



Immunotherapy

Inspire to Live
CCA

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8 februari 2018

Immunity is required to successfully reject cancer



A century of research
before we **understood**

Dr. William B. Coley, Surgeon - Oncologist. New York (1890-1936).

Discovered that bacterial infections sometimes coincide with tumor rejection.

Treated ~900 patients with bacterial extract known as 'Coley's Toxin' (1915)

Achieved up to 40% success rate in cancer patients.

Poorly understood and (too) toxic.

Immunity is the key to curing cancer

Science breakthrough of the past year: Immunotherapy

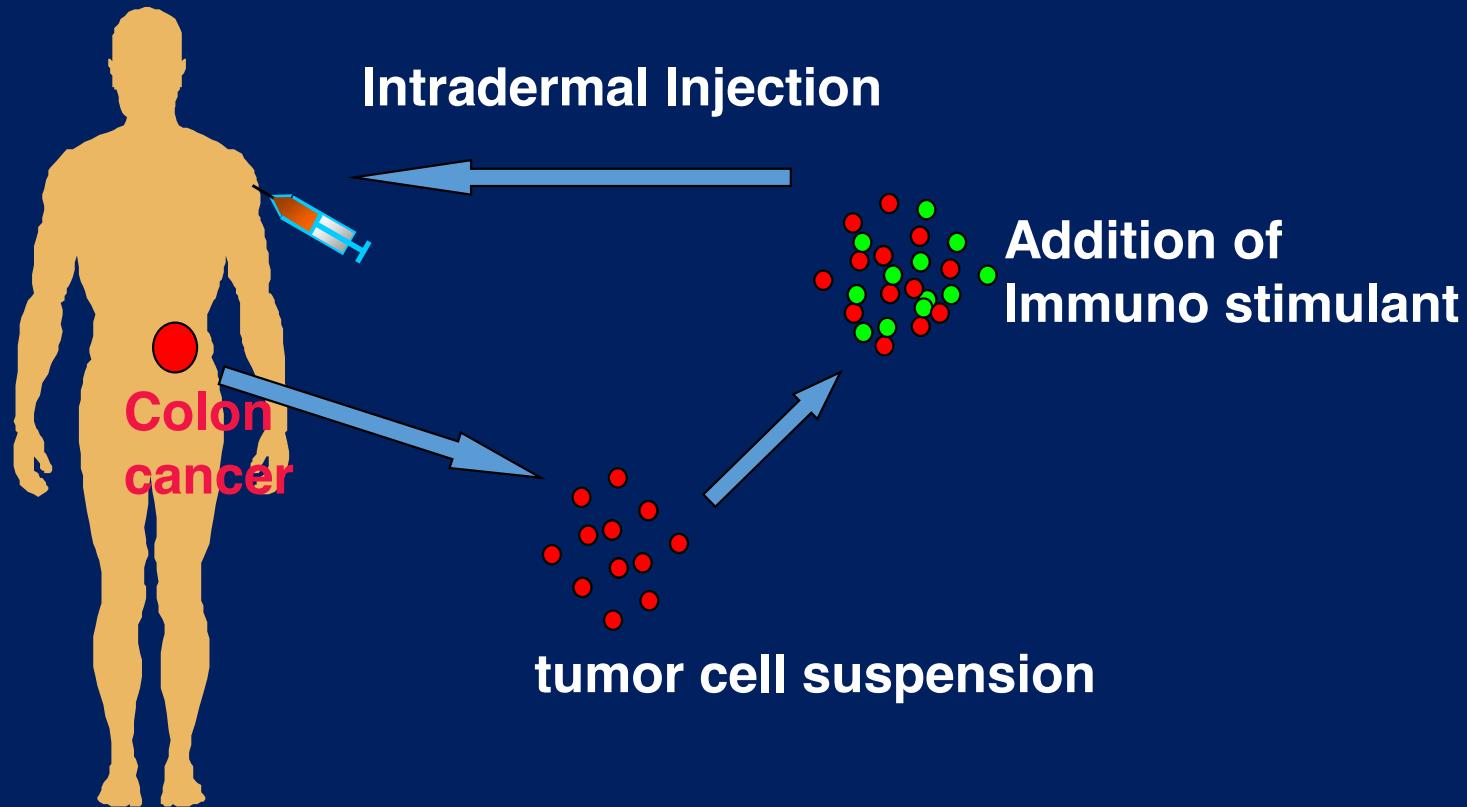
Evolving insights over the years at VUmc

- 1) Autologous whole tumor-cell immunization
- 2) Chemo-immunotherapy: *in vivo* vaccination
- 3) Allo-GVAX with ipilimumab/CTLA-4 blockade
- 4) Antibodies
- 5) Cytolytic viruses



Immunotherapy

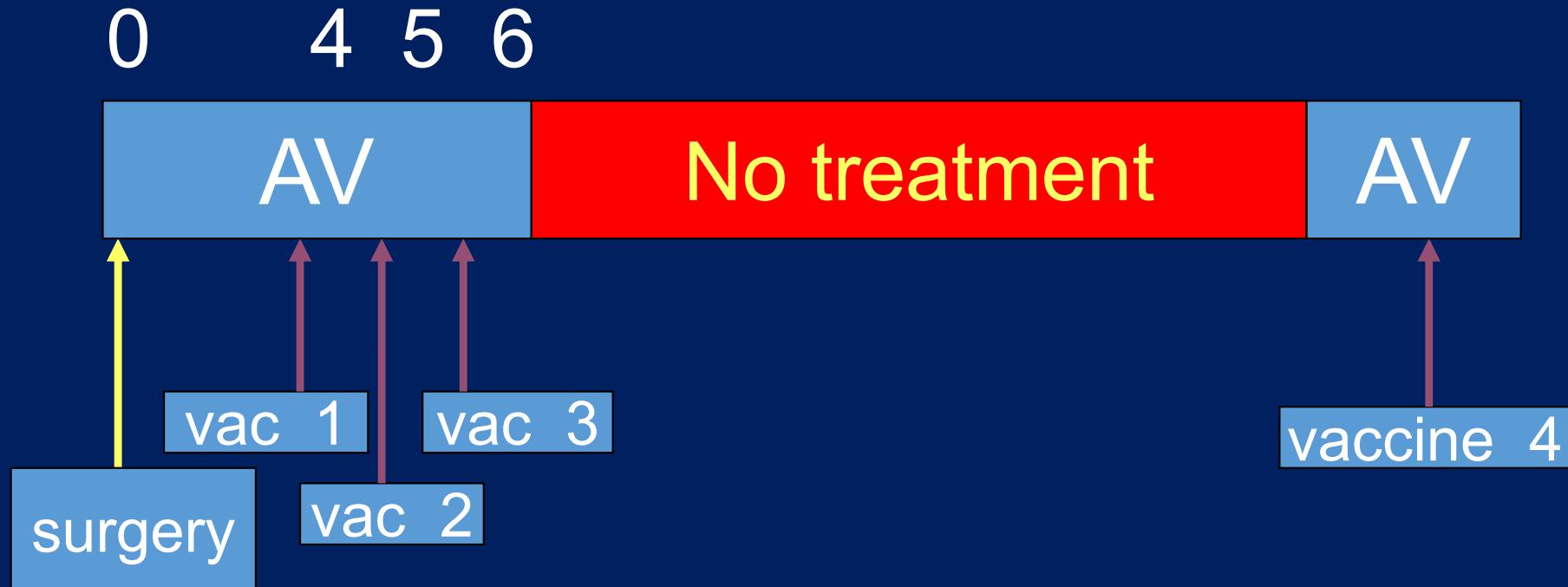
Active Specific Immunotherapy



Autologous vaccination in the thigh



Autologous vaccination in colon cancer

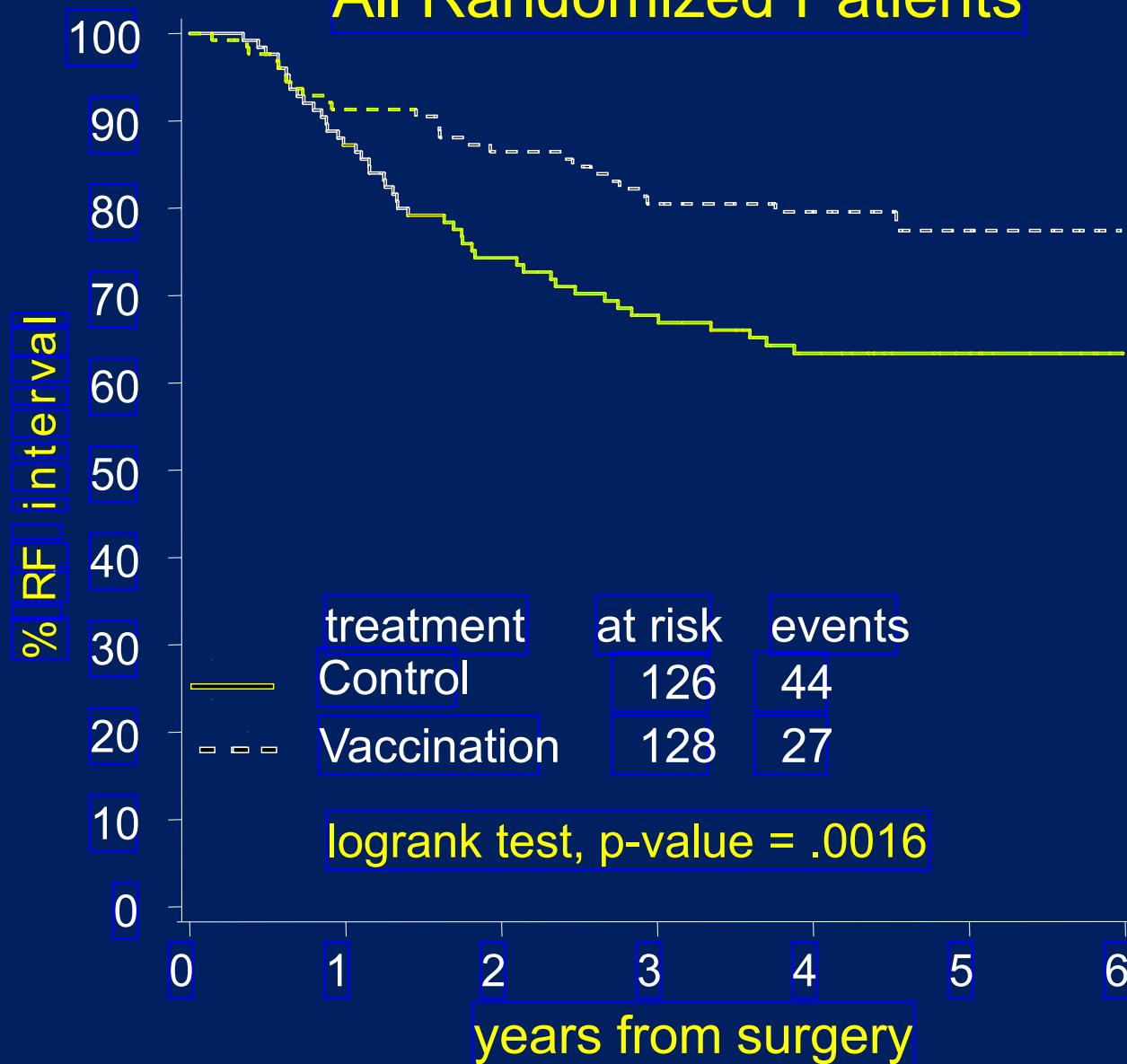


Vaccines 1 and 2: 10^7 autologous tumor cells + 10^7 BCG organisms

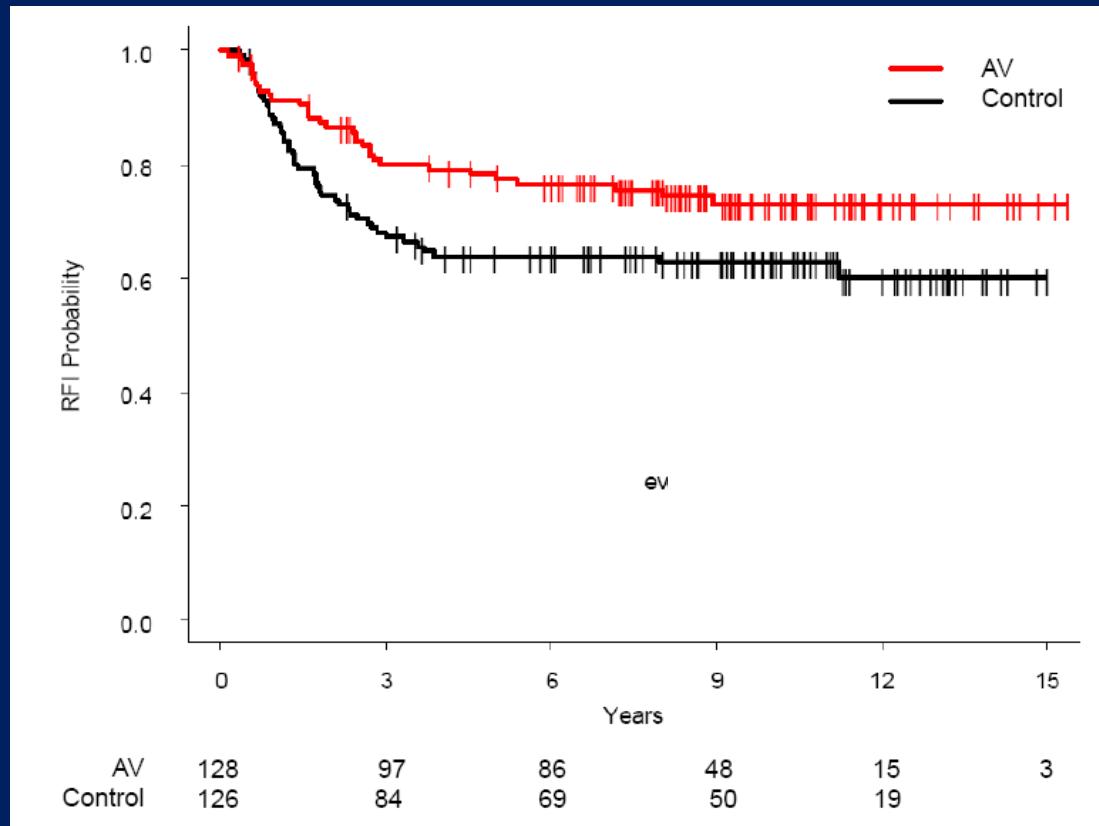
Vaccines 3 and 4: 10^7 autologous tumor cells

Recurrence Free Interval

All Randomized Patients

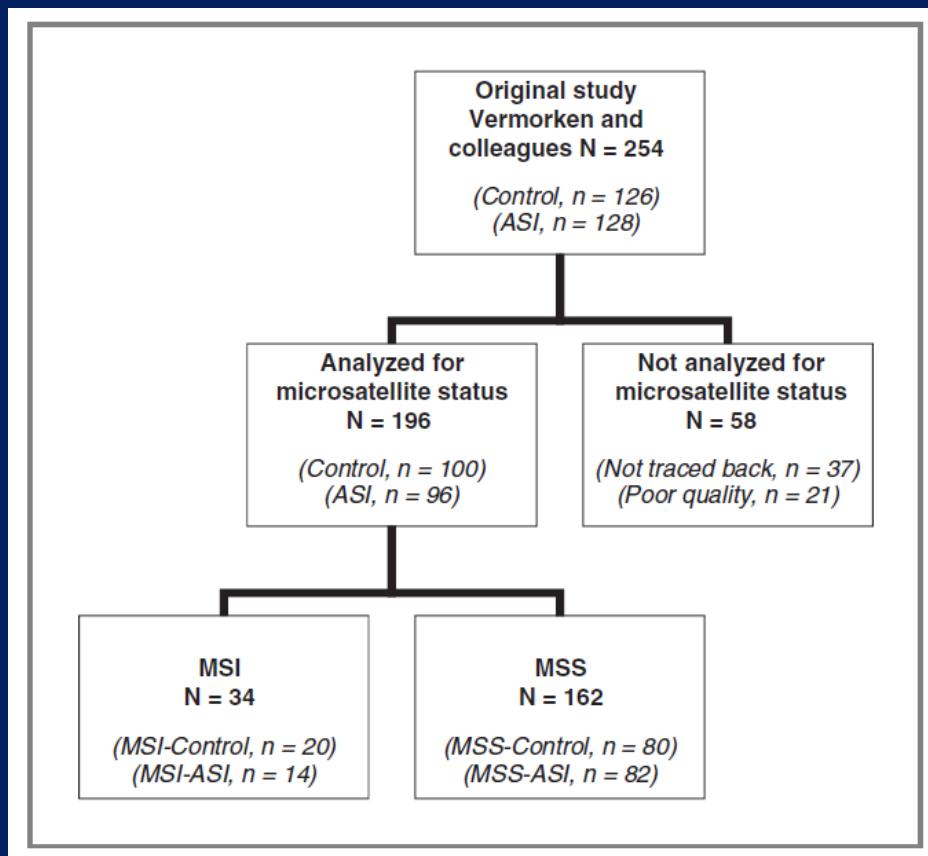


Recurrence-Free Interval following Adjuvant Autologous Vaccination (AV)

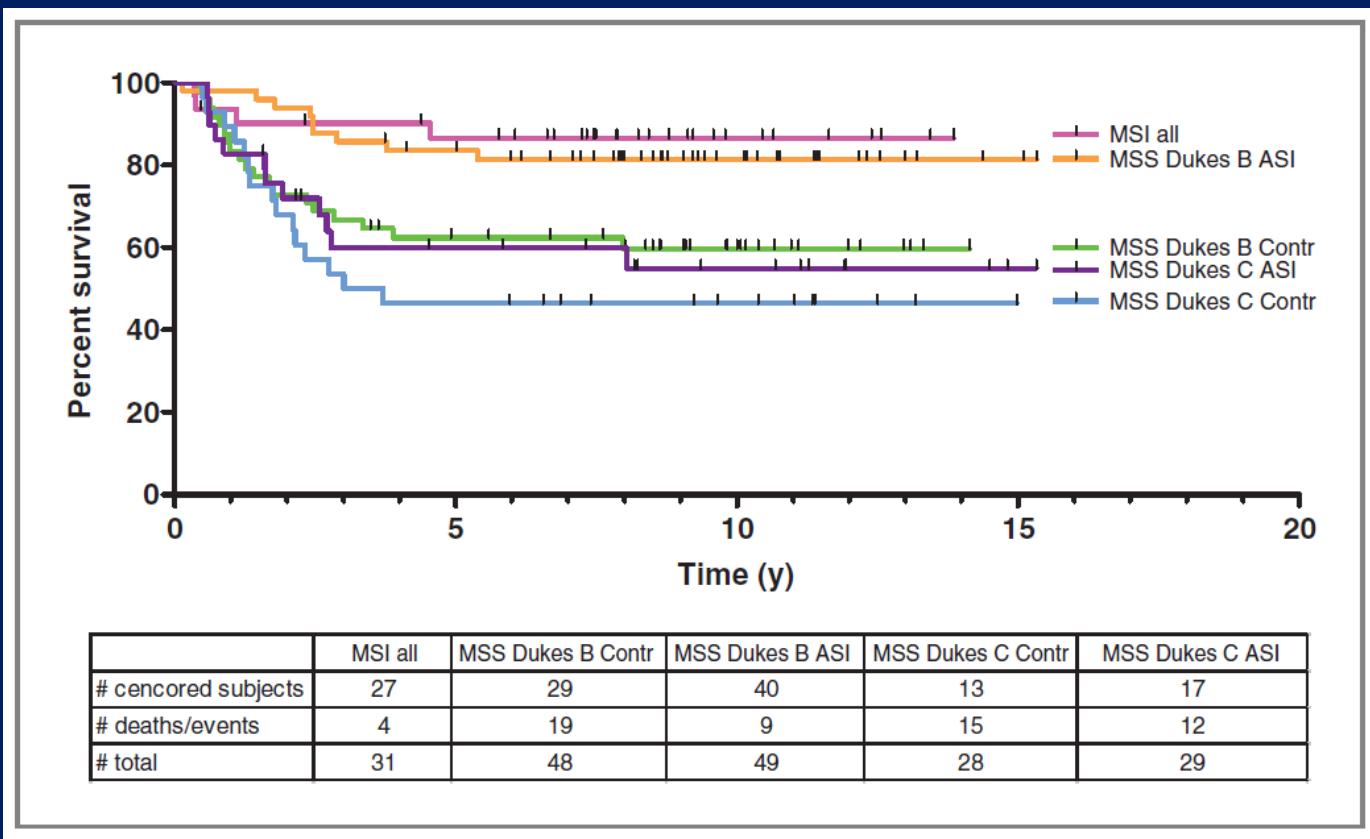


p-value 0.033

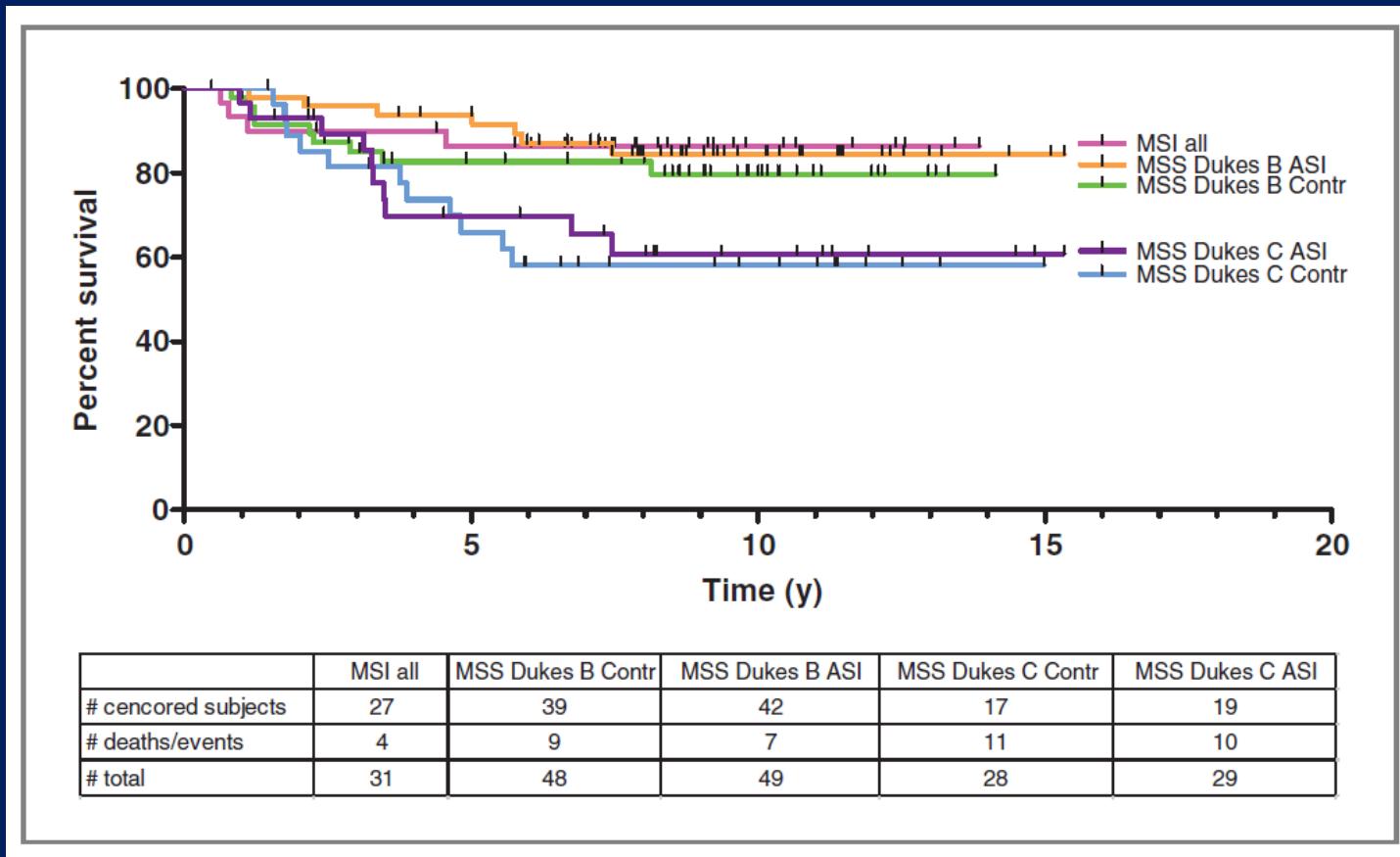
Study design



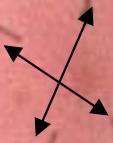
RFS in 2010 analysis: MSS+MSI



DSS in 2010 analysis: MSS+MSI



DTH response



Autologous Vaccination in Melanoma

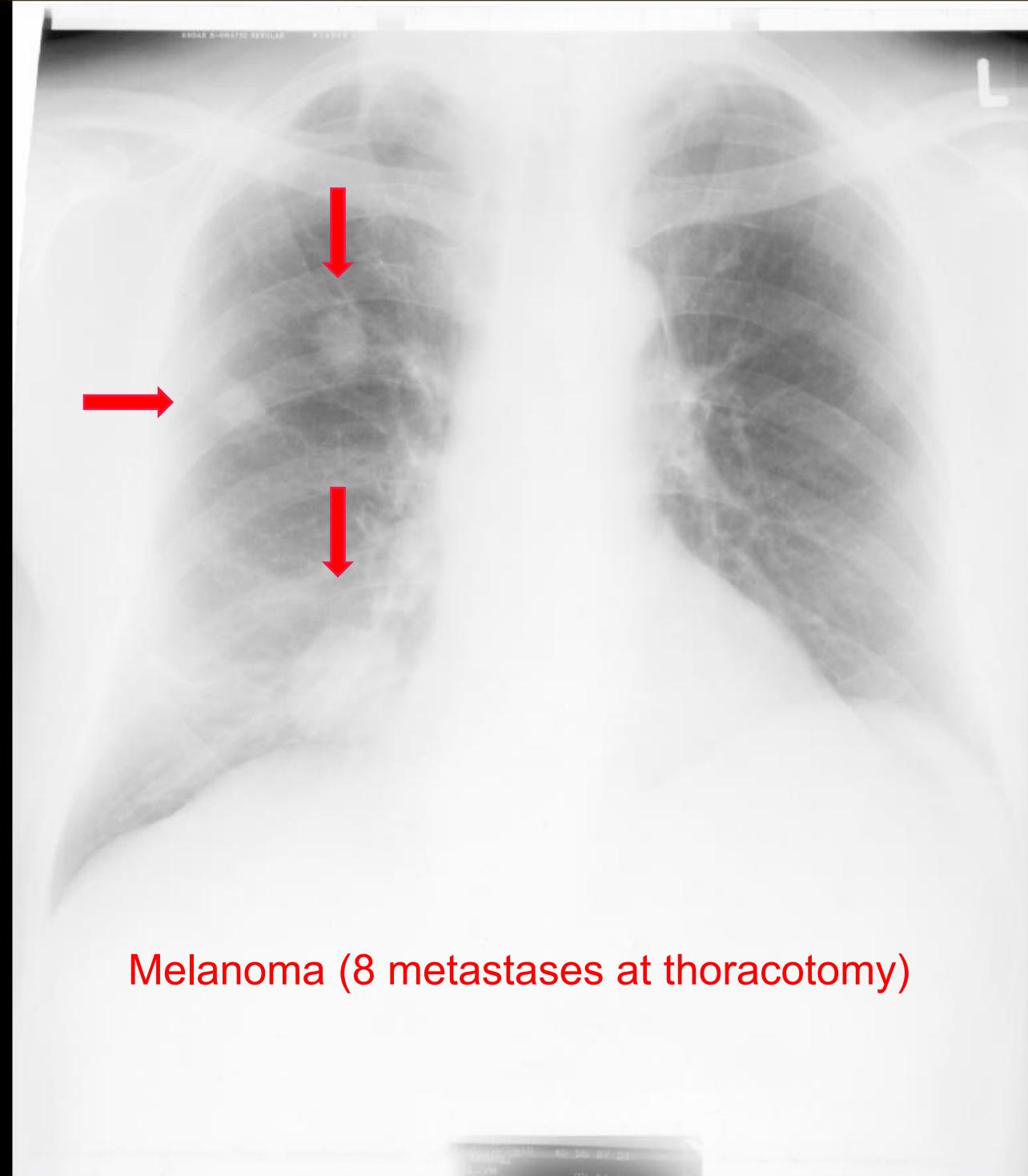
COURSE OF DISEASE AFTER REMOVAL OF METASTASES OF MELANOMA

- 58 yr old man presented with multiple metastases in right lung underwent resection of 8 metastases
- Autologous immunization (AV) every 3 months for 2 years
- At 60 yrs new metastasis removed
- AV resumed every 3 months for 2 more years
- At 68 yrs he died of unrelated disease

KRAUSZ L
58 years M 5558721
Acc: K12
22-6-1987

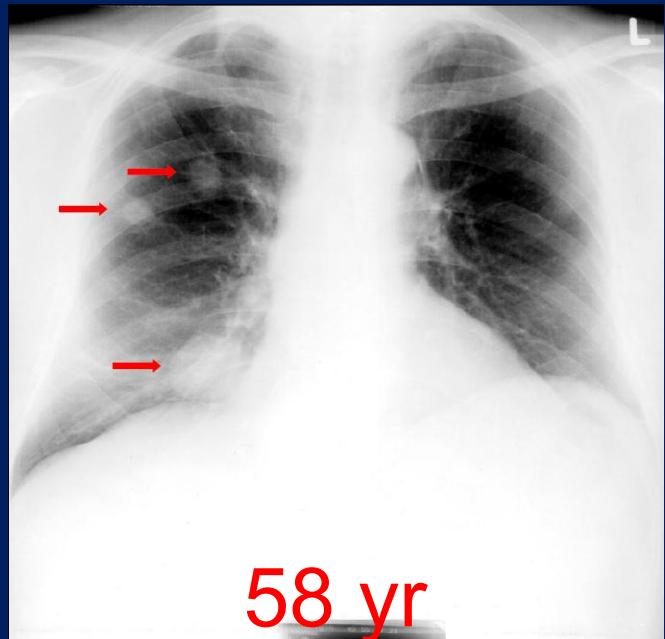
2007x2322
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Mag: 0.38x



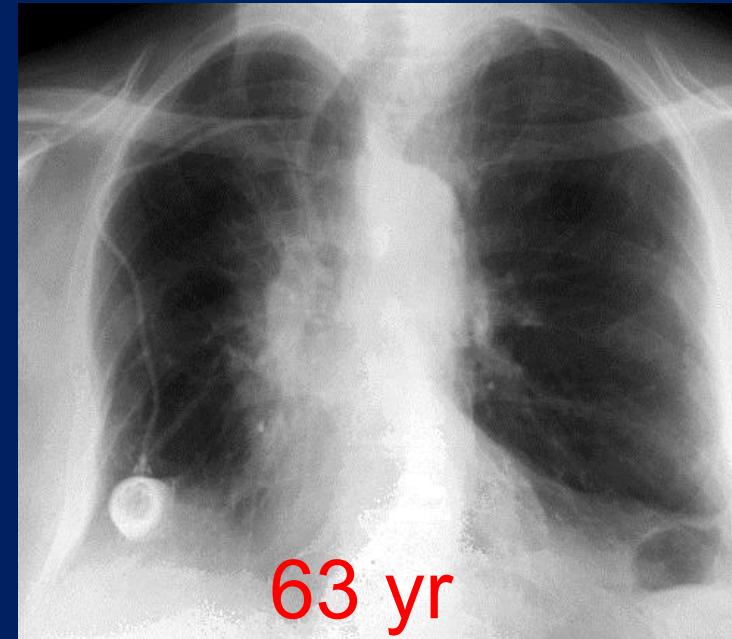
Melanoma (8 metastases at thoracotomy)

Melanoma: Metastectomy and Successful Use of the Cancer Cells as Autologous Vaccine (AV)



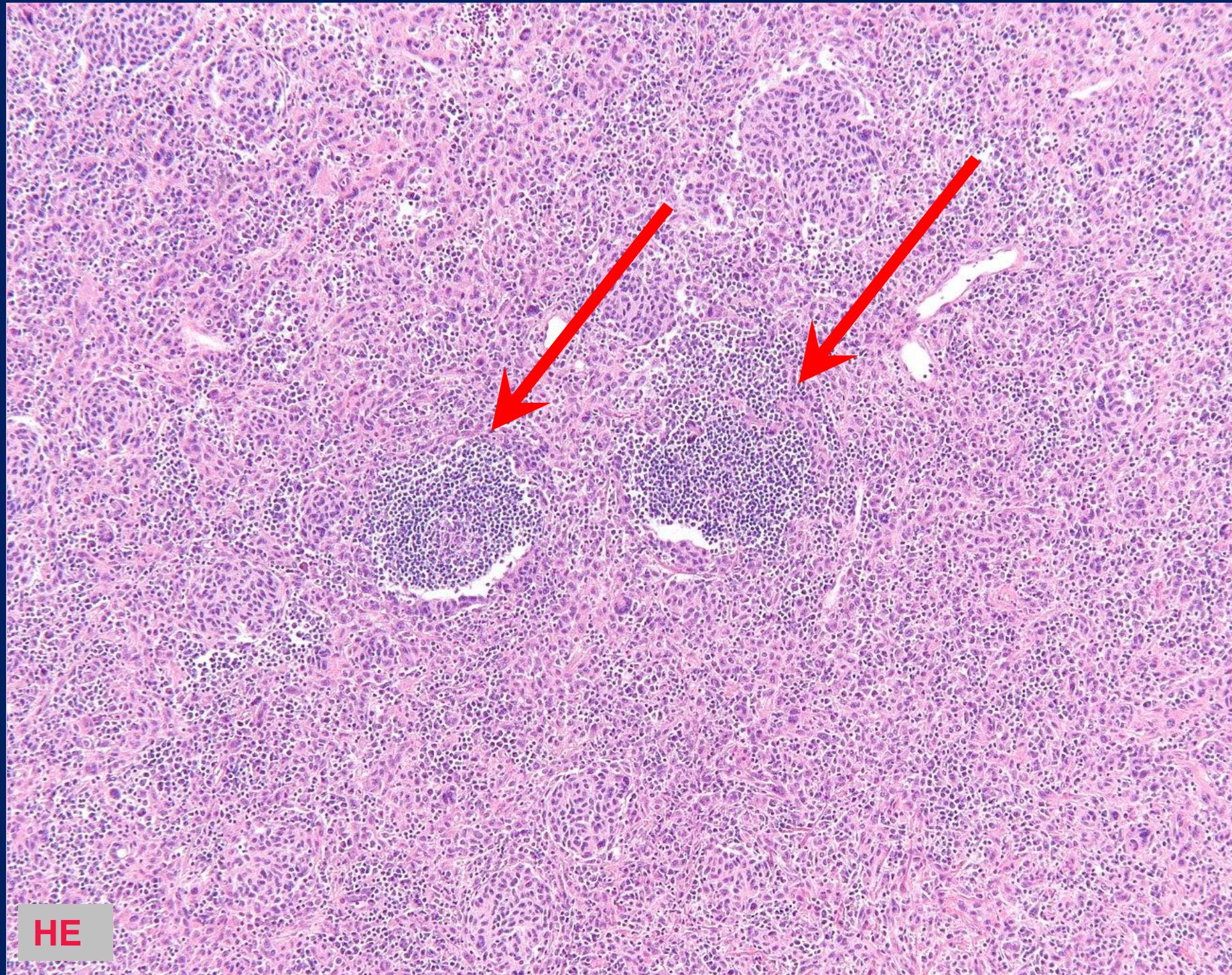
58 yr

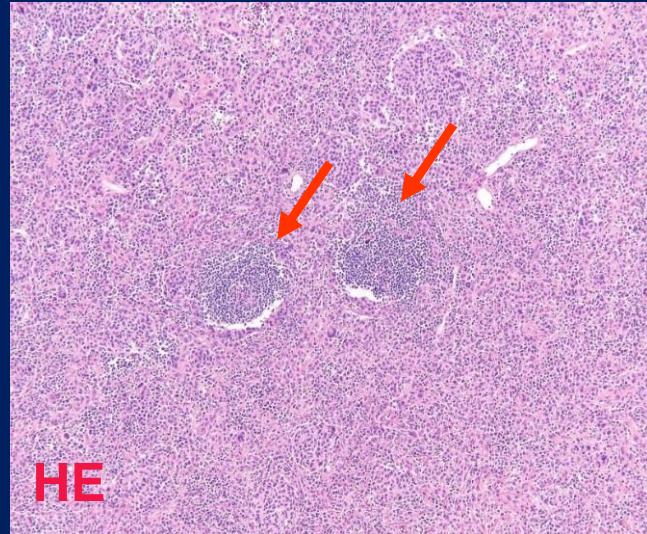
Resection of 8 lung mets
AV q 3 mths during 2 yrs
At 2 yrs new lung lesion resected
AV resumed q 3 mths for 2 more yrs



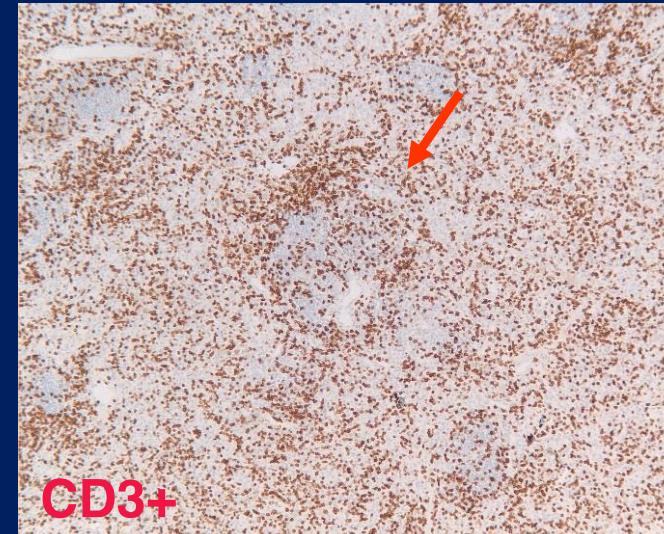
63 yr

PD in right groin after treatment-free period
Resistance to chemotherapy



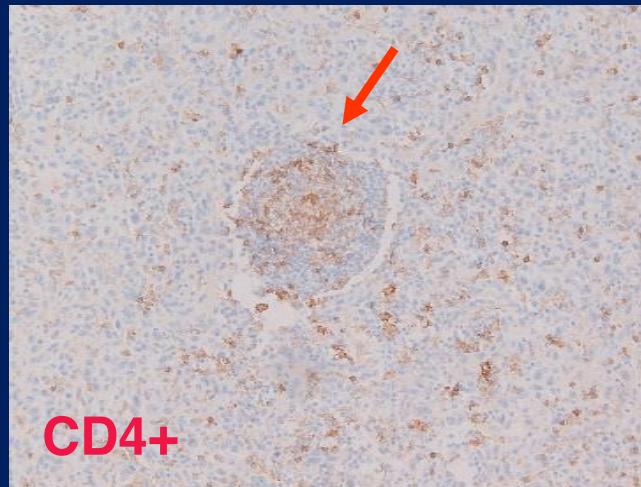


HE

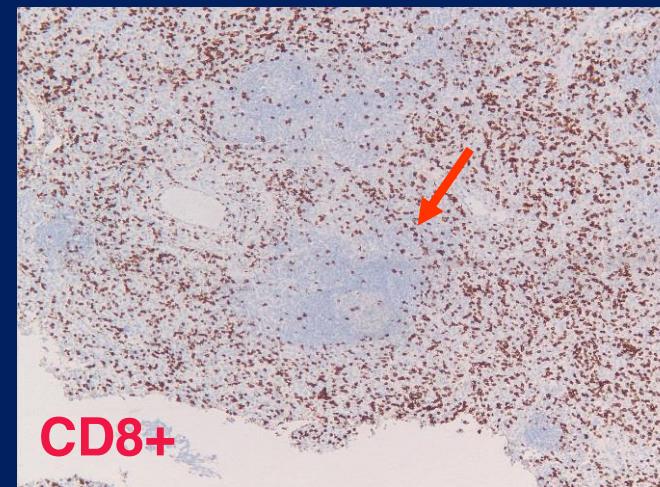


CD3+

Intra-metastatic Lymphoid Follicles

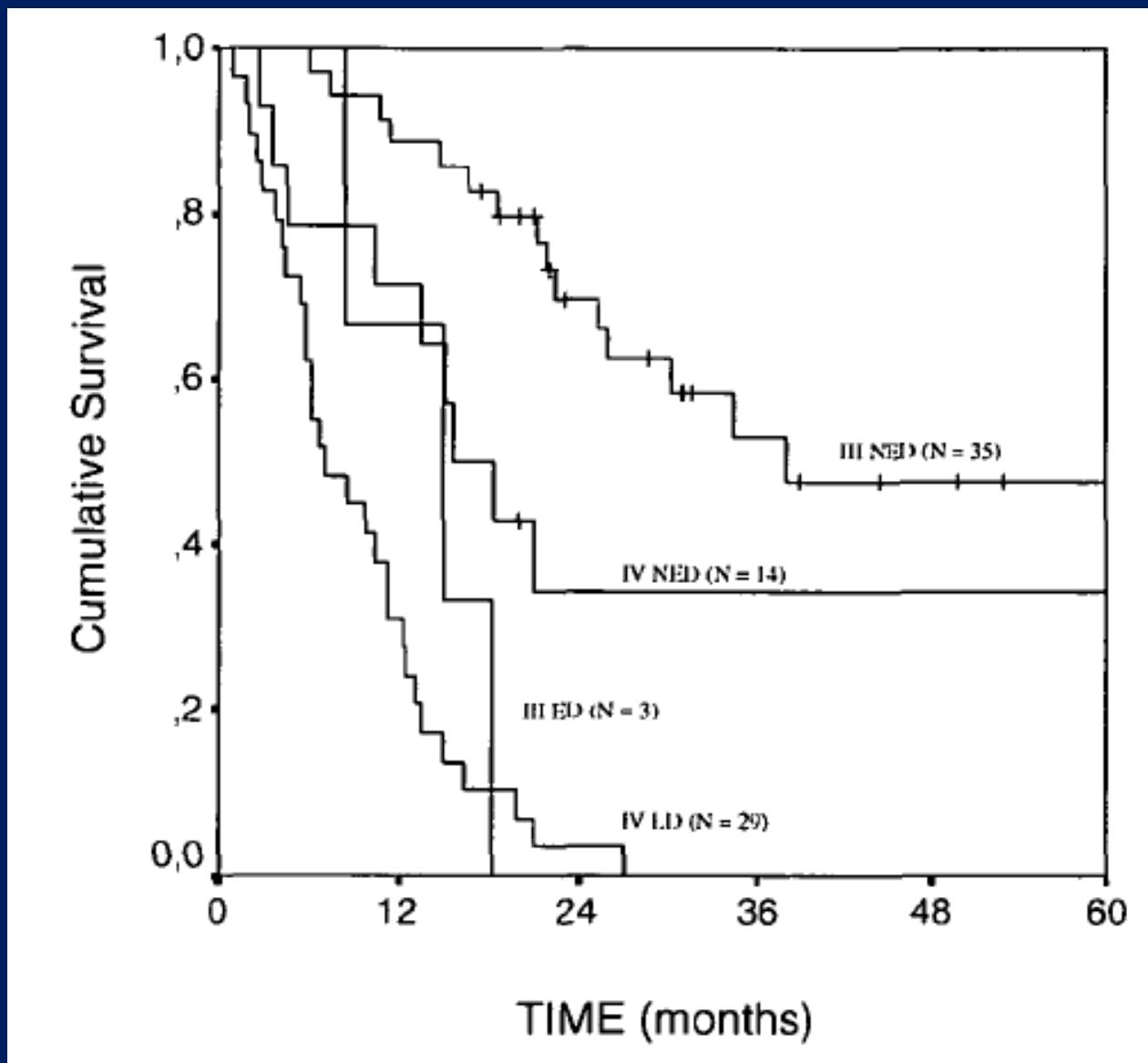


CD4+

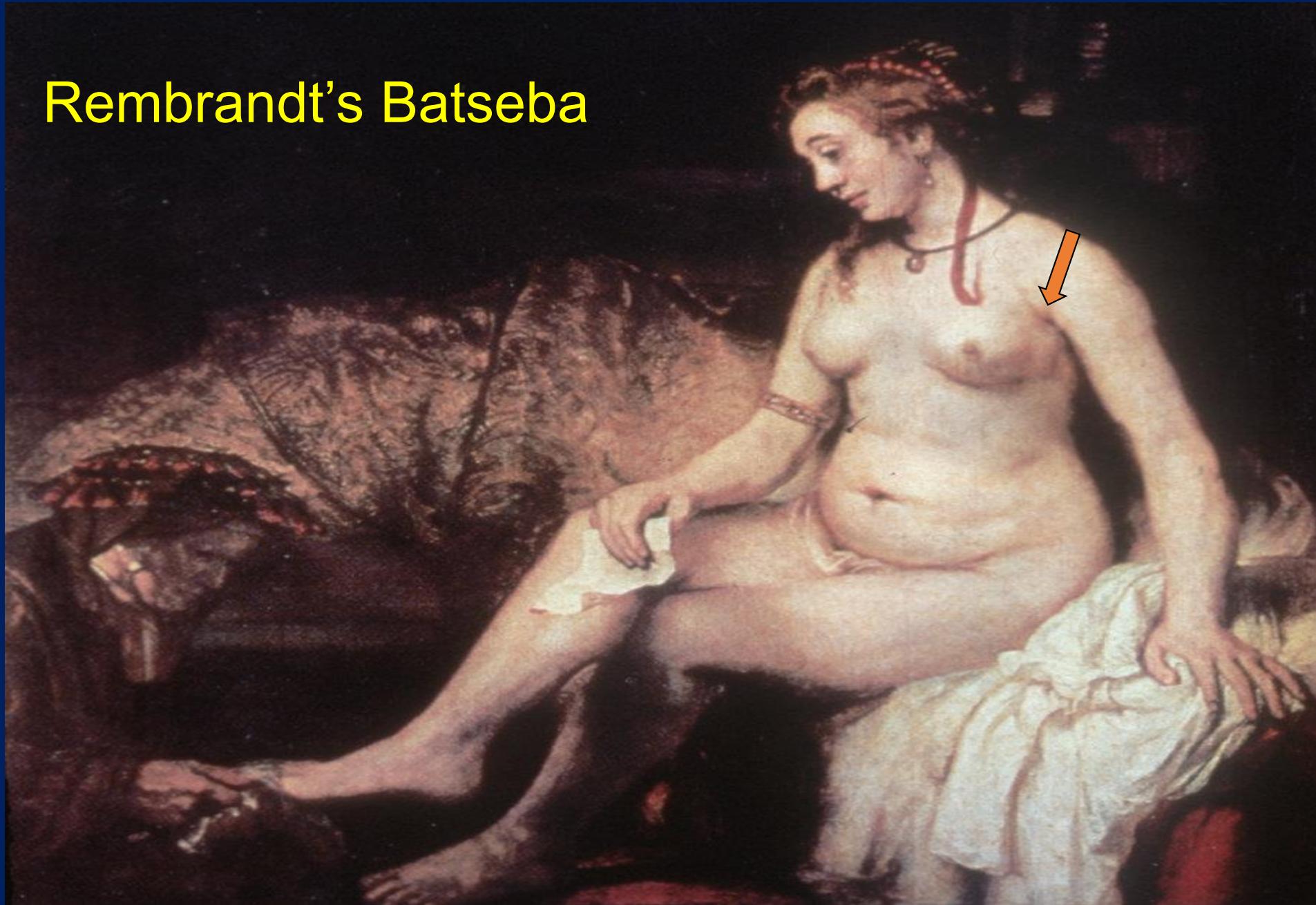


CD8+

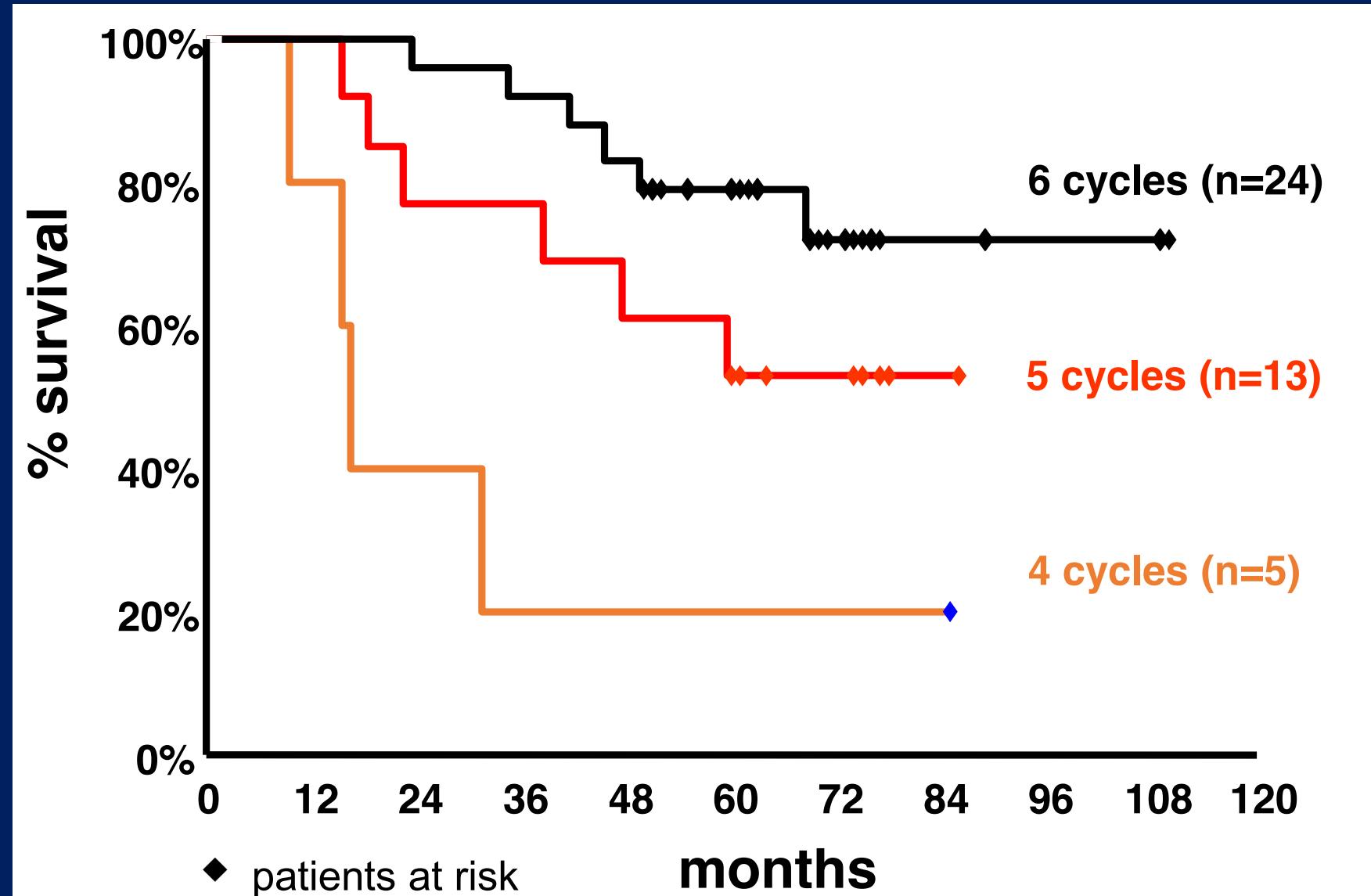
Survival according to remaining disease following surgery in melanoma stage III-IV



Rembrandt's Batseba

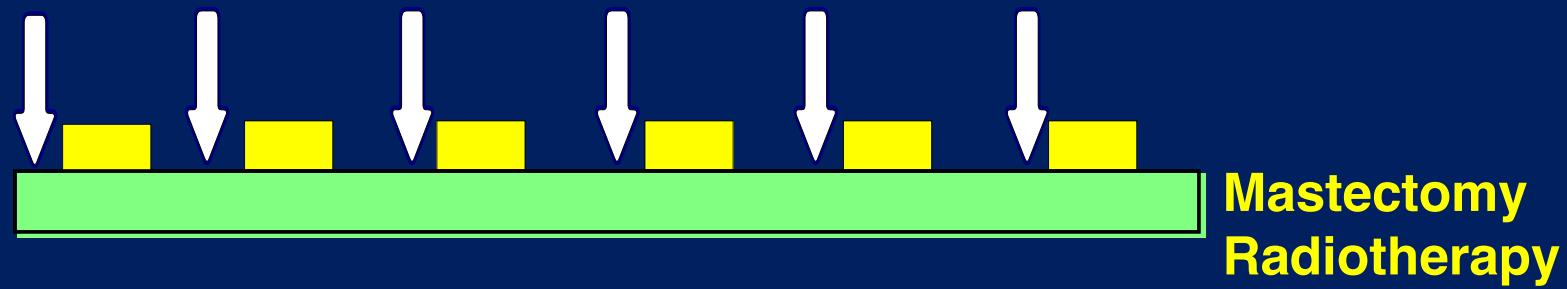


*Phase 2 study of neoadjuvant AC + GM-CSF
in LABC OS according to number of cycles*



Neoadjuvant Chemo-immunotherapy in LABC

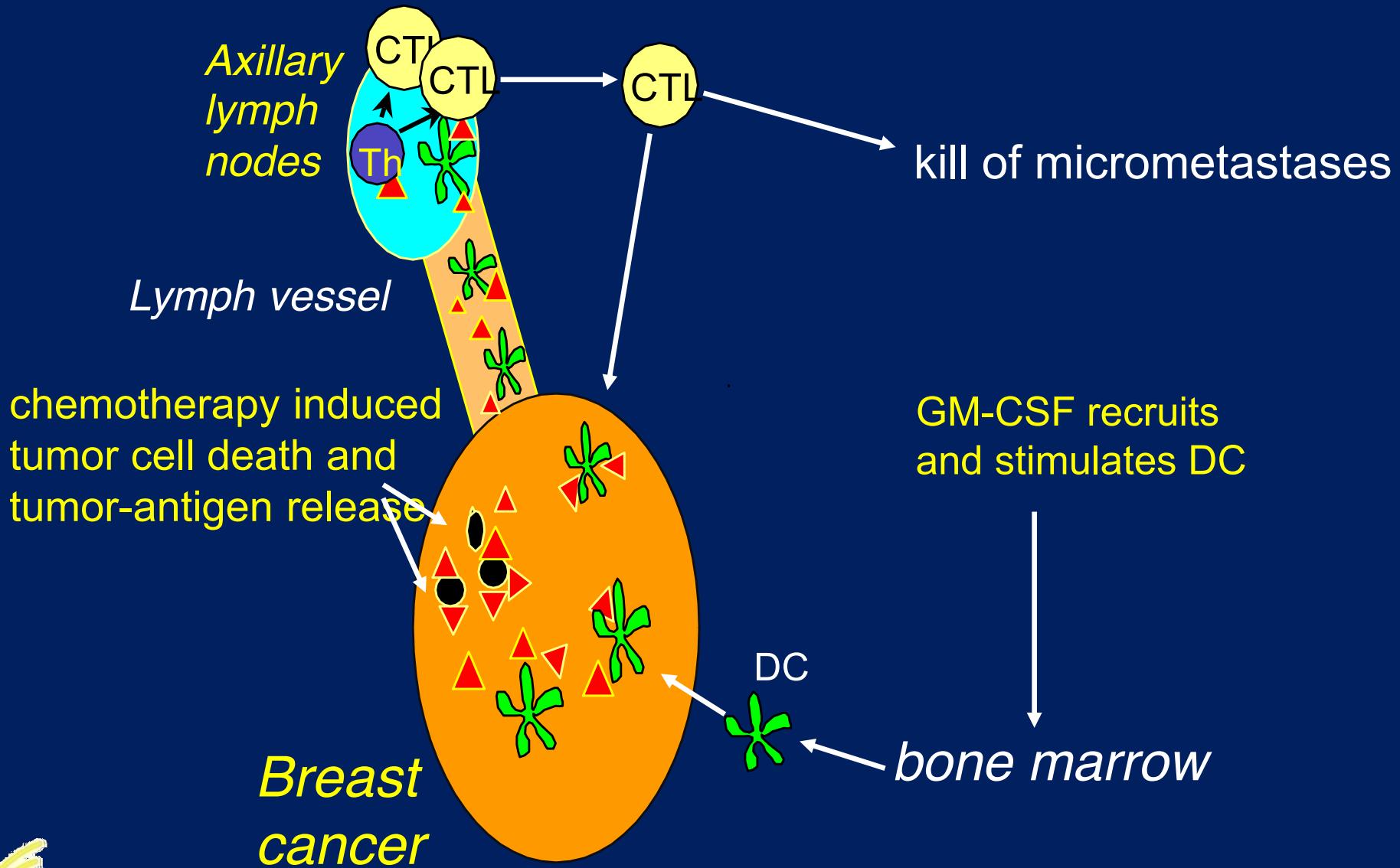
Change in Multidisciplinary Approach



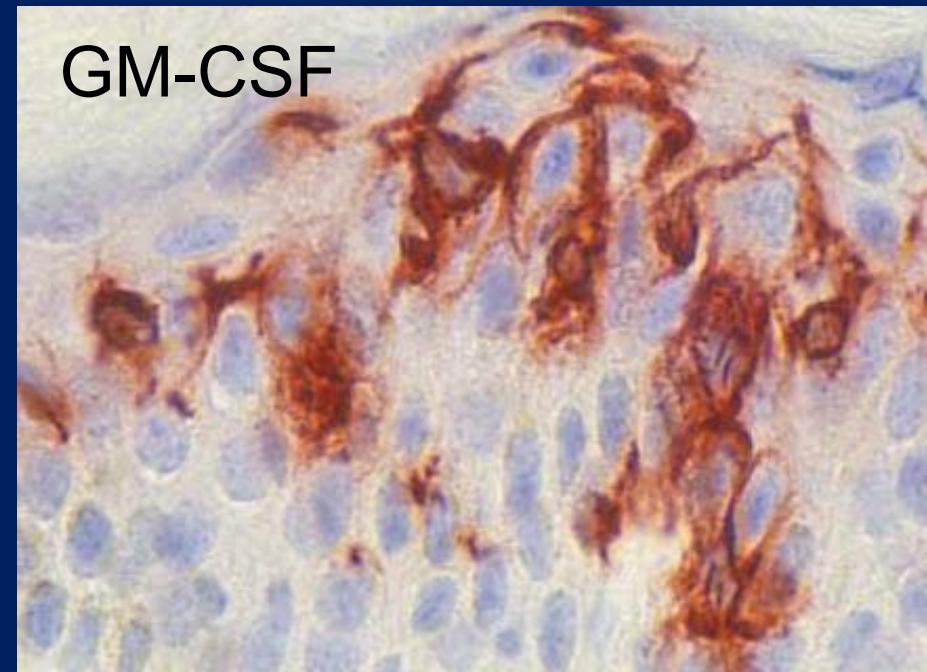
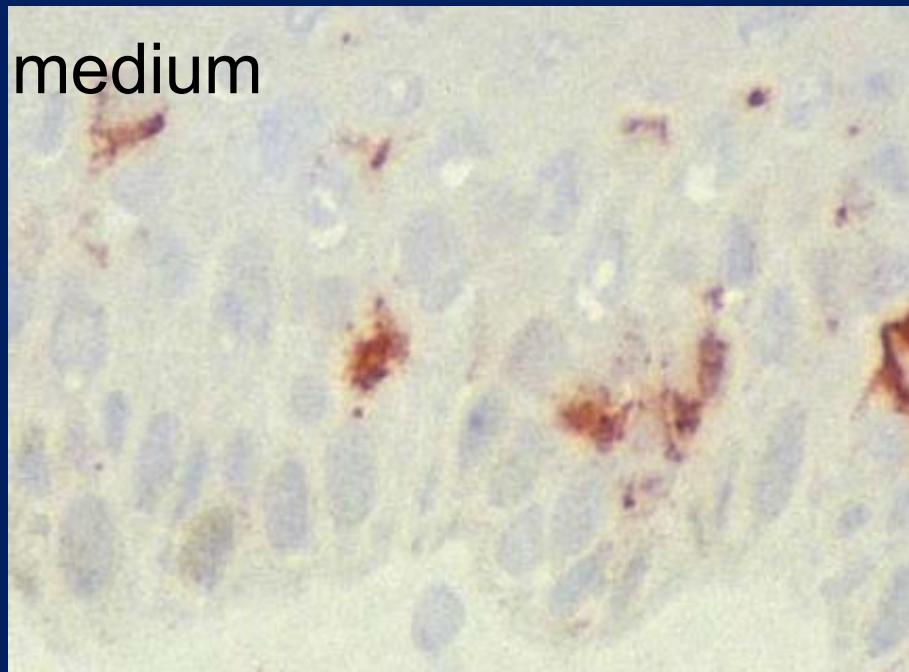
■ GM-CSF

AC

The Pre-existent idea...

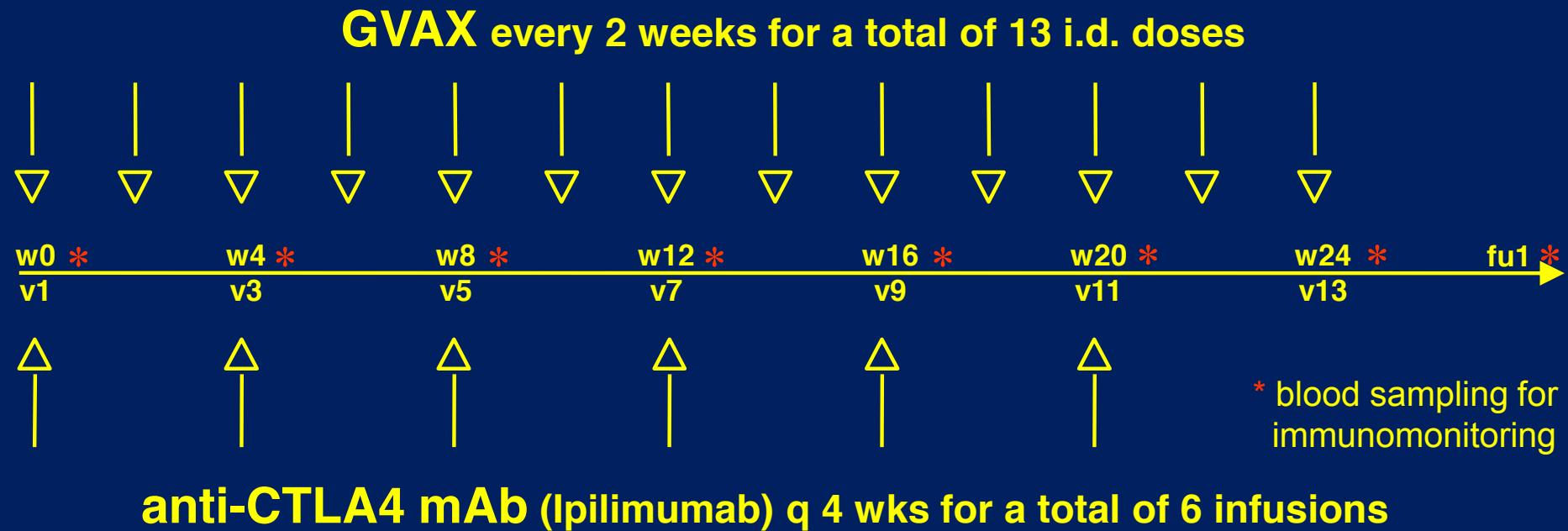


DC infiltration following GM-CSF injection in skin



Increase of number of DC's (HLA-DR+) in skin

Phase 1 study anti-CTLA4 Treatment schema



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
<hr/>		
Cohort 5	13-28	3.0 mg/kg

Skin reactions at the GVAX injection sites



GVAX IT alone

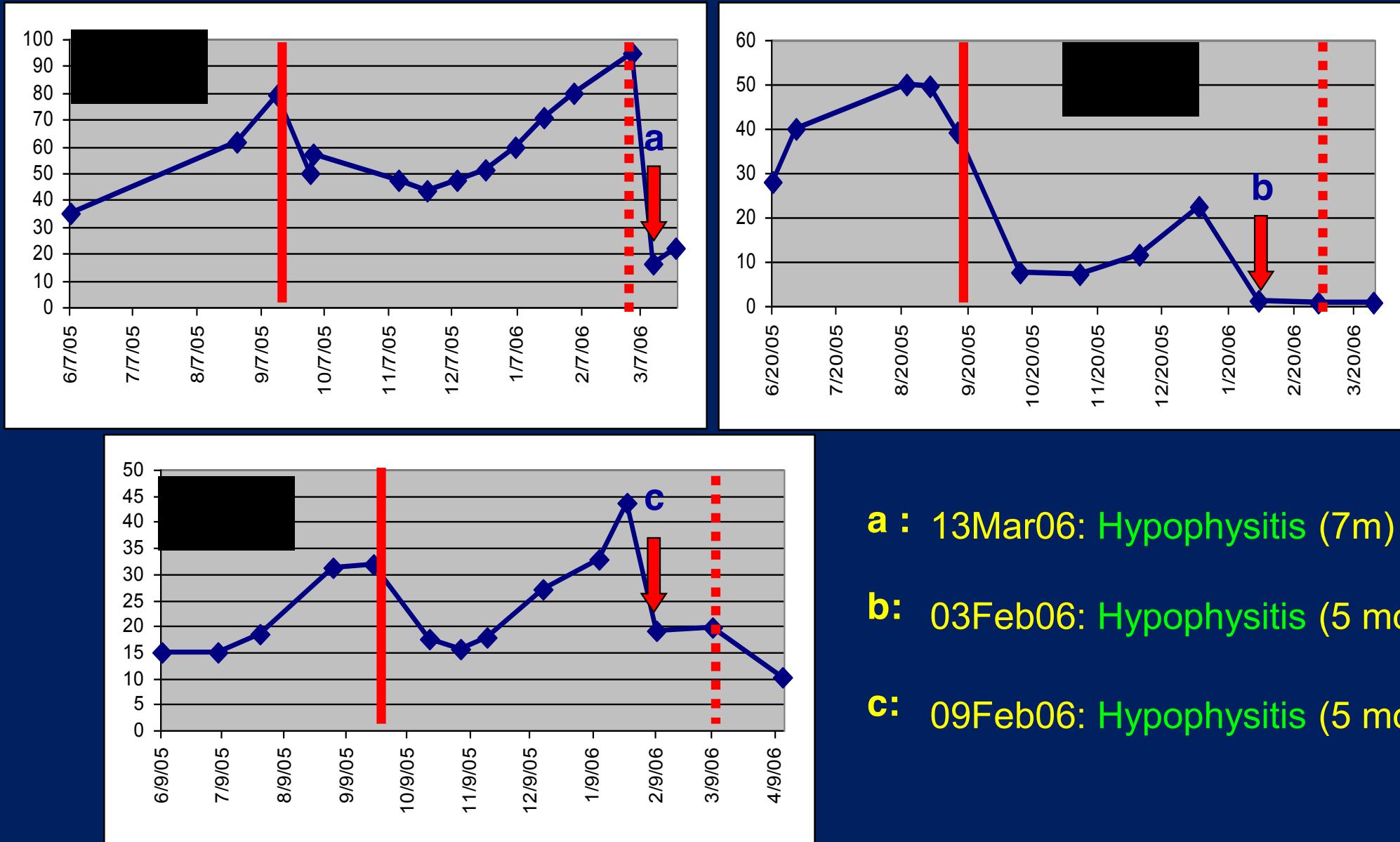


GVAX IT + MDX-010
(0.3 mg/kg)



GVAX IT + MDX-010
(3 mg/kg)
After 1 week

PSA curves – Dose Level 3 (3 mg/kg)



a : 13Mar06: Hypophysitis (7m)

b: 03Feb06: Hypophysitis (5 mo)

c: 09Feb06: Hypophysitis (5 mo)

Bone Scan Improvement in Patient 8 (3 mg/kg)



15 Sept 05

29 Mar 06

Breakthrough: Guidance by T-Cell Profiling in Blood, Tumor and Lymph nodes

TUMOR TYPE	STAGE	TREATMENT	IMMUNO-STIMULANT	PREDICTIVE FACTOR	REFERENCE
MELANOMA	METASTATIC DISEASE	EXCISION METS +AUTOLOGOUS TUMOR CELL VACCINATION	BCG	MELANOMA-SPECIFIC TILs, BUT NOT CIRCULATING CD8+ T CELLS, DTH	Haanen,Baars, Cancer Imm.Immunother. '06 Baars, Ann Oncol,2000
COLORECTAL CANCER	PRIMARY STAGE 2	SURGERY PLUS AUTOLOGOUS TUMOR CELL VACCINATION	BCG	MSI/MSS, CD8, CD8 T-CELL INFILTRATION	De Weger et al., Clin Cancer Res, '11 Turksma
LOCALLY ADVANCED BREAST CANCER (LABC)	PRIMARY STAGE 3/4	NEOADJUVANT CHEMOTHER; IN VIVO VACCINATION	GM-CSF	LYMPH NODE DENDRITIC CELLS Pre-treatment blood Tregs <i>CD4, CD8, CD68</i>	Pinedo et al, Eur.J. of Cancer, '03 Van Cruijsen et al,in pr <i>DeNardo, Cancer Discovery, '11</i>
PROSTATE CANCER	ADVANCED HORMONE RESISTANT	ALLO-GVAX VACCINATION	IPILIMUMAB/ GM-CSF	Teff/Treg ratio and CTLA-4 activated Th CELLS; High DC, low MDSC frequencies	Santegoets, Cancer Imm. Immunother, '13 and submitted.

..... Studies on profiling following anti-PD1 and others running.....



