

**Immunotherapie heeft geen plaats
bij de behandeling van
het gemetastaseerde niercelcarcinoom**

WIN-O symposium 2011

Dick Richel

AMC

IFN-alpha and IL-2 have exciting antitumor properties

IFN-alpha:

direct antitumour activity

- Inhibition of proliferation
- Inhibition of angiogenesis
- Immune stimulation
- Induction of apoptosis

IL-2:

Indirect antitumour activity

- Induction of interferon-gamma
- Induced increased antigen-activated T-cell proliferation
- Increased macrophage cytotoxicity
- Increase in Fas-mediated T-cell apoptosis
- Decrease of neutrophil chemotaxis

**Spontane remissies
Immunotherapy "succesvol"
INF α en IL2**

Bartsch, *Int J Cancer* 1989.

Ezekowitz, *N Engl J Med* 1992.

Grossberg *SE Interferon* 1985.

Gutterman, *Proc Natl Acad Sci USA* 1993.

Whittington, *Drugs* 1993.

Oppenheim, *Oncology* 1994.

Cellular and Molecular Immunology 1997.

Jablons, *J Immunol* 1990.

Interferon alpha (IFN- α)

- Response rates of 6-15%
- Survival benefit over hormonal therapy in mRCC¹
- Modest survival benefit of 2-3 months when compared with placebo-equivalent^{2,3}

Conclusion Cochrane review 2005⁴:

IFN provides a modest survival benefit compared with other commonly used treatments

¹ Medical Research Council Renal Cancer Collaborators. *Lancet* 1999;353(9146):14-17; ² Motzer RJ, et al. *J Clin Oncol* 2002;20(1):289-296;

³ Coppin C, et al. *Cochrane Database Syst Rev* 2005;(1):CD001425; 4. Coppin et al. *Cochrane Database Syst Rev* 2005;(1):CD001425

Interleukin-2 (IL-2)

- Response rates of 7-27%^{1,2,3}
- Long-term (>10 years) complete responders have been achieved with high-dose bolus IL-2⁴
- Toxicity substantially higher than IFN- α

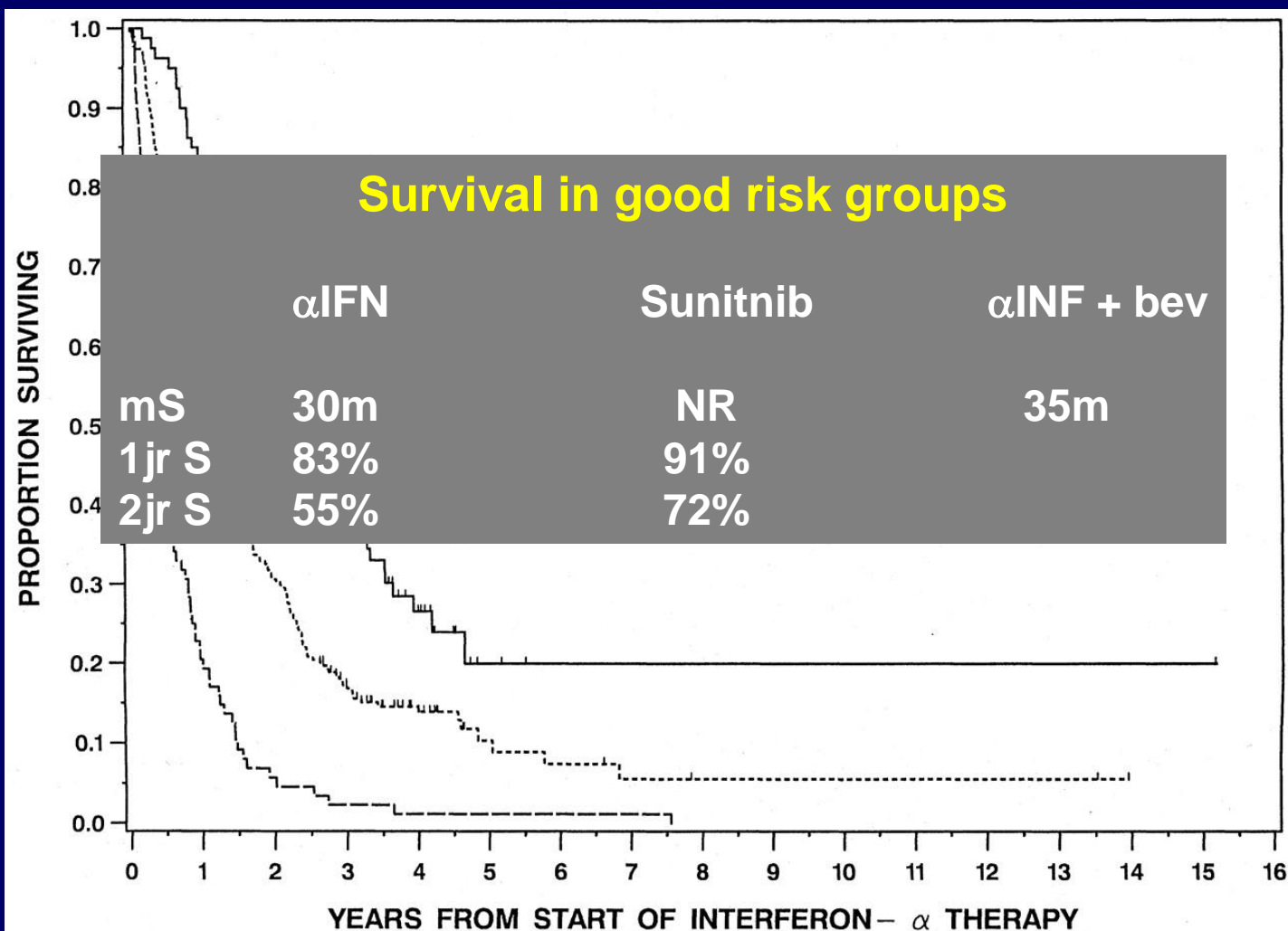
Conclusion Cochrane review 2005:

IL-2 has not been sufficiently validated in RCTs⁵

α IFN zou met name actief zijn in geselecteerde patiënt populaties

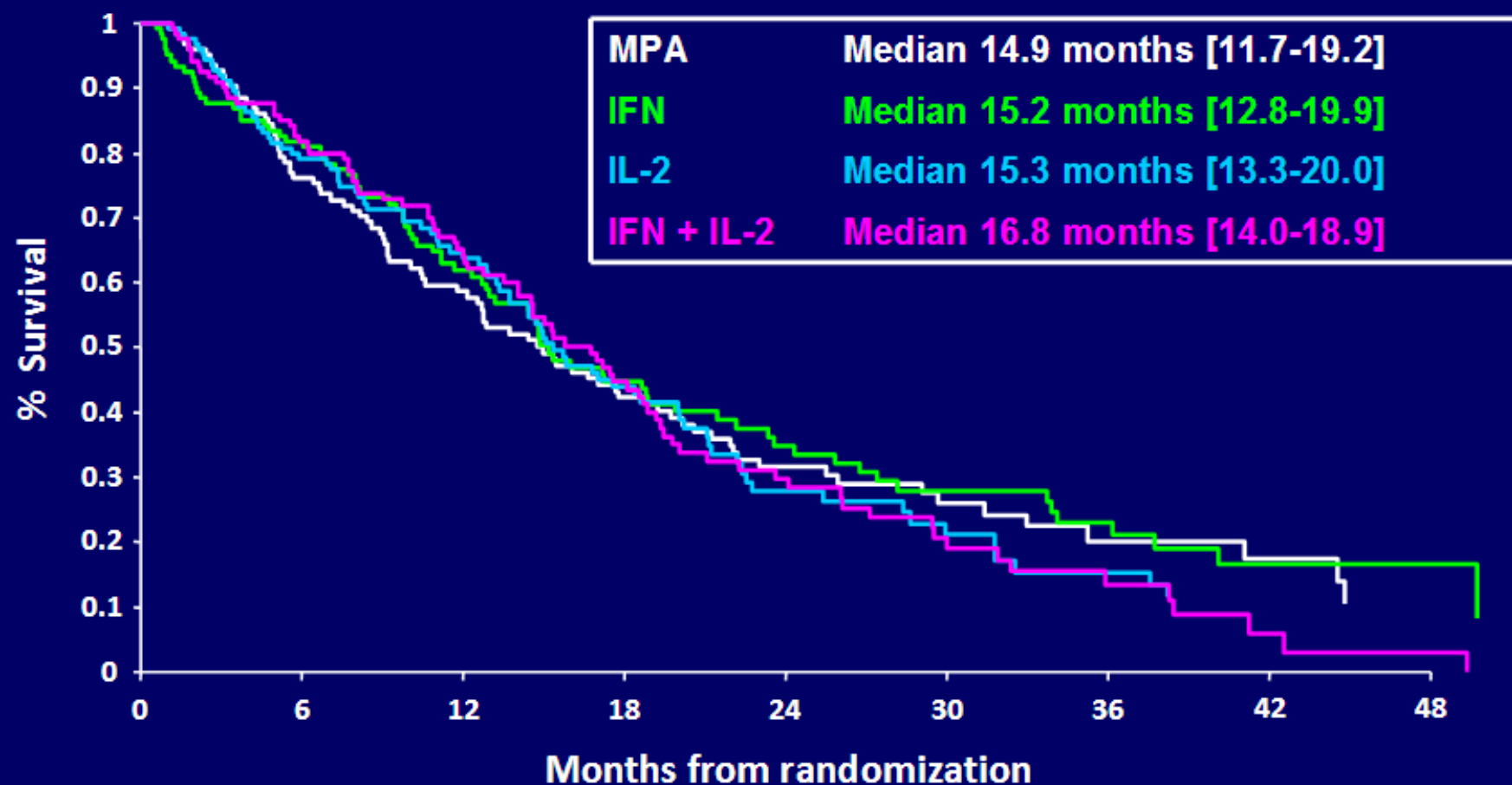
**Clear cell carcinoma
Good risk group (Motzer)
Lung metastases only**

Survival stratified by MSKCC risk group (n=437)



Risk factors: KPS <80%; low HGB; high LDH; high corrected calcium; time from Dx to IFN <1 year

No Survival Advantage for IFN/IL-2 or both in Intermediate Prognosis Pts (PERCY Quattro)

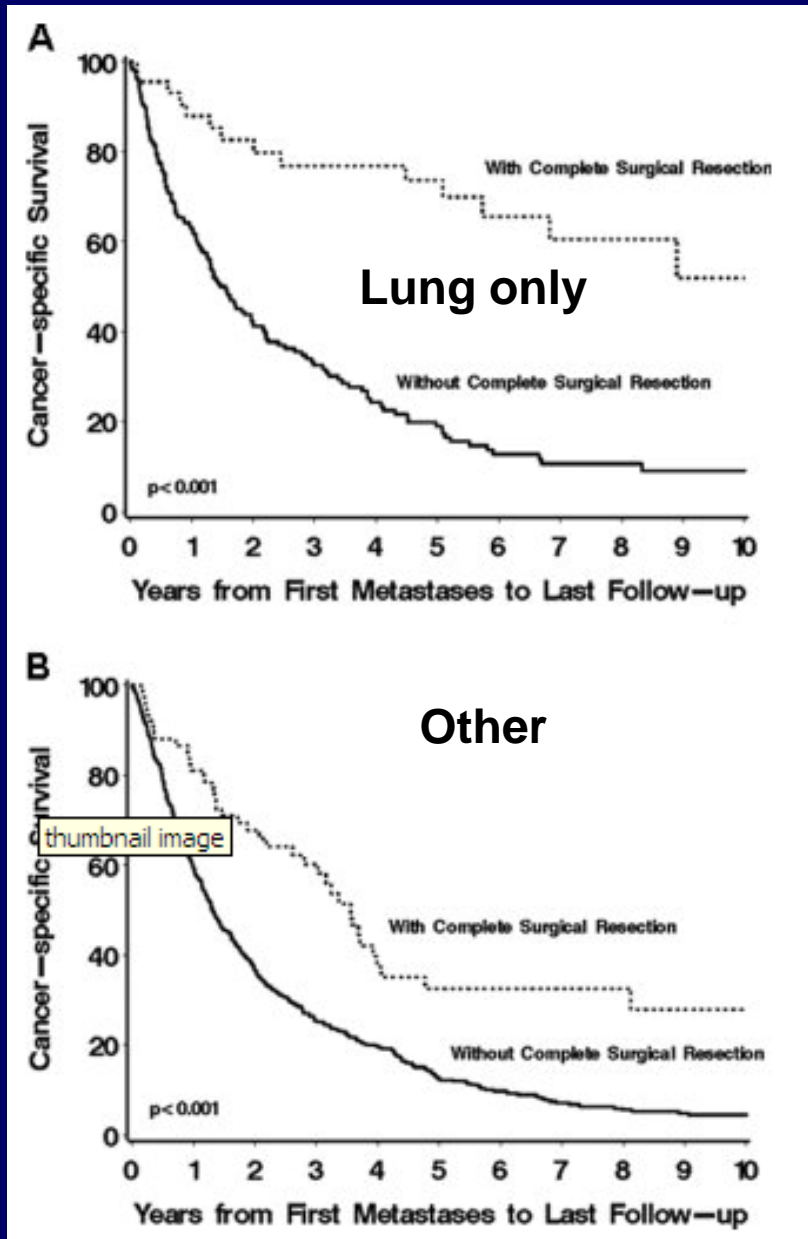


“Lung metastases only” ??

Geen goede data in de literatuur over te vinden.

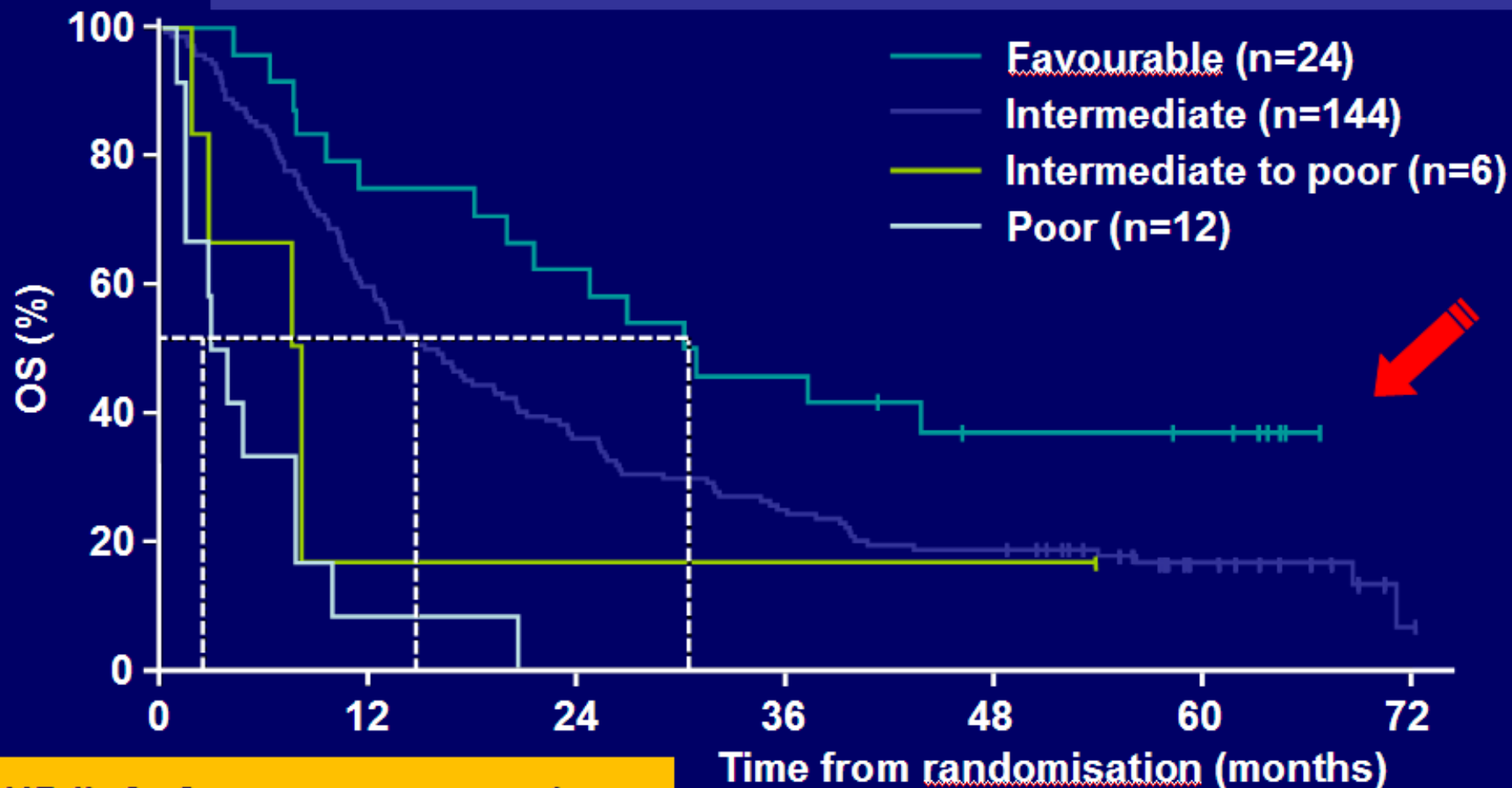
Alleen “personal experience”

Resectie van longmetastasen niercelcarcinoom



IL2

Cytokine Working Group phase III trial: OS by MSKCC criteria



HD IL-2: Cases not progressing after $\geq 30m$ ($\pm 4\%$) possibly cured

Ondanks vele jaren van klinische trials nog steeds niet mogelijk om patiënten voor α INF of IL2 te selecteren

Adjuvante trials immunotherapie

Adjuvante immunotherapy

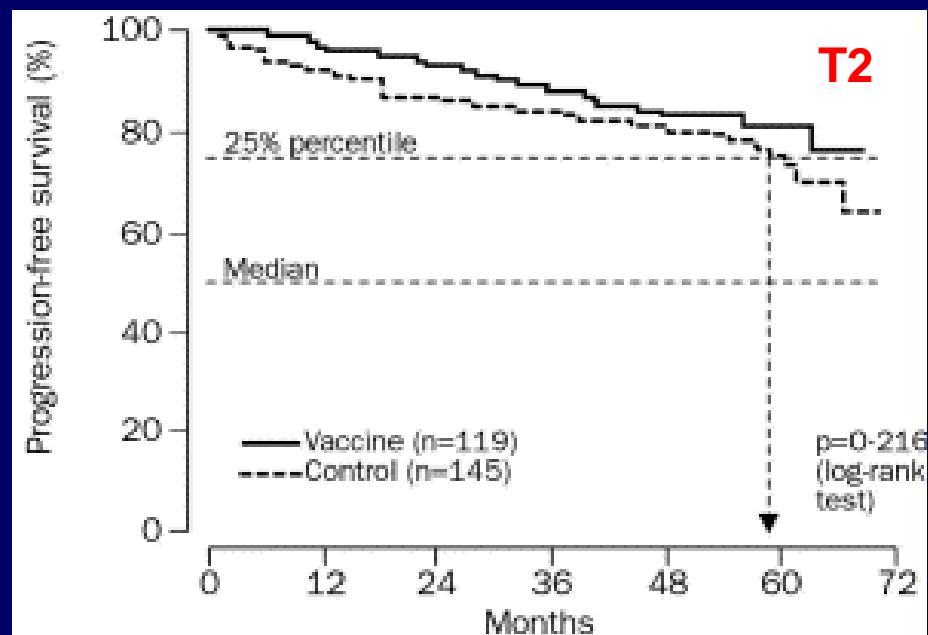
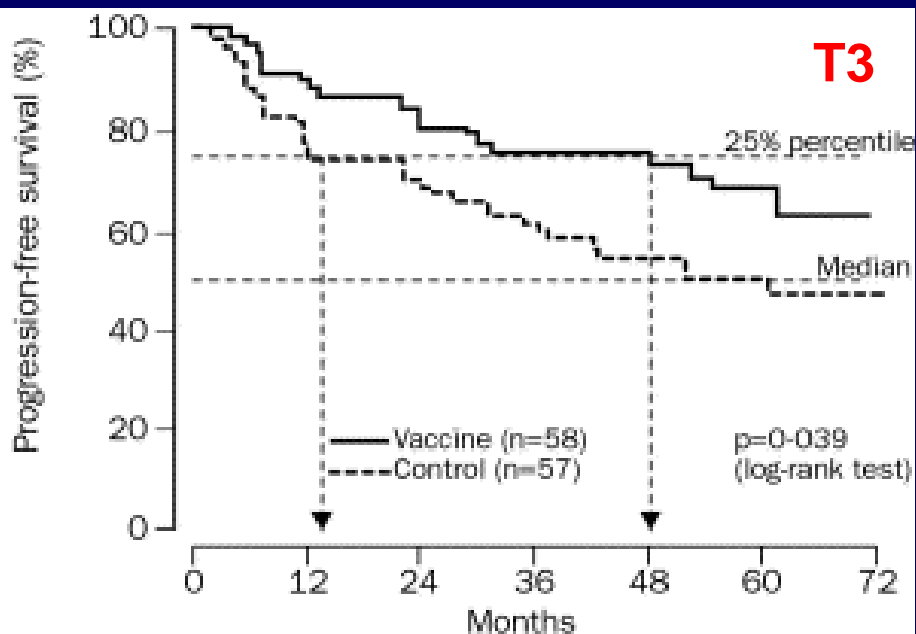
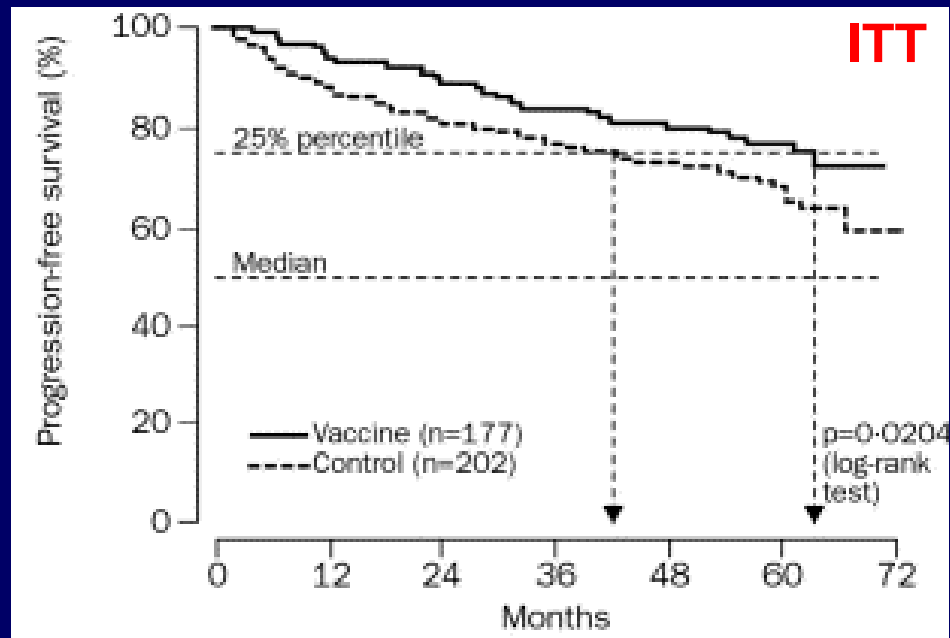
Geen voordeel tov observatie

Adjuvante trials immunotherapie

Autologe tumorvaccinatie na resectie

Lancet 2004;363:594

Survival?
1/3 kregen niet de therapie
waarvoor gerandomiseerd!





MAAR!



GMTV Gene modified tumor vaccines
Autologe tumor cellen
Dendritische cellen loaded with tumor antigens
Heat-shock protein (HSP)-peptide complex
Anti-CTL4

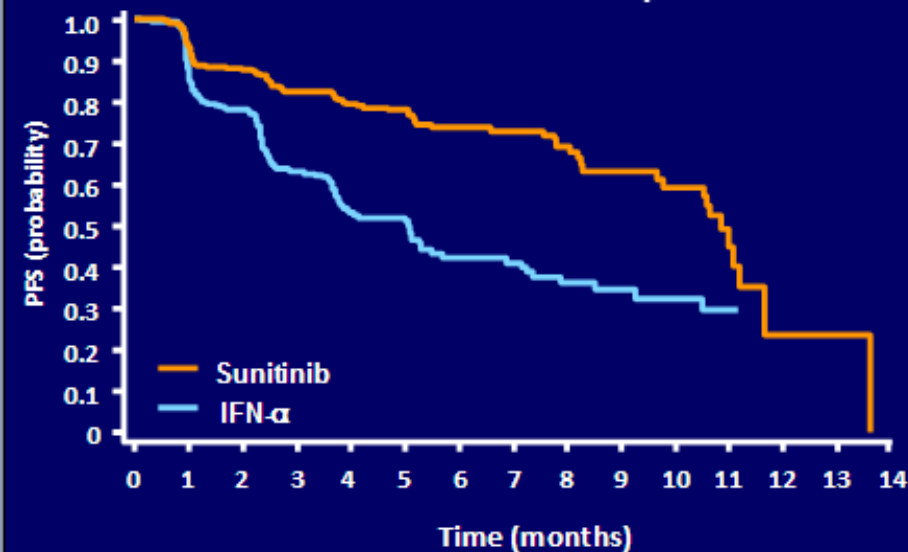
DCC

All phase I/II trials
Small number of renal cell carcinomas (197)
Pretreated
Sporadic responses, disease stabilization 30%
Eur Urol 2006 50 34

Targeted therapy has demonstrated superior efficacy (PFS) compared with cytokine therapy

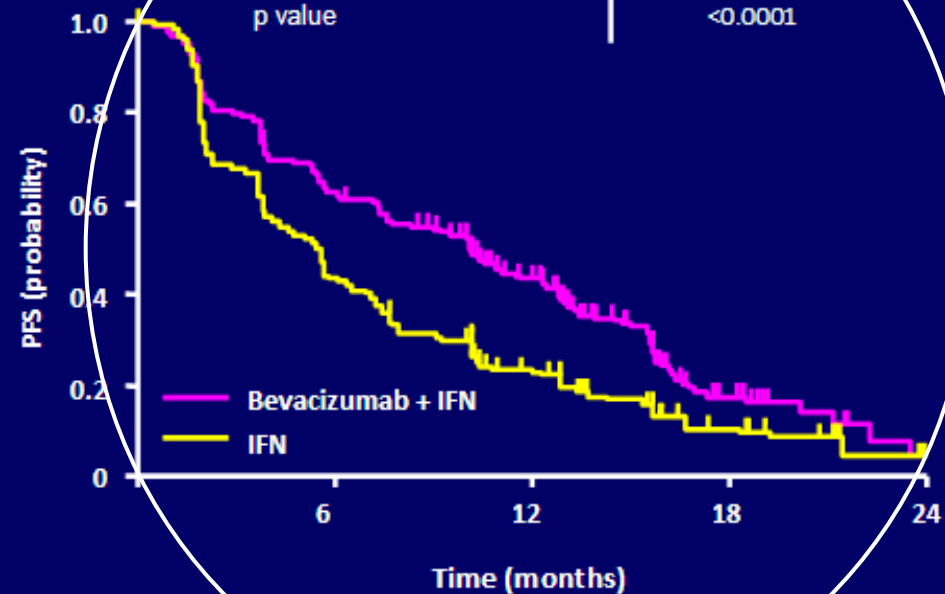
Median PFS (months)

Sunitinib	11.0
IFN- α	5.0
Hazard ratio (95% CI)	0.42 (0.32, 0.54)
p value (2-sided)	<0.001



Median PFS (months)

Bevacizumab + IFN	10.2
IFN	5.4
Hazard ratio (95% CI)*	0.61 (0.51, 0.73)
p value	<0.0001



Immunotherapie niercelcarcinoom

Wetenschappelijk zeer interessant

doch

Klinisch irrelevant

Hobbyisme

Immunother

**Cytokines en antiapoptotische moleculen die de CTL
Blokkeren**

**Epitope evansie
MHC1 down regulatie**