Lymphoid and myeloid biomarkers for clinical outcome of ipilimumab and Prostate GVAX treatment

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Tanja de Gruijl-disclosures

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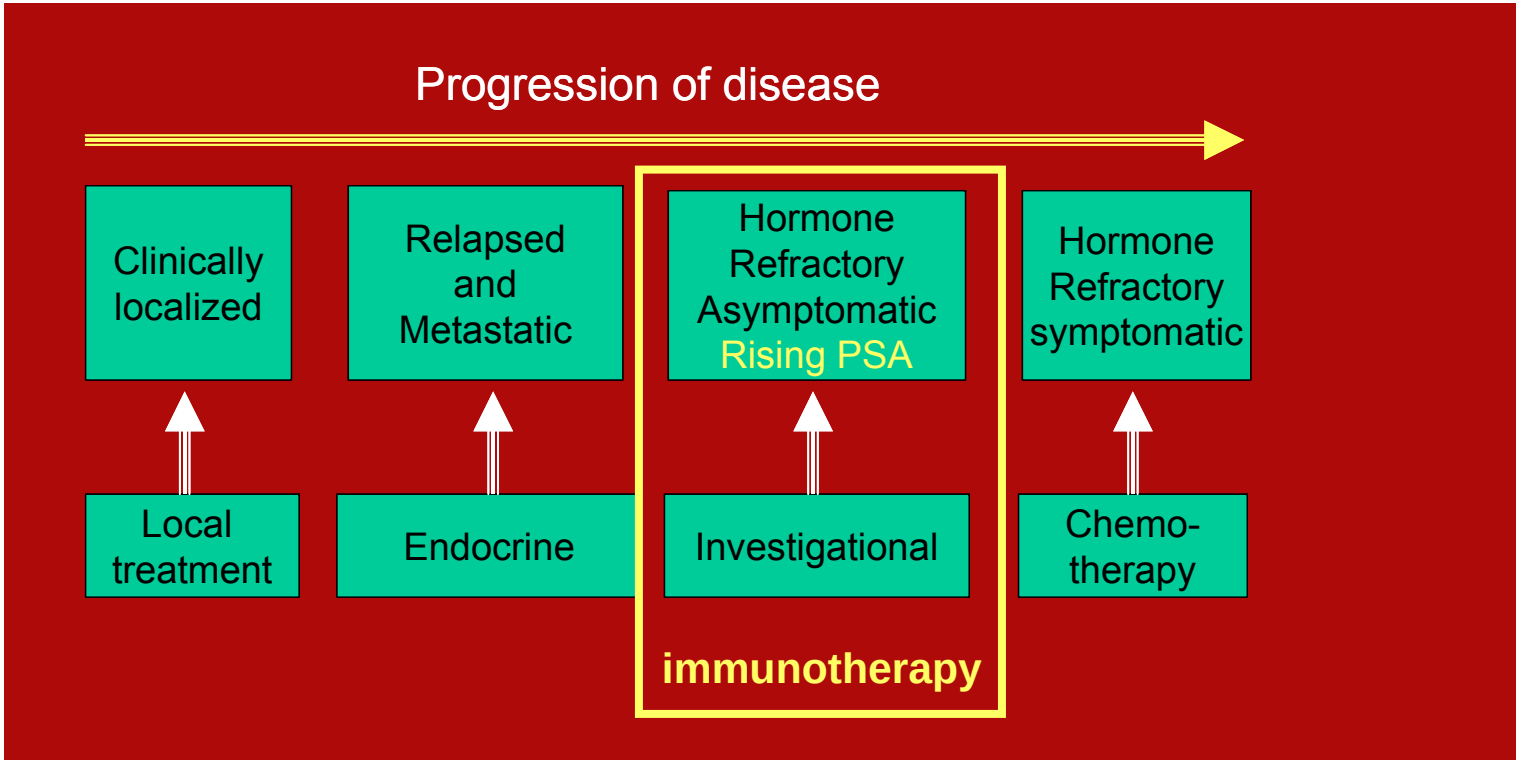
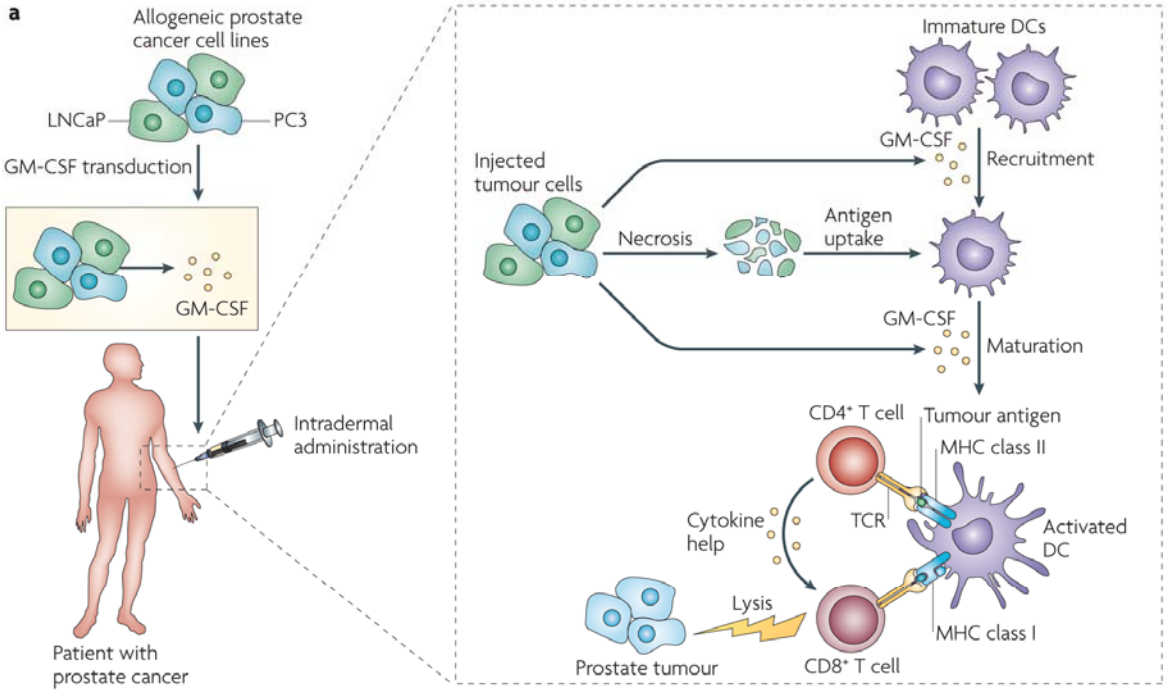
Prostate cancer

- Most common malignancy in elderly men
- Second leading cause of cancer deaths in western countries
- 1 in 6 men affected

(www.cancer.org)

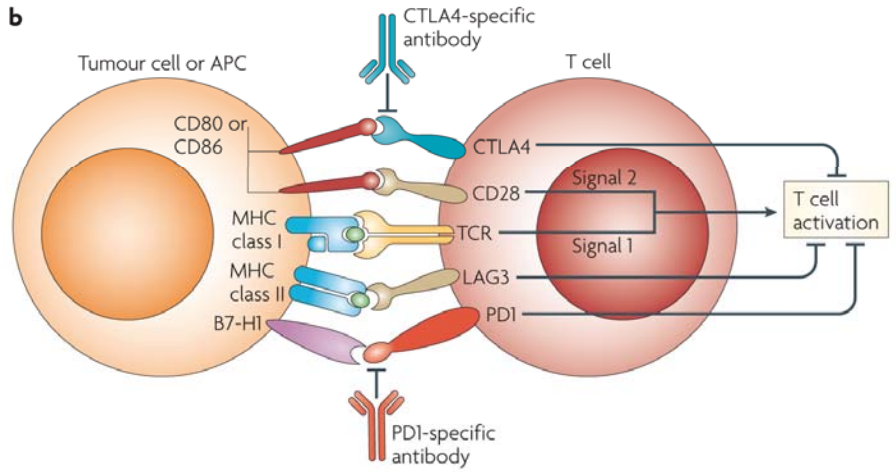




Prostate GVAX

Vaccine consisting of two AAV-GM-CSF transduced, irradiated prostate cancer cell lines (LNCaP, PC-3)

CELL GENESYS



Ipilimumab (Yervoy)

***anti-human CTLA-4 Antibody**
***high affinity and specificity**
***fully human IgG1k antibody**
***blocks the binding of CTLA-4 to B7**
***does not mediate ADCC**

Bristol-Myers Squibb

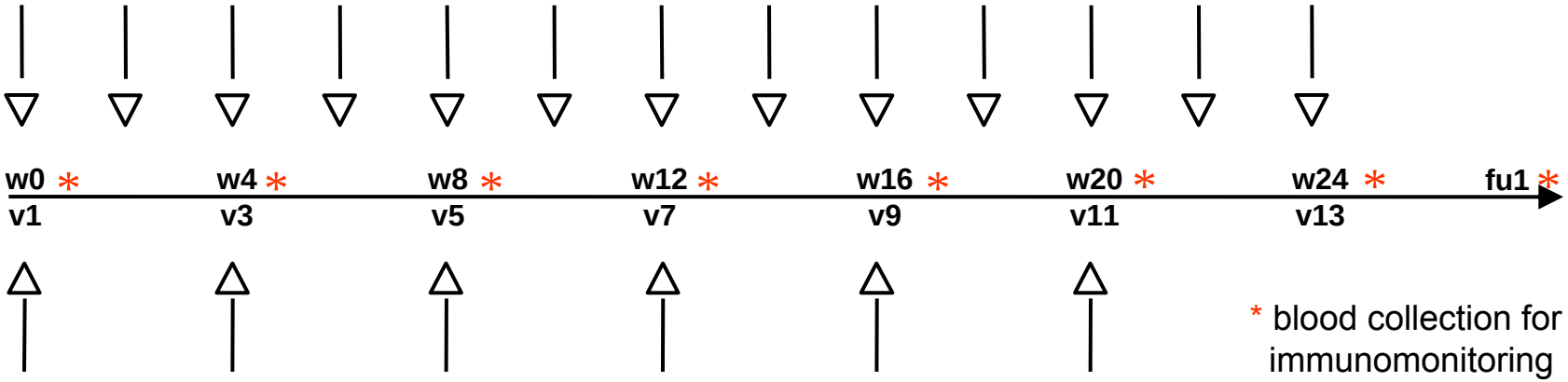
MEDAREX

Drake Nat Rev Immnol 2010

VUmc Cancer Center Amsterdam

Treatment and sampling scheme

GVAX every 2 weeks for a total of 13 i.d. doses

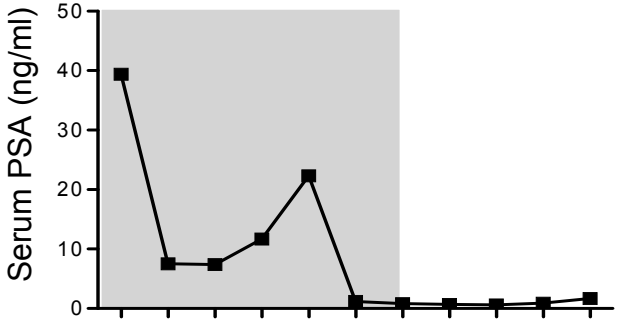


anti-CTLA4 mAb (Ipilimumab) every 4 weeks for a total of 6 infusions

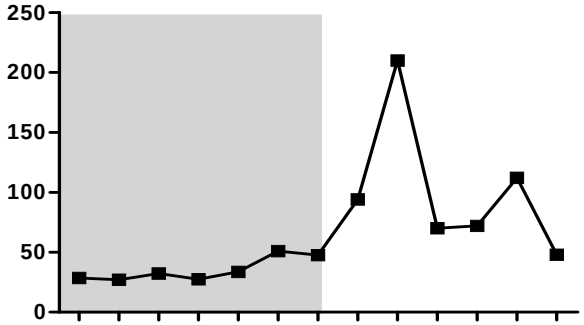
Dose level	patient #	anti-CTLA4 dose
Cohort 1	1-3	0.3 mg/kg
Cohort 2	4-6	1.0 mg/kg
Cohort 3	7-9	3.0 mg/kg
Cohort 4	10-12	5.0 mg/kg
Cohort 5	13-28	3.0 mg/kg

Clinical results

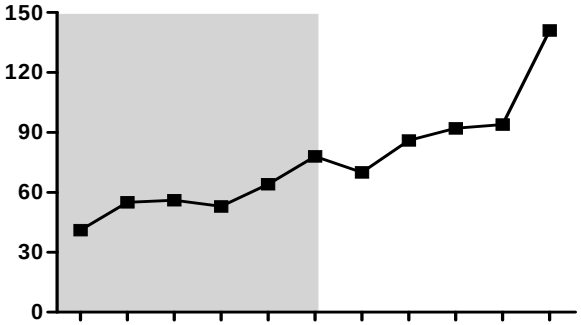
Partial Response (PR);
>50% PSA decline



Stable Disease (SD);
No PR or PD



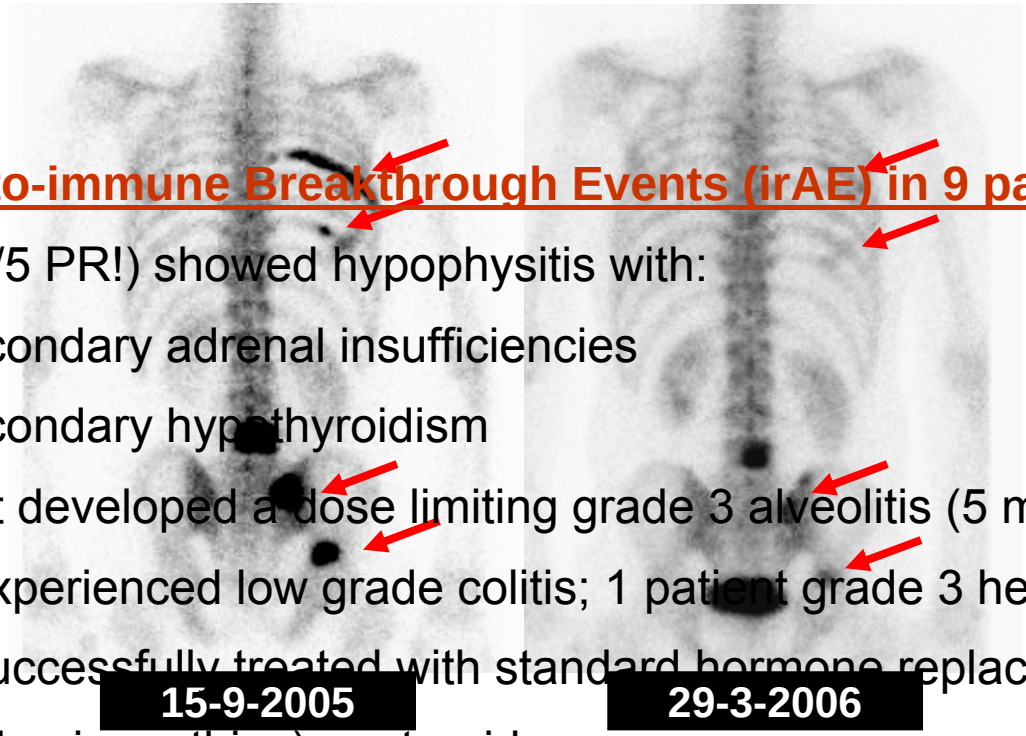
Progressive Disease (PD);
>25% PSA increase



Category:	Response	Number of patients	Duration of response (median and range in days)
PSA Partial Response (PR)	>50% on-study PSA decline	5 / 28	305 (51-919)
PSA Stable Disease (SD)	No PR or SD	12 / 28	85 (82-190)
PSA Progressive Disease (PD)	>25% on-study PSA increase	11 / 28	n.a.

Clinical results

- PSA declines were durable: 6 to 31 months
- Stable disease by bone scan was observed in 11 patients (>5 mns)
- Regressing bone and lymph node metastasis were observed in 2 patients



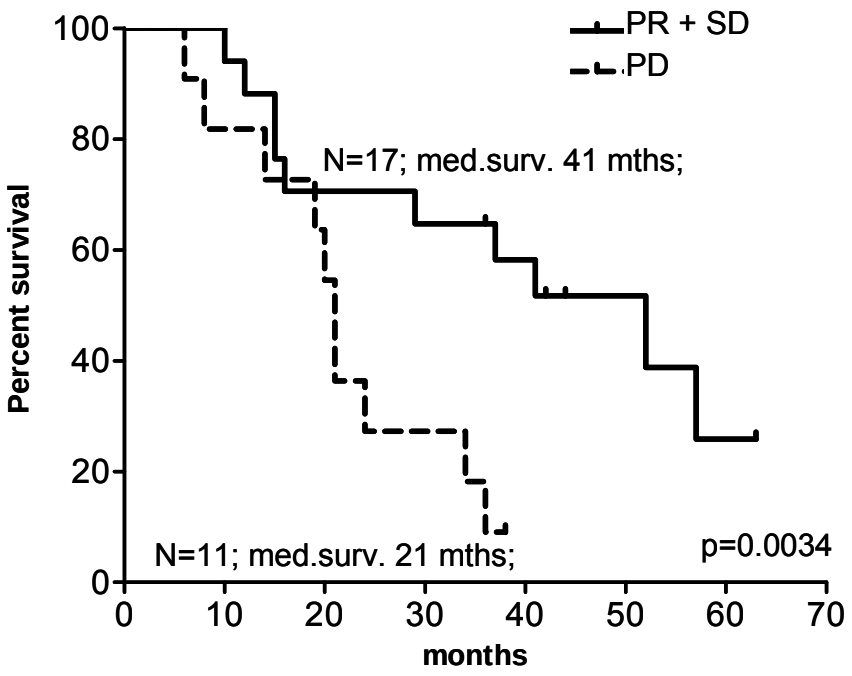
Toxicity: Auto-immune Breakthrough Events (irAE) in 9 patients

•7 patients (5/5 PR!) showed hypophysitis with:

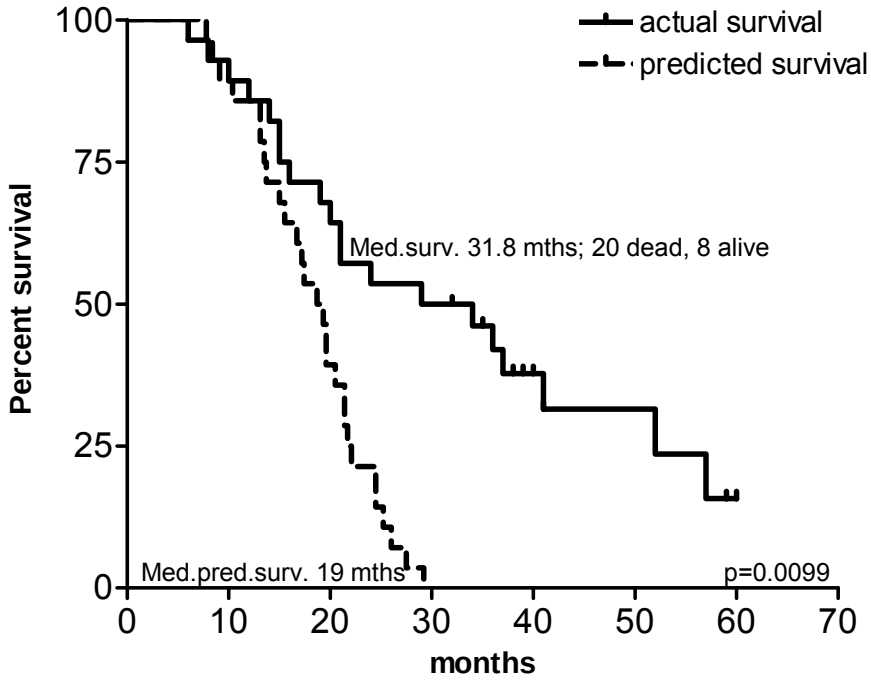
- secondary adrenal insufficiencies
- secondary hypothyroidism

- 1 PR patient developed a dose limiting grade 3 alveolitis (5 mg/kg Ipilimumab)
- 2 patients experienced low grade colitis; 1 patient grade 3 hepatitis
- irAE were successfully treated with standard hormone replacement therapy (endocrinopathies) or steroids.

Clinical results:



Treatment response correlated with survival



Actual survival was longer than Halabi-predicted survival

Immunomonitoring: principal question

Prostate Cancer as a learning model

Can we identify immune parameters that correlate with clinical activity and may be useful for clinical response prediction?

…or treatment resistance prediction? >>avoid autoimmune side effects

NB: Phase I study with non-randomized Phase II study: hypothesis generating.

Further validation of identified immune biomarkers in randomized trials with GVAX and/or ipilimumab required!

Immunomonitoring: principal question

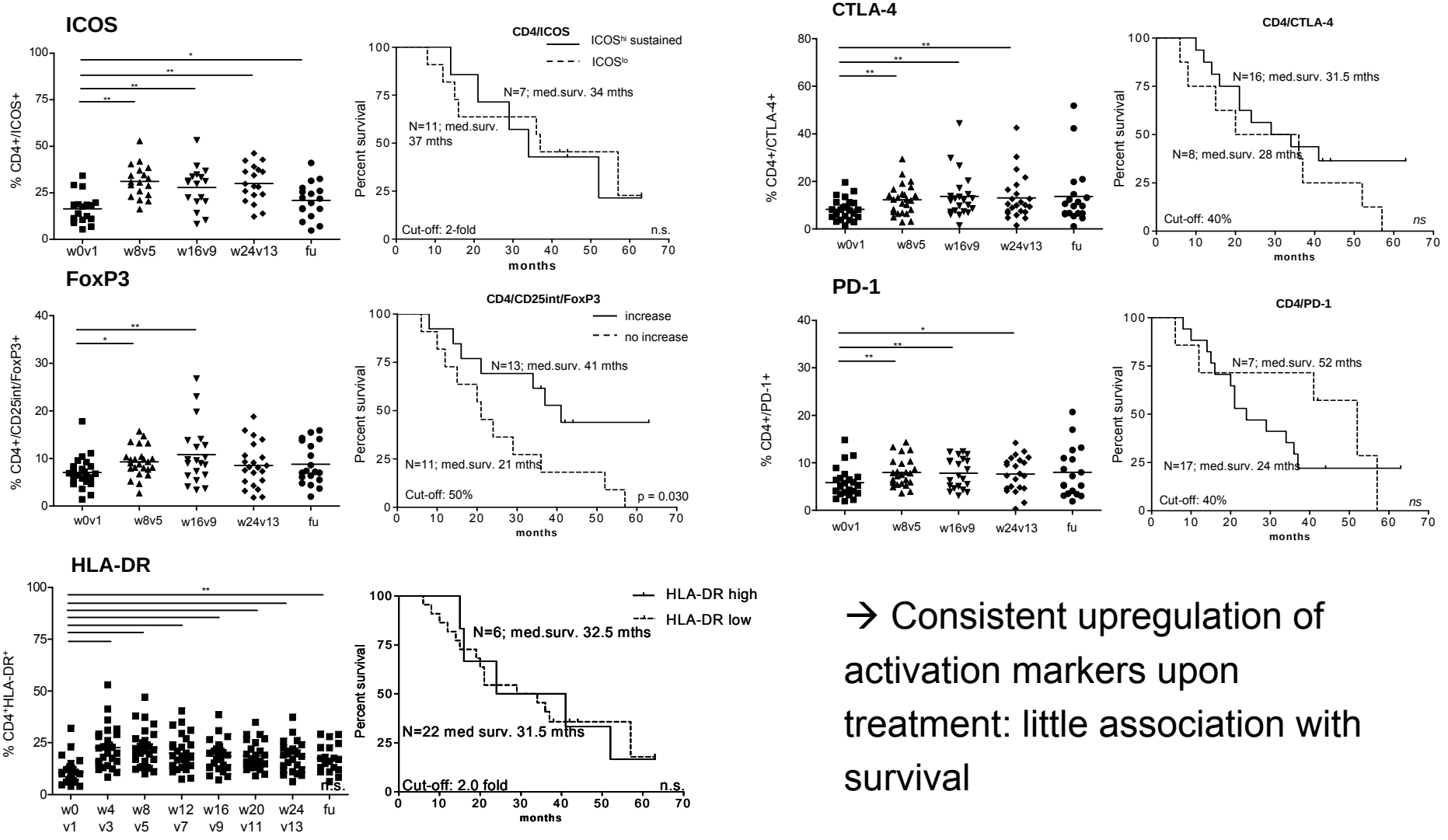
Prostate Cancer as a learning model

Can we identify lymphoid and myeloid immune parameters that correlate with clinical activity and may be useful for clinical response prediction?

…or treatment resistance prediction? >>avoid autoimmune side effects

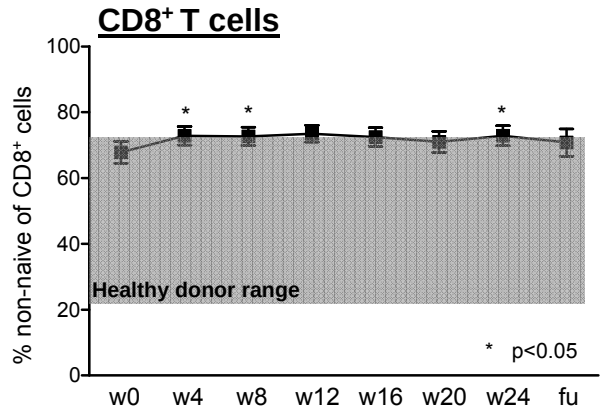
1. **Serology**
   - **tumor-specific antibodies**
2. **Peripheral blood T_{eff}-/T_{reg} cells**
   - **frequency**
   - **activation status**
   - **effector/memory phenotype**
3. **T cell Functionality**
   - **TAA-specific reactivity**
   - **suppression assays**
   - **cytokine profiles**
4. **Peripheral Blood DC (PBDC) and Myeloid Derived Suppressor Cells (MDSC)**
   - **frequency**
   - **activation status**

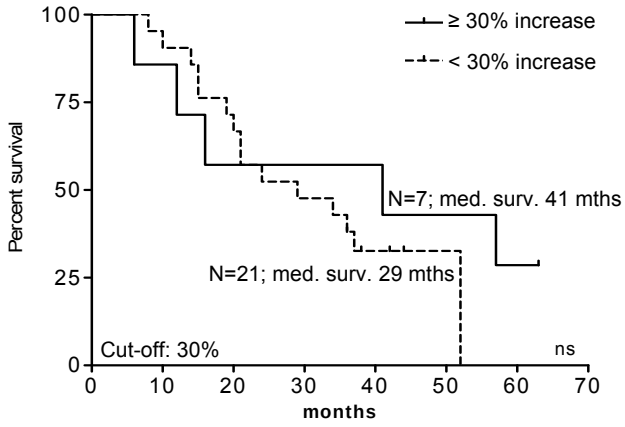
T cell activation: ICOS, FoxP3, CTLA-4, PD-1

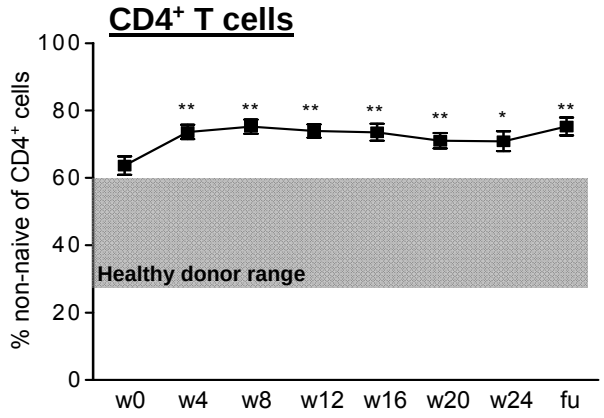


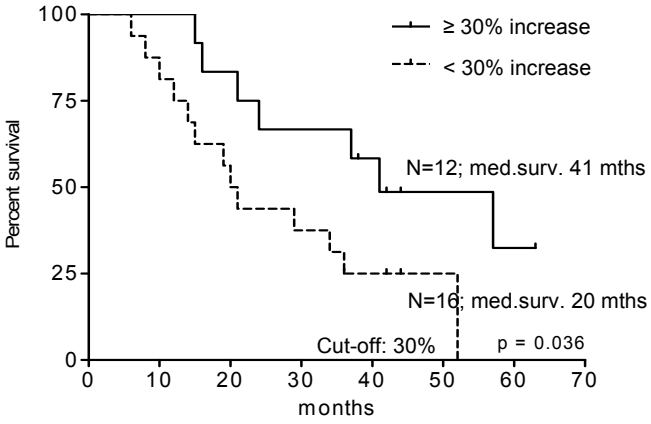
→ Consistent upregulation of activation markers upon treatment: little association with survival

T cell activation: effector/memory phenotype



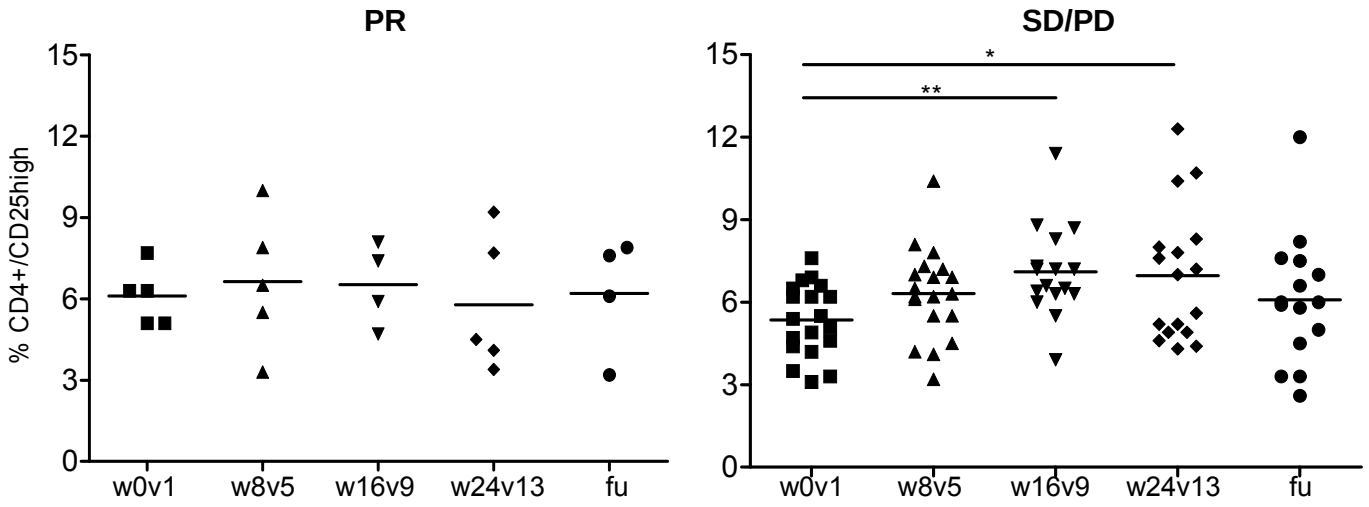


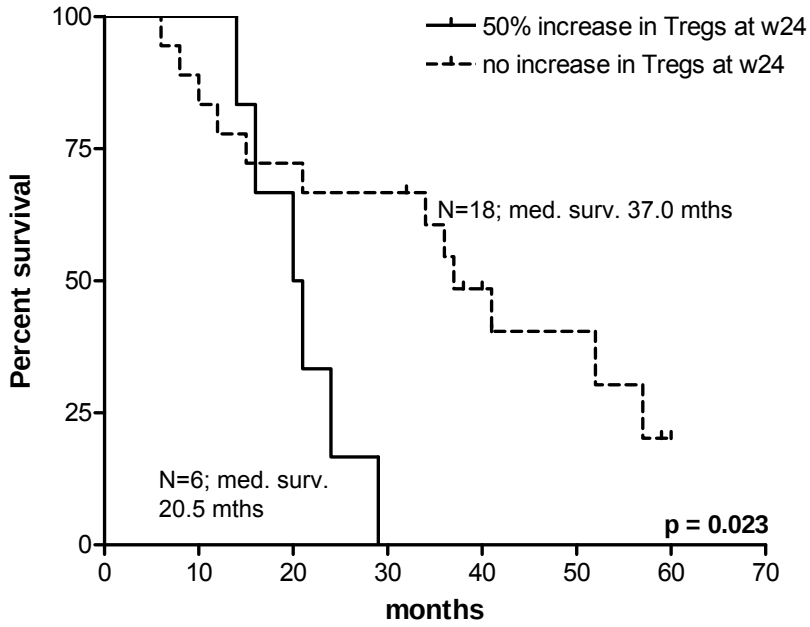


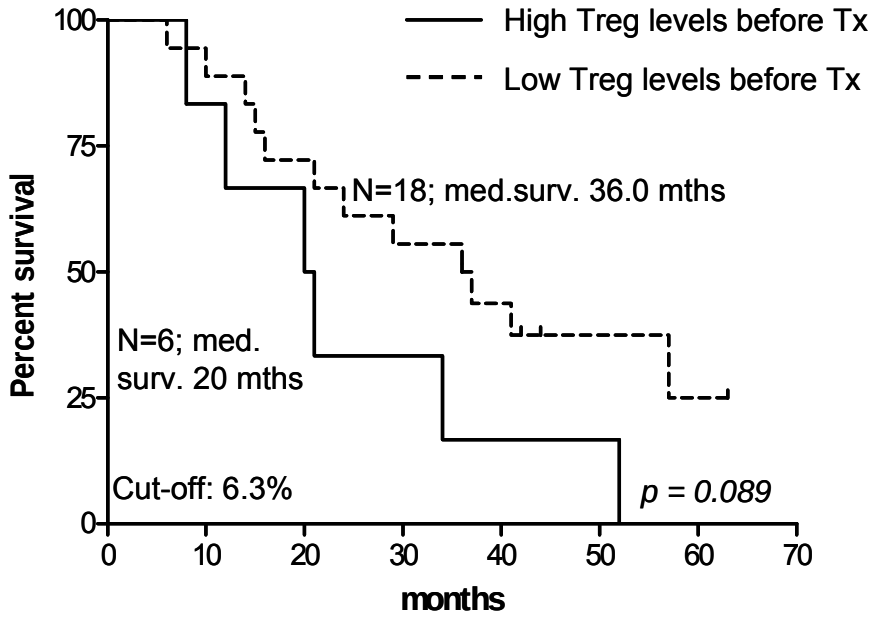


→Increased Th differentiation on treatment: relation with survival

Regulatory T cells (nTregs)







→ High Treg rates: associated with SD/PD and reduced survival

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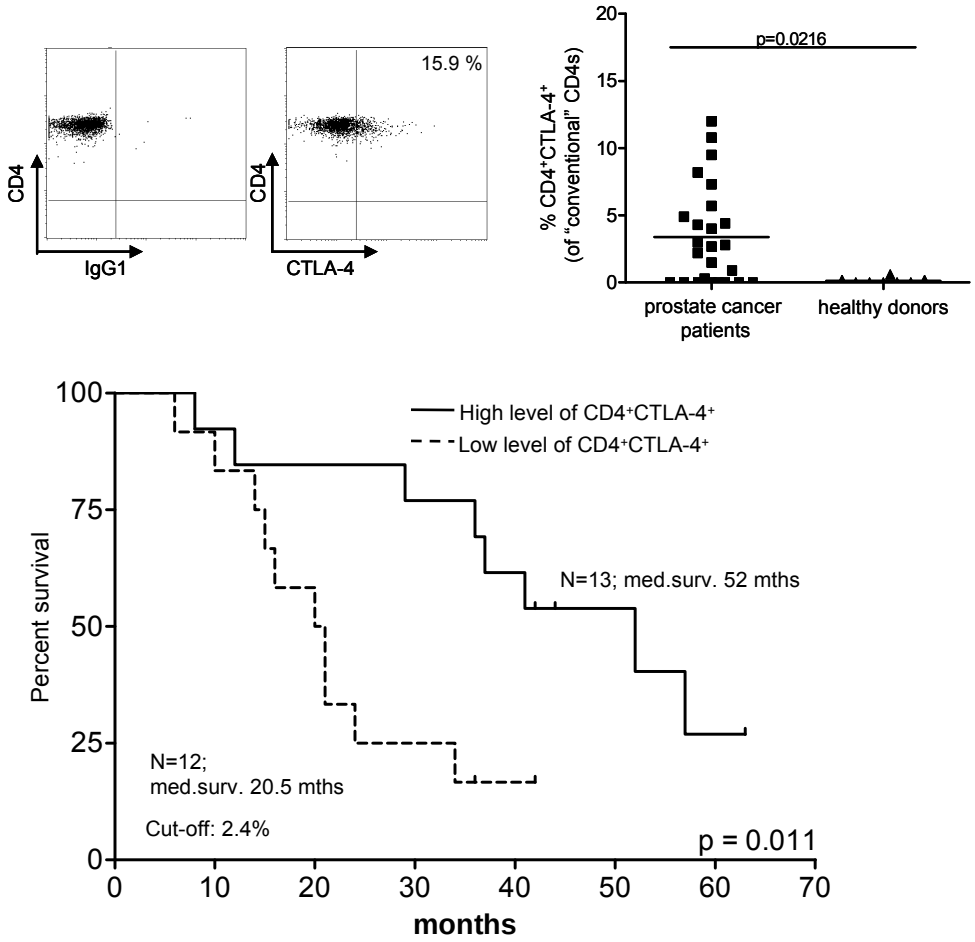
Pre-treatment CTLA4$^+$ Th cells



→ Tumor-related elevated pre-treatment frequencies of CD4$^+$CTLA4$^+$ Tcells have predictive value for survival on treatment

T cell activation profile

Potential biomarkers:

predictive vs prognostic; no relation according to Halabi-predicted survival

On-treatment predictive

Immune parameter	Median Survival between groups	P-value	Median Halabi Predicted Survival	P-value
Non-naïve CD4+ cells	41.0 vs. 20.0	**0.036**	16.5 vs. 21.4	0.086
CD8+ICOS+	21.0 vs. 57.0	**0.043**	16.7 vs.19.3	0.622
CD4+CD25intFoxP3+	41.0 vs. 21.0	**0.030**	19.6 vs. 15.0	0.401
CD4+CD25hiFoxP3+ Tregs	37.0 vs. 21.0	**0.045**	15.0 vs 19.6	0.201

Pre-treatment predictive

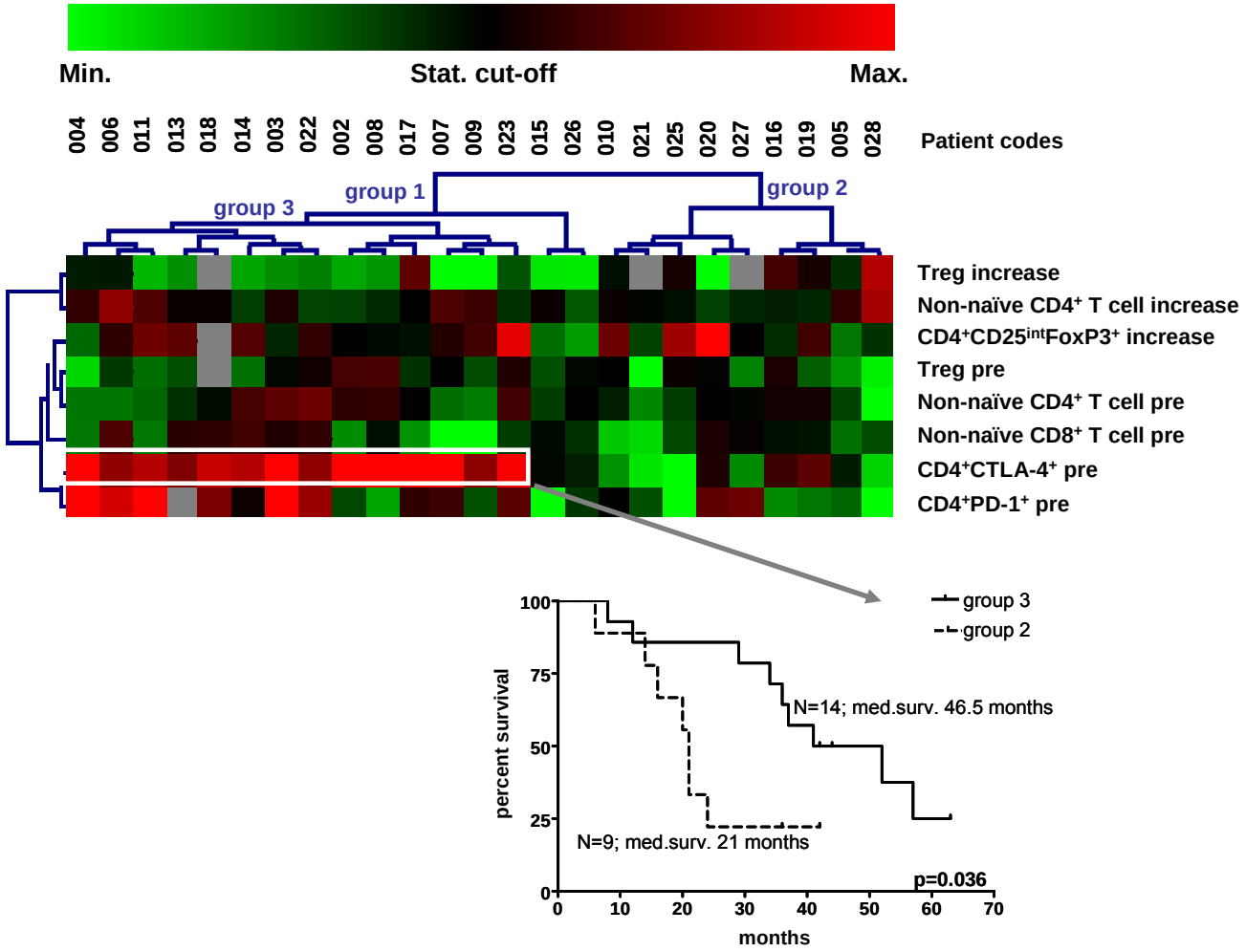
Immune parameter	Median survival between groups	P-value	Median Halabi Predicted Survival	P-value
Non-naïve $CD8^+$ cells	n.r. vs. 20.5	**0.028**	21.6 vs. 17.3	0.222
Non-naïve $CD4^+$ cells	19.0 vs. 41.0	**0.02**	21.4 vs. 16.7	**0.021**
$CD4^+PD\text{-}1^+$	41.0 vs. 18.0	**0.014**	20.5 vs. 15.9	0.194
$CD4^+CTLA\text{-}4^+$ (conv. T cells)	52.0 vs. 20.5	**0.011**	19.0 vs. 15.9	0.097
$CD4^+CD25^{hi}FoxP3^+$ Tregs	20.0 vs. 36.0	0.087	20.9 vs. 19.0	0.230

n.r.= not reached

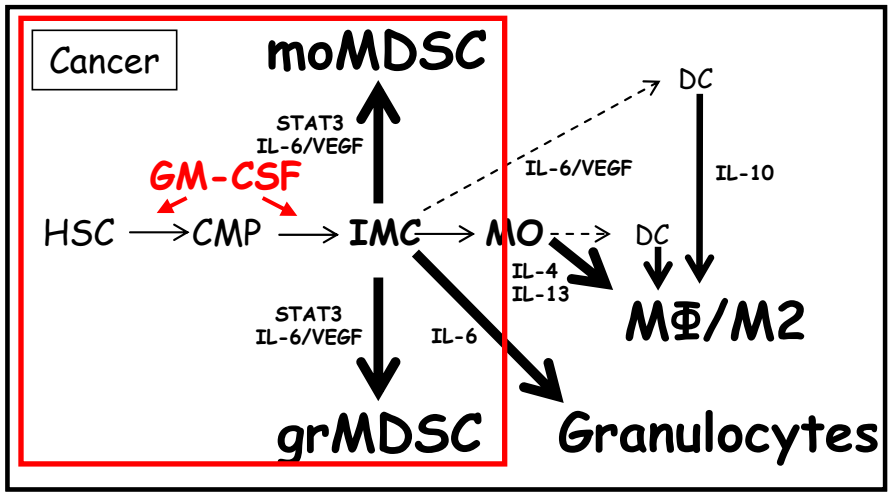
T cell activation profile

Unsupervised cluster analysis:

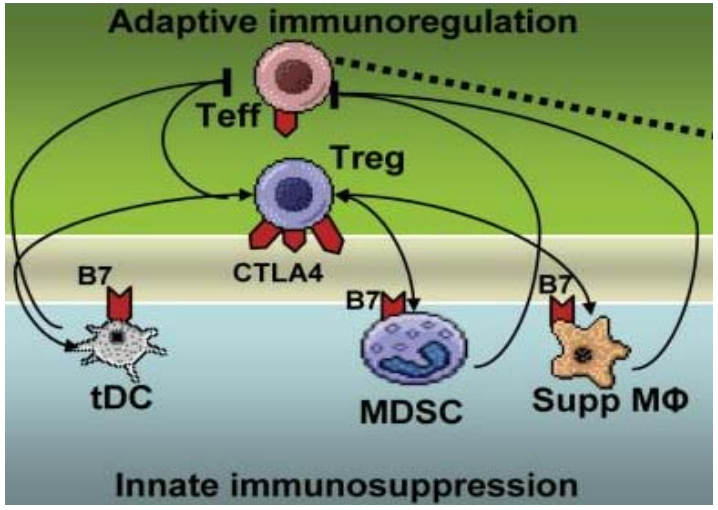
CD4+CDTLA4+ as dominant predictor of survival on treatment



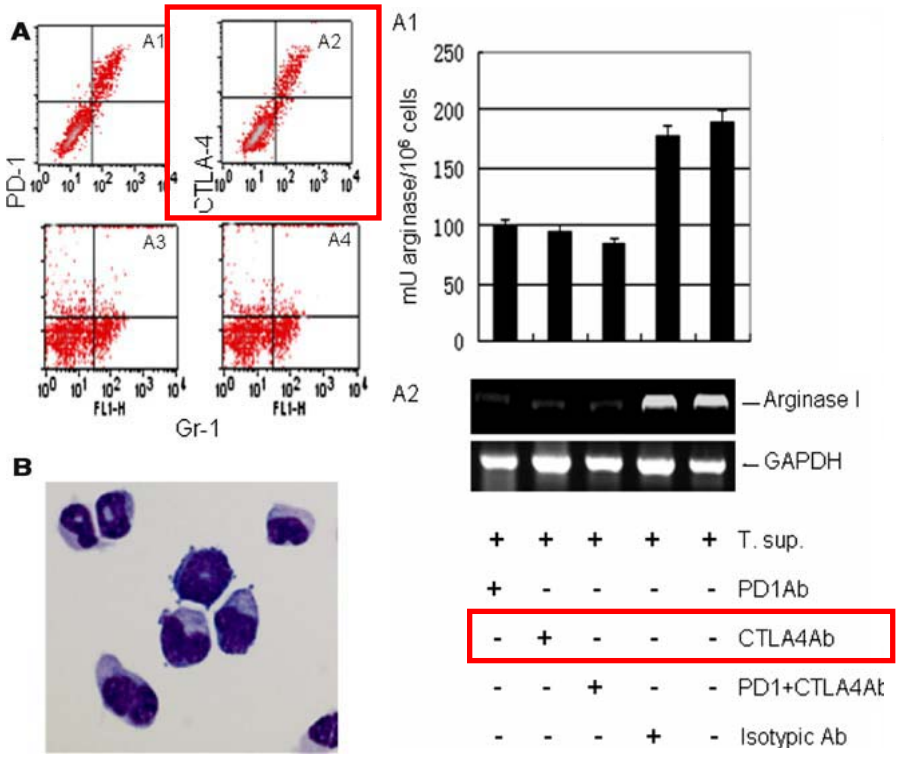
Myeloid subsets: also targets for GVAX and ipilimumab?



Oosterhoff Immunother 2011

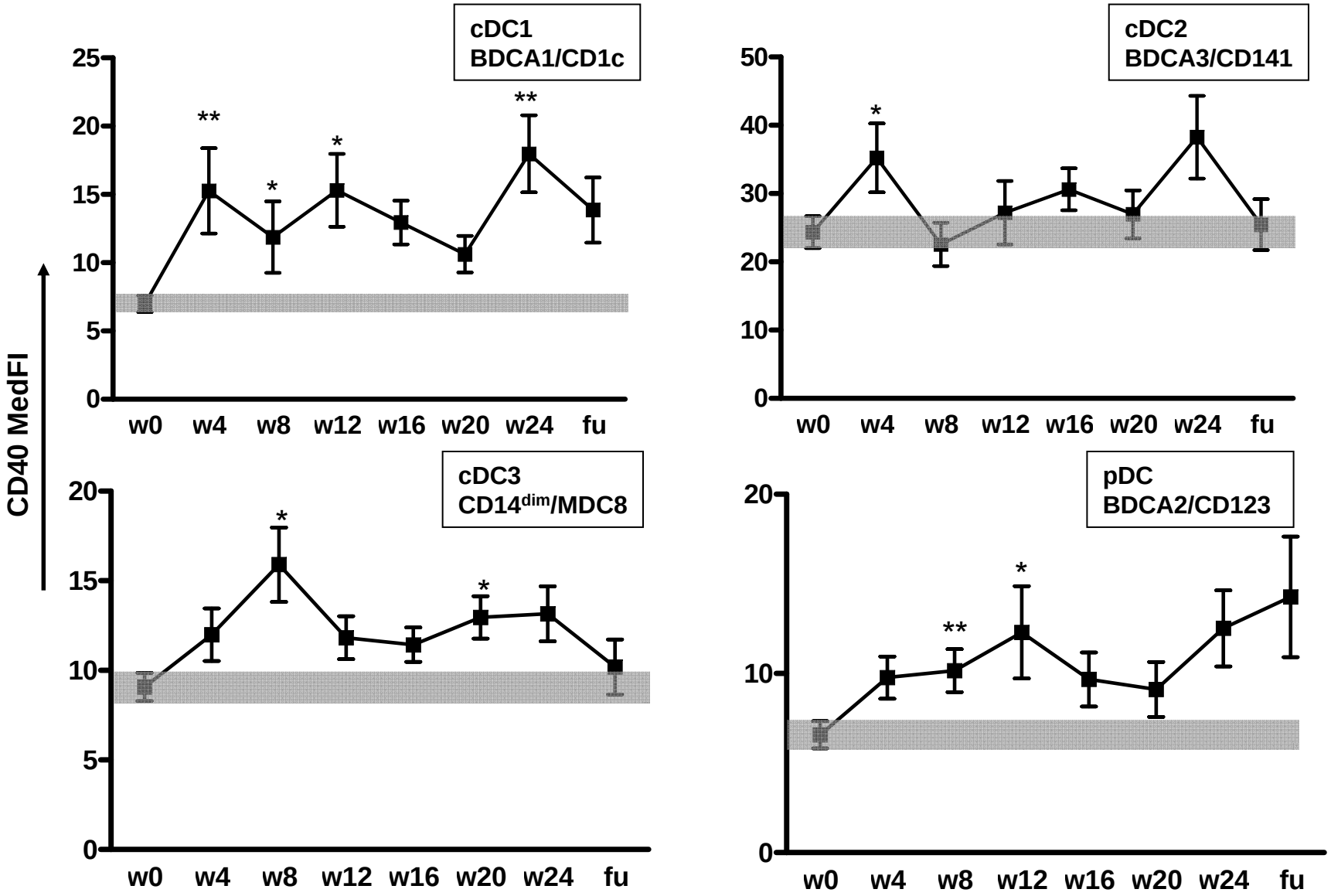


Suzuki Cell Transplant 2010

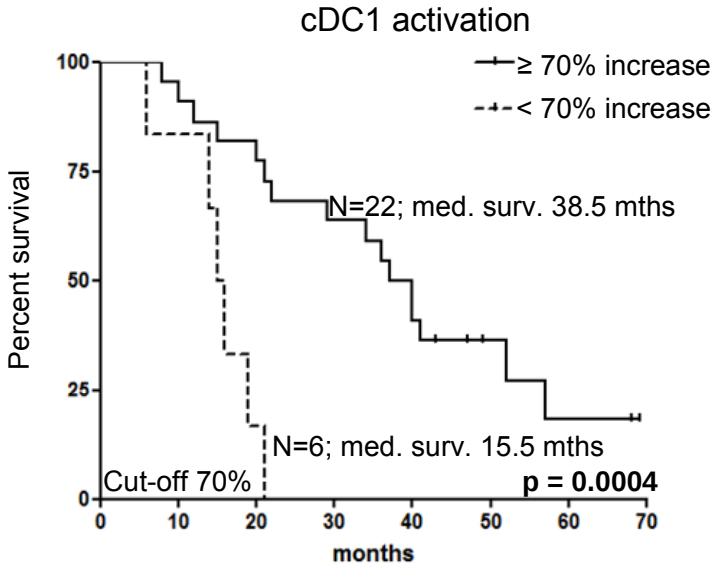


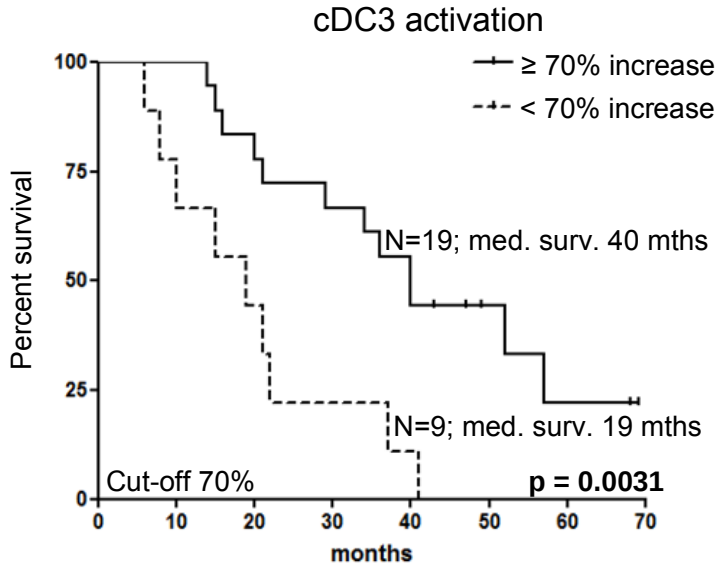
Liu CII 2009

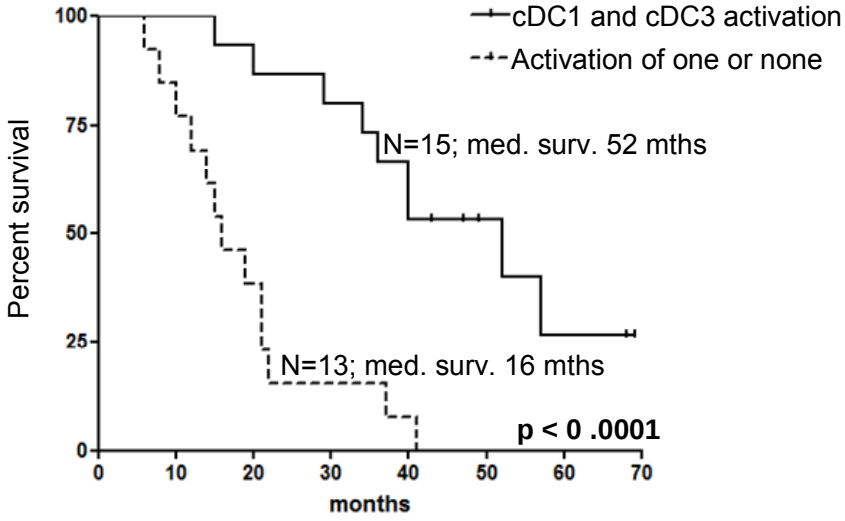
PBDC: subset activation



PBDC: cDC1 and cDC3 activation

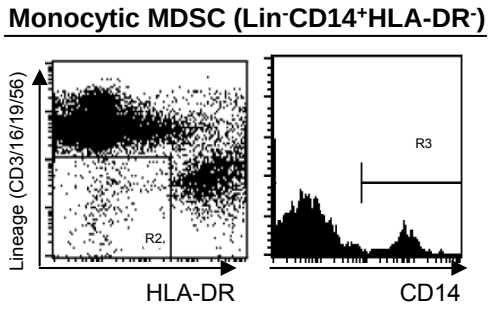




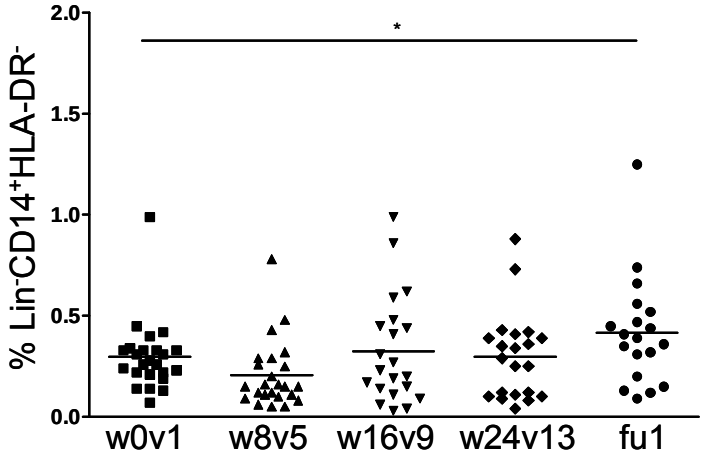


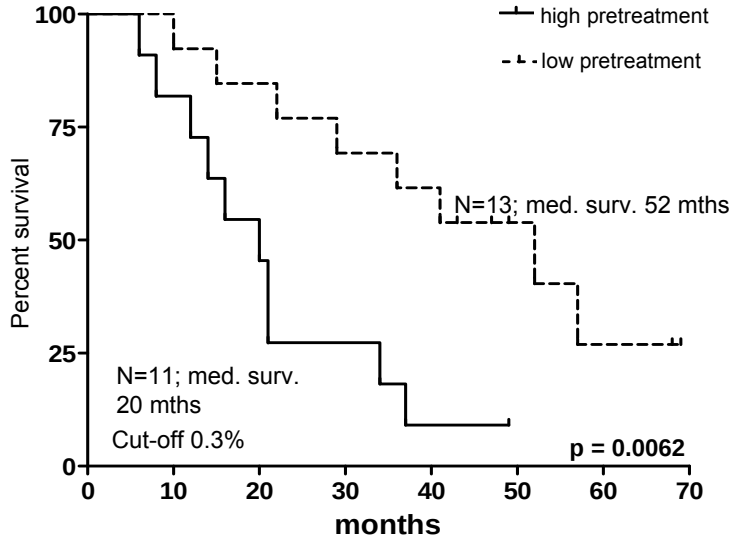
Increased activation of cDC1 and cDC3 (also known as 6-sulfo LacNAc+ or SLAN-DC) is related to survival

MDSC: monocytoid



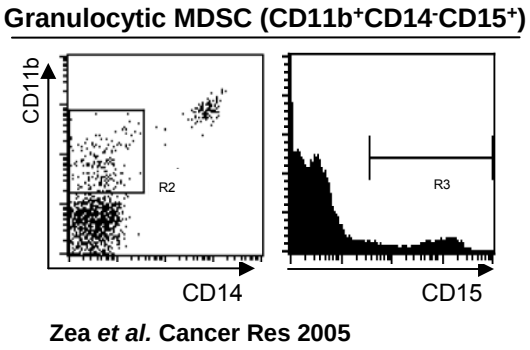
Filipazzi et al. JCO 2007

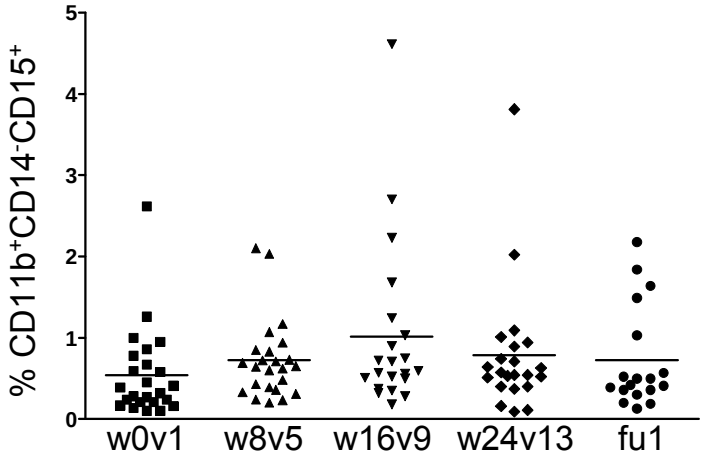


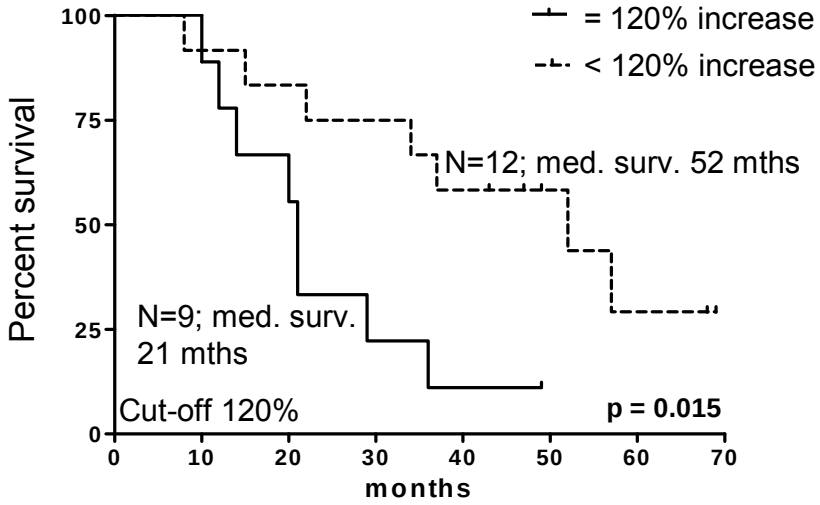


High pre-treatment levels of mMDSC are associated with poor survival

MDSC: granulocytic





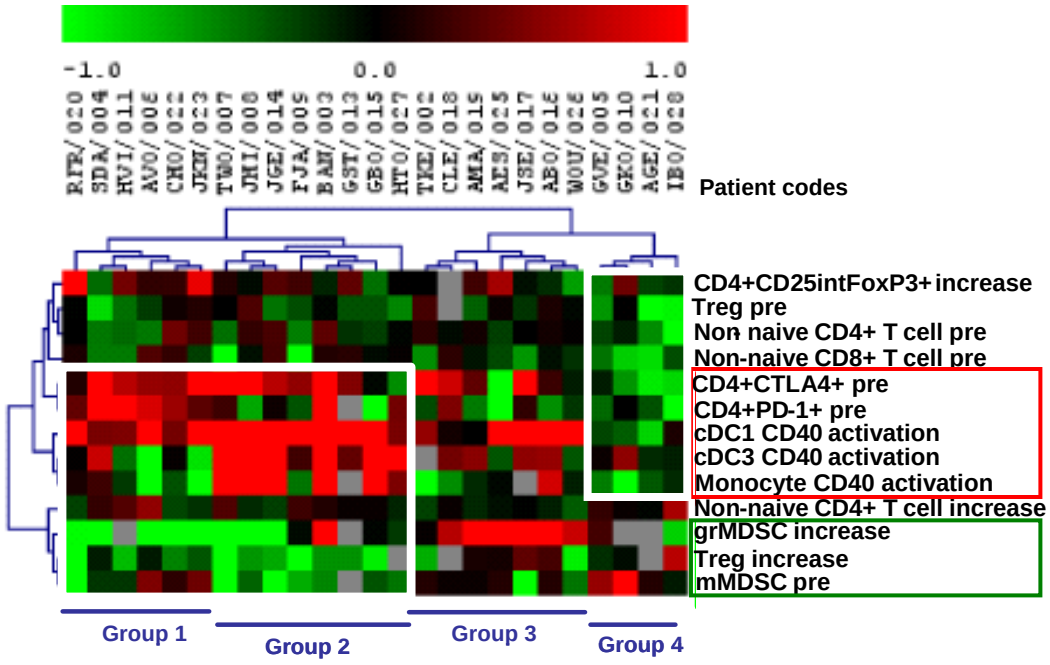


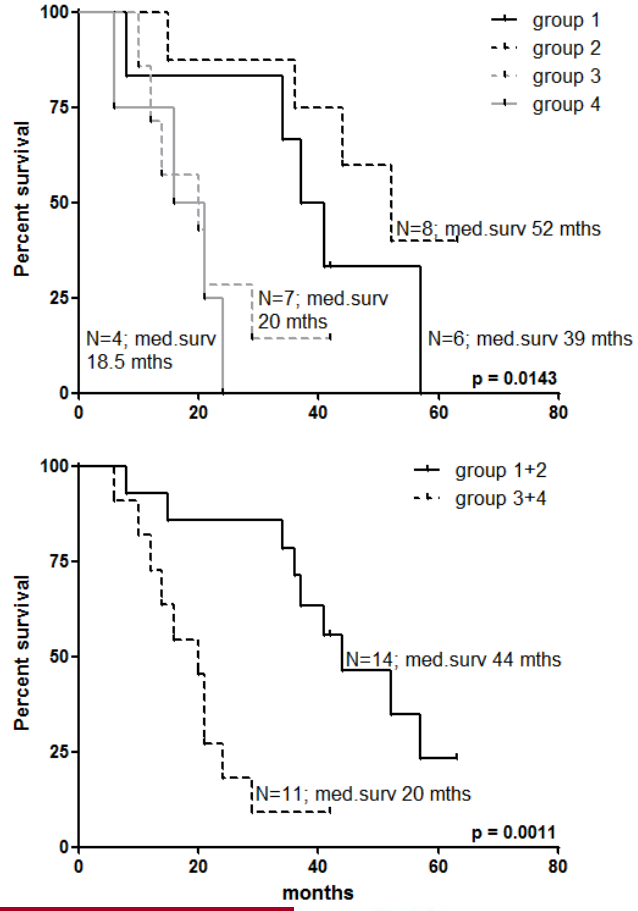
On-treatment increases in grMDSC are associated with poor survival

A predictive T cell and myeloid marker profile

Unsupervised cluster analysis:

High DC activation and Th CTLA4 and PD-1 expression and low suppressive MDSC and Treg levels together predict survival on GVAX+ipilimumab treatment





Conclusions

→**Potential immune biomarkers for patient selection *prior* to treatment:**

→**mMDSC, Tregs, effector/memory and CD4+PD-1+/CD4+CTLA4+ T cell rates**

Next: validation

- Treatment specific? (GVAX, ipilimumab monotherapies; other therapies?)
- Disease stage specific? (Early versus advanced prostate cancer?)
- Disease specific? (Melanoma vs prostate cancer)

Anita Stam & Saskia Santegoets

Fighting the Blues…

…with wine…

…and awards

VU university medical center

Immunotherapy lab

Saskia Santegoets

Anita Stam

Sinéad Lougheed

Petra Scholten

Martine Reijm

Mary von Blomberg

Rik Scheper

Tanja de Gruijl

Medical Oncology Clinic

Helen Gall

Fons van den Eertwegh

Winald Gerritsen

CELL GENESYS

Karin Jooss

Natalie Sacks

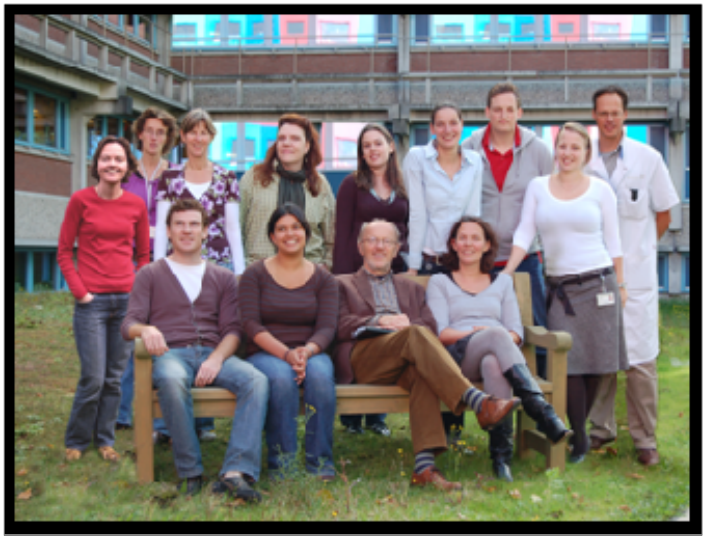
Kristen Hege

MEDAREX

Israel Lowy

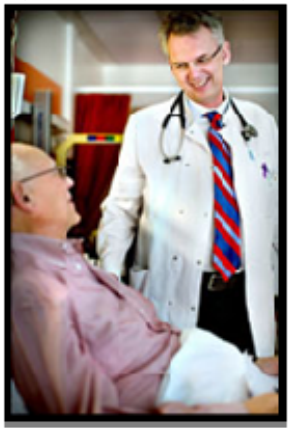
Bristol-Myers Squibb

Jean-Marie Cuillerot



NEDERLANDSE KANKERBESTRIJDING

KONINGIN WILHELMINA FONDS



Prostate Cancer Foundation

VUmc Cancer Center Amsterdam