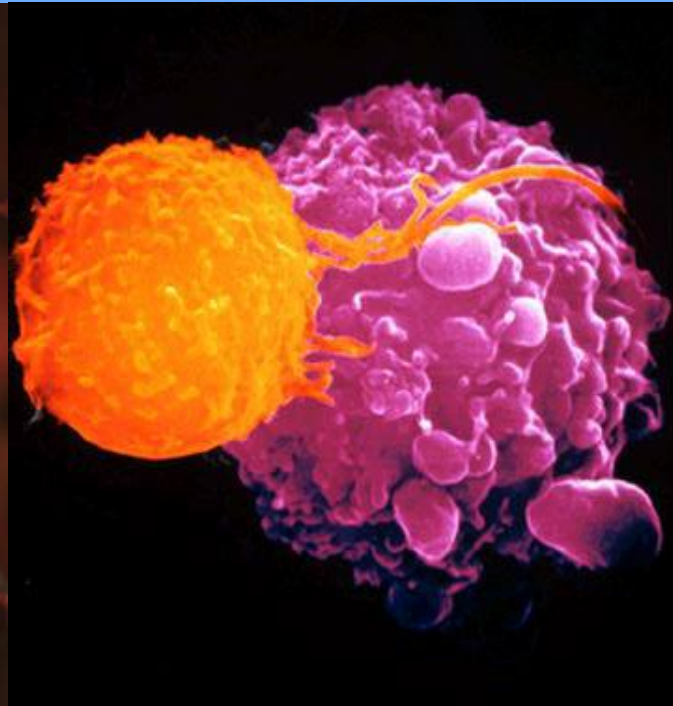
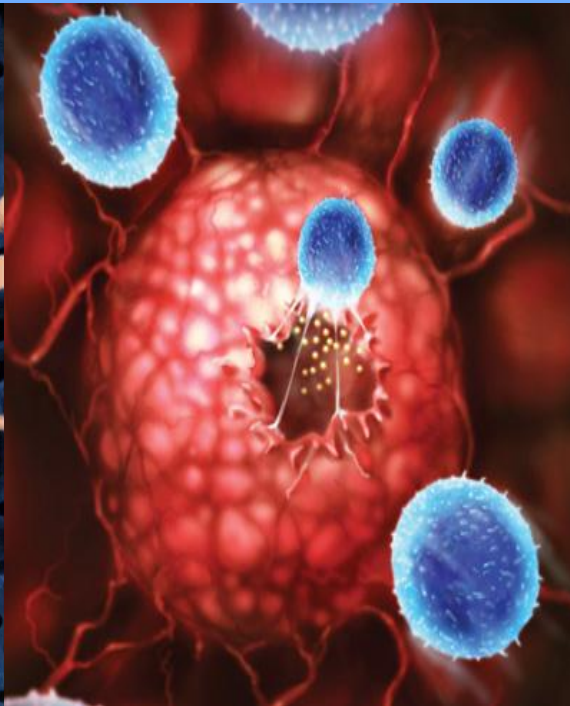
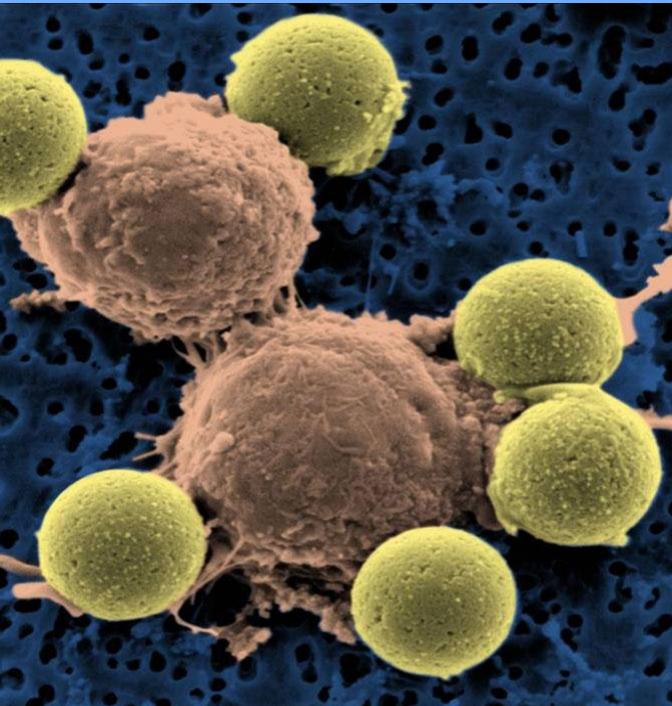


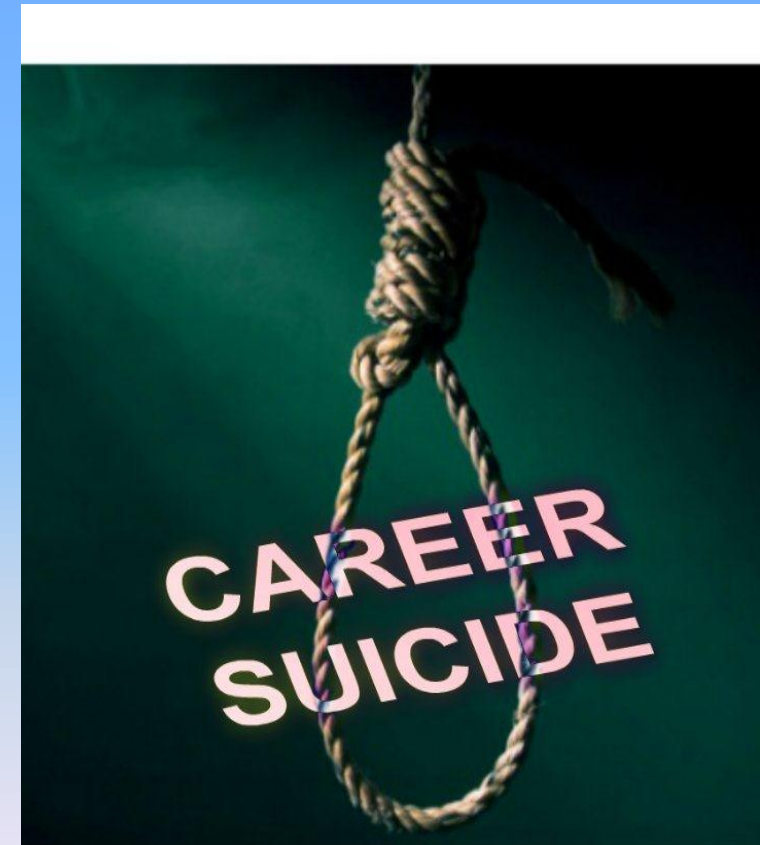
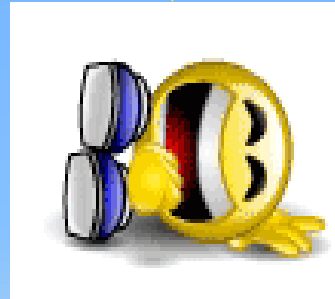
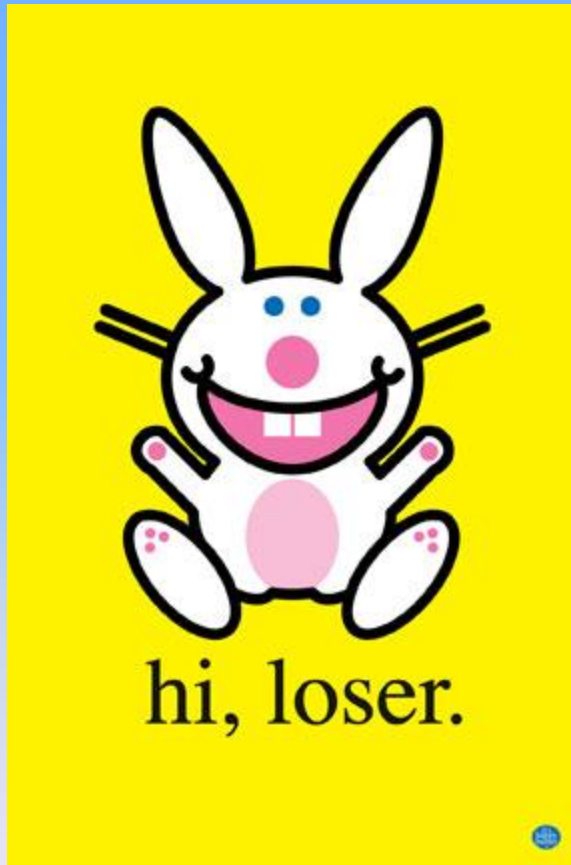
# Randomised Clinical Trial Of Epstein-Barr Virus-Specific Autologous Cytotoxic T-Lymphocyte For The Treatment Of Advanced Nasopharyngeal Carcinoma Patients



**DR TOH HAN CHONG**  
**DIVISION OF MEDICAL ONCOLOGY**  
**NATIONAL CANCER CENTRE SINGAPORE**

# ***CANCER IMMUNOTHERAPY ?***

## **THE USUAL REACTION FROM THE CANCER COMMUNITY**



20 December 2013 | \$19

# Science

Breakthrough of the Year

## Cancer Immunotherapy

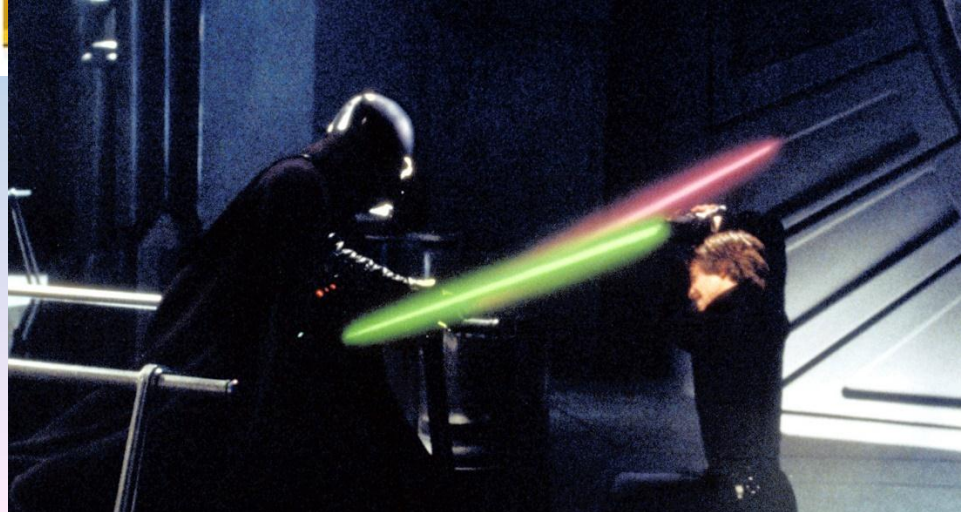
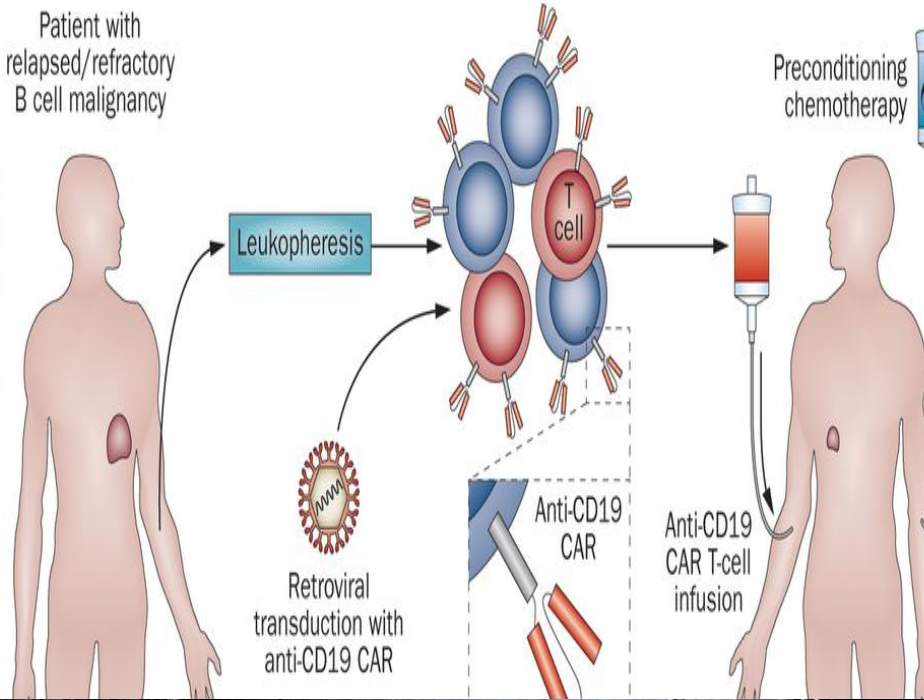
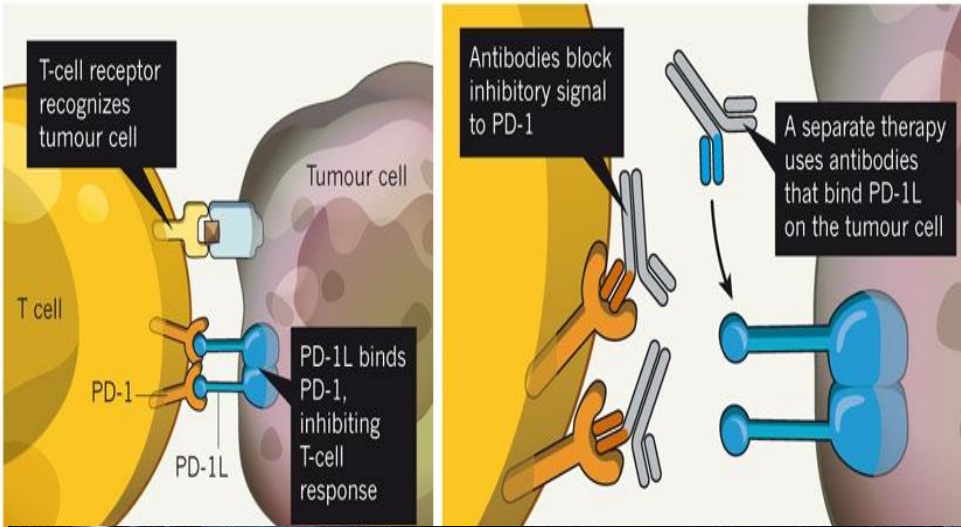
T cells on the attack



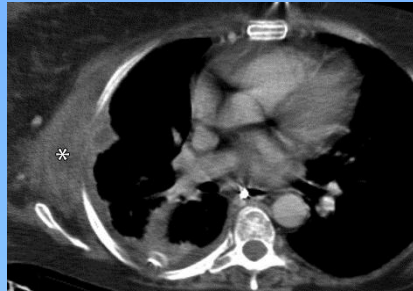
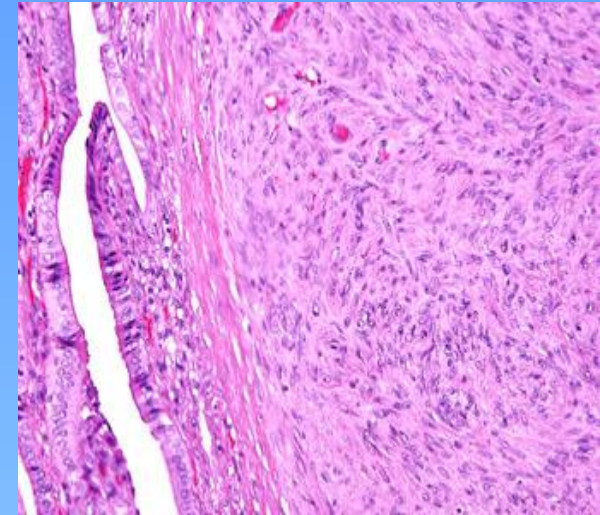
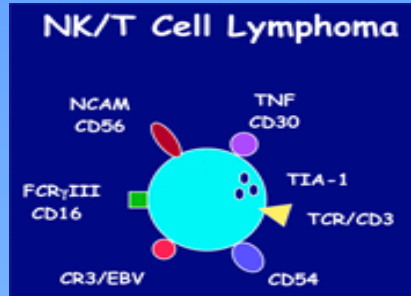
# THE DARLINGS OF IMMUNO-ONCOLOGY

## WAKING UP THE BODY'S DEFENCES

Tumour cells can inhibit the body's immune response by binding to proteins, such as PD-1, on the surface of T cells. Antibody therapies that block this binding reactivate the immune response.



# EPSTEIN-BARR VIRUS AND CANCER



# NASOPHARYNGEAL CANCER

## BACKGROUND

- Nasopharyngeal carcinoma (NPC) is endemic in South-East Asia and Southern China
- Associated with Epstein-Barr virus (EBV) transformation
- The median survival of advanced NPC is < 12 months and chemotherapy is not curative



# CT scan images for patient 16 at dy-13 (pre-NST), dy+104 and dy+336

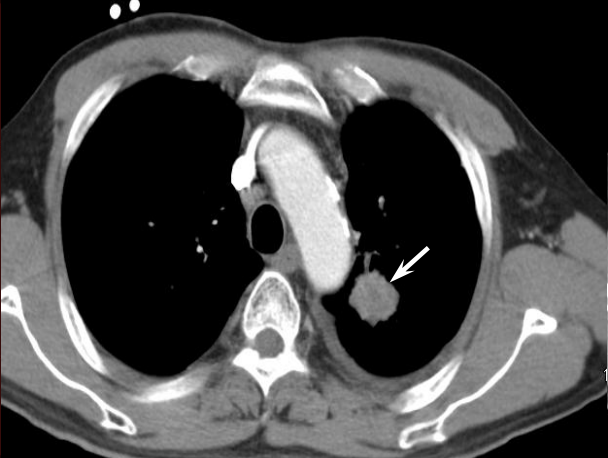
**A** **Pre-NST**

National Cancer Centre  
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120kV, 113mAs  
SC 500 mm  
SW 8.0 mm  
Study Desc: (HEAD/NECK/CHEST/ABD)



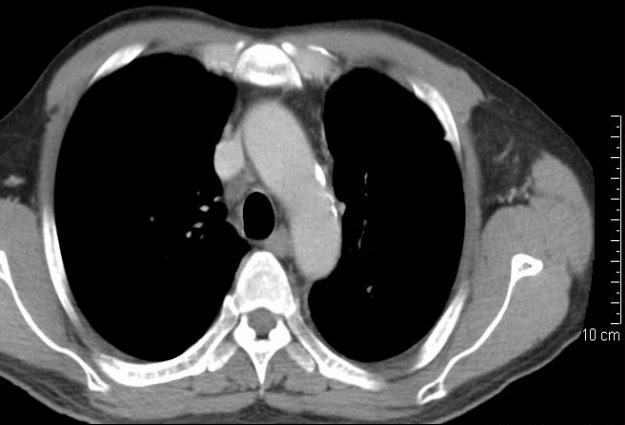
**Day +104**

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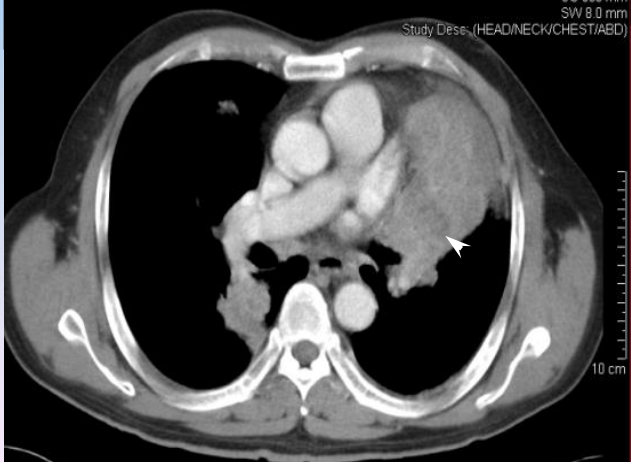


**Day +336**

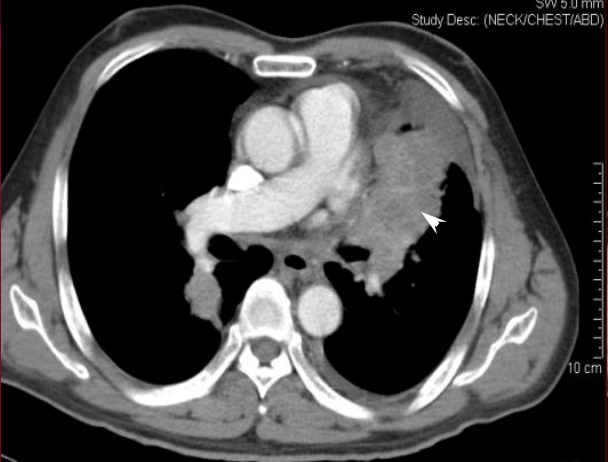
National Cancer Centre  
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Study Desc: CHEST/ABD



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Study Desc: (HEAD/NECK/CHEST/ABD)



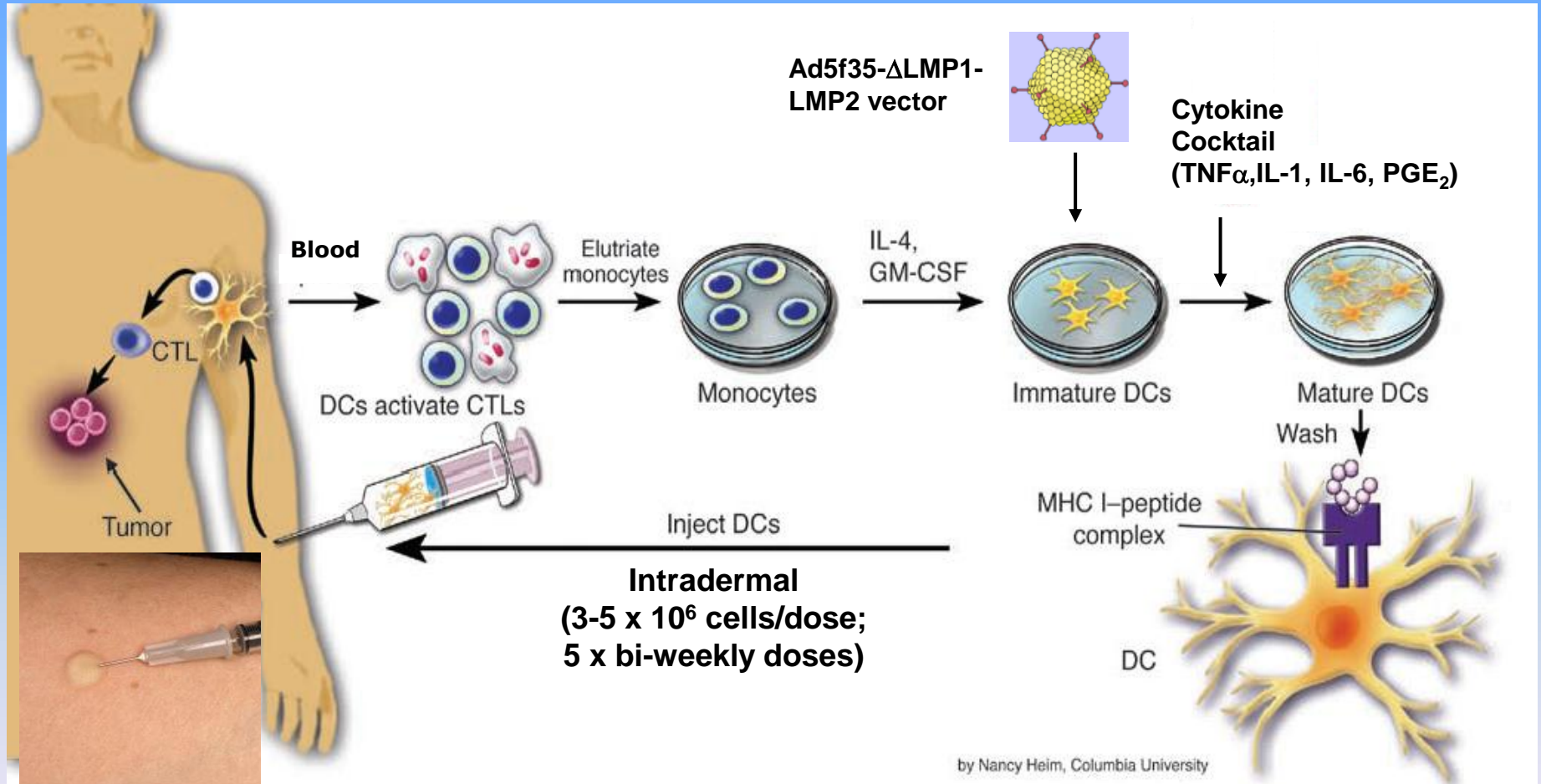
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Study Desc: (NECK/CHEST/ABD)



National Cancer Centre  
GE MEDICAL SYSTEMS LightSpeed VCT  
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SC 500 mm  
SW 5.0 mm  
Study Desc: CHEST/ABD



# TREATMENT OF METASTATIC NASOPHARYNGEAL CARCINOMA WITH AUTOLOGOUS DENDRITIC CELLS TRANSDUCED WITH ADENOVIRAL VECTOR (AD5F35) EXPRESSING LATENT MEMBRANE PROTEIN (LMP)-1 AND LMP-2 GENES IN PATIENTS



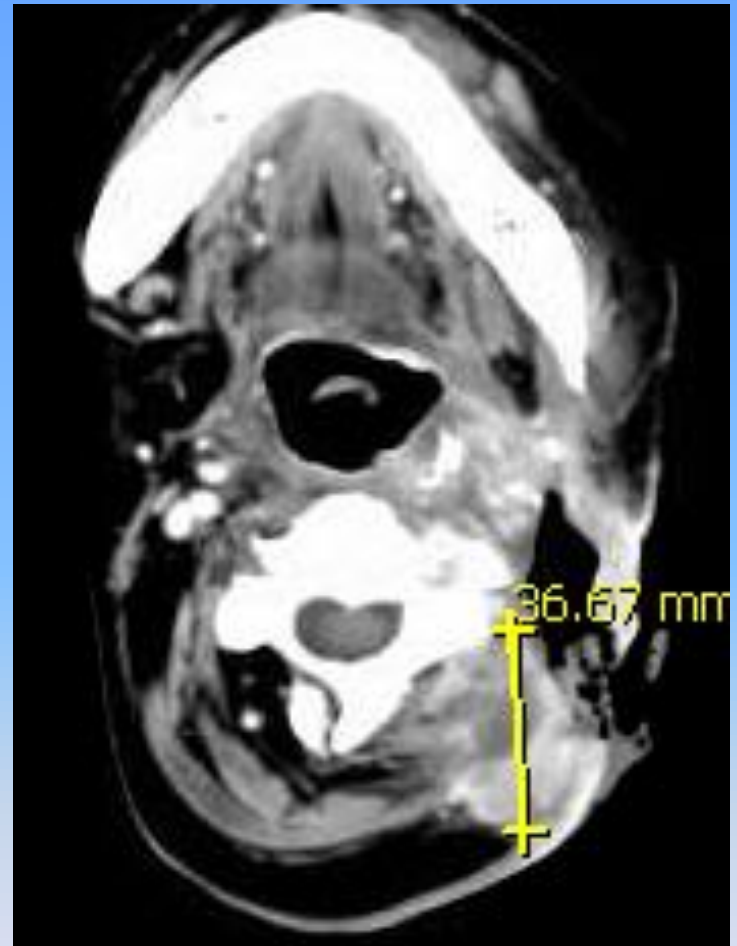
A Phase II clinical trial, n=16



# PATIENT 004 – PARTIAL RESPONSE

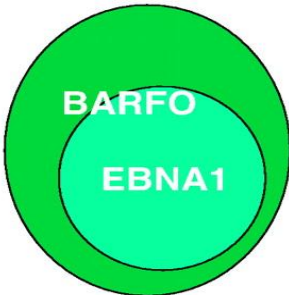
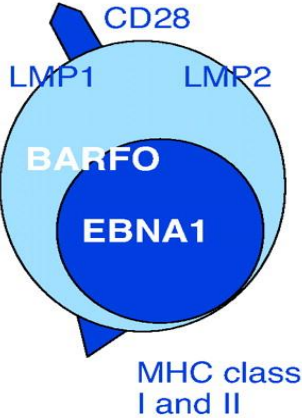
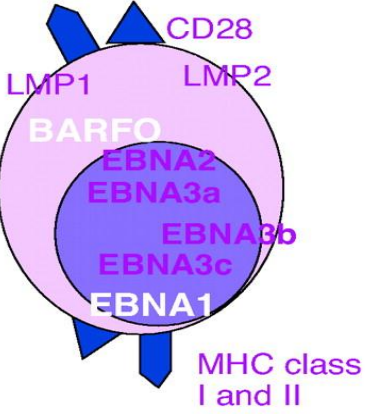


**Baseline Date: 24/10/07**

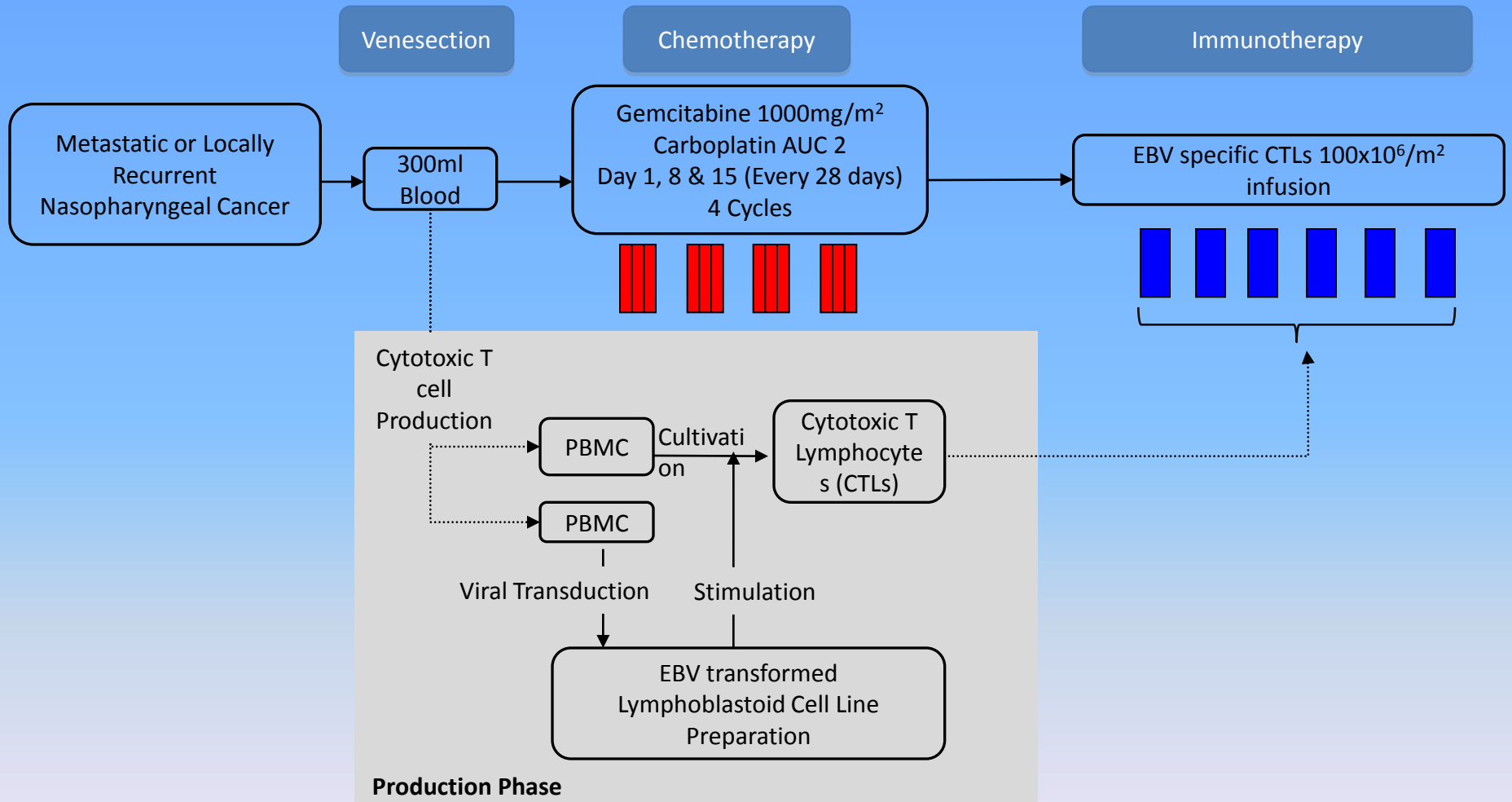


**Date: 5/3/08**

# Treatment of nasopharyngeal carcinoma with Epstein-Barr virus-specific T lymphocytes

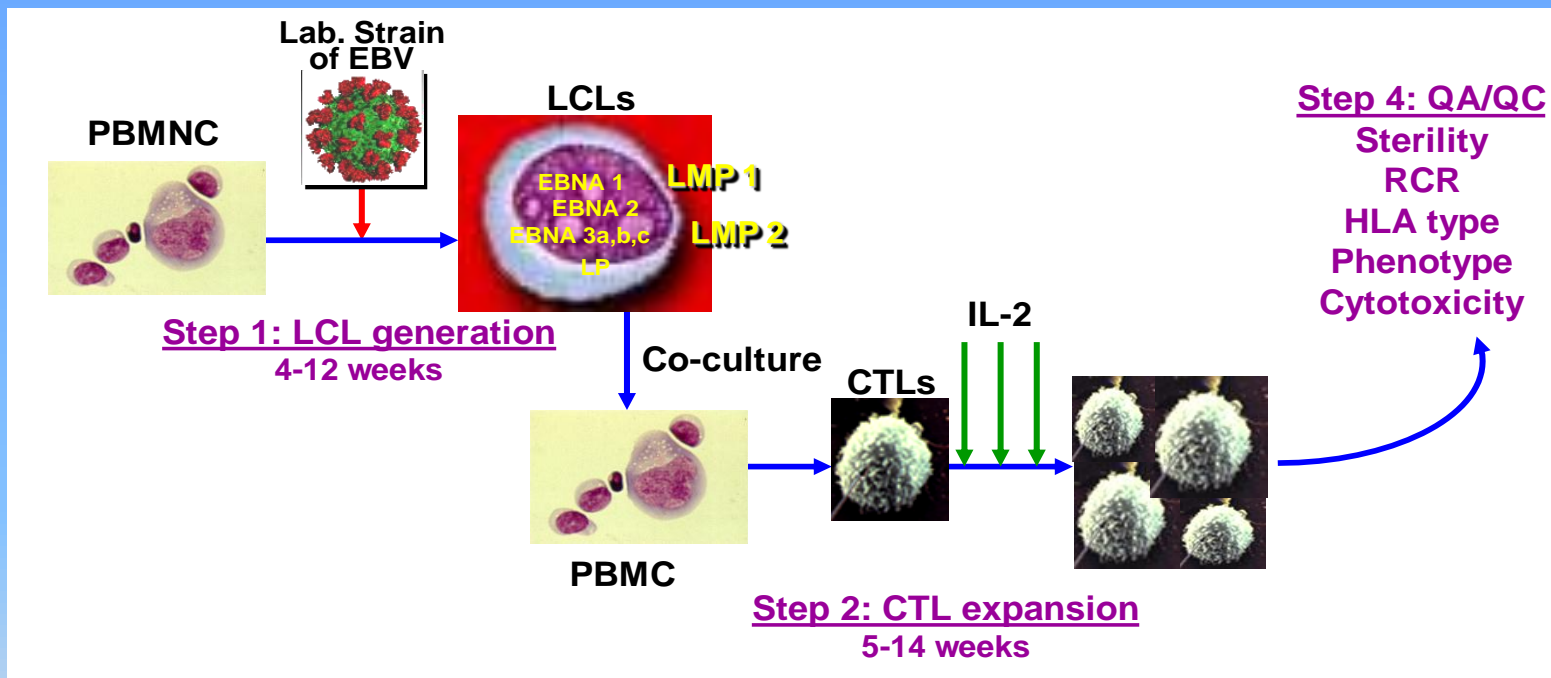
Type I latency	Type II latency	Type III latency
		
Burkitt's lymphoma	Hodgkin's lymphoma Nasopharyngeal carcinoma	Lymphoproliferative disease in immunocompromised, LCL

# CTL THERAPY IN ADVANCED NPC



# Treatment of nasopharyngeal carcinoma with Epstein-Barr virus-specific lymphocytes

## EBV Specific CTL Generation



- Phase II Trial: Evaluating efficacy of a strategy employing combination of gemcitabine and carboplatin chemotherapy followed by EBV-specific cytotoxic T lymphocytes in patients with metastatic or locally recurrent EBV-positive Nasopharyngeal carcinoma (n = 38)
- 4 cycles of Gemcitabine + Carboplatin Chemotherapy, followed by 6 doses i.v.  $1.0 \times 10^8$  CTLs/m<sup>2</sup>

# CELL THERAPY IS VERY LABOUR INTENSIVE

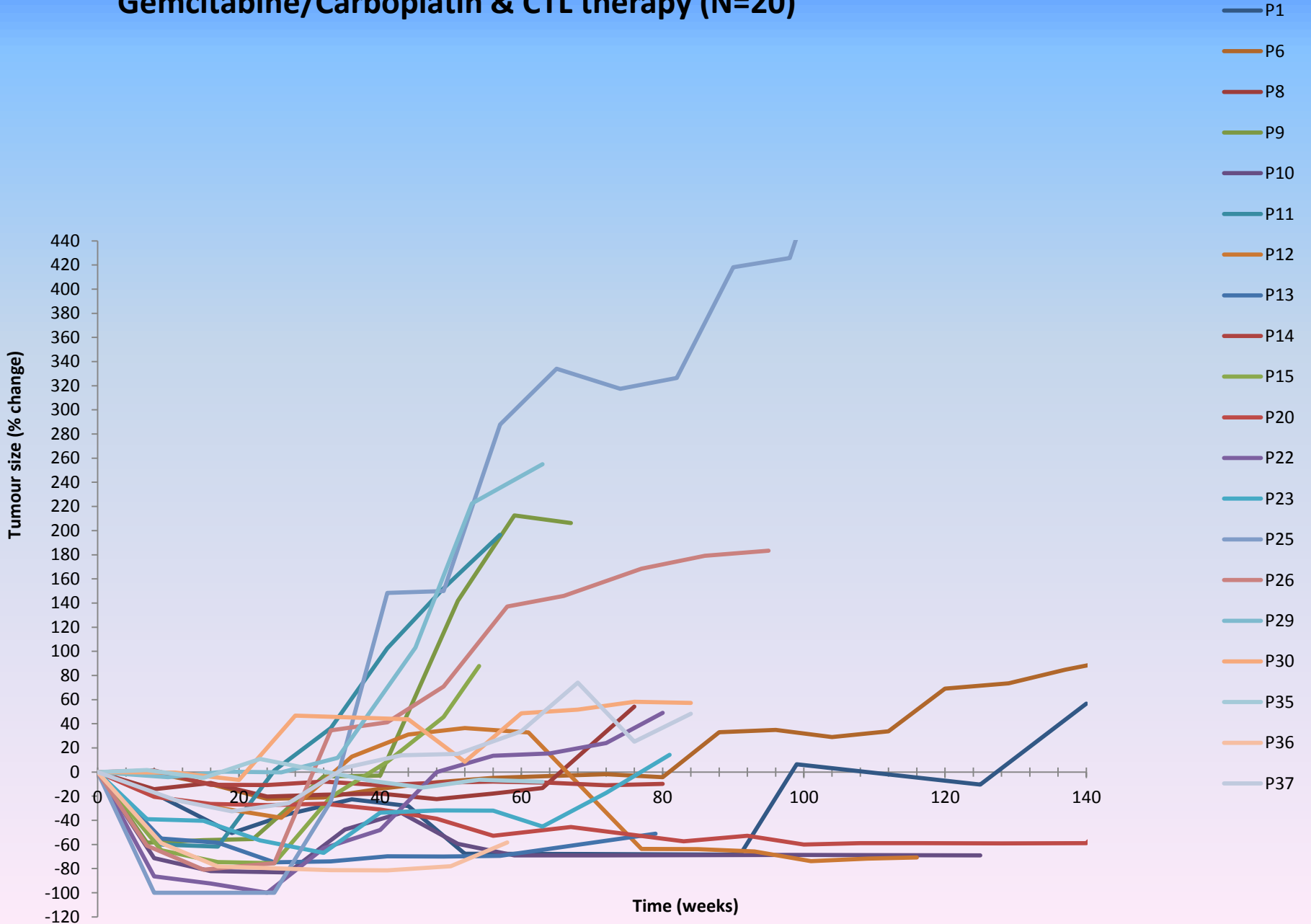


# Results

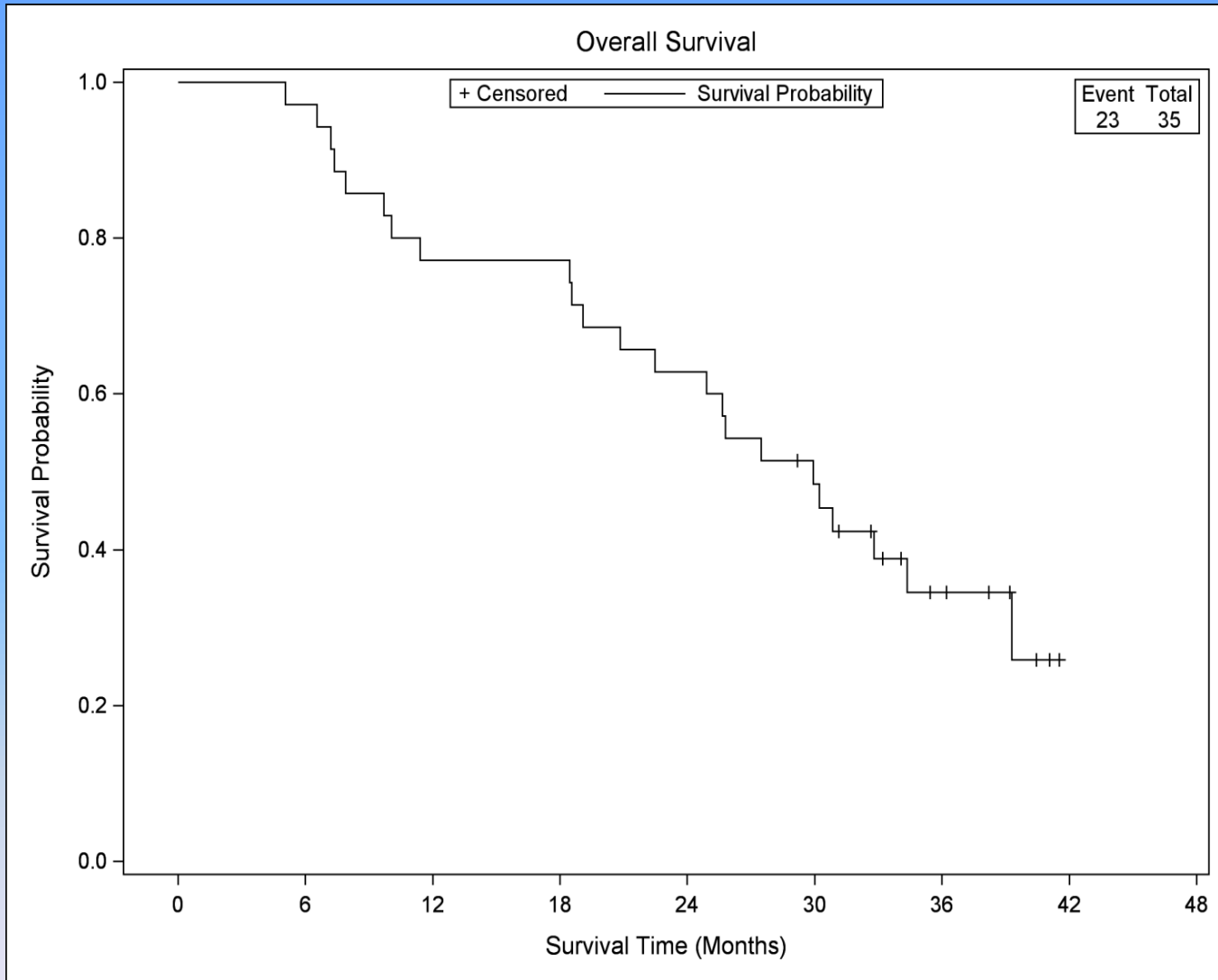
- **Median follow up** 29.2 mths
- **Median OS** 29.9 mths (95% CI, 20.8 – 39.3 mths)
- **1-year OS** 77.1%
- **2-year OS** 62.9%
  
- **PFS1 (chemo + CTL)** 7.6 mths (95% CI: 7.4 to 8.4 mths)
- **PFS2 (CTL)** 3.7 mths (95% CI: 2.4 to 4.0 mths, range 2.0 – 35.3 mths)
  
- **ORR (chemo + CTL)** 71.4%
- **ORR (T cells)** 20%, (SD 42.9%)
  
- **Clinical Benefit Response** 100%

# SPIDER PLOT OF TUMOUR SIZES

Gemcitabine/Carboplatin & CTL therapy (N=20)

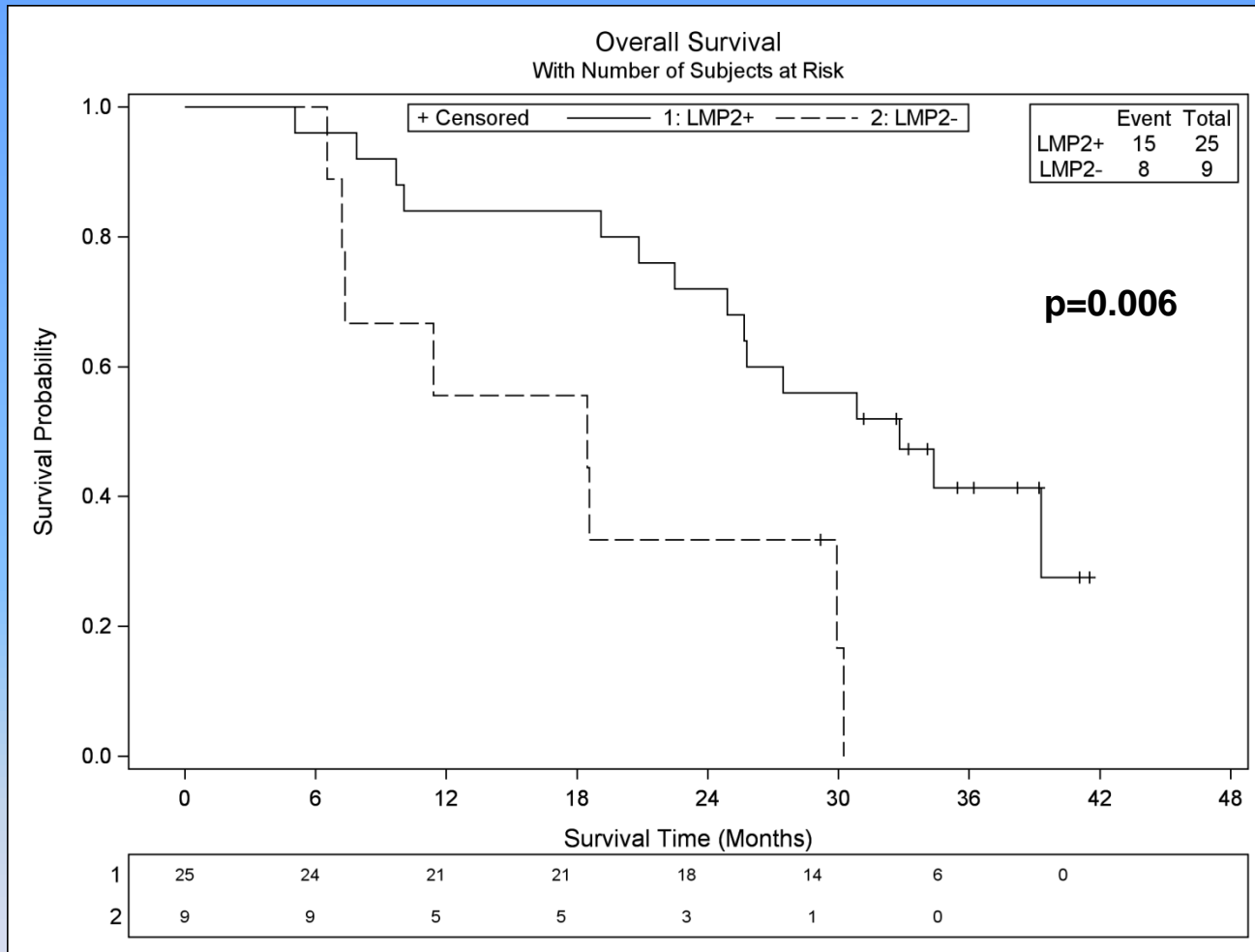


# Overall Survival





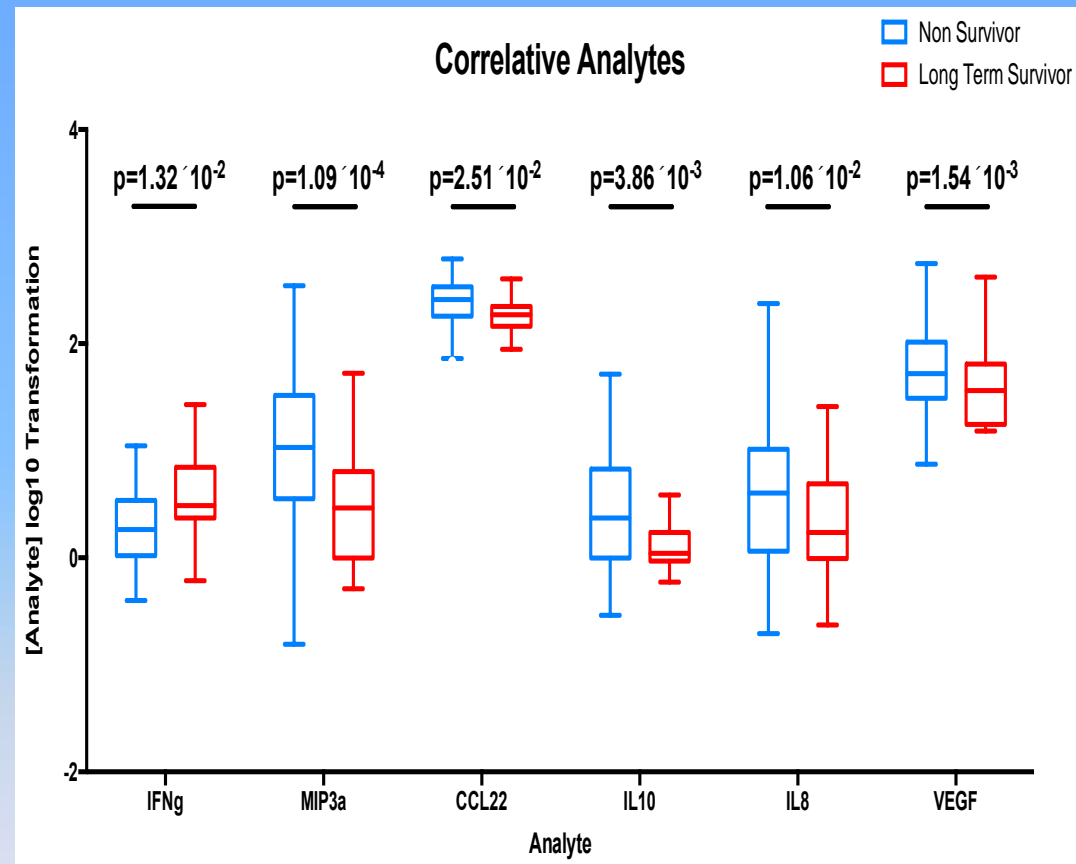
# LMP2 dependent outcome



**Kaplan-Meier estimated OS according to status of detectable LMP2-specific CTLs (Elispot) in infusion product**

# Phase II EBV-CTL Trial Updates...

- Median follow-up of 29.9 months; Median overall survival (OS) of 29.9 months
- 2-year OS: 62.9%, 3-year OS: 37.1%, and 4-year OS: 25.7%.
- As of 31 December 2013, 6 patients remained alive with a median follow-up of 51.7 months.
- Individuals who survived longer than 3-years exhibited higher sera levels of the antiviral cytokine IFN $\gamma$ , compared to non-survivors ( $p = 0.032$ ).
- Long-term survivors secreted lower levels of regulatory T-cell associated proteins CCL22 and IL10 and lower levels of pro-angiogenesis proteins IL8 and VEGF. The chemokine CCL20 (MIP3a) is also lower in long-term survivors.



# Comparison with other Clinical Trials in Metastatic NPC Patients

Author	Journal	Regimen	Line	n	ORR	PFS	Median OS	1yr OS	2yr OS
Ngan et al	Ann Oncol. 2002 Aug;13(8):1252-8	Gem 1000 Day 1,8,15 CDDP 50 Day 1,8	1st/2nd	44	73%	10.6mths	15mths	62%	20%
Ma BB et al	Ann Oncol. 2009 Nov;20(11):1854-9	Gem 1000 Day 1,8 Ox 20 Day 2,9	1st	42	64%	8.9mths	19.6mths	70%	0%
Leong SS et al	Cancer. 2005 Feb 1;103(3):569-75	Gem 1000 Day 1,8 Carbo AUC 5 Day 1 Tax 70 Day 1,8	1st	32	78%	8.1mths	18.6mths	83.5%	15%
Leong SS et al	Cancer. 2008 Sep 15;113(6):1332-7	Gem 1000 Day 1,8 Carbo AUC 2.5 Day 1,8 Tax 70 Day 1,8 5FU 450 wkly	1st	28	86%	8mths	22mths	75%	44%
Siu L et al	J Clin Oncol. 1998 Jul;16(7):2514-21	CAPABLE	1st	51	80%		14mths	55%	25%
Toh HC et al	<i>unpublished</i>	4 cycles: Gem1000 & Carbo(AUC2) Day 1,8,15 4 cycles: EBV specific cytotoxic T lymphocytes	1st	38	71%	PFS1 = 7.6mths PFS2 = 3.7mths	28.7mths (n=35)	77.1%	61.8%

# Phase III Study Design

	Stage 1	Stage 2	Follow-up
ARM A (n=165)	4 Cycles of Chemotherapy (Gemcitabine + Carboplatin)	6 Cycles of Immunotherapy (CTL Infusion)	Follow-up
ARM B (n=165)	6 Cycles of Chemotherapy (Gemcitabine + Carboplatin)	Follow-up	

- Chemotherapy:** Gemcitabine-Carboplatin infusions at Day 1, Day 8 and Day 15
- Immunotherapy:** CTL infusions at Day 1 and Day 14 (Day 1 CTL Infusion - between 14 to 28 days from last chemotherapy), followed by 4 CTL

# Phase III Global NPC CTL Trial: 330 Patients From 5 Countries and 17 Hospital Sites



