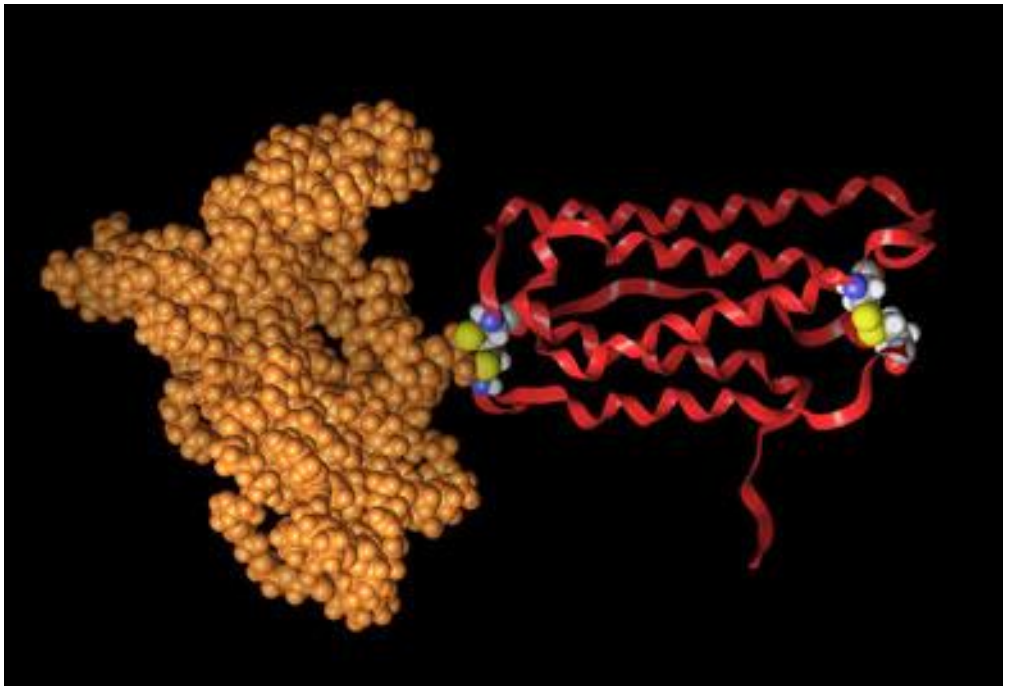
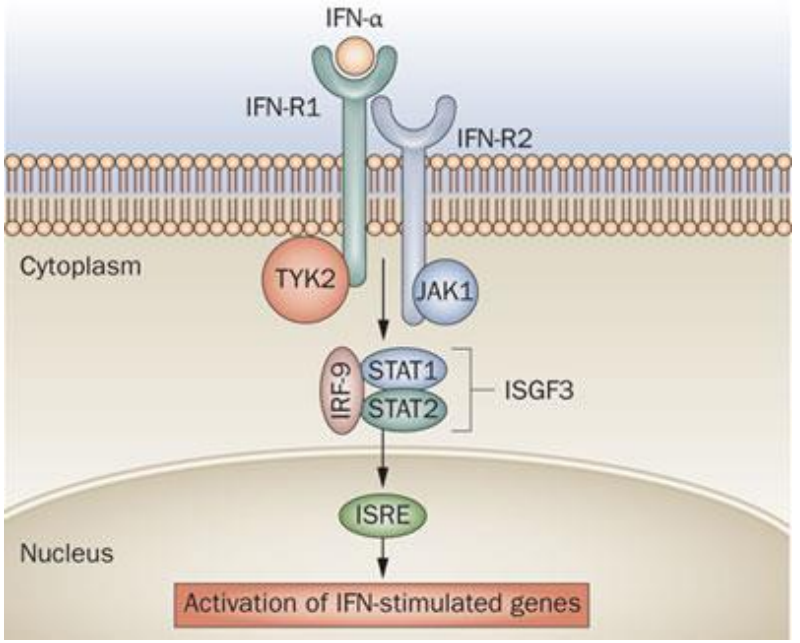
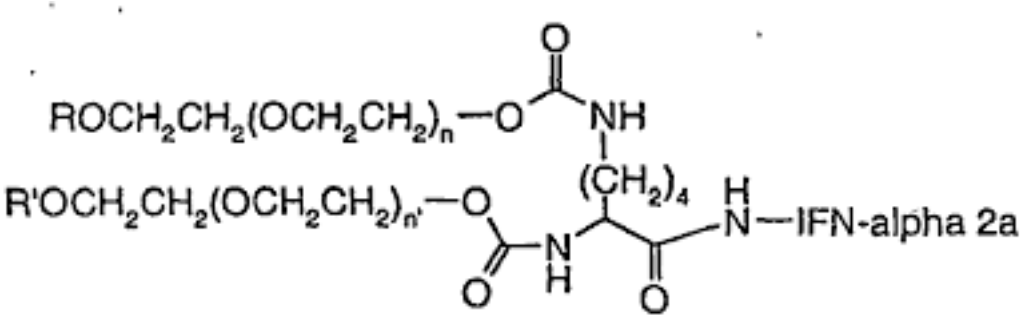



IFN-α
IFN-R1
IFN-R2
Cytoplasm
TYK2
JAK1
IRF-9
STAT1
STAT2
ISGF3
ISRE
Nucleus
Activation of IFN-stimulated genes


ROCH2CH2(OCH2CH2)n—O
NH
(CH2)4
R'OCH2CH2(OCH2CH2)n'—O
N
H
H
N—IFN-alpha 2a
O

EORTC 18991 vs. ECOG 1684

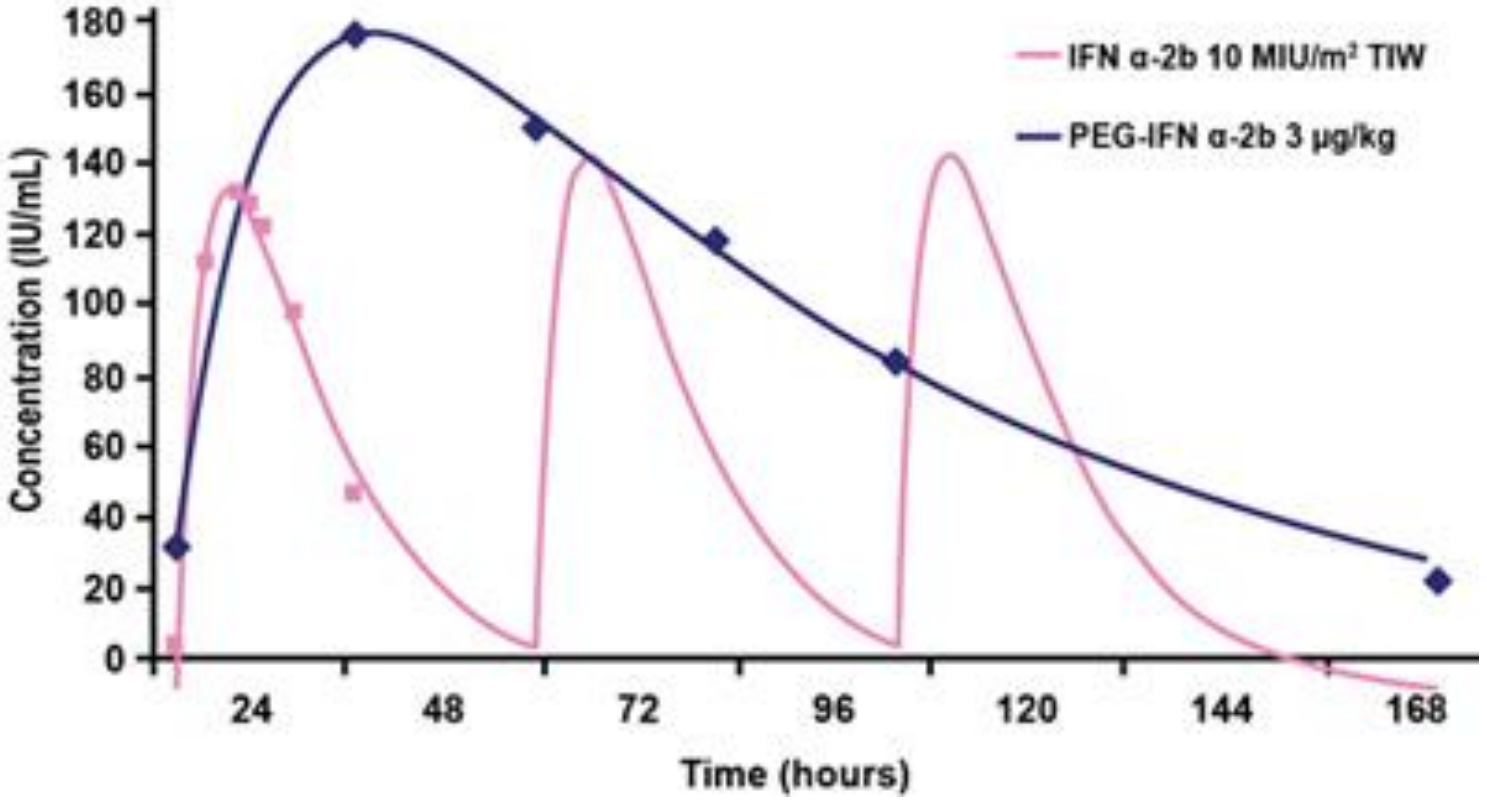
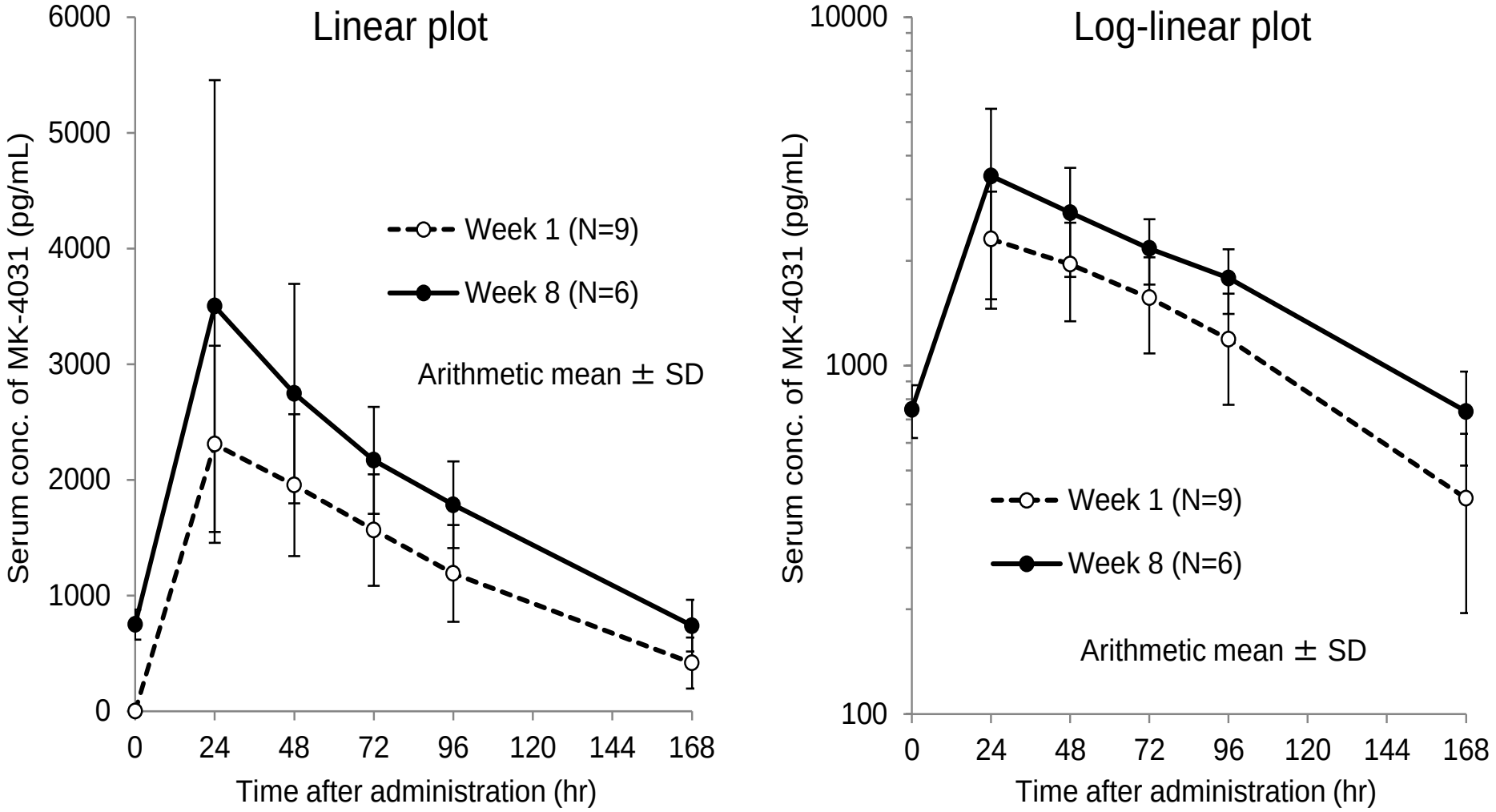


Figure 3.

(a) Serum concentration – time profile by 6 μg/kg/week dosing of PEG-IFN α-2b (arithmetical mean ± standard deviation).

(One patient data who did not administer at Week 7 is excluded from calculation at Week 8.)

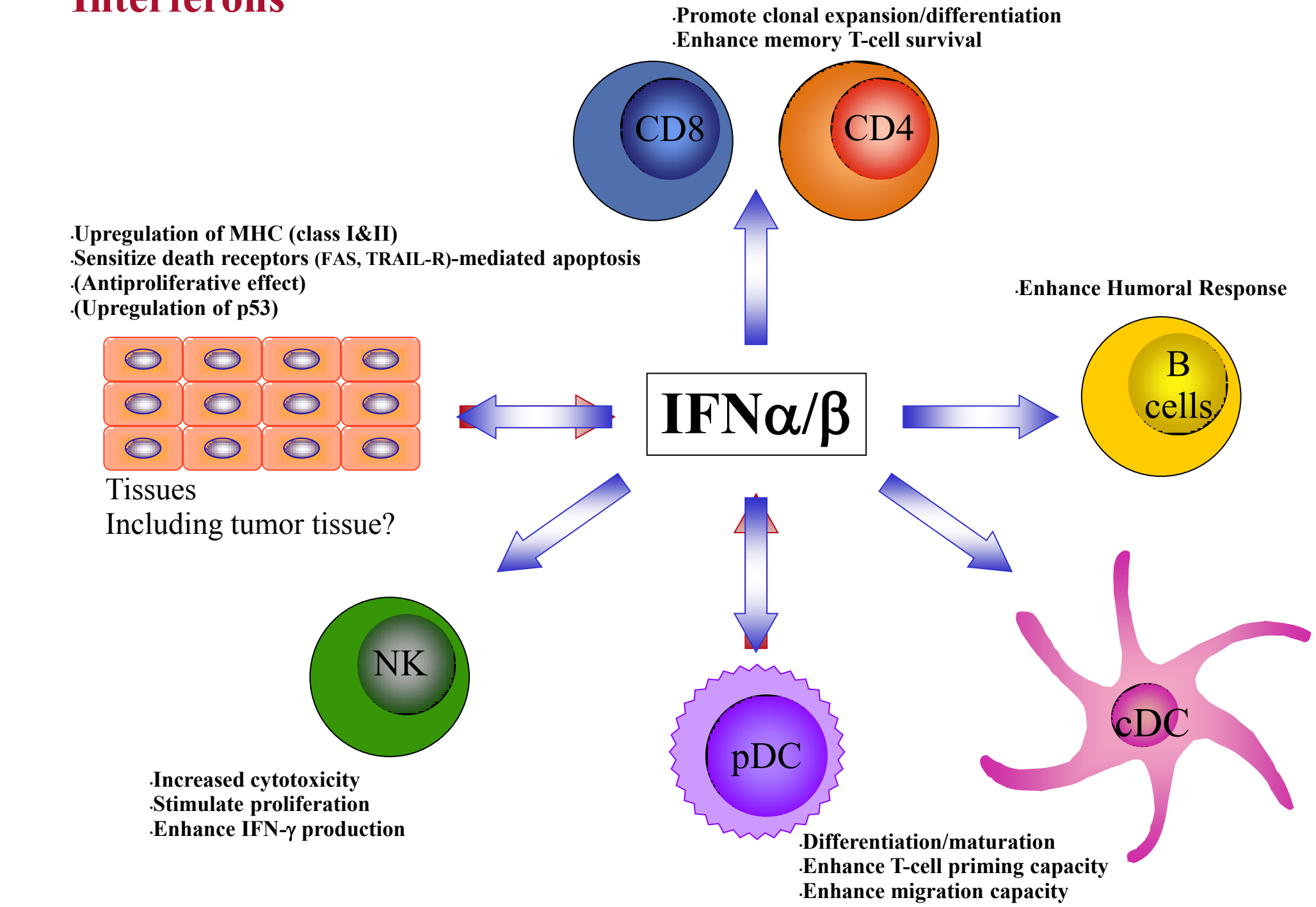


Adjuvant therapy with pegylated interferon alfa-2b versus observation alone in resected stage III melanoma: final results of EORTC 18991, a randomised phase III trial **Alexander MM Eggermont**, MD, Stefan Suciu, PhD, Mario Santinami, MD, Alessandro Testori, MD, Wim HJ Kruit, MD, Jeremy Marsden, MD, Prof Cornelis JA Punt, MD, François Salès, MD, Prof Martin Gore, MD, Prof Rona MacKie, MD, Prof Zvonko Kusic, MD, Prof Reinhard Dummer, MD, Prof Axel Hauschild, MD, Elena Musat, MD, Alain Spatz, MD, Prof Ulrich Keilholz, MD, for the EORTC Melanoma Group‡

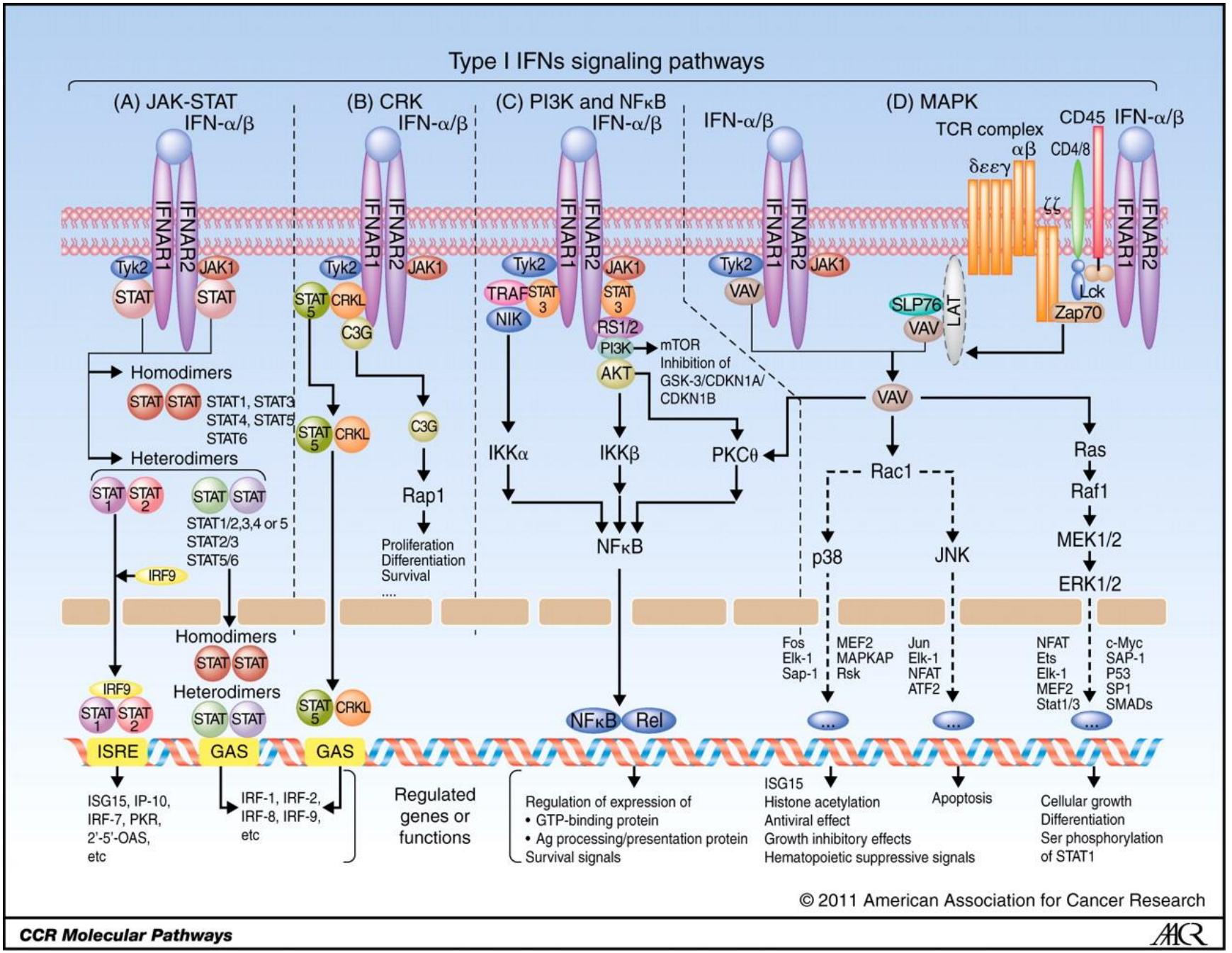
1256 patients with resected stage III melanoma were randomly assigned to observation (n=629) or pegylated interferon alfa-2b (n=627) 6 µg/kg per week for 8 weeks (induction) then 3 µg/kg per week (maintenance)

The 4-year rate of recurrence-free survival was 45·6% (SE 2·2) in the interferon group and 38·9% (2·2) in the observation group. There was no difference in overall survival between the groups. Grade 3 adverse events occurred in 246 (40%) patients in the interferon group and 60 (10%) in the observation group; grade 4 adverse events occurred in 32 (5%) patients in the interferon group and 14 (2%) in the observation

Immunological properties of Type I Interferons



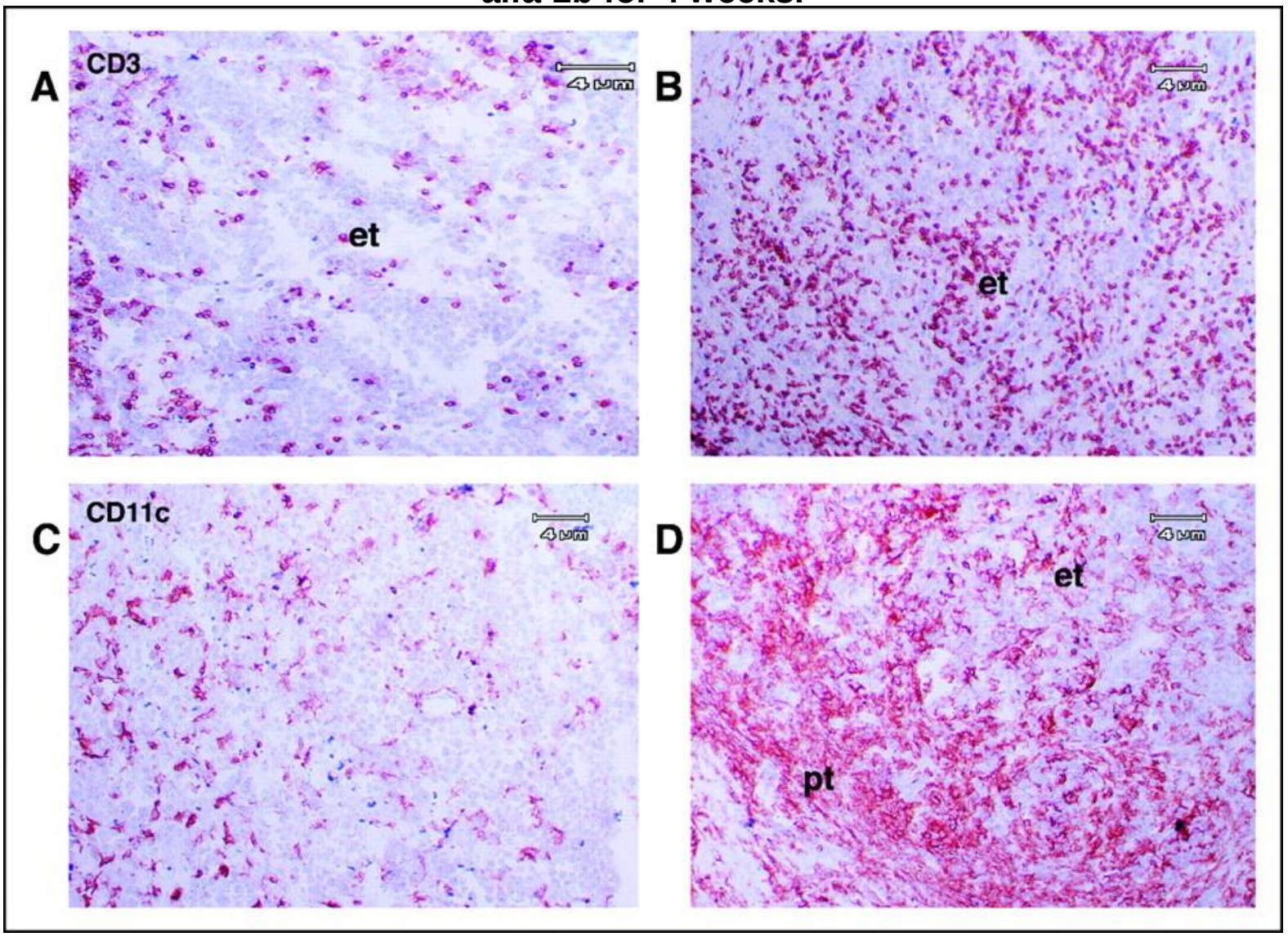
Signaling pathways activated by the IFN-I receptor.



Sandra Hervas-Stubbs et al. Clin Cancer Res 2011;17:2619-2627

Clinical Cancer Research
AACR American Association for Cancer Research

Immunohistochemical staining for CD3 (A, B) and CD11c (C, D) in melanoma-infiltrated lymph nodes from a clinical responder before (A, C) and after (B, D) treatment with high-dose interferon alfa-2b for 4 weeks.



Stergios J. Moschos et al. JCO 2006;24:3164-3171

Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial

Alexander M M Eggermont, MD, Vanna Chiarion-Sileni, MD, Prof Jean-Jacques Grob, MD, Prof Reinhard Dummer, MD, Jedd D Wolchok, MD, Henrik Schmidt, MD, Omid Hamid, MD, Prof Caroline Robert, MD, Prof Paolo A Ascierto, MD, Jon M Richards, MD, Prof Céleste Lebbé, MD, Virginia Ferraresi, MD, Michael Smylie, MD, Jeffrey S Weber, MD, Michele Maio, MD, Cyril Konto, MD, Axel Hoos, MD, Veerle de Pril, MSc, Ravichandra Karra Gurunath, MD, Gaetan de Schaetzen, PhD, Stefan Suciu, PhD, Alessandro Testori, MD

951 patients were randomly assigned to ipilimumab (n=475) or placebo (n=476)

Median recurrence-free survival was 26·1 months (95% CI 19·3–39·3) in the ipilimumab group versus 17·1 months (95% CI 13·4–21·6) in the placebo group (hazard ratio 0·75; 95% CI 0·64–0·90; p=0·0013); 3-year recurrence-free survival was 46·5% (95% CI 41·5–51·3) in the ipilimumab group versus 34·8% (30·1–39·5) in the placebo group.

FDA News Release
FDA approves Yervoy to reduce the risk of melanoma returning after surgery
October 28, 2015

Five (1%) participants died because of drug-related adverse events in the ipilimumab group;

FDA Approves Ipilimumab to Reduce the Risk of Melanoma Recurrence After Surgery

A new use as adjuvant therapy for patients with stage III melanoma

Date: 03 Nov 2015

Topic: **Melanoma** / **Immuno-oncology**

On 28 October 2015, the US Food and Drug Administration (FDA) expanded the approved use of ipilimumab (Yervoy) to include a new use as adjuvant therapy for patients with stage III melanoma, to lower the risk that the melanoma will recur following surgery.

In stage III melanoma, the cancer has spread to one or more lymph nodes. Patients with stage III melanoma are generally treated by surgery to remove the melanoma skin lesions and the nearby lymph nodes.

Yervoy, administered intravenously, was originally approved in 2011 to treat late-stage melanoma that cannot be removed by surgery. Yervoy is a monoclonal antibody that blocks cytotoxic T-lymphocyte antigen-4 (CTLA-4). CTLA-4 may play a role in slowing down or turning off the body's immune system, and affects its ability to fight off cancerous cells. Yervoy may work by allowing the body's immune system to recognise, target and attack cells in melanoma tumours.

The safety and effectiveness of Yervoy for this new use were studied in 951 patients who received Yervoy or a placebo as adjuvant therapy following complete surgical removal of melanoma. The study measured recurrence-free survival and overall survival.

It the study, 49% of participants treated with Yervoy had their cancer return after an average of 26 months, compared to 62% of those receiving a placebo, whose cancer returned after an average of 17 months. The analysis of overall survival data has not yet occurred.

So what to do with type I IFNs in melanoma?

1. Combinations
2. Intratumoral administration (a local cytokine system)
3. Gene therapy
4. Get it induced by virotherapy (T-Vec)

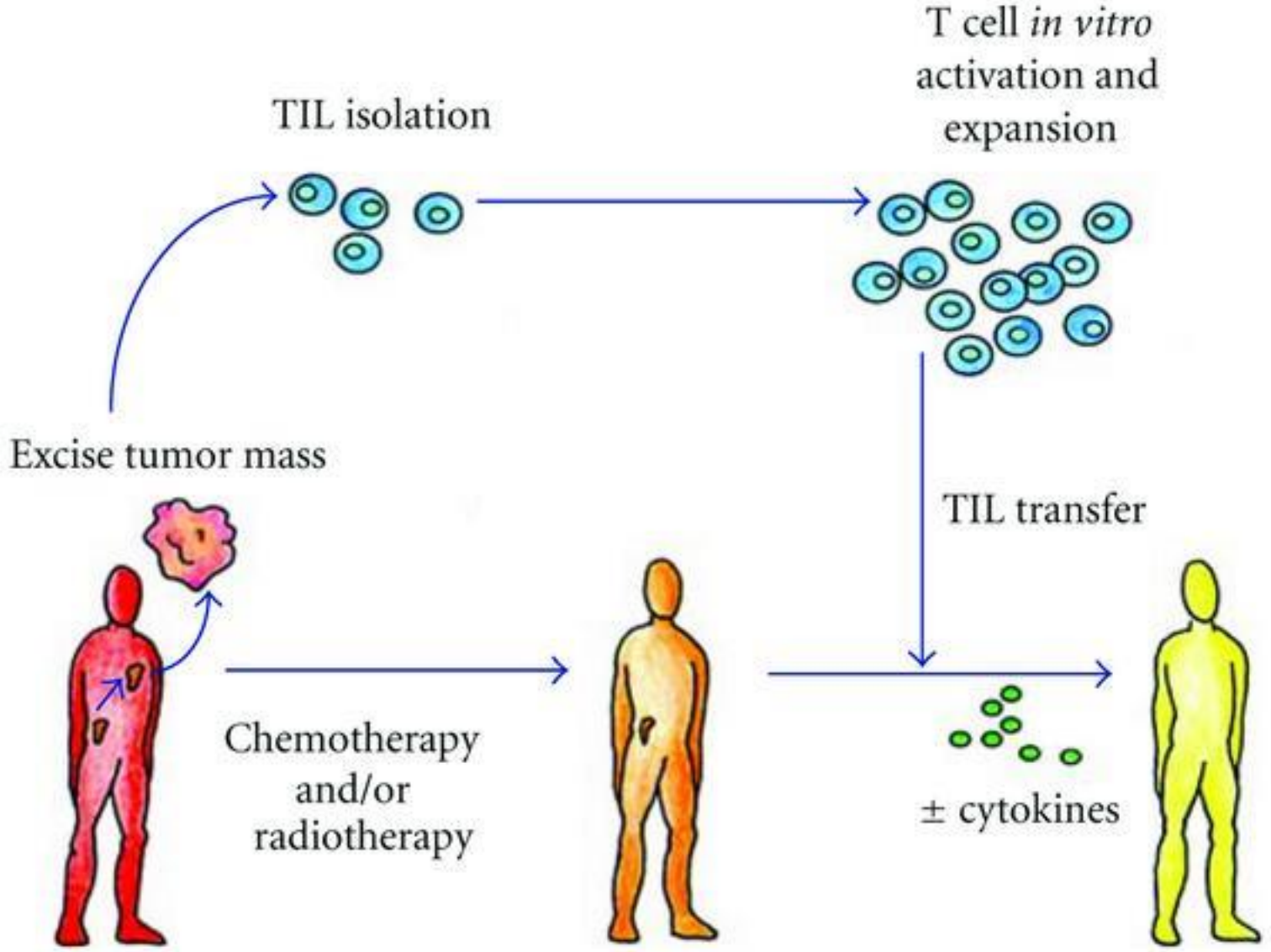

T cell *in vitro* activation and expansion
TIL isolation
Excise tumor mass
TIL transfer
Chemotherapy and/or radiotherapy
± cytokines

Table 4: Patients with HCC treated with adoptively transferred TILs

Subject code	Days of T-cell infusion after the tumor tissue was obtained	Cells per infusion	Number of infusions	Clinical response	DFS (d)	OS (d)
01	26	3×10^9	2	Recurrence	170	462^+
02	26	8.5×10^8	2	NED	454^+	454^+
03	27	3.4×10^8	1	NED	438^+	438^+
04	31	3.1×10^8	1	NED	438^+	438^+
05	32	8.8×10^8	1	NED	431^+	431^+
06	31	1×10^9	1	NED	431^+	431^+
07	25	9.0×10^8	1	NED	427^+	427^+
08	35	8.6×10^8	1	NED	427^+	427^+
09	22	9×10^8	2	NED	425^+	425^+
10	28	8.2×10^8	1	NED	424^+	424^+
11	26	2.6×10^9	1	Recurrence	105	418^+
12	26	2.5×10^9	1	Recurrence	261	418^+
13	26	9.2×10^8	1	NED	404^+	404^+
14	27	1.8×10^9	1	NED	355^+	355^+
15	27	10^9	1	NED	355^+	355^+

+: ongoing
NED: no evidence of disease

Figure 2: The impact of autologous TIL infusion on HBV load A and AFP level B. Plasma samples taken prior to the surgery and after T cell infusion were assessed for HBV load and AFP level.

Figure2A

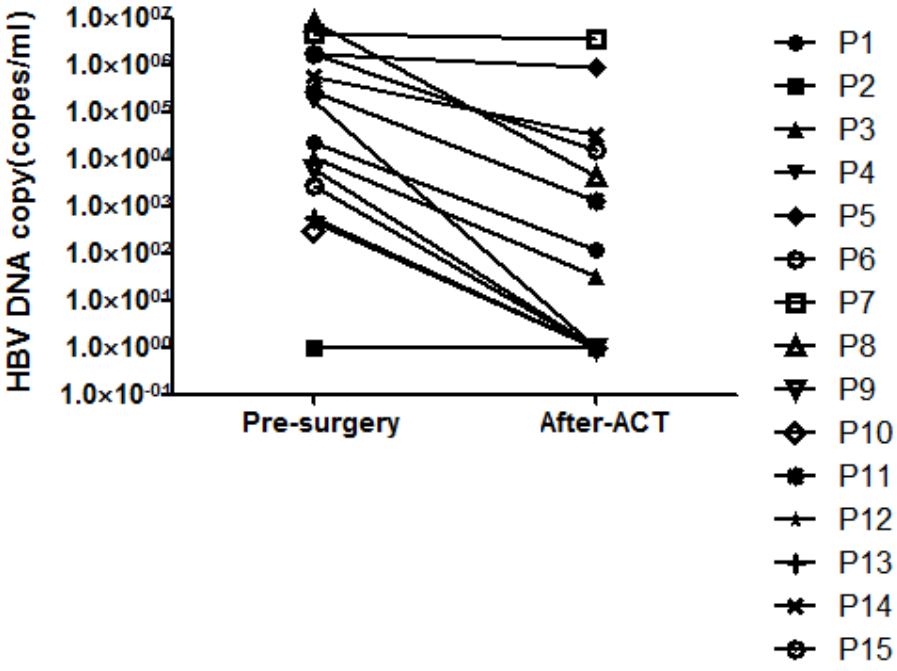
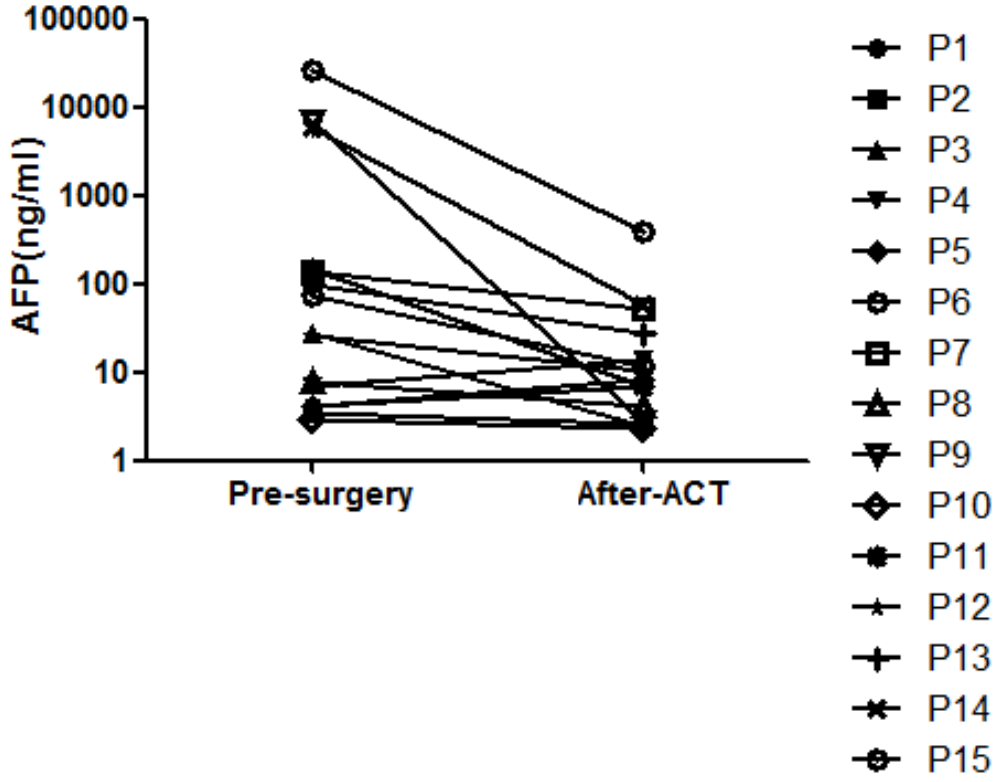


Figure2B



Questions and comments

- Only 15 patients surgically amenable (since transplantation was not considered probably high risk of relapse).
- Underlying liver HBVdisease?
- Preconditioning regimen and surgery?

- Excellent technical T-cell culture results
- Was IL-2 used and if so at what doses?
- Abundance of CD4 T cells.

- Results are very encouraging with over a year follow-up
- Only suggestive but not compelling.