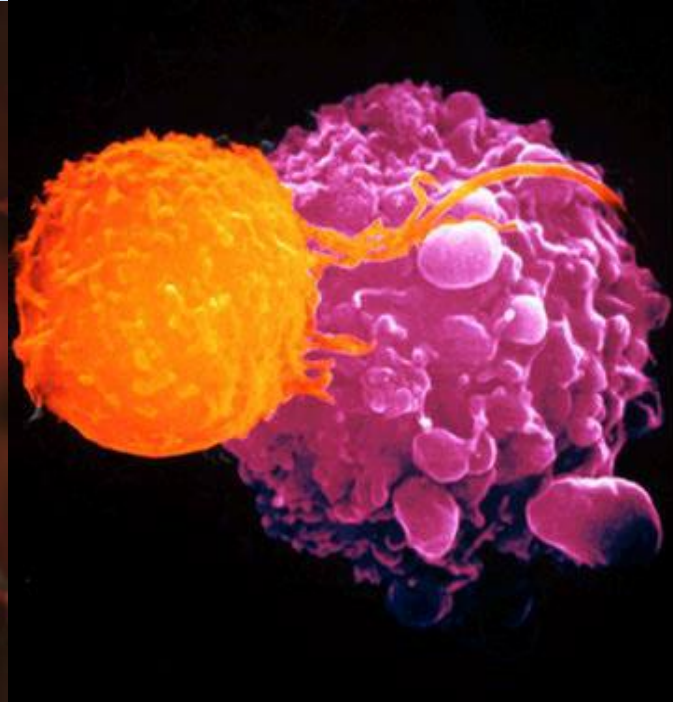
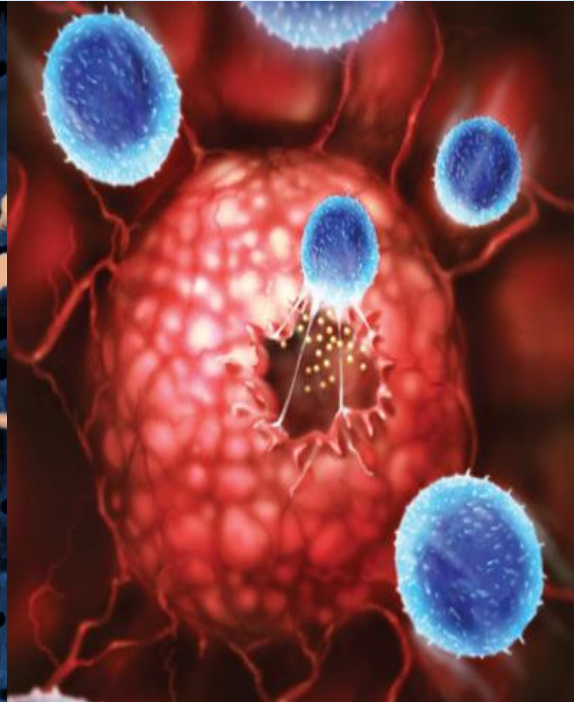
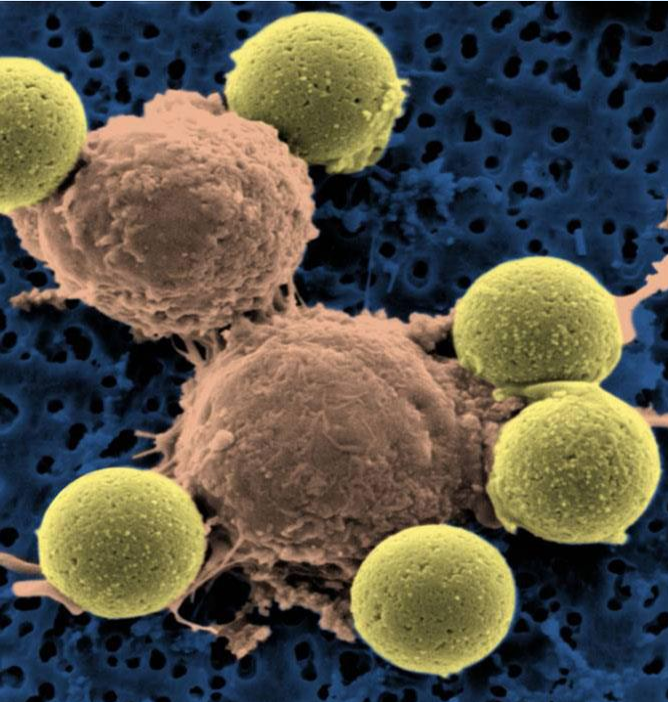


# CANCER IMMUNOLOGY AND INFLAMMATION

## HOW WE FULFILLED OUR ASPIRATIONS THROUGH NMRC FUNDING

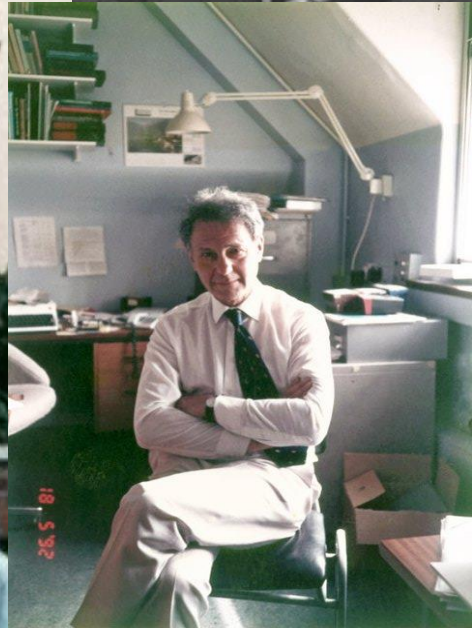


**DR TOH HAN CHONG**

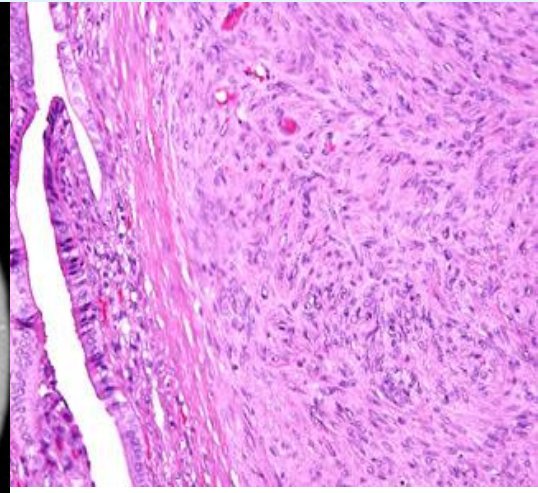
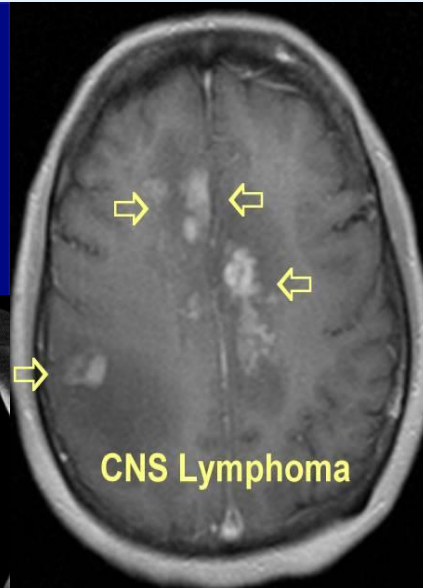
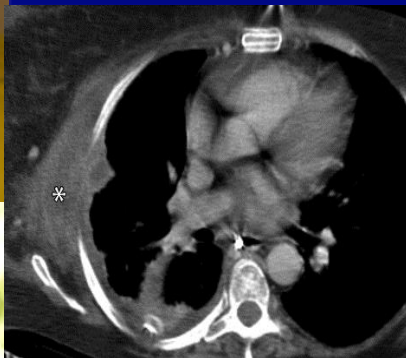
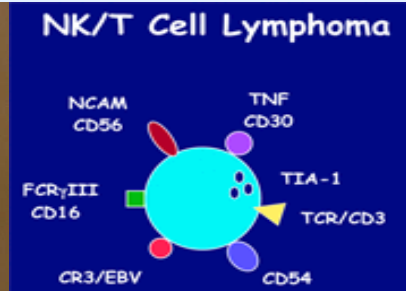
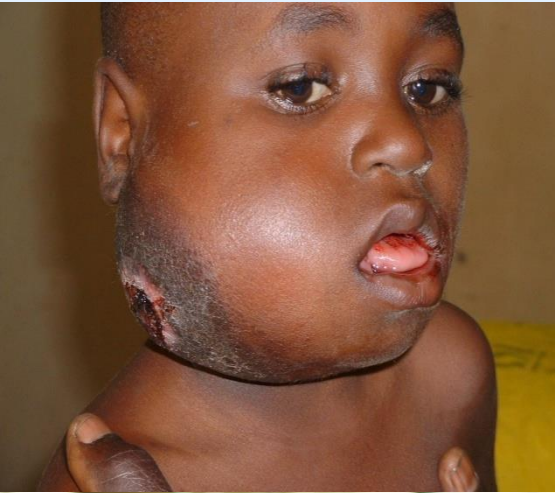
**BSc(Lond) MBBChir(Camb) MRCP(UK) FRCP(Edin)**

**DIVISION OF MEDICAL ONCOLOGY**

**NATIONAL CANCER CENTRE SINGAPORE**



# EPSTEIN-BARR VIRUS AND CANCER



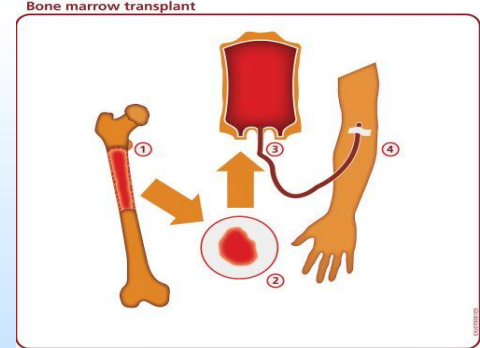
# NASOPHARYNGEAL CANCER

## 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



# MINITRANSPLANT FOR ADVANCED NPC



1. When a matched donor has been found some of their bone marrow is extracted from their hip, via a needle. Meanwhile, the recipient has had all their stem cells destroyed and receives blood transfusions until they are ready to receive new stem cells.
2. The extracted bone marrow is treated to remove the 'adult' cells.
3. The purified stem cells are then collected for transplant.
4. The stem cells are injected via a central line, and re-populate the bone marrow. Within a few months the 'new' bone marrow will start to produce 'healthy' blood cells.

Achieve mixed chimaera

Achieve full donor chimaera

Nonablative  
preparative  
regimen to  
achieve  
engraftment

allo  
PBPC  
or  
BMT

short-  
time  
GvHD-  
prophy-  
laxis

DLI if  
residual  
disease



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

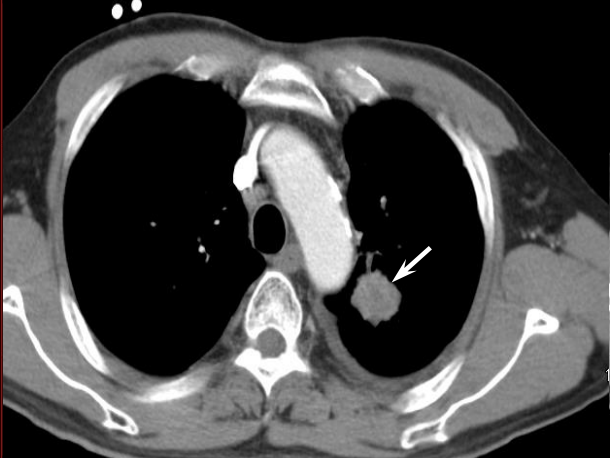
**A** **Pre-NST**

National Cancer Centre  
SIEMENS SOMATOM PLUS 4  
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120kV, 113mAs  
SC 500 mm  
SW 8.0 mm  
Study Desc: (HEAD/NECK/CHEST/ABD)



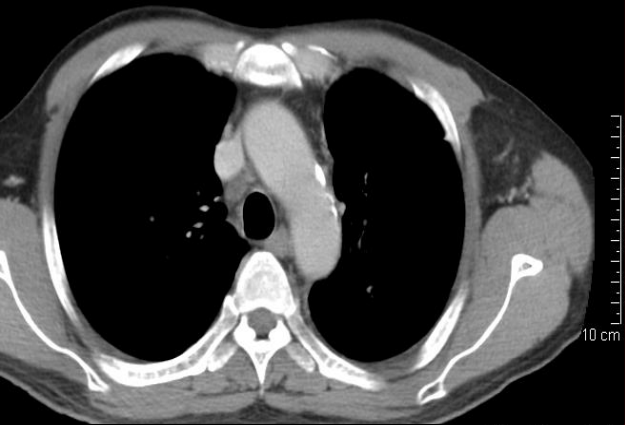
**Day +104**

National Cancer Centre  
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120kV, 11  
SC 50  
SW 5:  
Study Desc: (NECK/CHEST)

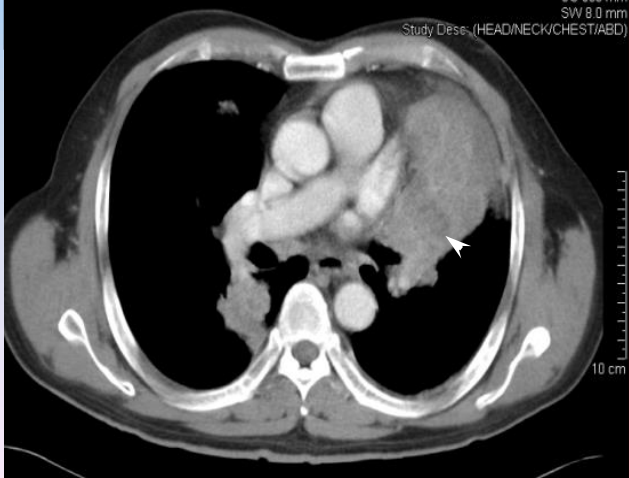


**Day +336**

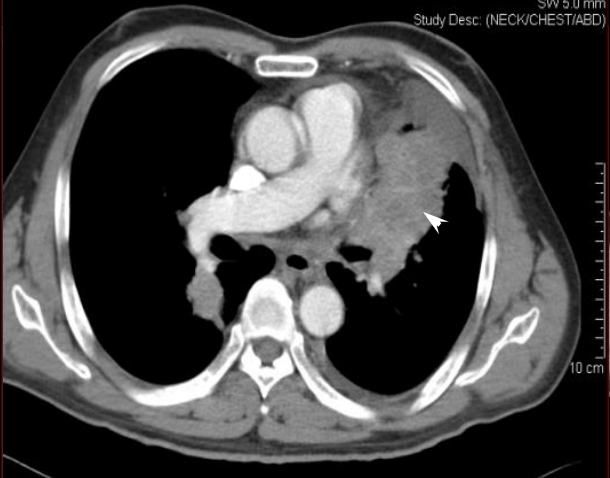
National Cancer Centre  
GE MEDICAL SYSTEMS LightSpeed VCT  
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SW 5.0 mm  
Study Desc: CHEST/ABD



National Cancer Centre  
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Study Desc: (HEAD/NECK/CHEST/ABD)



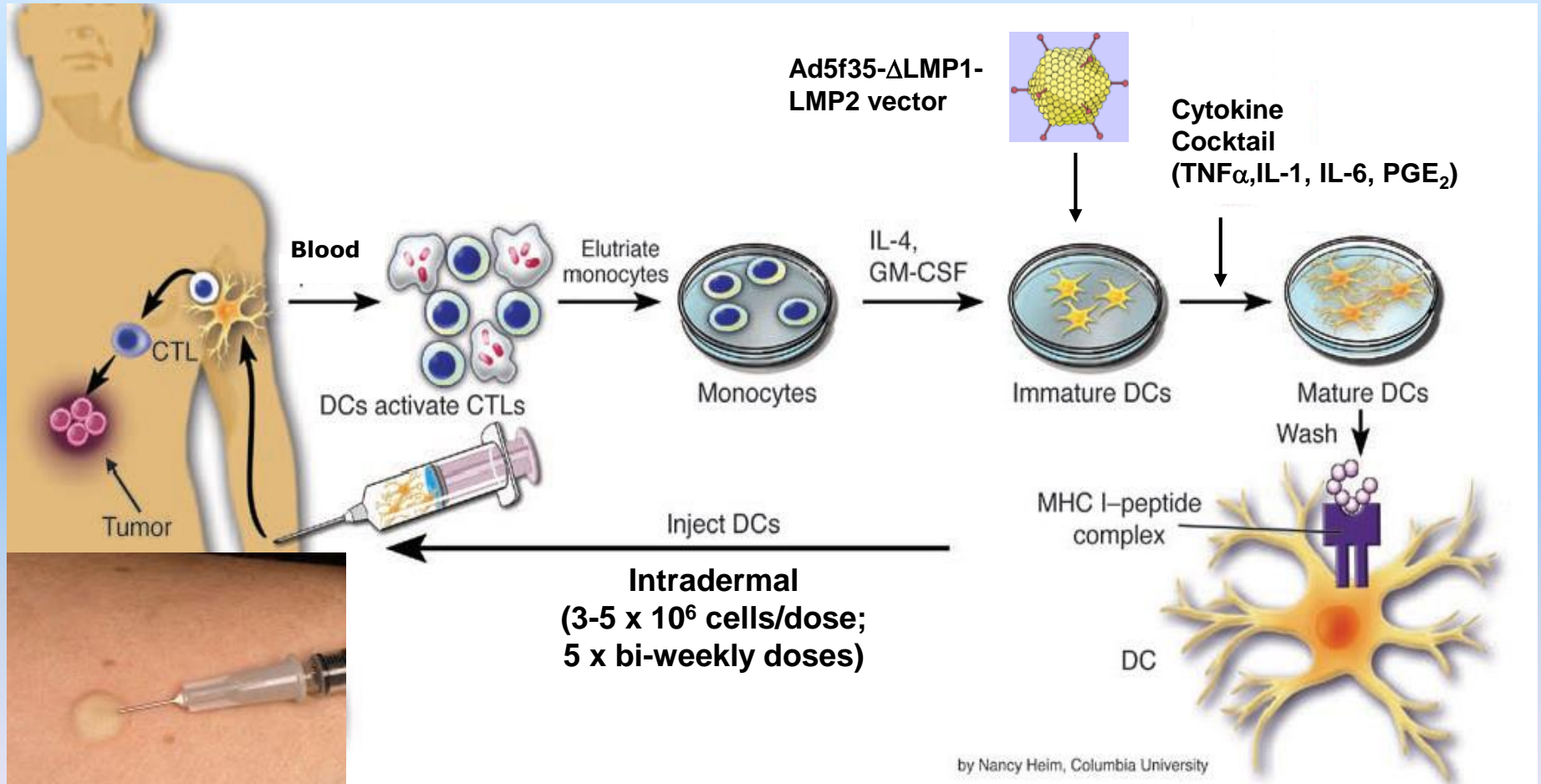
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Study Desc: (NECK/CHEST/ABD)



National Cancer Centre  
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Study Desc: CHEST/ABD

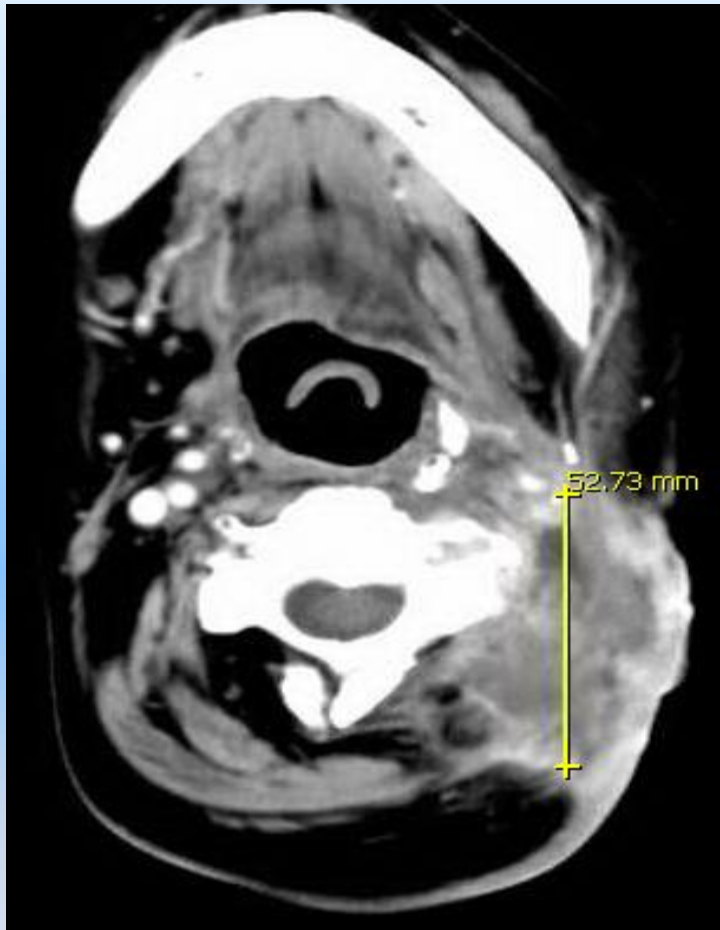


# TREATMENT OF METASTATIC NASOPHARYNGEAL CARCINOMA WITH AUTOLOGOUS DENDRITIC CELLS TRANSDUCED WITH ADENOVIRAL VECTOR (AD5F35) EXPRESSING LATENT MEMBRANE PROTEIN (LMP)-1 AND LMP-2 GENES IN PATIENTS

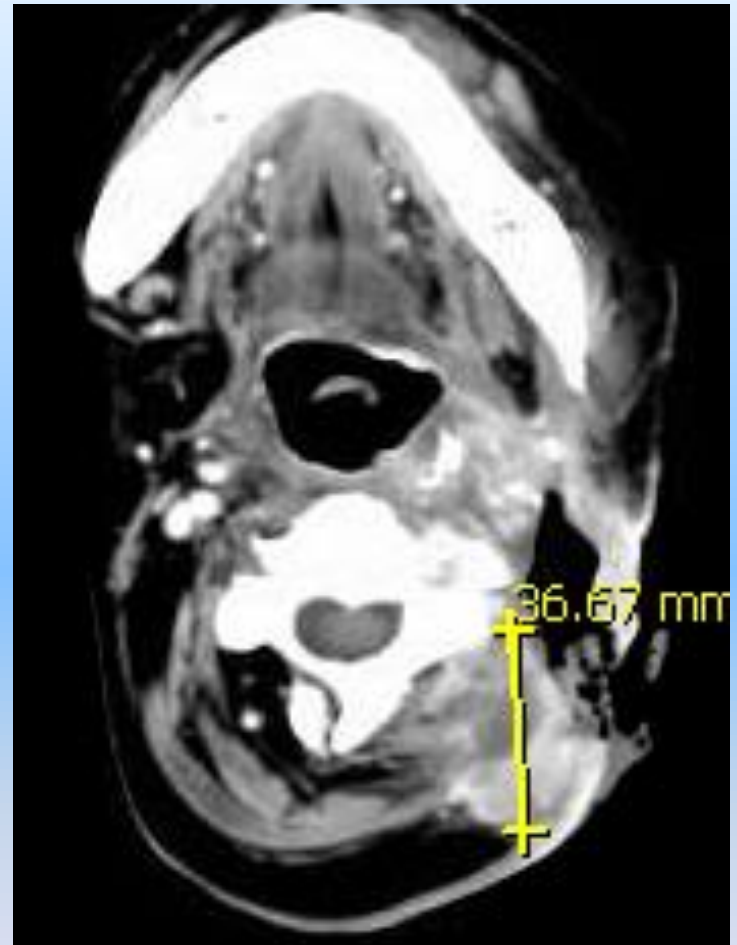


clinical trial, n=16

# PATIENT 004 – PARTIAL RESPONSE



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

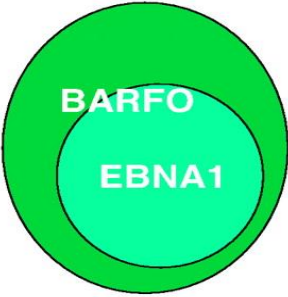
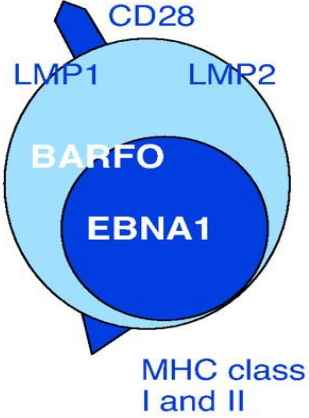
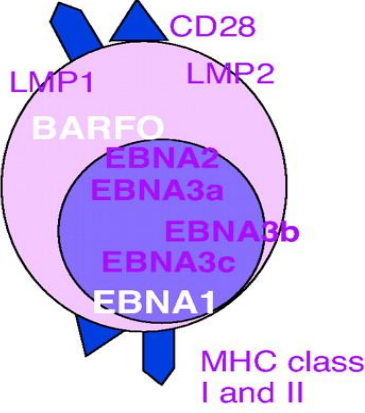


**Date: 5/3/08**



Treat  
Eps

na with  
cytes

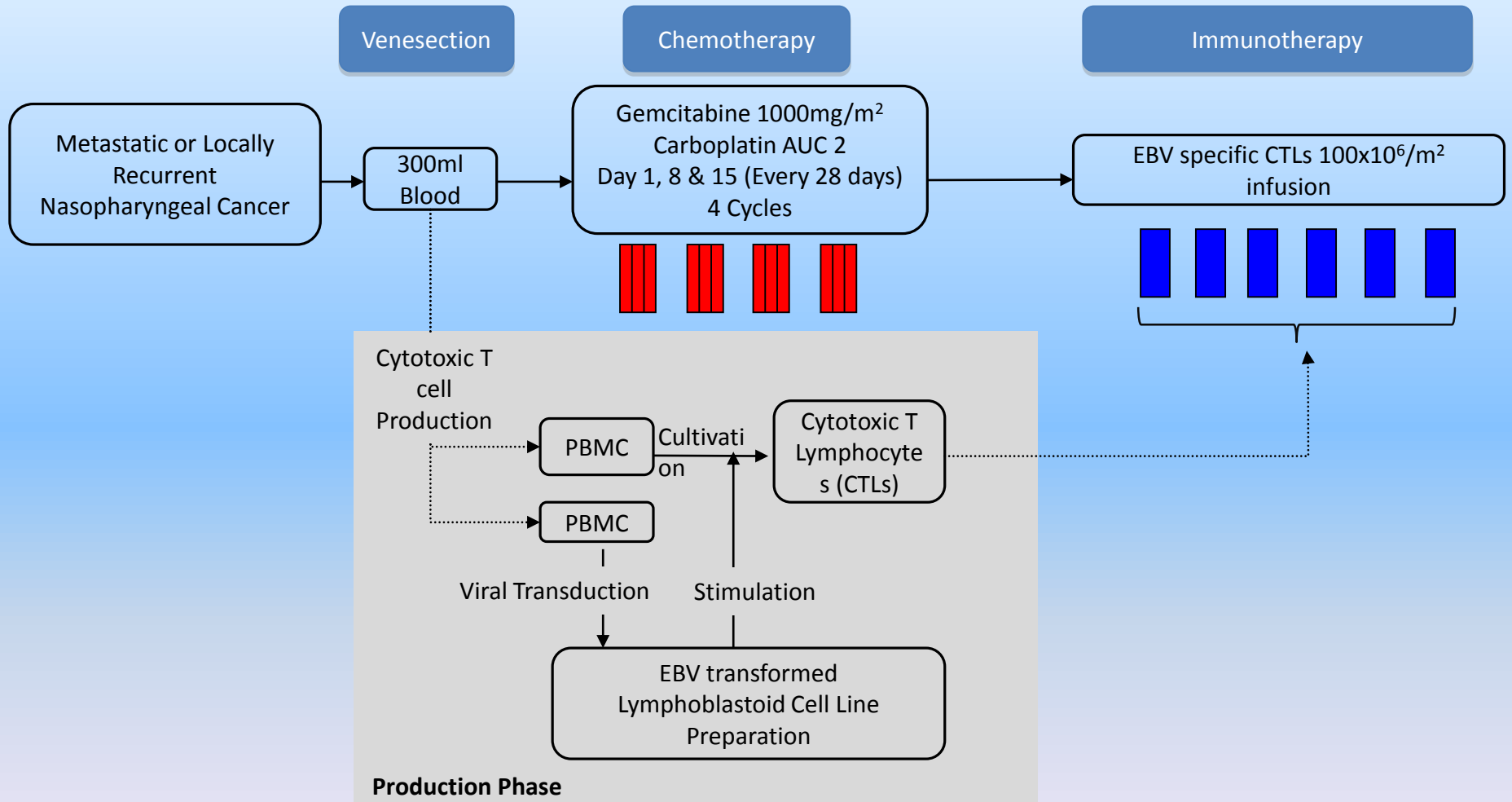
Type I latency	Type II latency	Type III latency
		
Burkitt's lymphoma	Hodgkin's lymphoma Nasopharyngeal carcinoma	Lymphoproliferative disease in immunocompromised, LCL



## T CELLS AS LIVING THERAPY

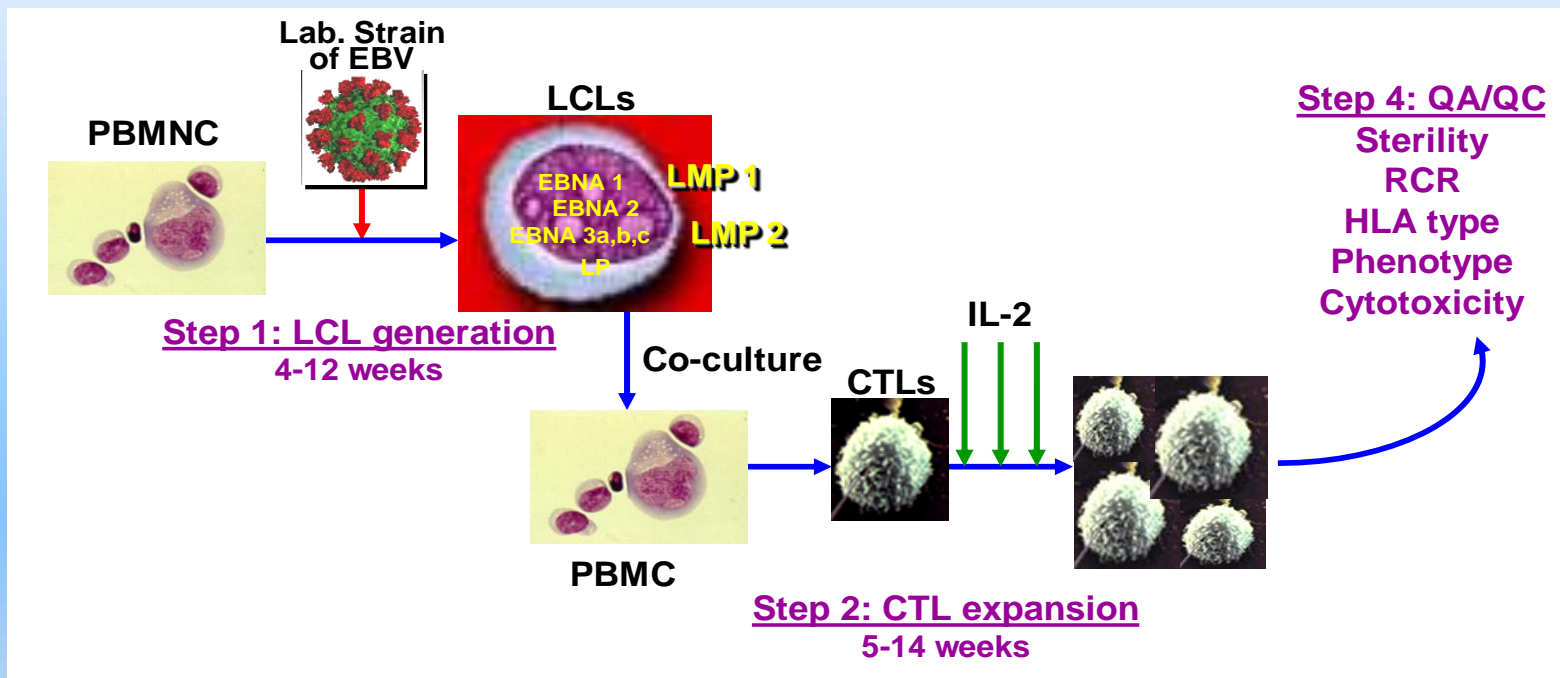


# CTL THERAPY IN ADVANCED NPC



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

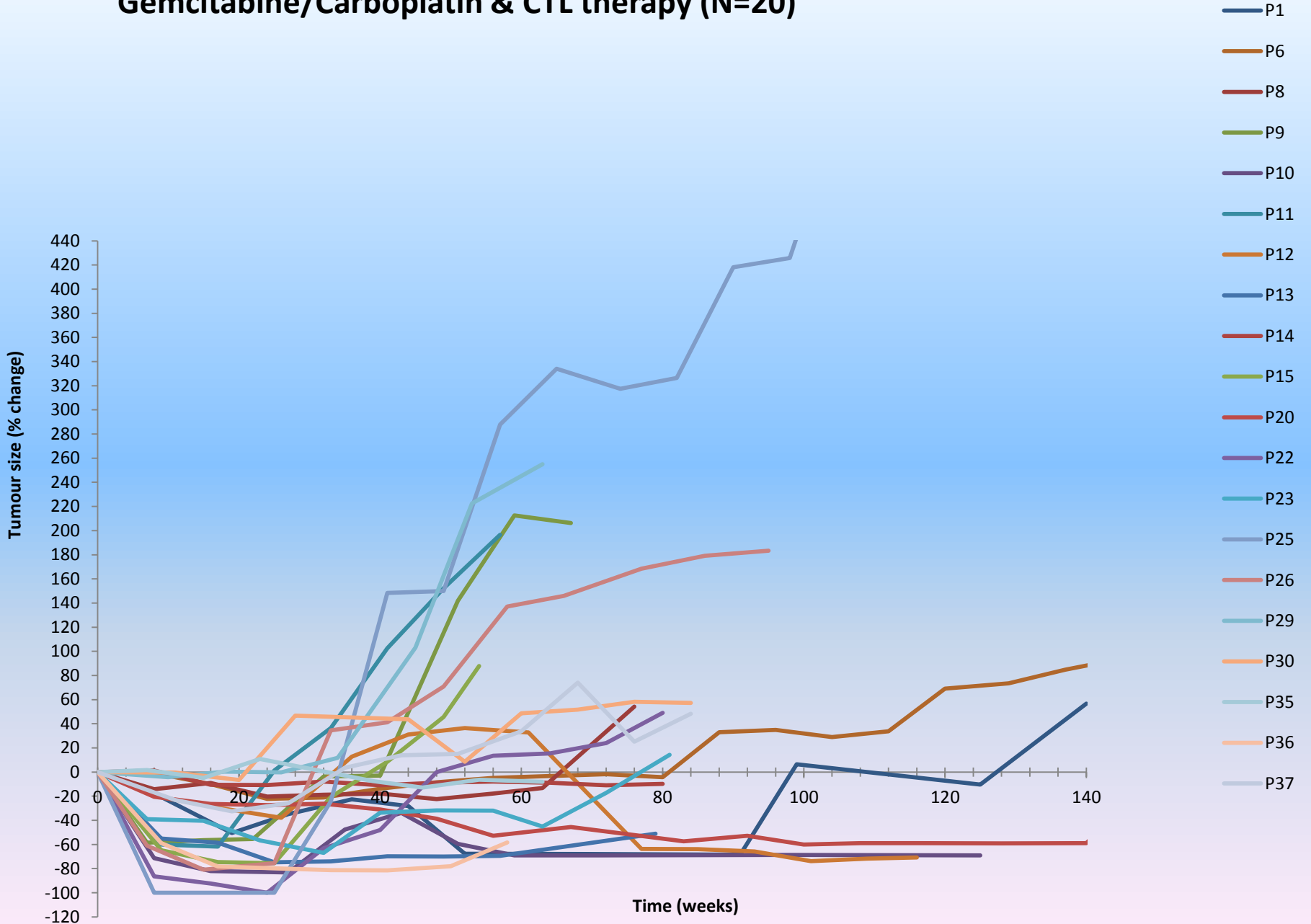
## EBV Specific CTL Generation



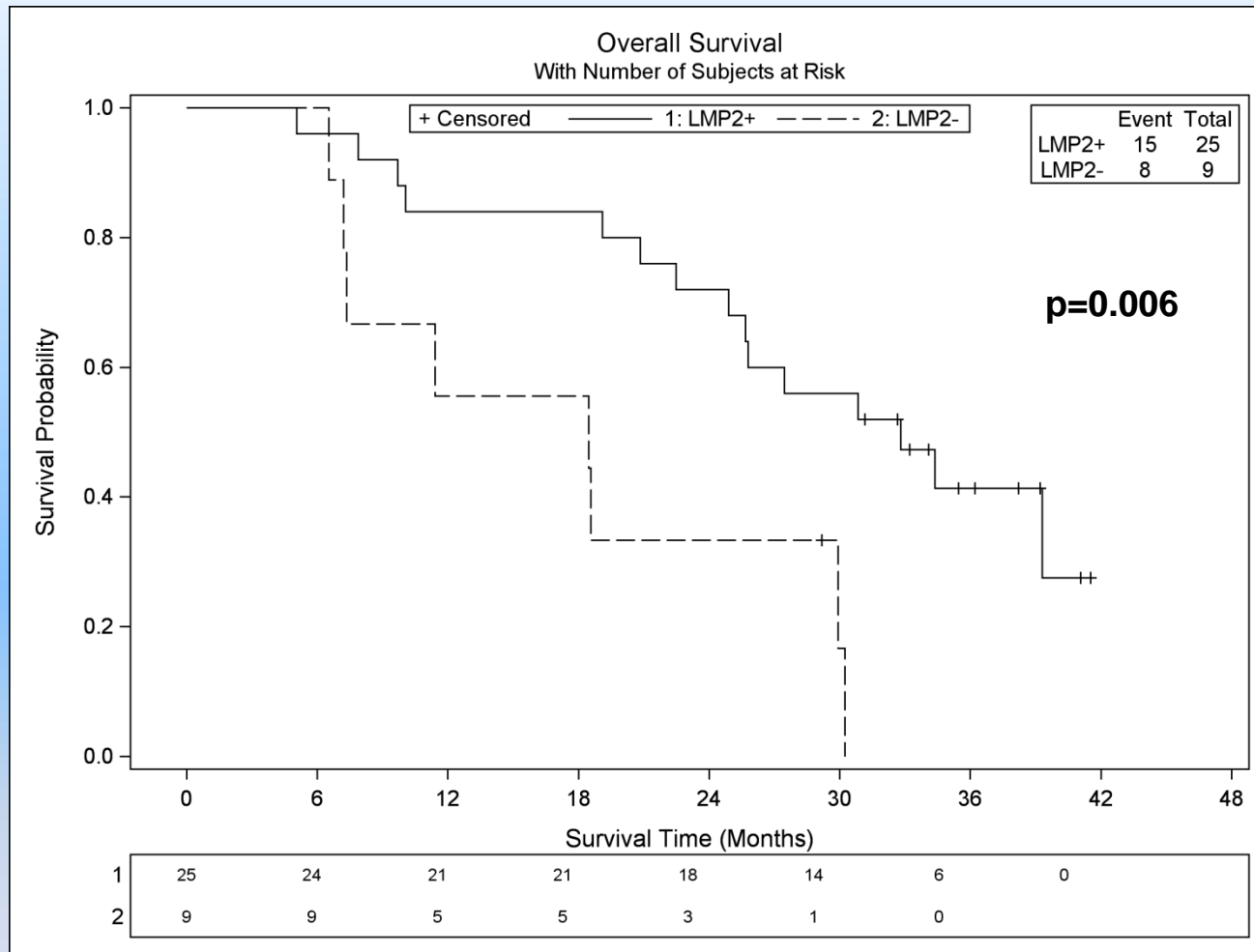
- **Phase II Trial: Evaluating efficacy of a strategy employing combination of gemcitabine and carboplatin chemotherapy followed by EBV-specific cytotoxic T lymphocytes in patients with metastatic or locally recurrent EBV-positive Nasopharyngeal carcinoma (n = 38)**
- **4 cycles of Gemcitabine + Carboplatin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

# SPIDER PLOT OF TUMOUR SIZES

Gemcitabine/Carboplatin & CTL therapy (N=20)



# LMP2 dependent outcome

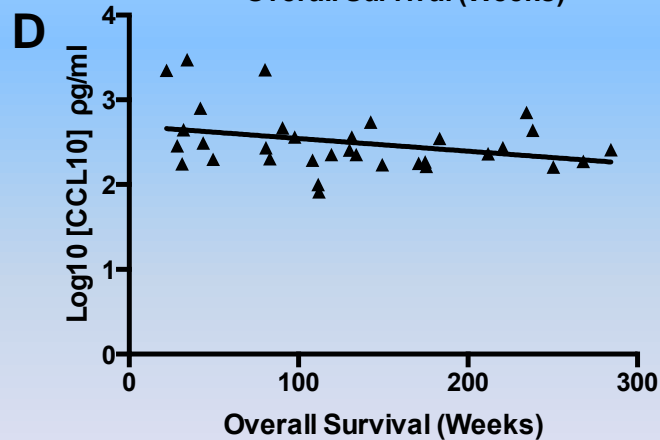
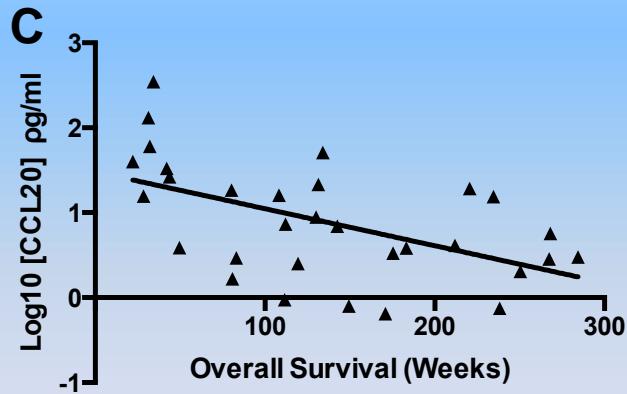
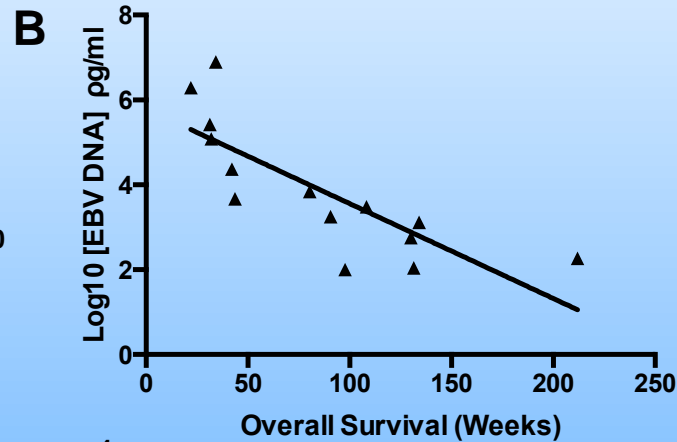
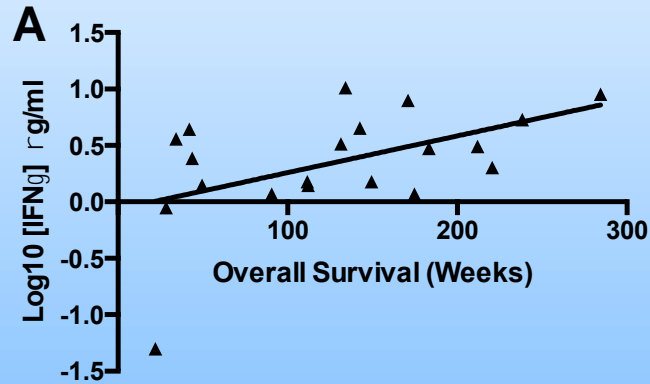


**Kaplan-Meier estimated OS according to status of detectable LMP2-specific CTLs (Elispot) in infusion product**

# 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%

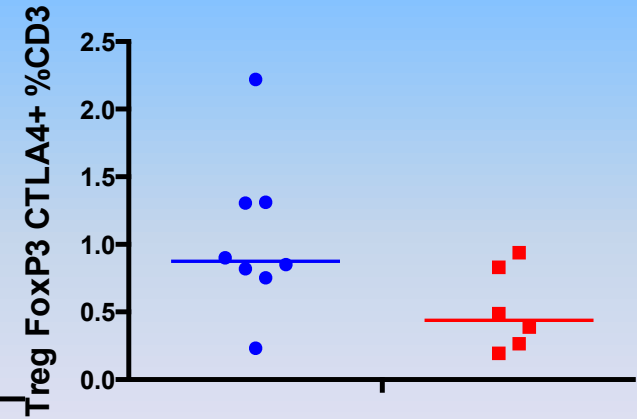
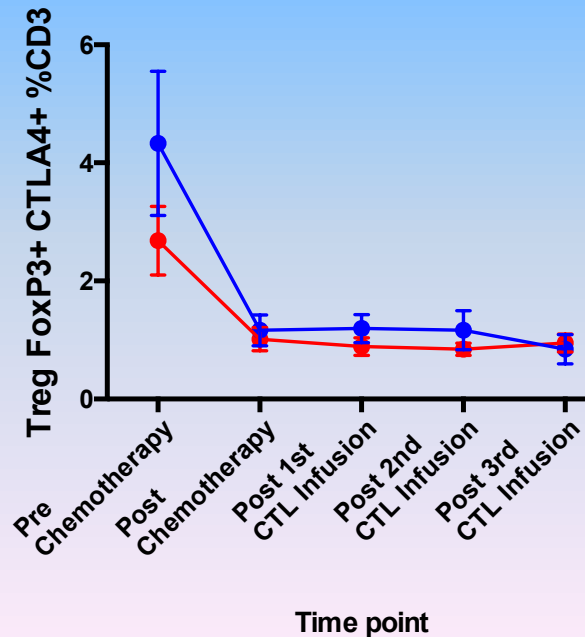
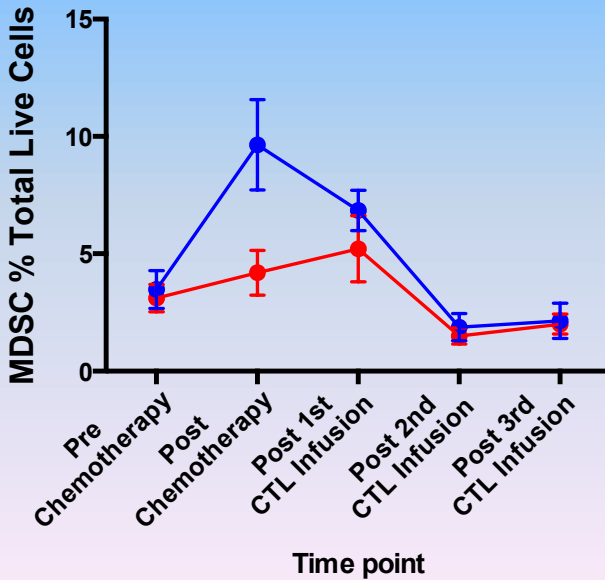
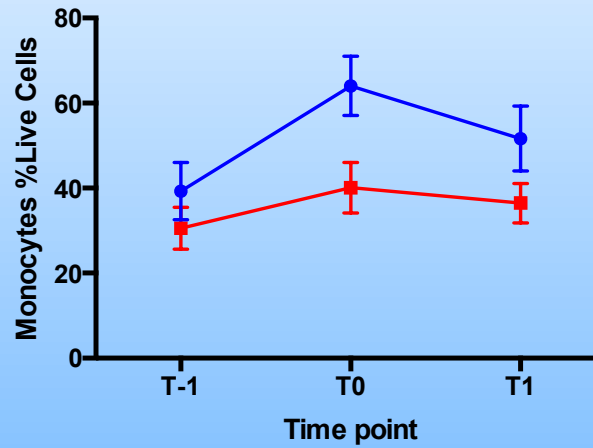
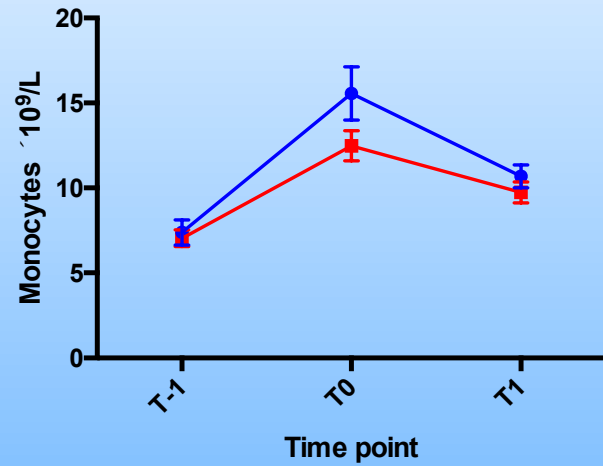
# Successful CTL Immunotherapy Causes Increases in IFN $\gamma$ production and Decreases in Myeloid Chemokines



	T0	T1
IFN $\gamma$	r -0.04045	0.4637
	p 0.8511	<b>0.0395</b>
EBV DNA	r -0.8818	-0.8725
	p <b>0.0007</b>	<b>0.0001</b>
CCL20	r -0.3951	-0.5472
	p <b>0.0339</b>	<b>0.0014</b>
CCL10	r -0.2425	-0.3155
	p 0.1671	0.0737



# ***Non-Survivors Experience an Increase of Myeloid-Derived Suppressor Cells Post Chemotherapy***



# 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 25 Hospital Sites



# $\gamma\delta$ T cell Summary

- We generated *ex vivo* populations of  $\gamma\delta$  T cells that exhibit high expression levels of both effector and antigen-presentation markers
- LMP2 peptide-loaded  $\gamma\delta$  T cells are more efficient than monocyte-derived DCs in stimulating antigen-specific CD8<sup>+</sup> T cells
- In addition, these  $\gamma\delta$  T cells loaded with EBV-derived LPM2 peptides are as capable as LCL in stimulating CD8<sup>+</sup> T cells that are cytolytic towards autologous LCL expressing LMP2 antigen

**and now it's time for something  
completely different**

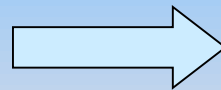


# ASCOLT Study



Dukes B, C  
**Colon** or  
**Rectal** Cancer

↓  
Surgery  
+ chemotherapy



R  
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**Aspirin 200mg  
daily (3yrs)**

Placebo (3yrs)

# THE LARGEST CLINICAL TRIAL TO BE LED OUT OF SINGAPORE

## Asia needs Large Clinical Trial Networks



**ASCOLT**



# Aspirin's Relevance is increasing



National Cancer Institute

U.S. National Institutes of Health | www.cancer.gov

## Provocative Questions

### Identifying Perplexing Problems to Drive Progress Against Cancer

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Aspirin was ranked one of the most important questions in Cancer by the NCI in 2013


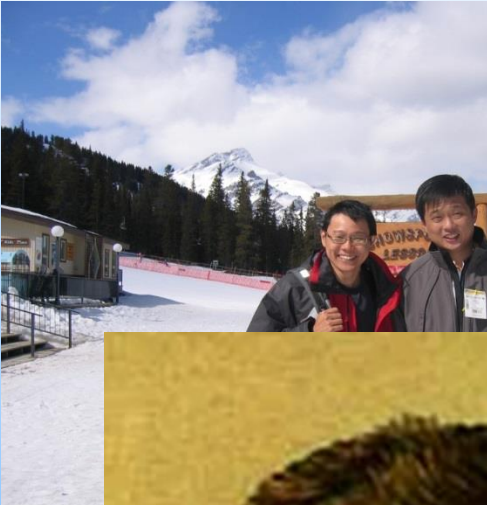
**What is the molecular mechanism by which a drug (such as aspirin or metformin) that is chronically used for other indications protects against cancer incidence and mortality?**

**Background:** Numerous observational studies indicate that some drugs commonly used to treat or prevent diseases other than cancer reduce the risk of developing some cancers or produce a better cancer prognosis. For example, a recently published meta-analysis shows that people taking low-dose aspirin to reduce risk of vascular disease have a 20 to 30% lower risk of death due to several types of cancer, including cancers of the esophagus, lung, and pancreas, as well as colon. Other commonly used drugs, such as metformin used for the treatment of Type 2 diabetes, are also associated with a lower risk of cancer. However, the mechanisms by which these agents affect cancer risk and outcome are not well understood, and research needs to move beyond observational studies. Successful applications will determine which changes induced by drugs that are used commonly and chronically for other diseases are key for cancer prevention. The drugs chosen for study should already show good preventative effects in previous studies.

“The new leaders at the NCI are eager to influence the state of cancer research by attempting to define more potentially **game-changing scientific questions** that could influence the directions taken by NCI-sponsored research in the future.”

“Elucidating the key molecular mechanisms by which these agents work would be a **major breakthrough in cancer prevention.**”





“... we choose to do these things not because they are easy but because they are hard.”

John F. Kennedy

