease stabilization	31 (39.7)	29 (38.7)	60 (39.2)
Disease progression	28 (35.9)	27 (36.0)	55 (35.9)
Response at month 6, <i>n</i> (%)*			
Missing value	1	0	1
Nonevaluable patients	8 (10.0)	1 (1.3)	9 (5.8)
Complete response	3 (3.8)	3 (4.0)	6 (3.9)
Partial response	9 (11.4)	15 (20.0)	24 (15.6)
Disease stabilization	17 (21.5)	13 (17.3)	30 (19.5)
Disease progression	42 (53.2)	43 (57.3)	85 (55.2)

*Ten patients were not evaluable at week 12 (because of death or missing data).

Immunotherapy for advanced Renal Cell Cancer A Cochrane review

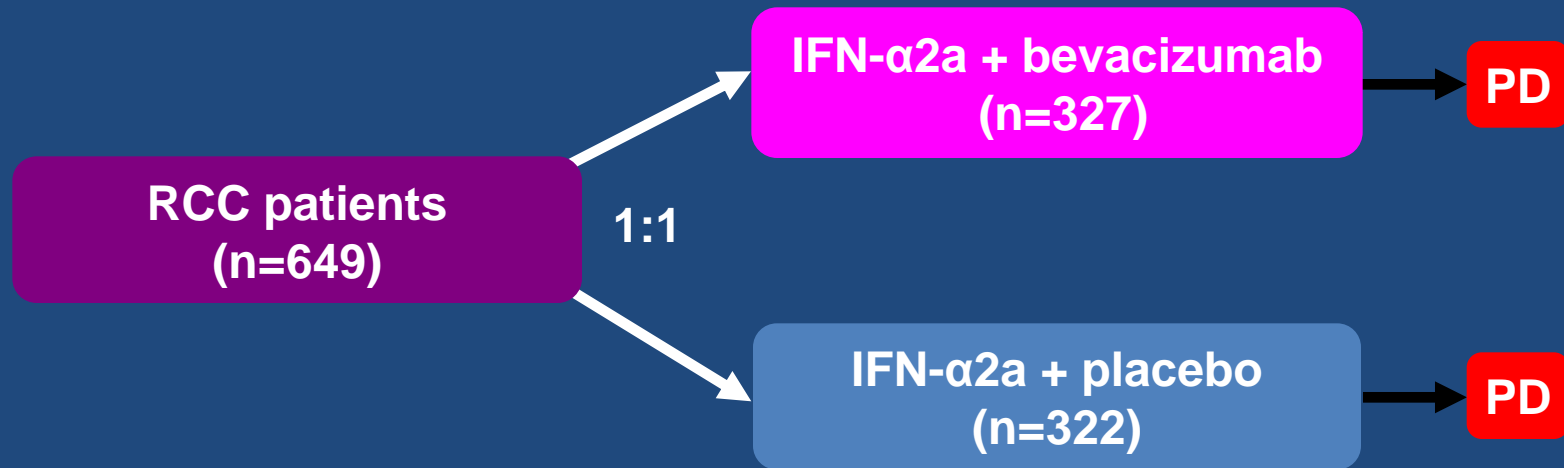
- 53 studies with 6117 patients
- Response rate 12.9 % versus 2.5-4.3% control
- Interferon-alpha treatment results in a 3.8 months survival benefit
- Optimal dose and duration is not known
- Fit asymptomatic nephrectomized patients seem to have the most benefit

Bevacizumab: anti-VEGF Monoclonal Antibody

- 93% human, 7% murine
- binds VEGF & blocks binding of VEGF to its receptors → neutralizes effects of VEGF
- inhibits tumor growth & leads to tumor regression
- half life: ~17-21 days
- broad potential applicability
- complementary with chemotherapy
- $K_{DVEGF} = 8 \times 10^{-10}$



AVOREN: study design



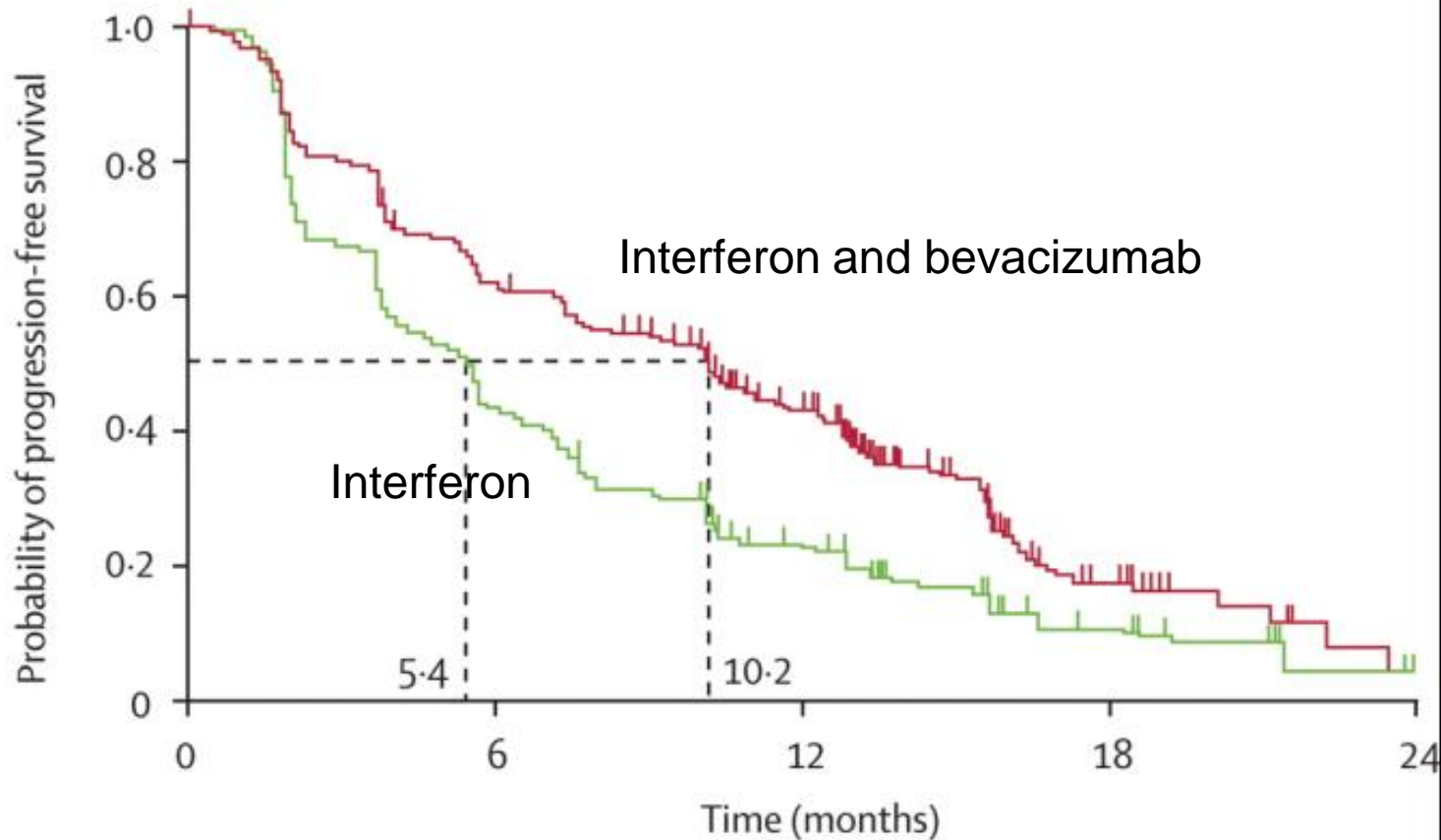
- Bevacizumab/placebo 10mg/kg i.v. q2w until progression
- IFN- α 2a 9MIU s.c. three times/week (maximum of 52 weeks) (dose reduction allowed)
- Multinational ex-US study: 101 study sites in 18 countries
- Stratification factors: country and Motzer score

PD = progression of disease; i.v. = intravenous; s.c. = subcutaneous

Avoren responses

	Bevacizumab plus interferon alfa (N=306)	Placebo plus interferon alfa (N=289)
Overall response*	96 (31%)	37 (13%)
Complete response	4 (1%)	6 (2%)
Partial response	92 (30%)	31 (11%)
Stable disease	141 (46%)	144 (50%)
Disease progression	61 (20%)	95 (33%)
Not assessable	8 (3%)	13 (5%)
Duration of response (months)	13.5 (1.8-20.3)	11.1 (3.7-19.5)
Duration of stable disease (months)	10.1 (2.1-23.5)	7.2 (2.3-24.0)
Time to response (months)	2.2 (2-14)	3.7 (1-10)

Avoren progression-free survival



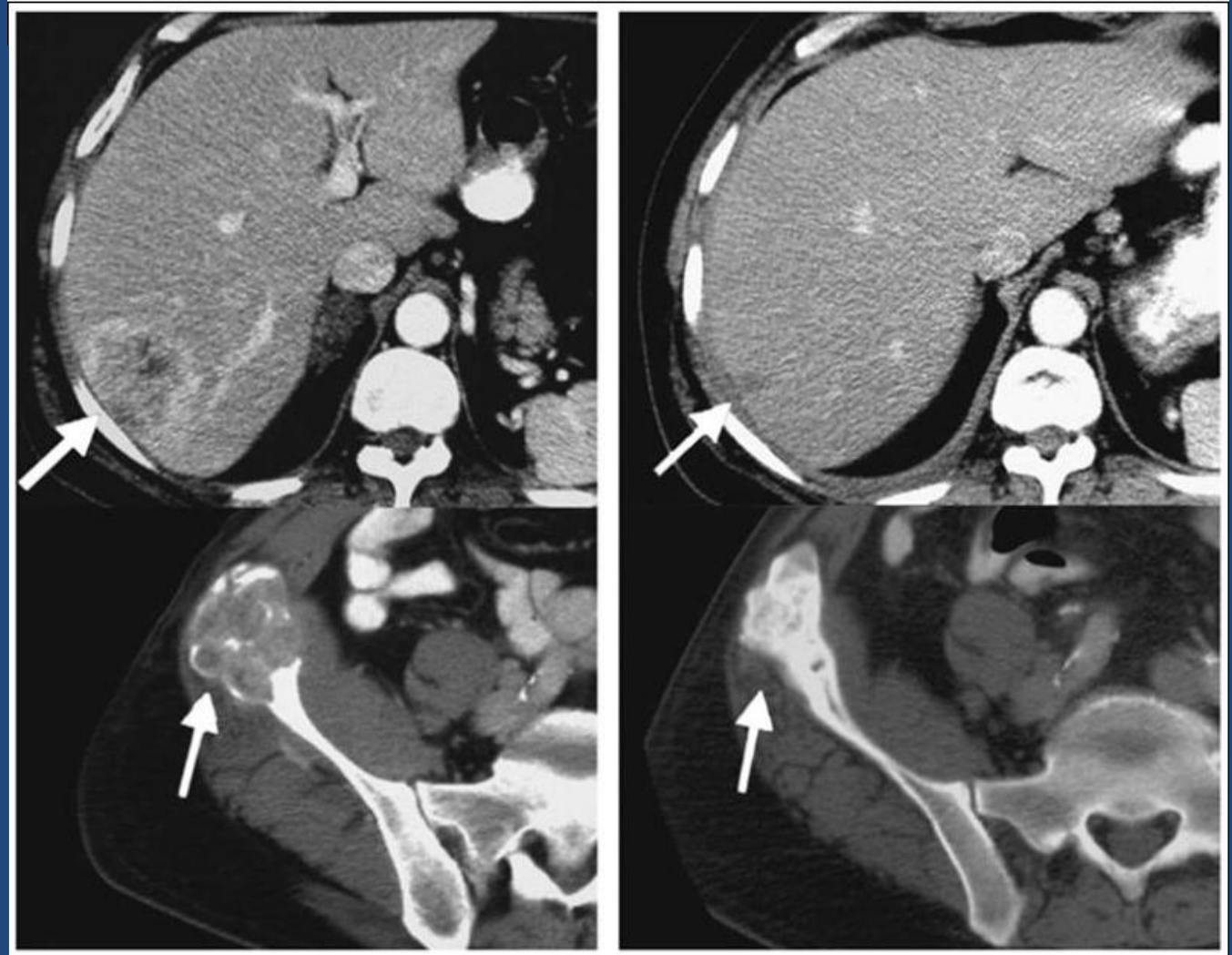
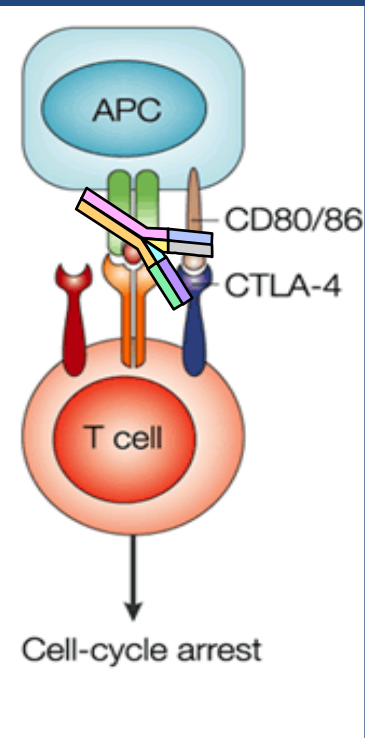
Number of patients at risk

Placebo plus interferon alfa	322	137	59	15	0
Bevacizumab plus interferon alfa	327	196	107	18	0

Metastatic Renal Cell Carcinoma



ipilimumab (PRs: 5/40)



Two years later

Metastatic RCC reduced-intensity allografting



Day 0



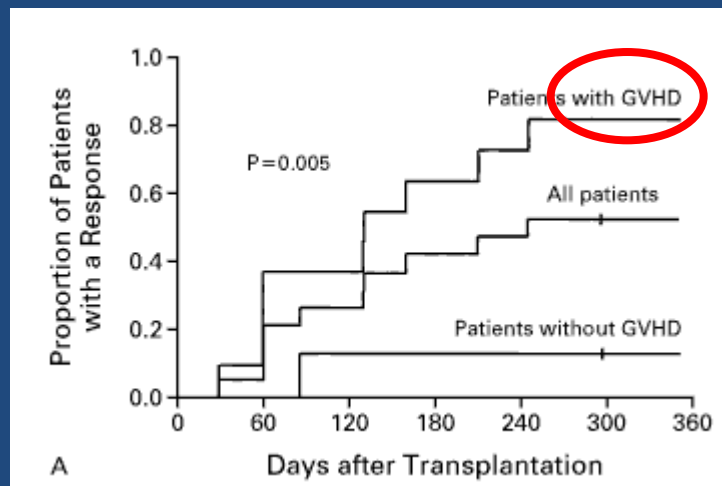
Day 64



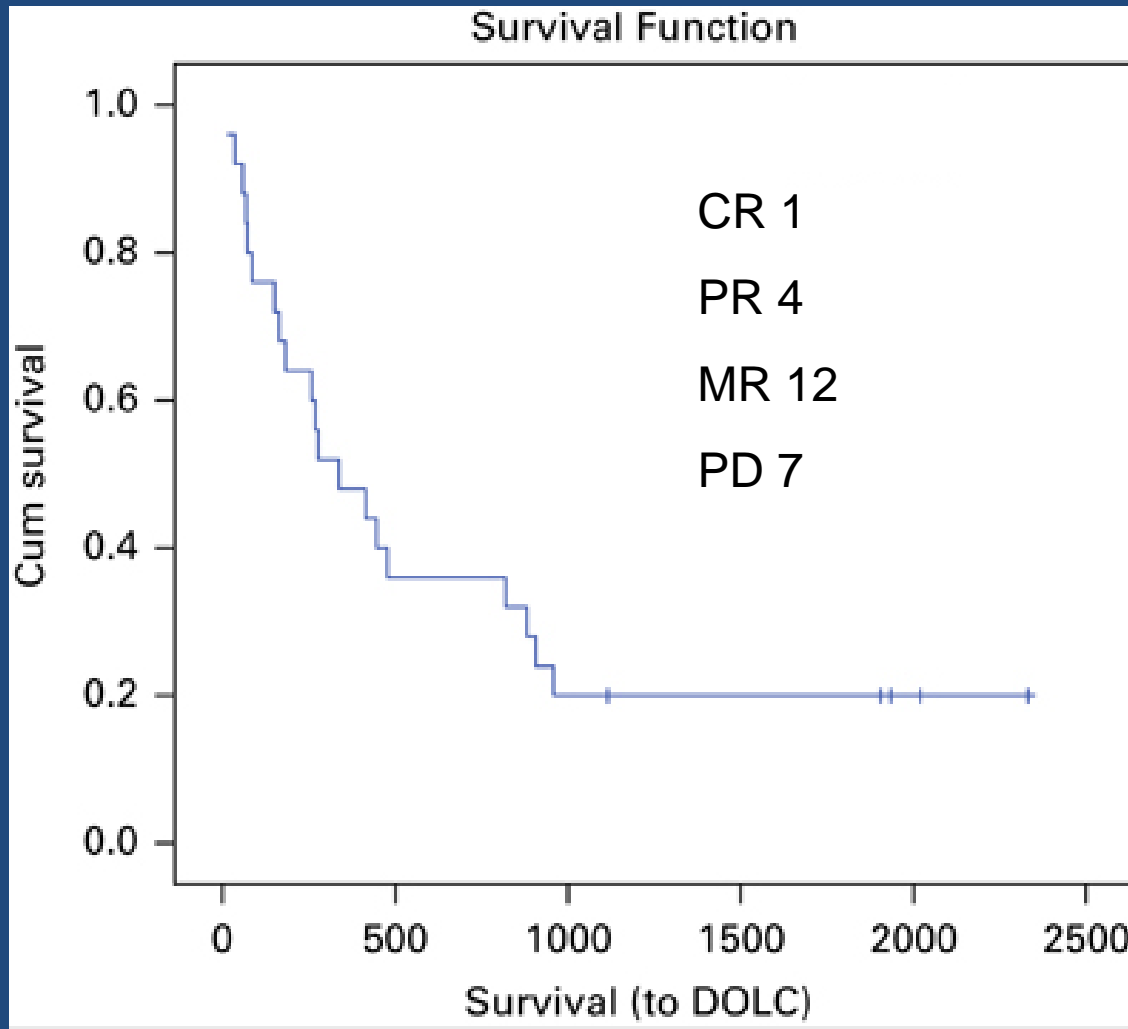
Day 110

Metastatic RCC reduced-intensity allografting

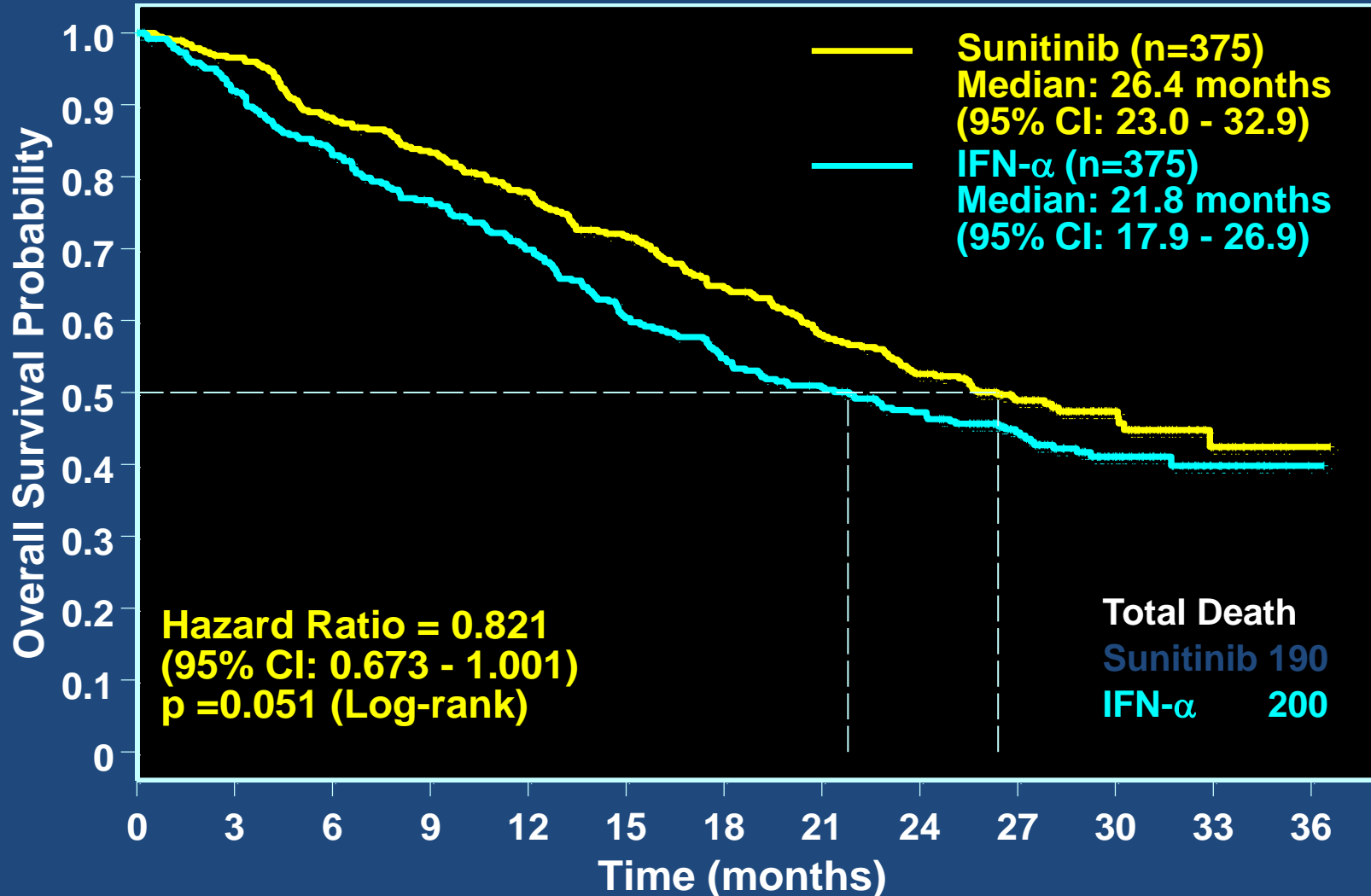
- 19 patients
- two died because of transplantation related toxicity
- 10 responses (3CR, 7 PR; 53%)
- regressions were late (median 129 days)
and often after withdrawal of ciclosporine



Metastatic RCC reduced-intensity allografting

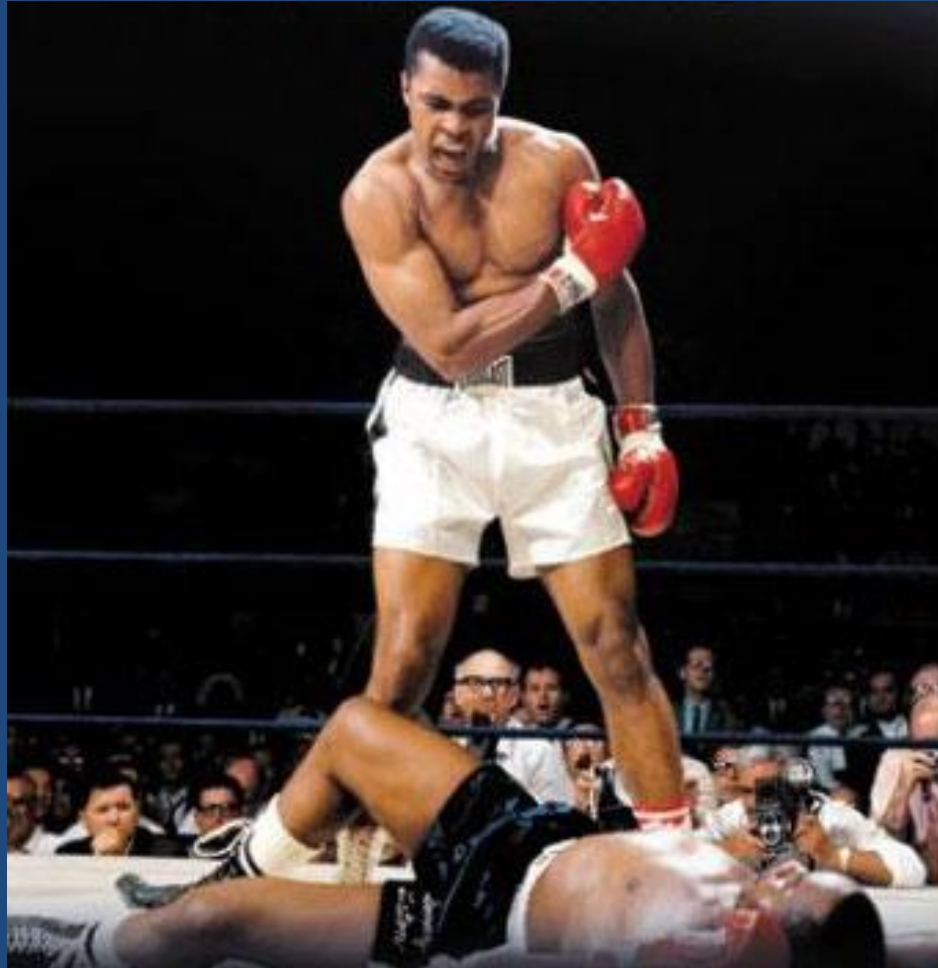


Final overall survival sunitinib versus interferon



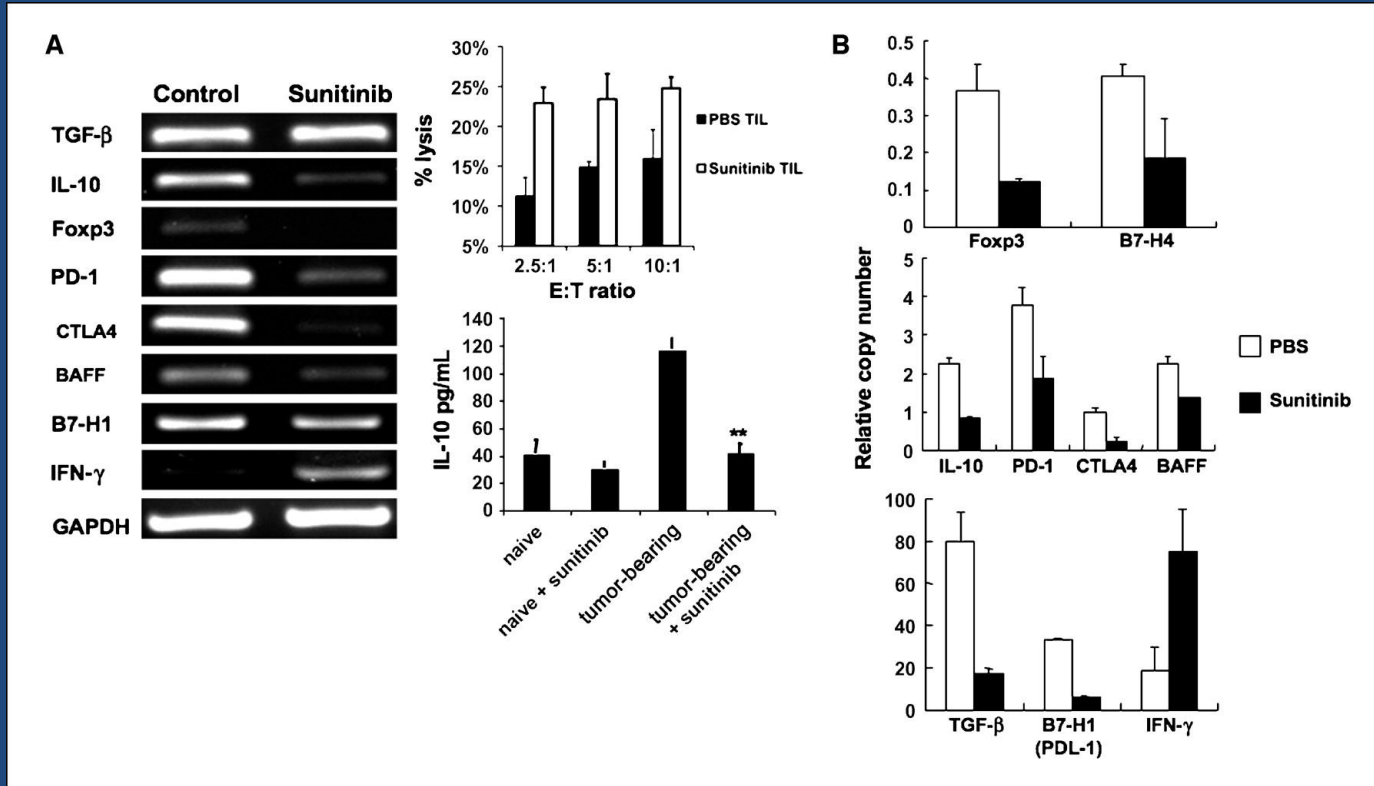
nDeath/nRisk Sunit	375	44 / 326	38 / 283	48 / 229	42 / 180	14 / 61	4 / 2
nDeath/nRisk IFN- α	375	61 / 295	46 / 242	52 / 187	25 / 149	15 / 53	1 / 1

Sunitinib



the end of immunotherapy ??

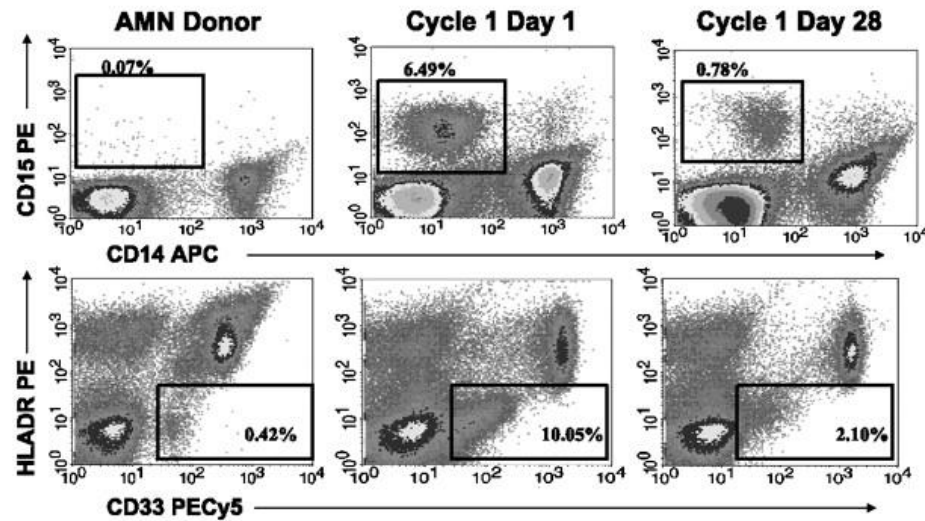
Sunitinib can reverse immune suppression of tumor microenvironment



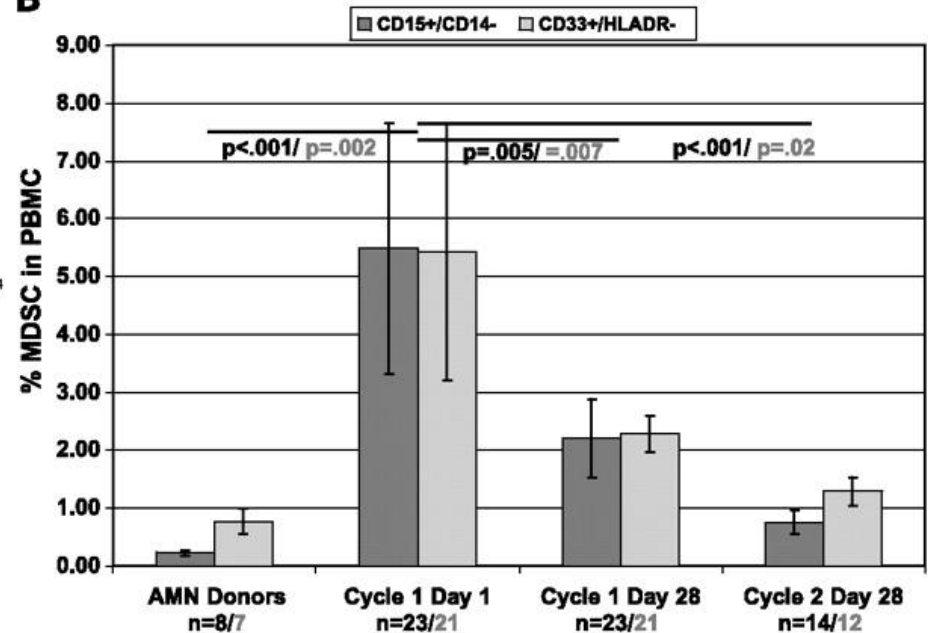
Ozao-Choy, J. et al. Cancer Res 2009;69:2514-2522

Elevated myeloid-derived suppressor cells in mRCC patients decline in response to sunitinib

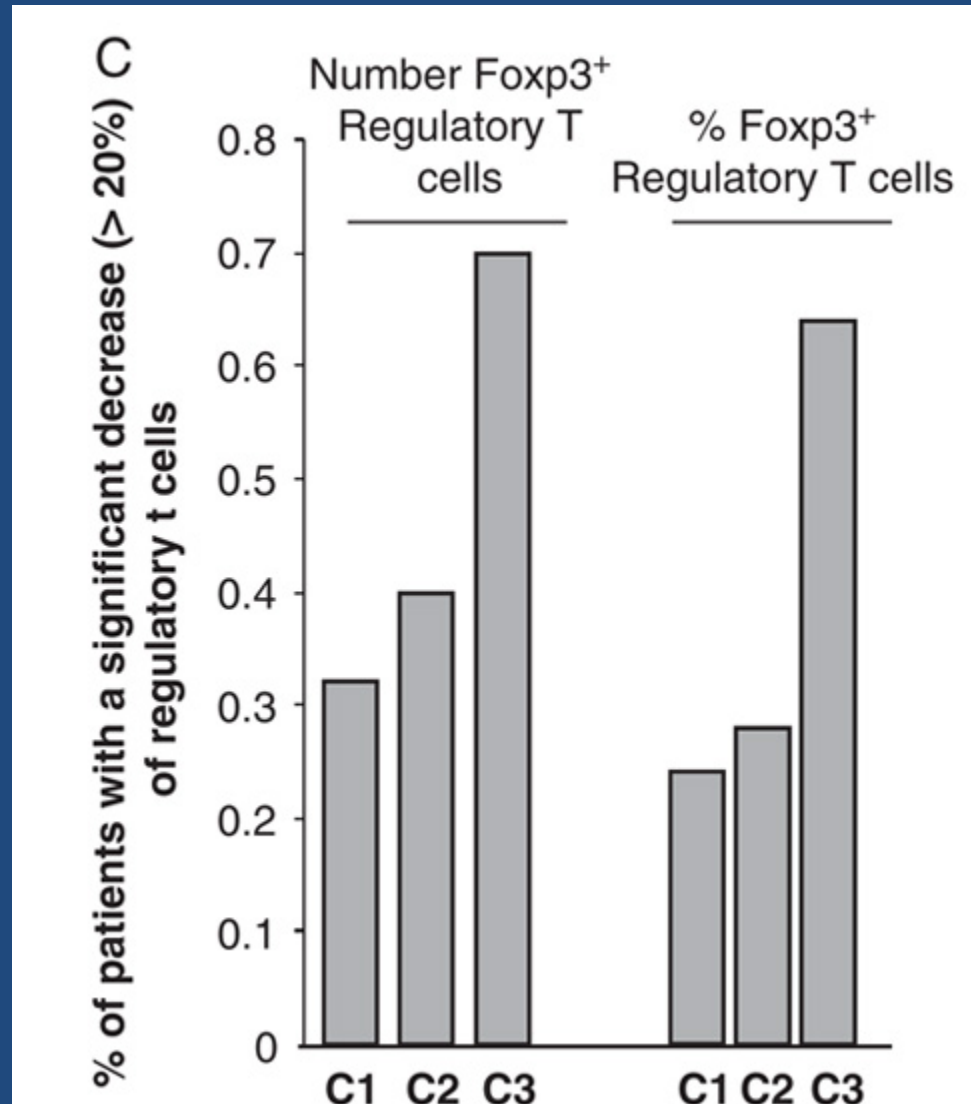
A



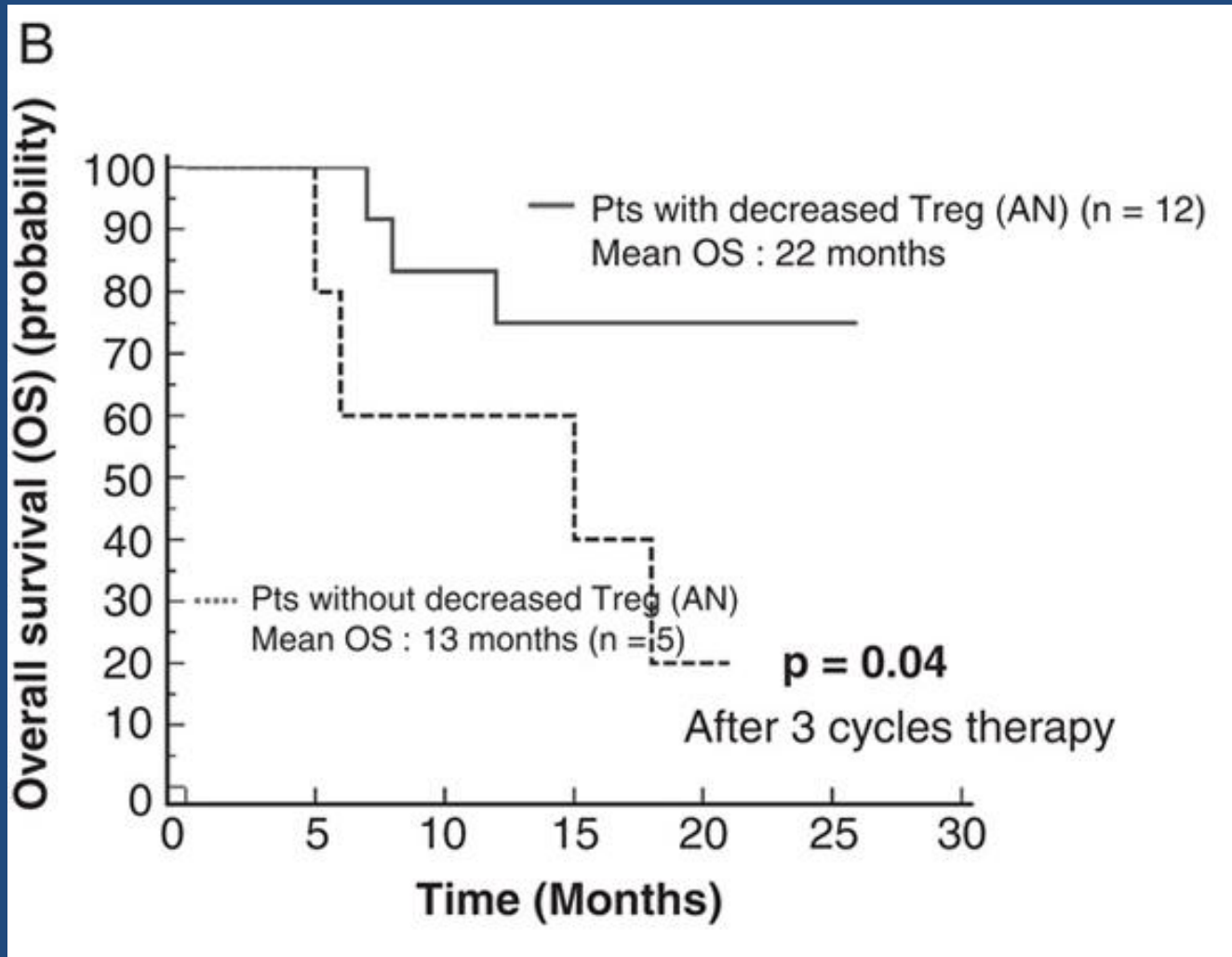
B



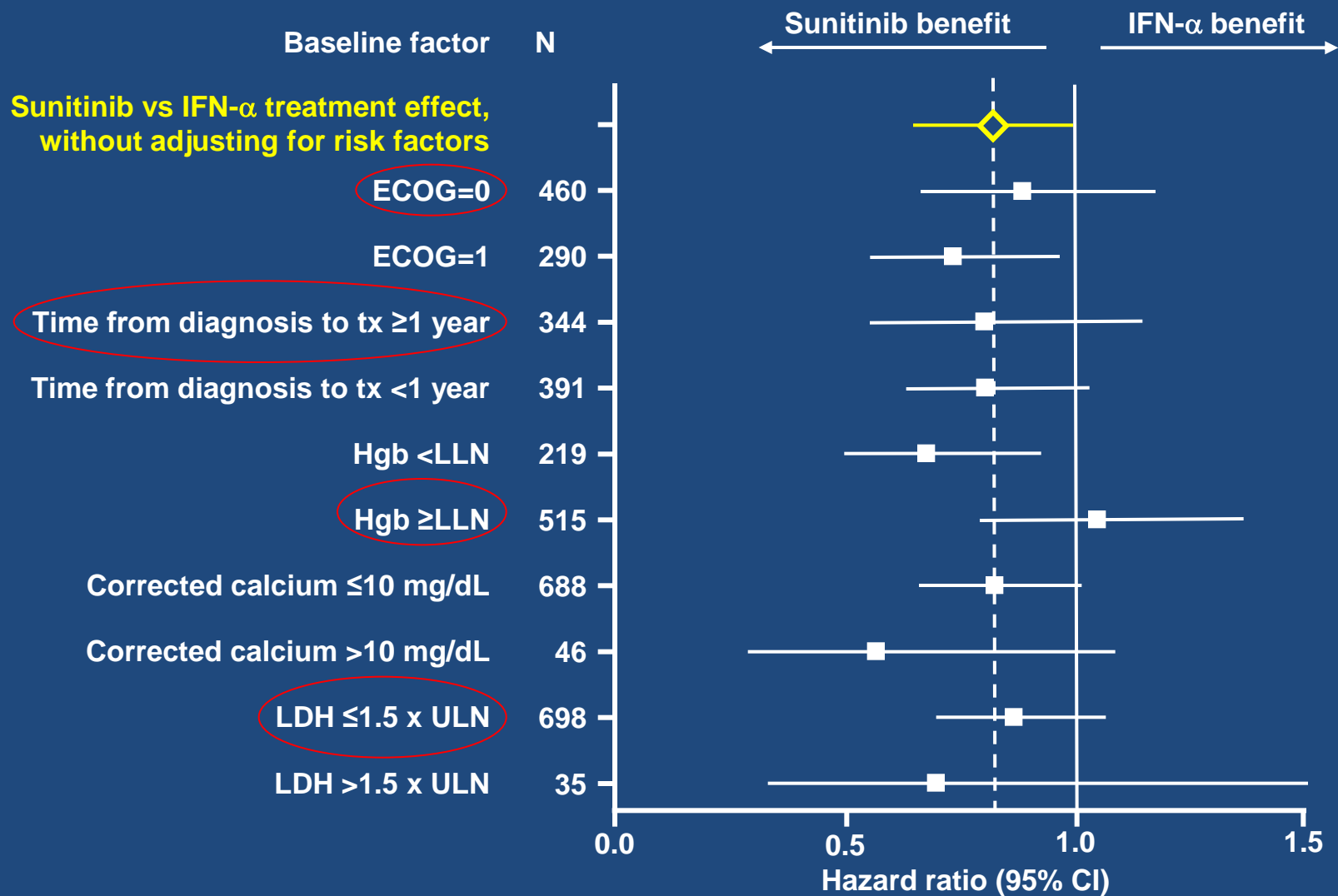
Regulatory T cells decrease after treatment with sunitinib in RCC patients



A decrease of regulatory T cells after sunitinib correlates with overall survival in RCC

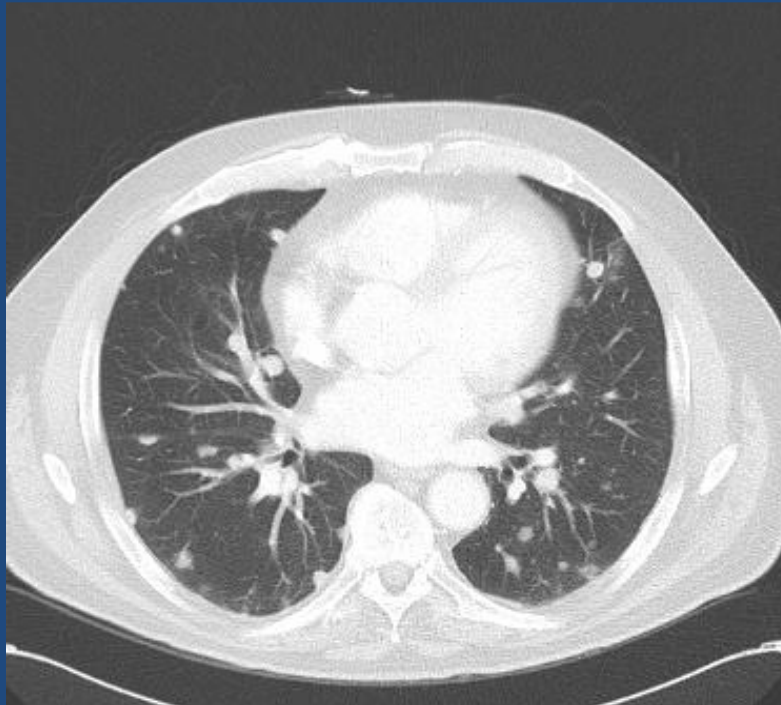


OS in Subgroups According to Individual Baseline Factors*

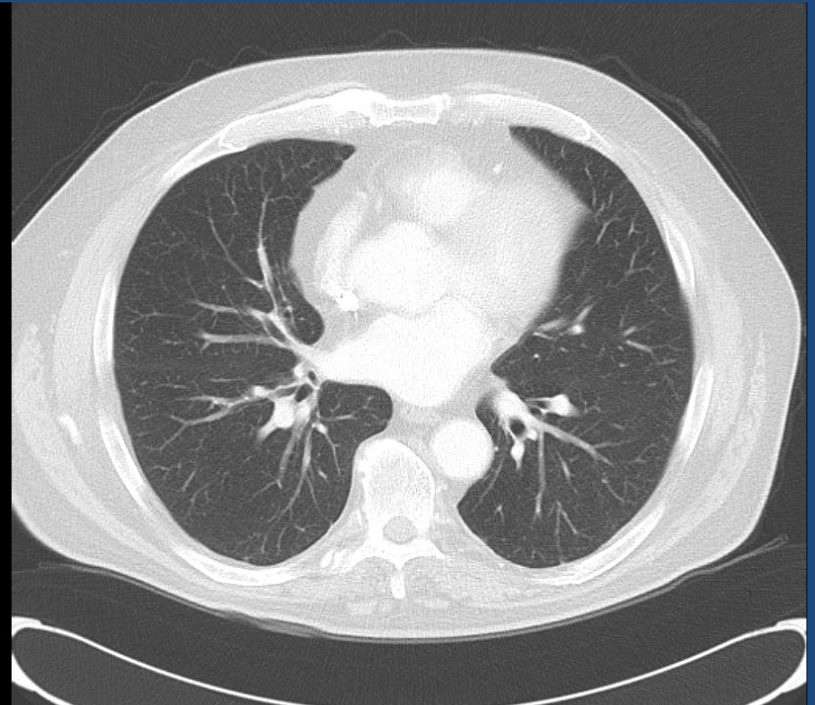


Metastatic Renal Cell Carcinoma

Immunotherapy a chance to cure



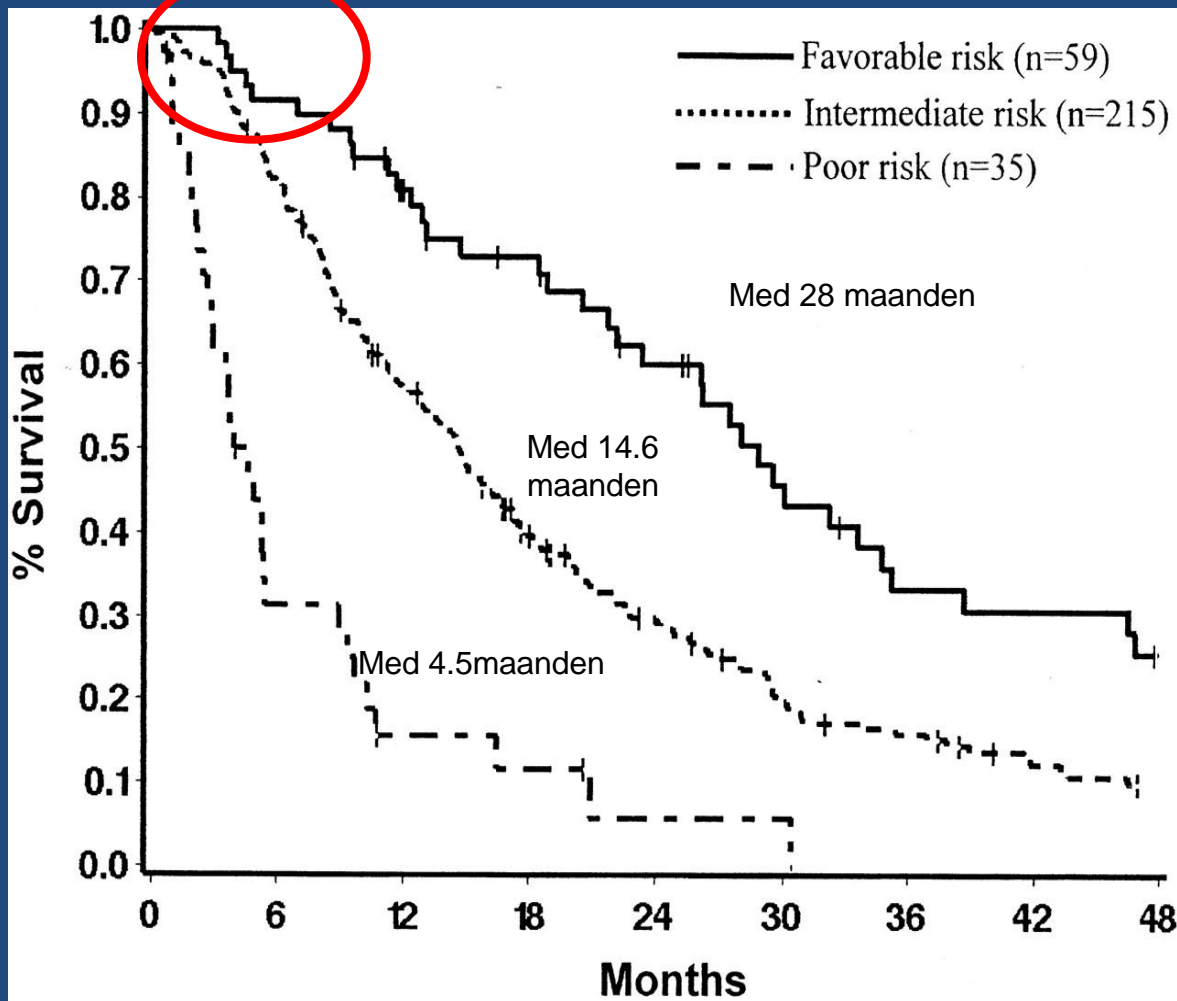
5-8-2005



7-1-2011

Metastatic Renal Cell Carcinoma prognosis

Timing of immunotherapy

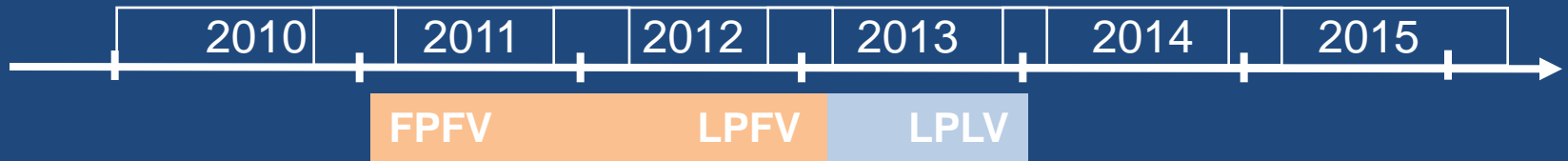


Motzer criteria

- Performance
- LDH
- Calcium
- Hemoglobin
- time to metastases



Phase I and II study of everolimus and low-dose oral cyclophosphamide in patients with metastatic renal cell cancer



Phase I: 2nd Line mRCC

N= 5 per dose level

Everolimus
10 mg/day until
progression

+

Dose level	<i>Week on, week off</i>	Dose level	<i>Continuous</i>
0	no cyclophosphamide		
1	50 mg cyclophosphamide; od	2	50 mg cyclophosphamide; od
3	50 mg cyclophosphamide; bid	4	50 mg cyclophosphamide; bid
5	100 mg cyclophosphamide; bid	6	100 mg cyclophosphamide; bid
7	150 mg cyclophosphamide; bid	8	150 mg cyclophosphamide; bid

Study endpoints

- Dose
- Safety
- Immunologic (e.g. Treg depletion)
- Angiogenesis
- RR
- PK

Phase I: 2nd Line mRCC

Everolimus
10 mg/day until
progression

+

Cyclophosphamide
Selected dose level

N= 56

Study endpoints

- PFS
- Safety
- Immunologic (e.g. Treg depletion)
- Angiogenesis
- RR

Immunotherapy in RCC

conclusions

- Immune system has an important role in the pathogenesis of RCC
- Immunotherapy can induce long term remissions and stabilizations
- **IMMUNOTHERAPY CAN CURE PATIENTS**
- An extra chance for fit RCC patients
- Immunotherapy has no chronic toxicity
- Subgroup of RCC patients that has benefit from immunotherapy should be identified