

Dendritic and T cell functions in patients with metastatic hormone-refractory prostate cancer treated with GVAX immunotherapy for prostate cancer and ipilimumab

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A Phase I Dose Escalation Trial of GVAX Immunotherapy for Prostate Cancer and Ipilimumab (α CTLA-4 Ab) in Patients with Metastatic Hormone-Refractory Prostate Cancer

Phase 1 dose escalation trial:

GVAX Immunotherapy for prostate cancer + Ipilimumab (α CTLA-4 mAb)

GVAX = GM-CSF-secreting tumor cell immunotherapy

- Tumor cells as source of antigen: PC-3 and LNCaP
- GM-CSF: growth and maturational effects on:
dendritic cells, macrophages and neutrophils
 - activation of immune system; breaking tolerance
 - inducing DC antigen presentation



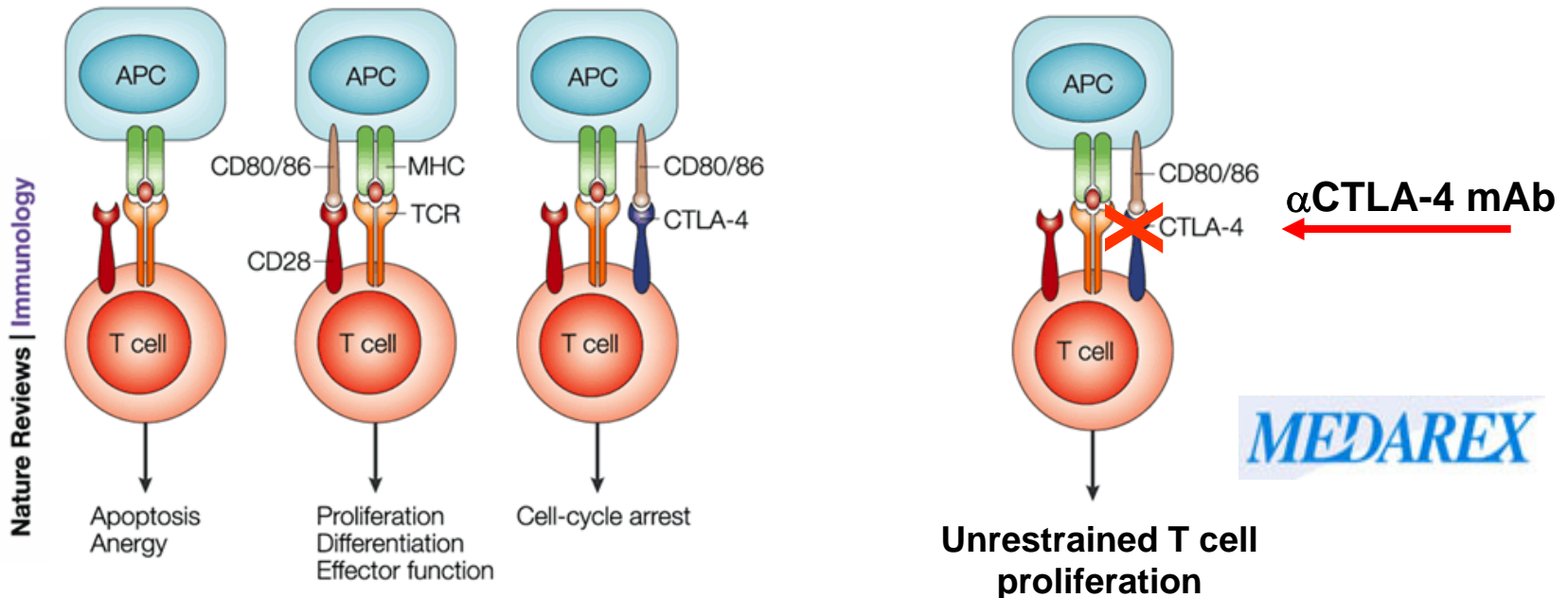
CELL GENESYS

Ipilimumab (α CTLA-4)

Human IgG_{1K} antibody directed against CTLA-4

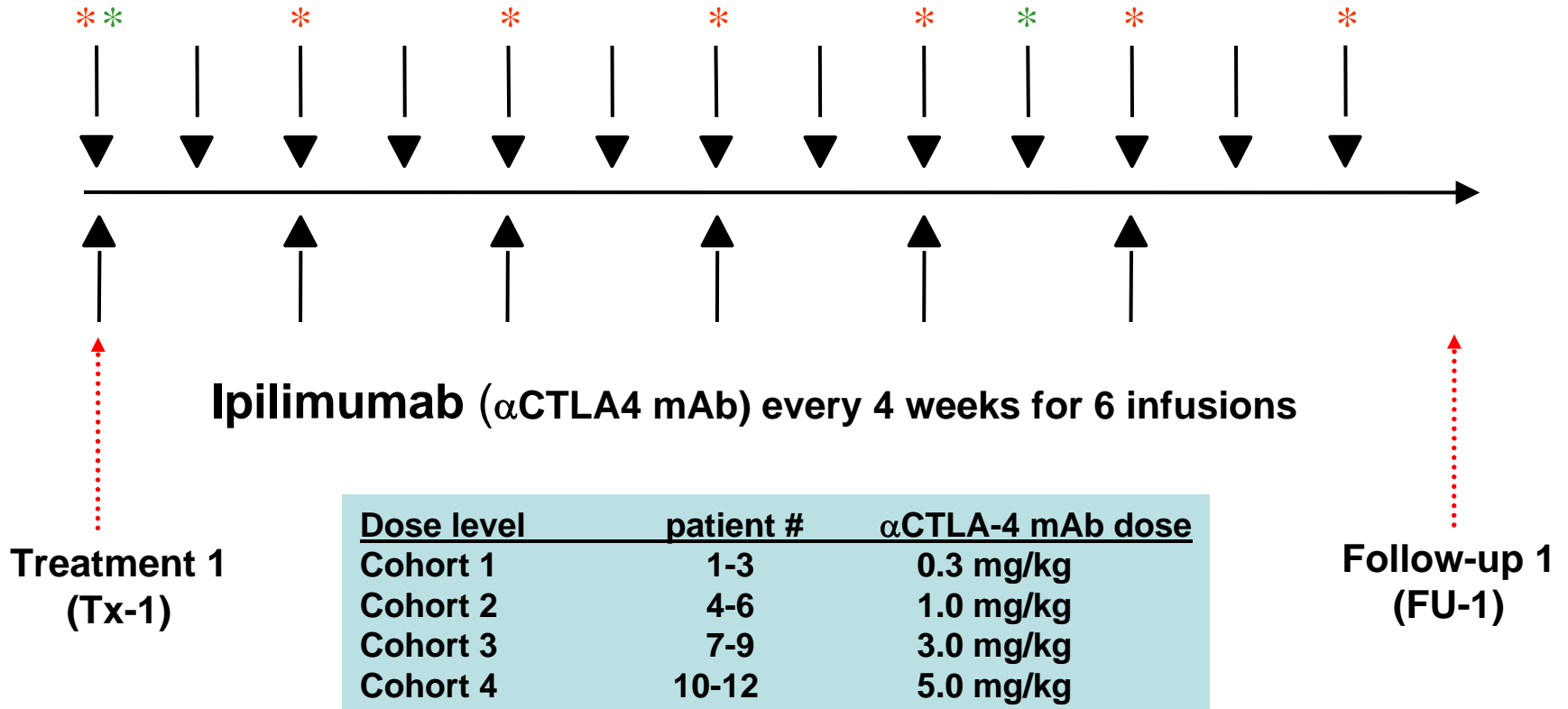
CTLA-4 = CTL Antigen-4

- Expressed on activated CD8⁺ and CD4⁺ T cells and on regulatory T cells
- Receptor for CD80/86; binds with higher affinity than CD28
- Plays an inhibitory role in regulation of T cell responses and maintenance of homeostasis
- CTLA-4 KO mice: die of lymphoproliferative disease with multi-organ infiltration and tissue destruction. *Tivol et al, Immunity, 1995* and *Waterhouse et al, Science, 1995*



Blood/Tissue sampling for immunomonitoring

GVAX every 2 weeks for a total of 13 doses

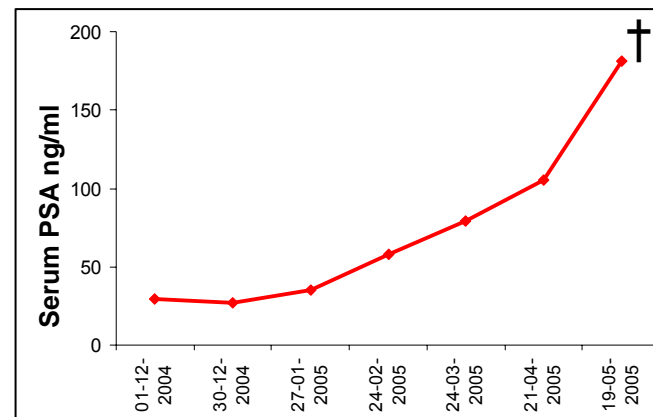


- * blood collection for PBDC and T cell immunomonitoring
- * skin biopsy, 48 hours after immunotherapy

GVAX + α CTLA-4 mAb: objectives

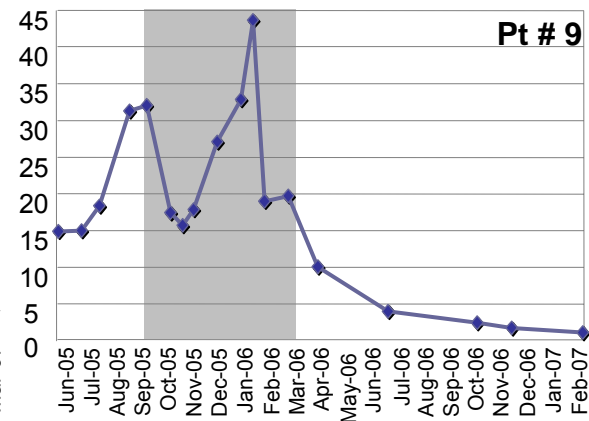
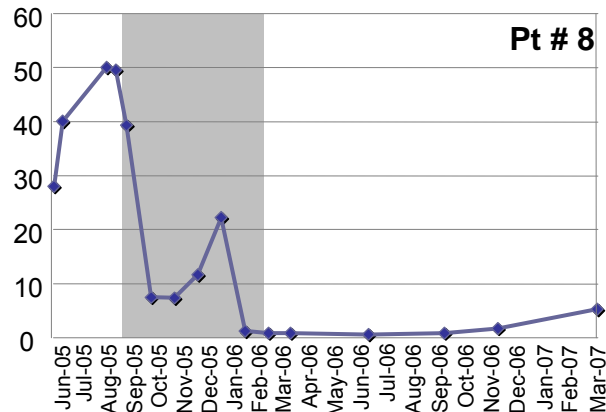
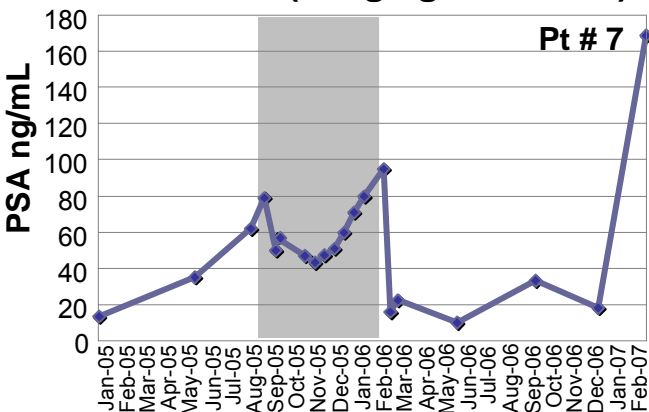
- Primary:**
- safety
 - determine maximum tolerated dose of α -CTLA-4 mAb in combination with GVAX
- Secondary:**
- time to clinical disease progression
 - time to PSA progression and PSA response
 - immune response to CG1940 and CG8711 (GVAX)
 - reduction in metabolic bone activity
 - survival

**Serum prostate-specific antigen (PSA)
as a read-out for tumor load:**

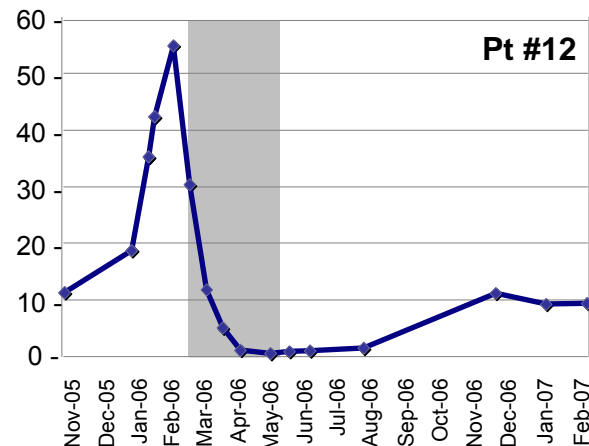
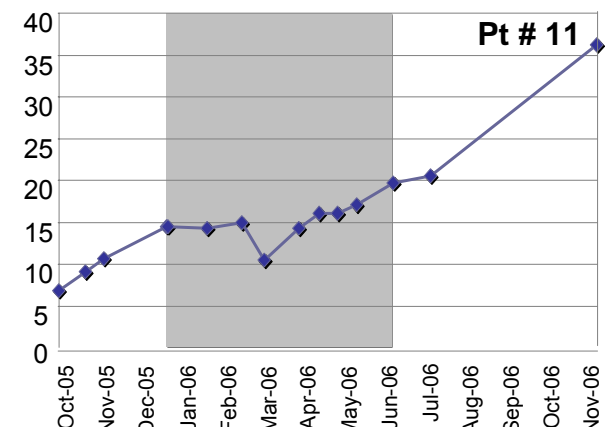
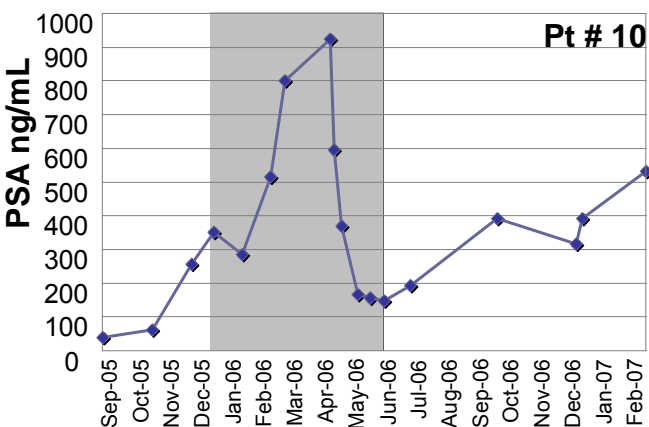


Clinical results

Dose level 3 (3 mg/kg α -CTLA-4)



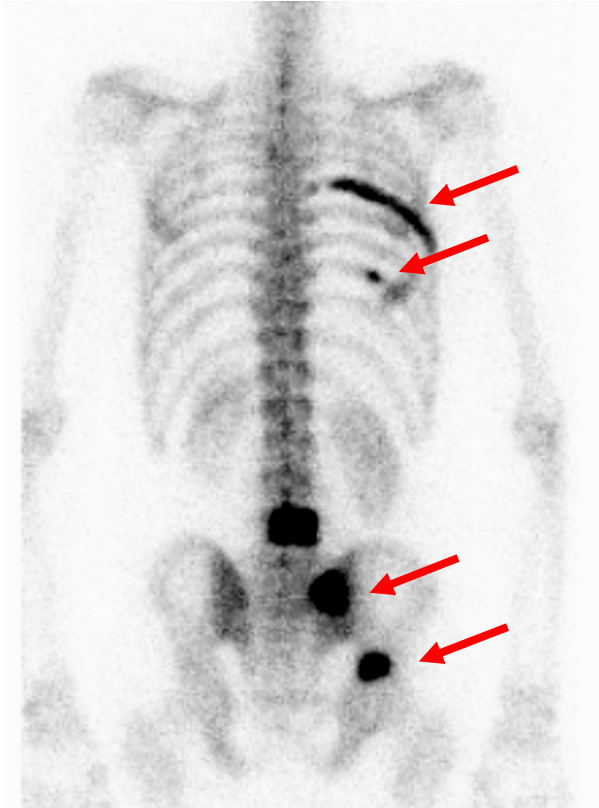
Dose level 4 (5 mg/kg α -CTLA-4)



- No PSA responses observed in dose level 1 and 2
- PSA declines of >50 % in 5/6 patients in dose level 3 and 4
- 4 PSA declines were durable > 6 months including 3 of 3 in dose level 3

Clinical results

Bone Scan Response in Patient 8 (dose level 3)



15-9-2005



29-3-2006

Ongoing as of 5/07

Clinical results

Tumor Response

- 11 patients had abnormal bone scans at baseline.
- Stable disease on bone scan was observed in 6 patients at 3 months, and is ongoing for 3 patients at 9 months and 1 patient at 12 months. 2 patients showed resolution of lesions (both in 3 mg/kg cohort)
- Regressing lymph node metastasis was observed in patient 12 (5 mg/kg)
- Improvement in bone pain

Clinical results

2nd PSA drop was accompanied by **immune related adverse events**

- 5/6 patients showed hypophysitis with secondary adrenal insufficiencies (4 of 5 patients) and secondary hypothyroidism (2 of 5 patients)
- 1 patient in 5 mg/kg dose level showed a dose limiting grade 3 alveolitis
- endocrinopathies successfully treated with standard hormone replacement therapy
- Two patients showed recovery of thyroid function within 6 months

Objective clinical responses correlate with autoimmunity. *Attia et al, JCO 2005.*

Immunomonitoring: principal question

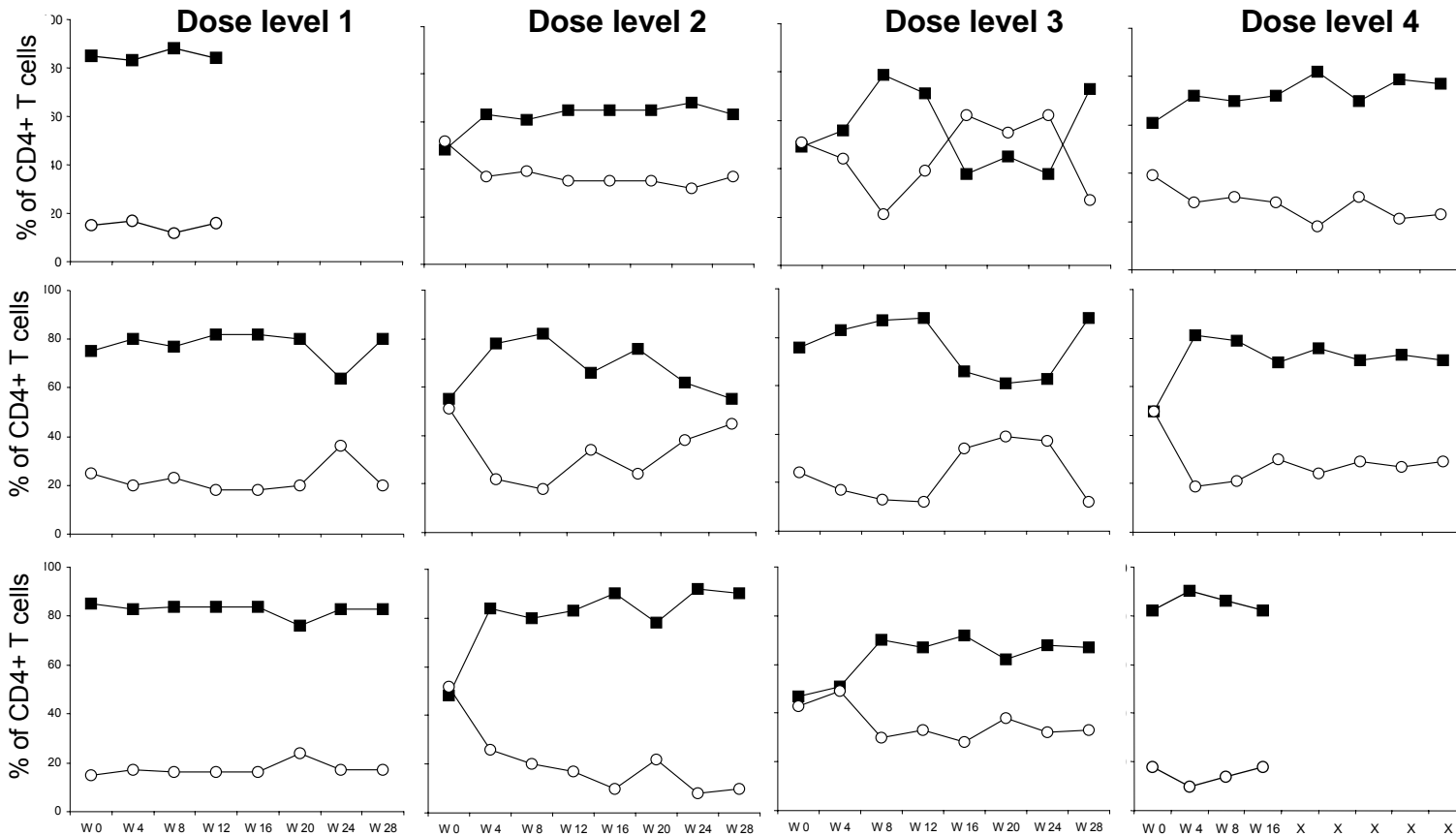
Can we identify immune parameters that correlate with clinical activity and facilitate rational design of future immunotherapeutic approaches?

Immunomonitoring

- **Peripheral Blood DC (PBDC) monitoring**
 - subsets
 - activation status
- **Peripheral blood T-/ T_{reg}/NKT cell monitoring**
 - activation status
 - phenotype
- **CTL / T helper cell monitoring**
 - tumor antigen-specific
 - peripheral blood and site of vaccination
- **Serological monitoring**
 - immunosuppressive factors
 - tumor-specific antibodies

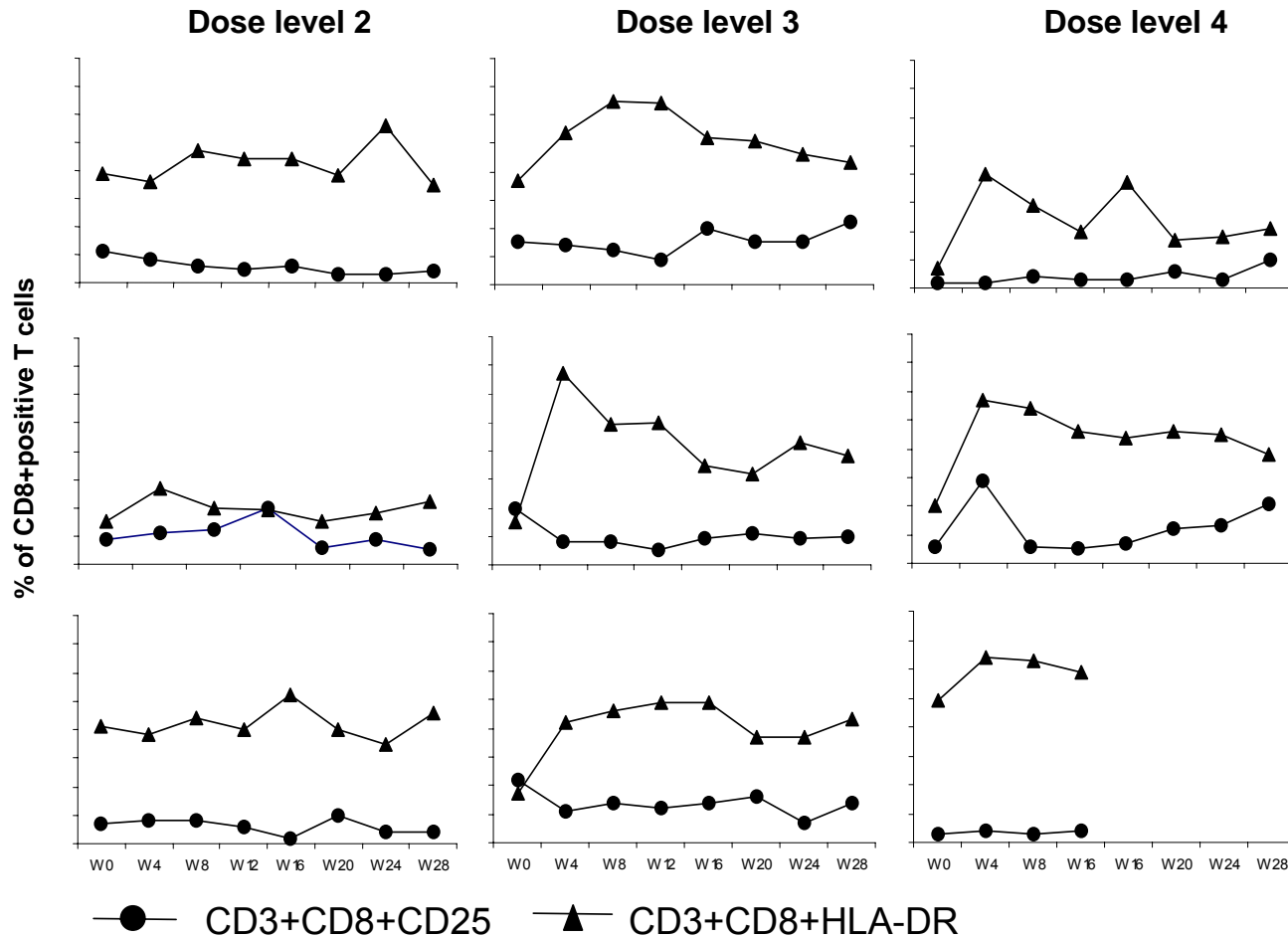
Peripheral blood T cell monitoring

T memory CD4+CD45RO++
 T naive CD4+CD45RO-



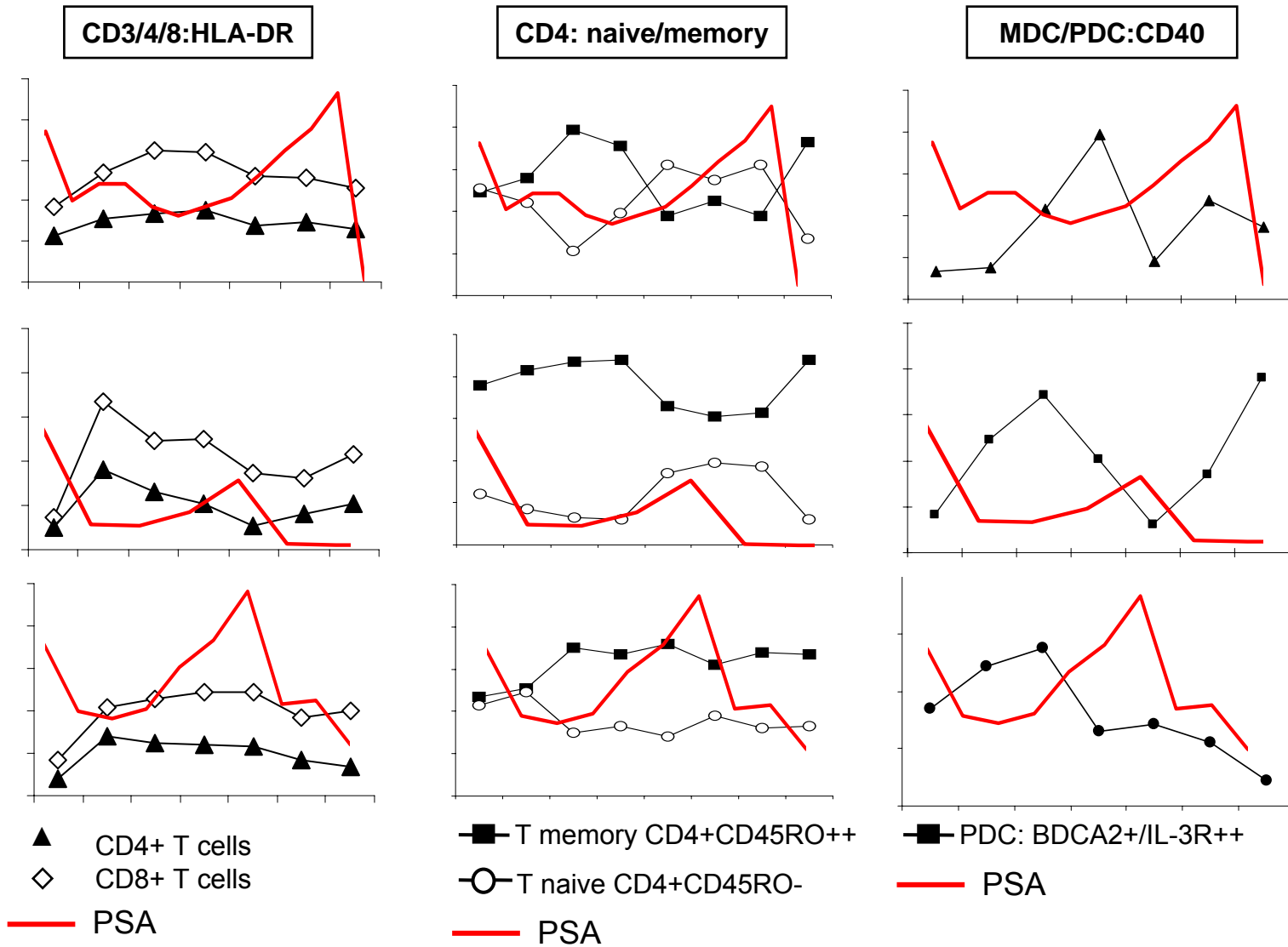
- Shifts from CD4+/CD45RA+ naive to CD4+/CD45RO+ memory phenotype in dose level 2, 3 and 4; not in dose level 1
- Transient decrease of naive CD8+ T cells in 4/6 patients in dose level 3 and 4 (not shown)

Peripheral blood T cell monitoring



Increase of HLA-DR levels on both CD4+ (not shown) and CD8+ T cells in dose level 3 and 4; not observed for CD25 (Maker et al, JI 2005)

Association of immune parameters with clinical activity: Reverse association



Conclusions

Immunomonitoring

- **Transient shift from naive to memory phenotype in dose levels 2-4 (CD4 and CD8)**
- **Increase of activation status of CD4+ and CD8+ T cells in dose levels 3 and 4**
- **Transient increase of MDC/PDC activation at dose level 3; not in 1, 2 and 4**
- **Reverse association observed between PSA and activation state of PBDC, T cells and levels of naive/memory CD4+ and CD8+ T cells**

Conclusions

Immunomonitoring

- **No anti-PSA antibodies were detected in the serum of GVAX and α -CTLA-4 mAb combination-treated patients (not shown)**
- **GVAX and α -CTLA-4 mAb combination induces IgG responses to a panel of PCa tumor associated antigens including PSMA, NY-ESO-1, Her2/Neu and filamin B (not shown)**

Our data suggest that the GVAX immunotherapy for prostate cancer + α CTLA-4 mAb combination may result in:

- durable objective clinical responses and**
- the activation of the immune system**

Future Plans

- Expansion cohort of 16 patients at 3 mg/kg α -CTLA-4 mAb has started
- Expansion of Th and CTL from immunotherapy injection site biopsies → TAA-specific T cell monitoring



**GVAX + α -CTLA-4 mAb
(0.3 mg/kg) after 48 hours**



**GVAX + α -CTLA-4 mAb
(3 mg/kg) after 1 week!**

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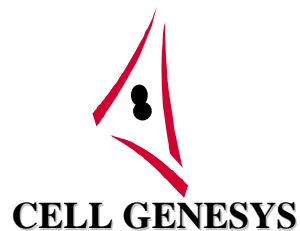
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