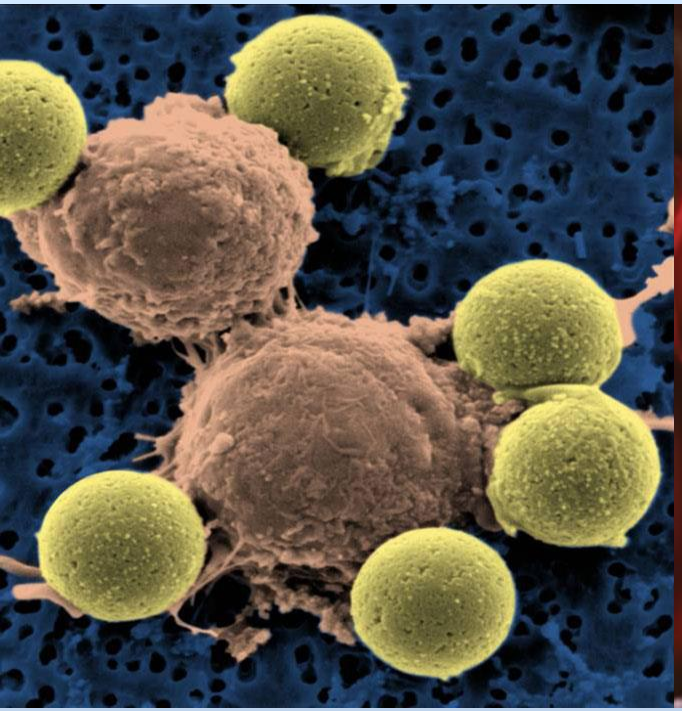
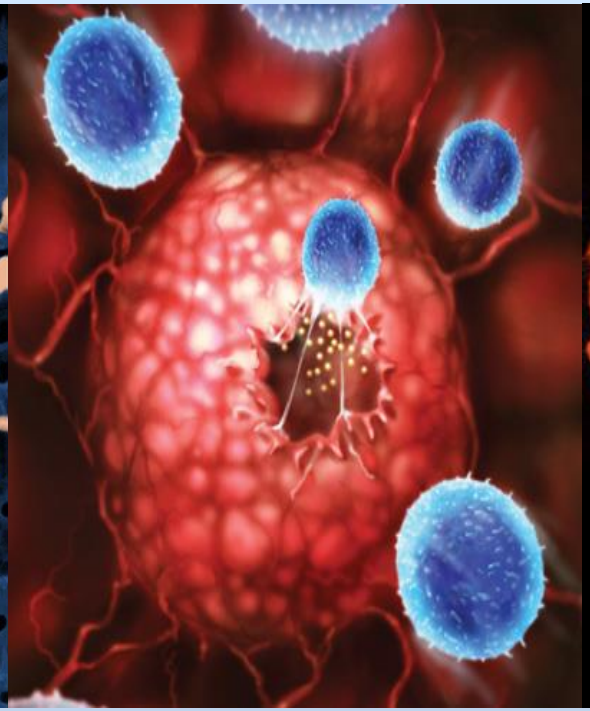
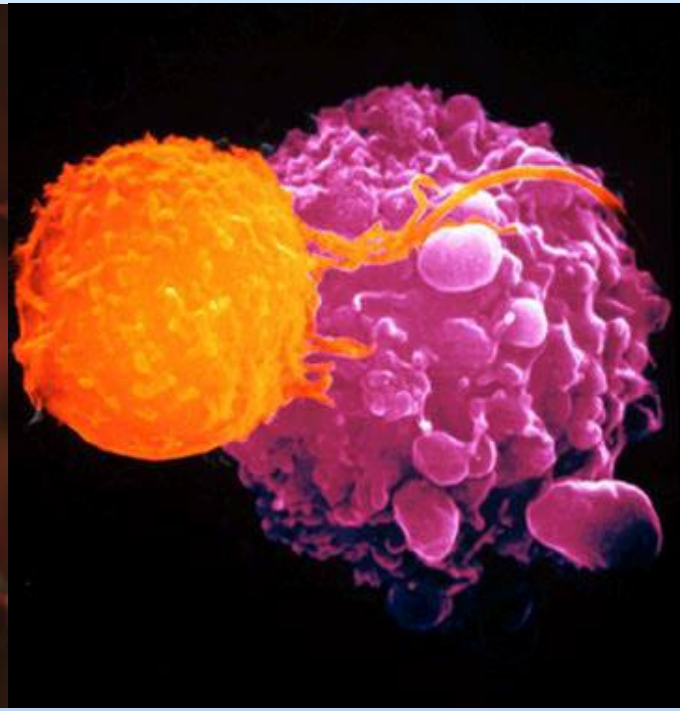
CANCER IMMUNOLOGY AND INFLMMATION
HOW WE FULFILLED OUR ASPIRATIONS THROUGH NMRC FUNDING

DR TOH HAN CHONG

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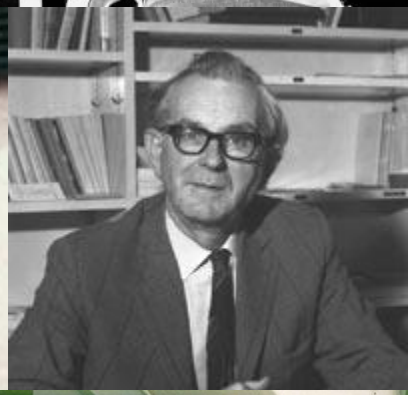
DIVISION OF MEDICAL ONCOLOGY

NATIONAL CANCER CENTRE SINGAPORE

National Cancer Centre Singapore

SingHealth

DUKE NUS GRADUATE MEDICAL SCHOOL SINGAPORE

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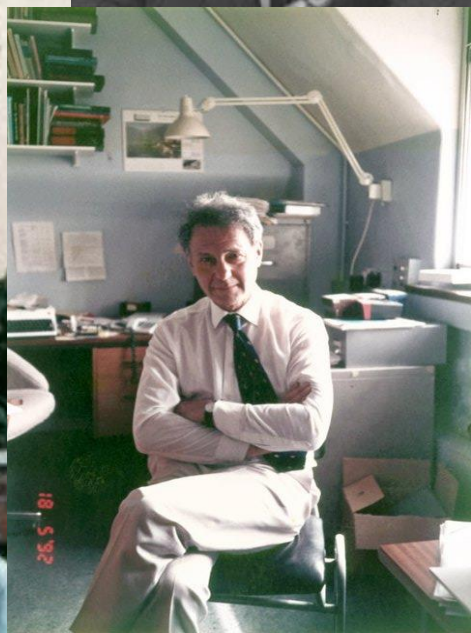
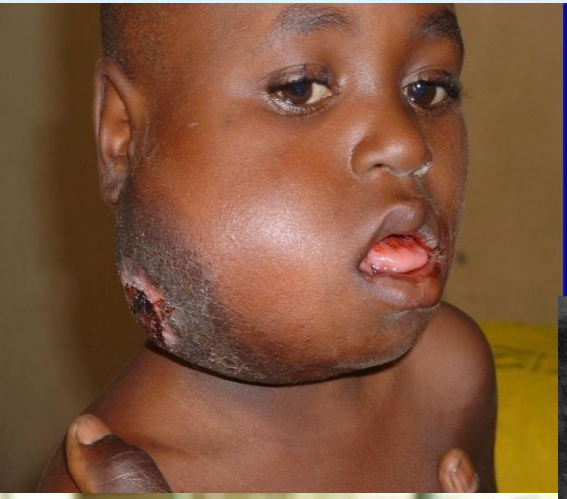
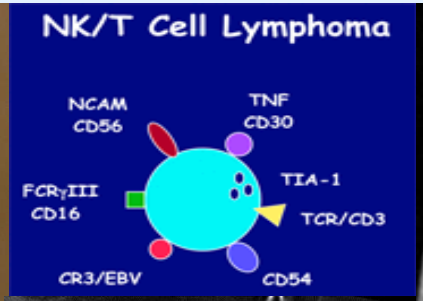
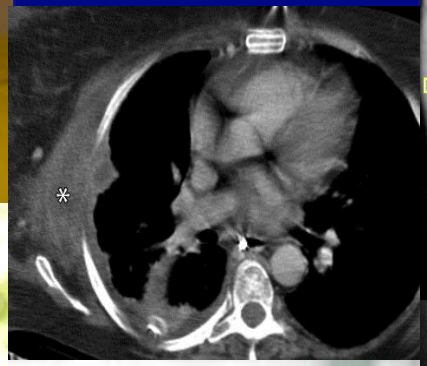
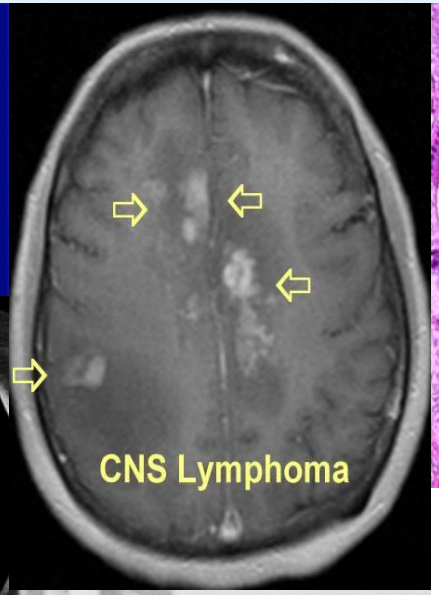


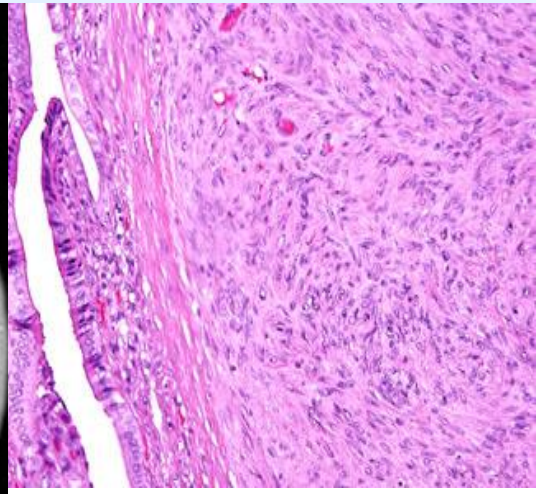
EPSTEIN-BARR VIRUS AND CANCER









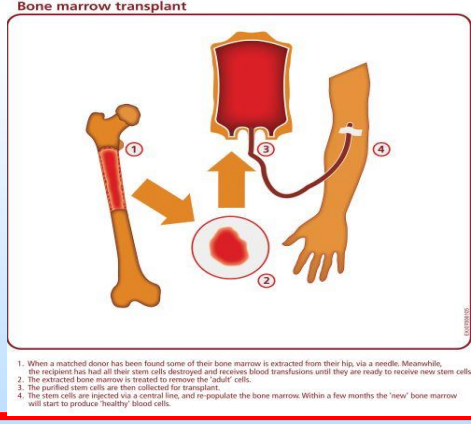


NASOPHARYNGEAL CANCER

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

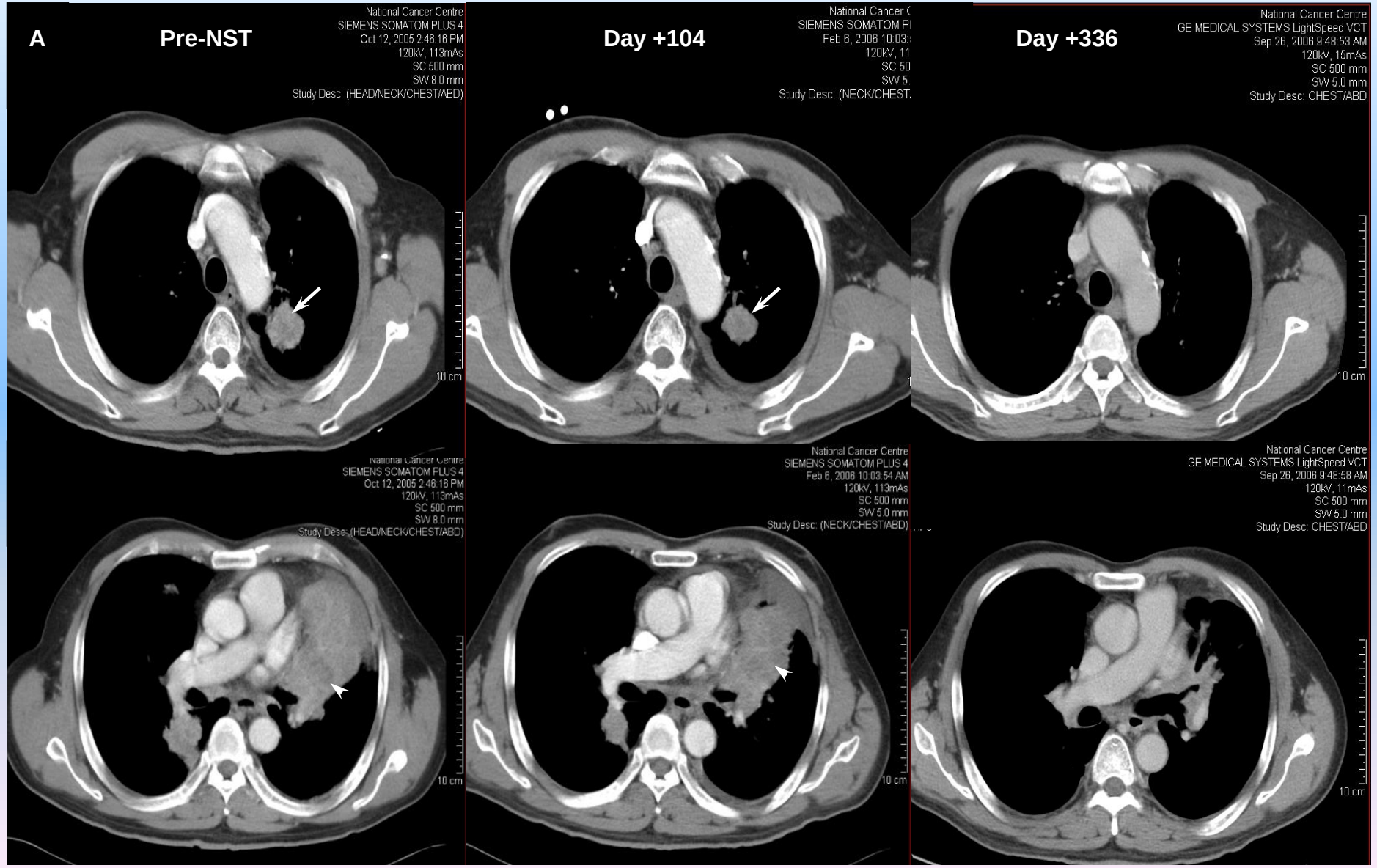


Achieve mixed chimaera

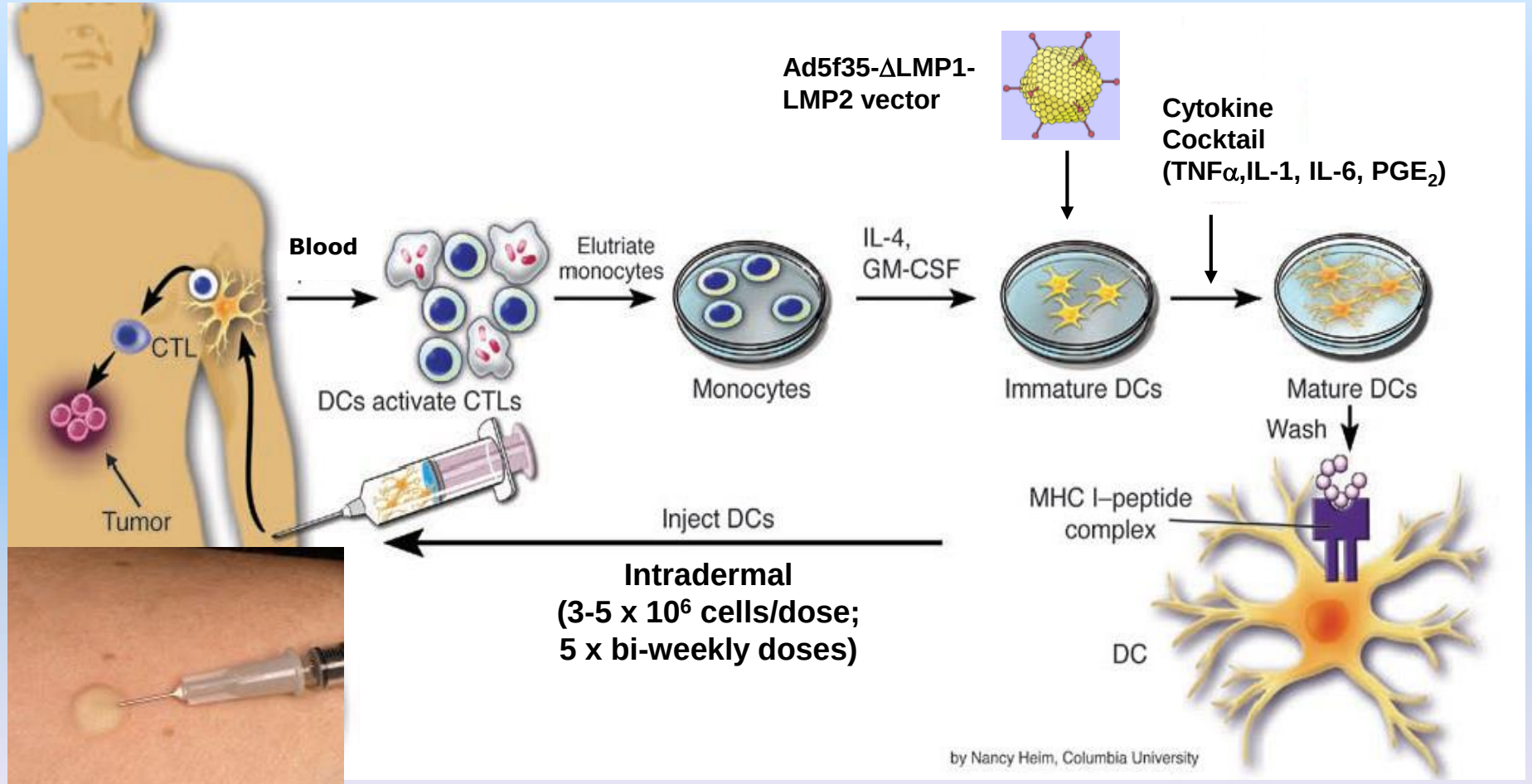
Achieve full donor chimaera

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

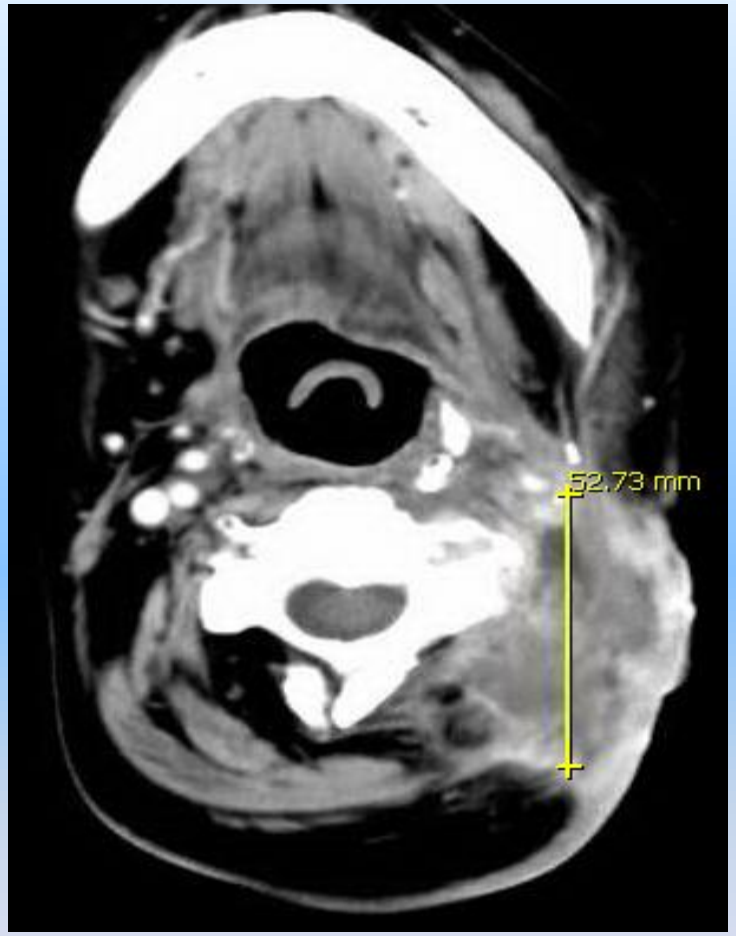


TREATMENT OF METASTATIC NASOPHARYNGEAL CARCINOMA WITH AUTOLOGOUS DENDRITIC CELLS TRANSDUCED WITH ADENOVIRAL VECTOR (AD5F35) EXPRESSING LATENT MEMBRANE PROTEIN (LMP)-1 AND LMP-2 GENES IN PATIENTS

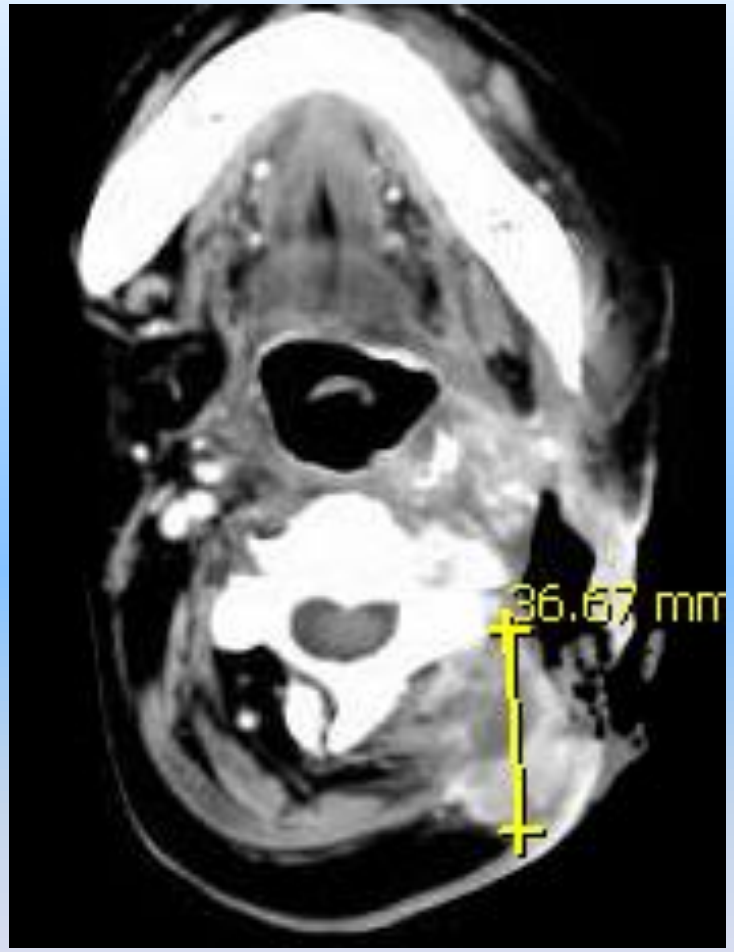


cal trial, n=16

PATIENT 004 – PARTIAL RESPONSE



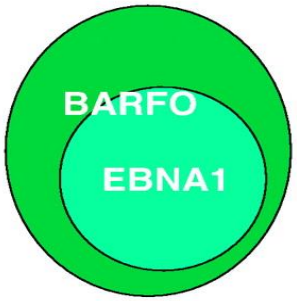
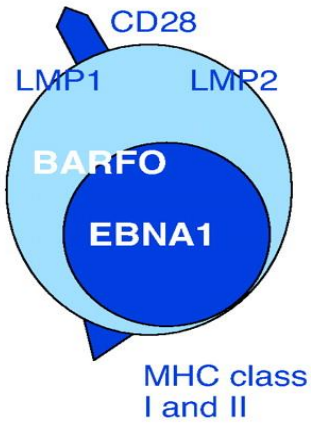
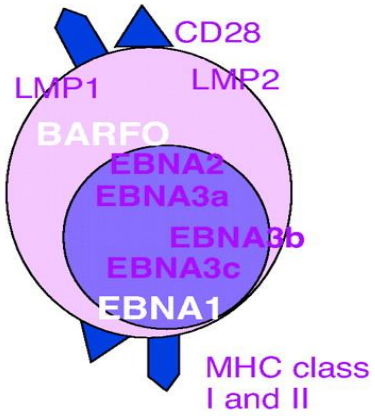
Baseline Date: 24/10/07



Date: 5/3/08

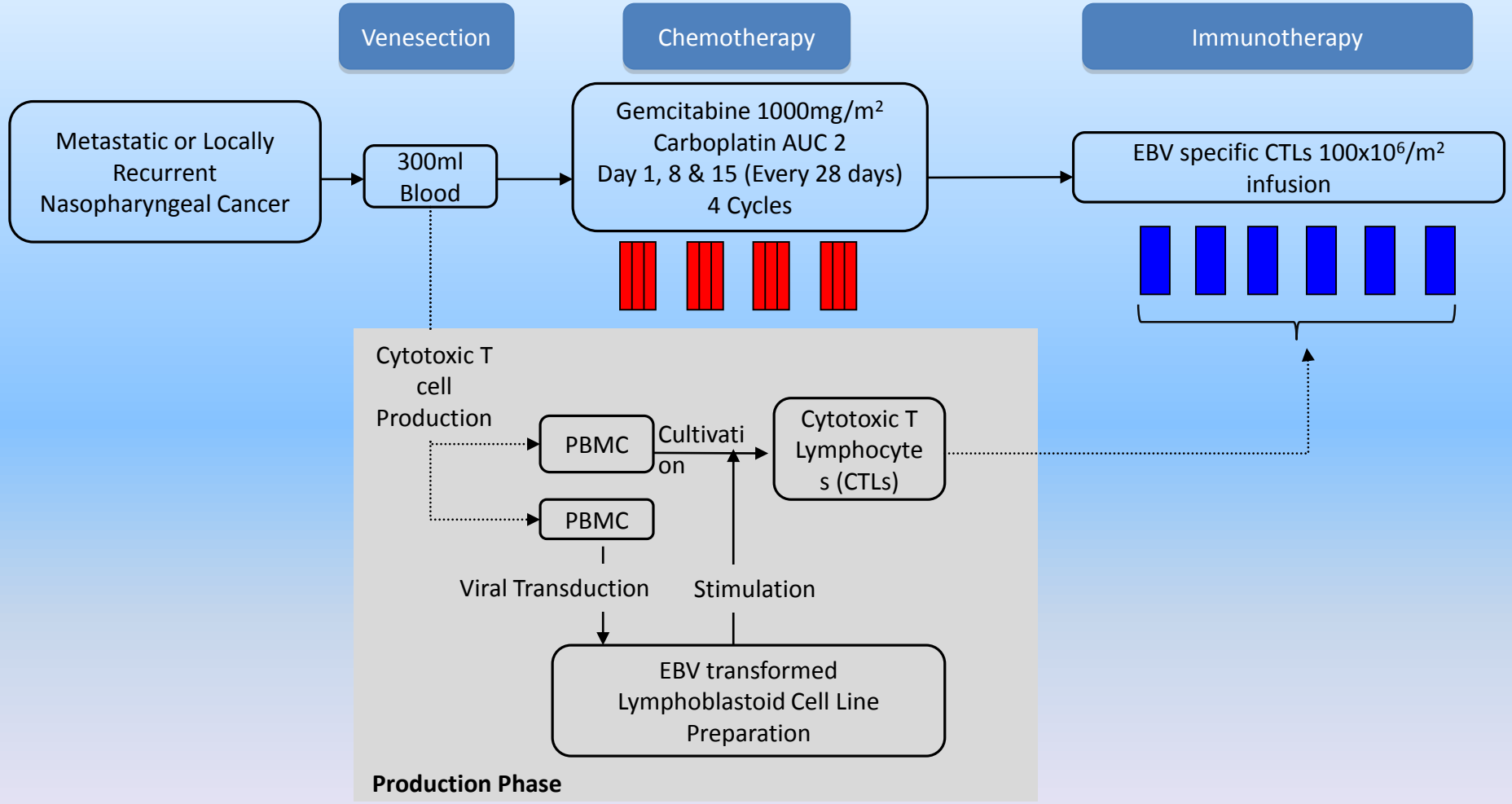
National Cancer Centre Singapore
SingHealth

Treat…na with Eps…cytes

Type I latency	Type II latency	Type III latency
		
Burkitt's lymphoma	Hodgkin's lymphoma Nasopharyngeal carcimona	Lymphoproliferative disease in immuno-compromised, LCL

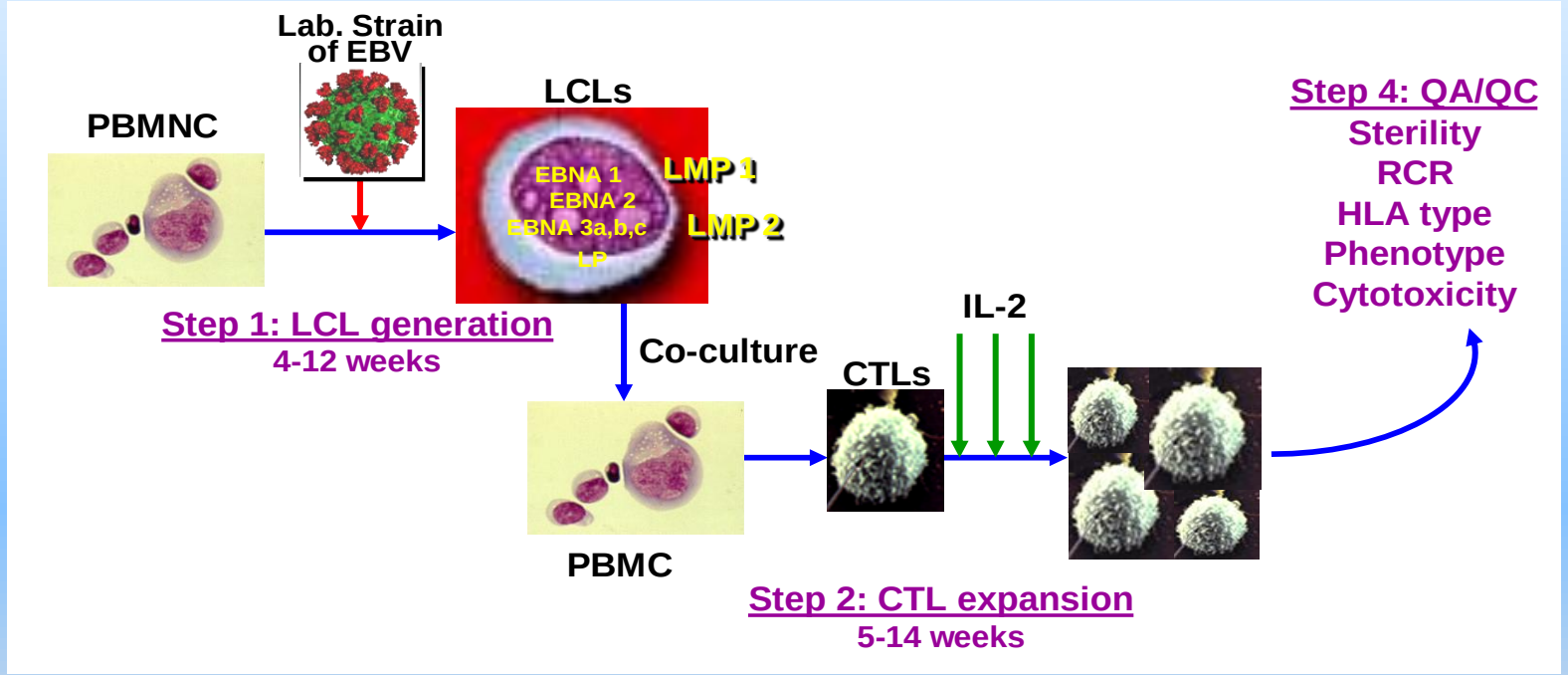
T CELLS AS LIVING THERAPY

CTL THERAPY IN ADVANCED NPC



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

EBV Specific CTL Generation

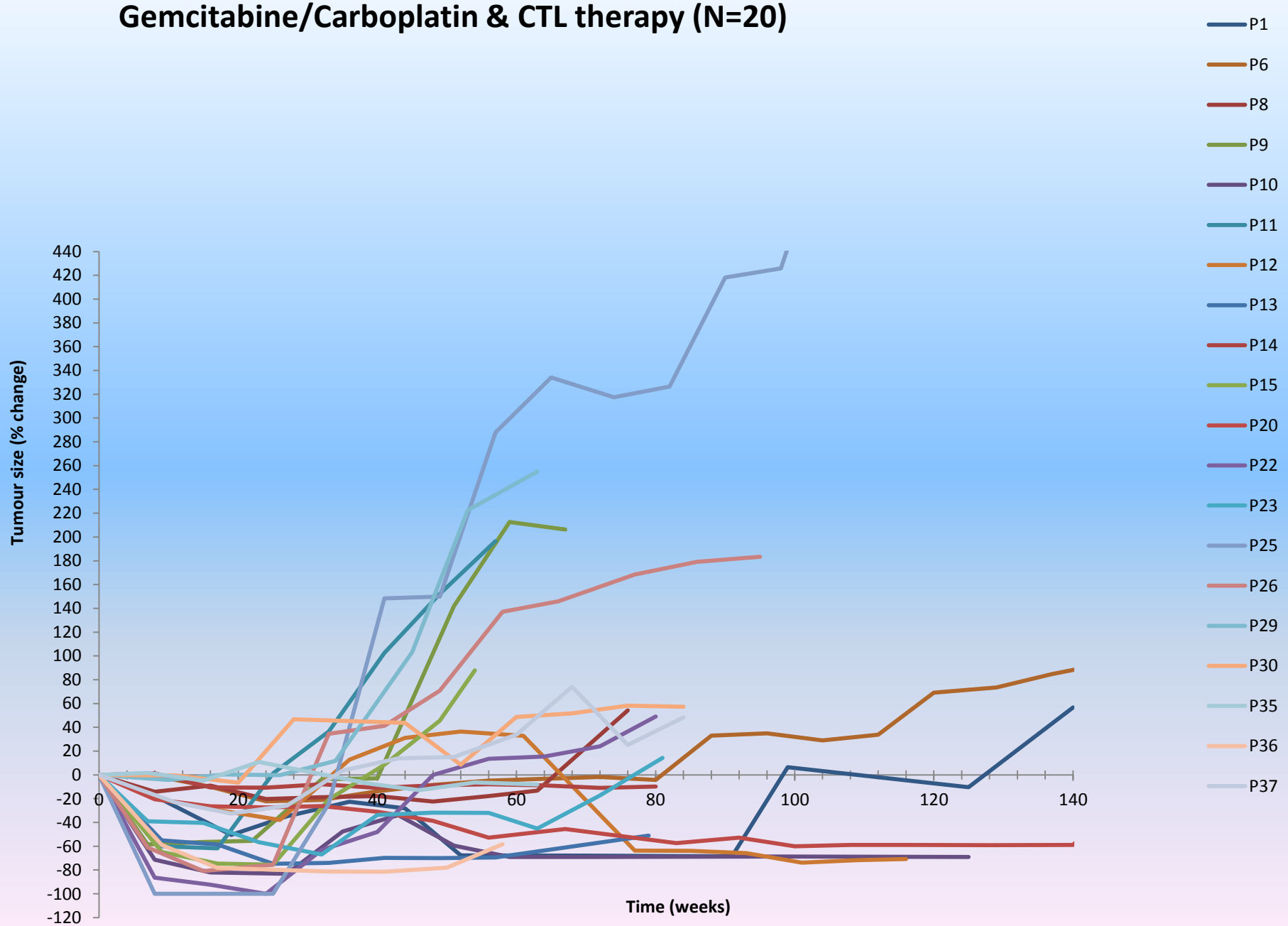


- **Phase II Trial: Evaluating efficacy of a strategy employing combination of gemcitabine and carboplatin chemotherapy followed by EBV-specific cytotoxic T lymphocytes in patients with metastatic or locally recurrent EBV-positive Nasopharyngeal carcinoma (n = 38)**

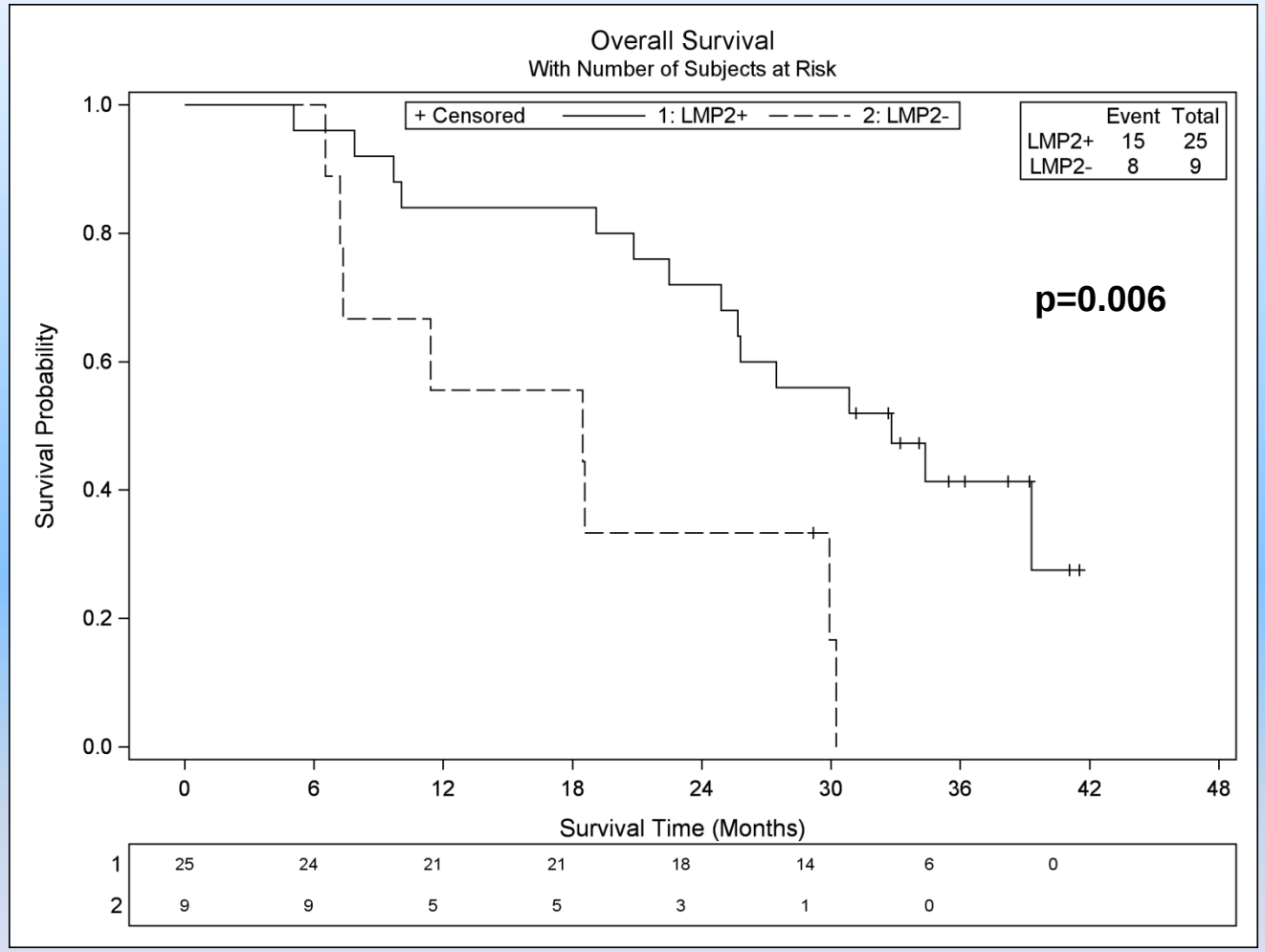
- **4 cycles of Gemcitabine + Carboplatin Chemotherapy, followed by 6 doses i.v. 1.0 x 10^8 CTLs/m^2**

SPIDER PLOT OF TUMOUR SIZES

Gemcitabine/Carboplatin & CTL therapy (N=20)



LMP2 dependent outcome

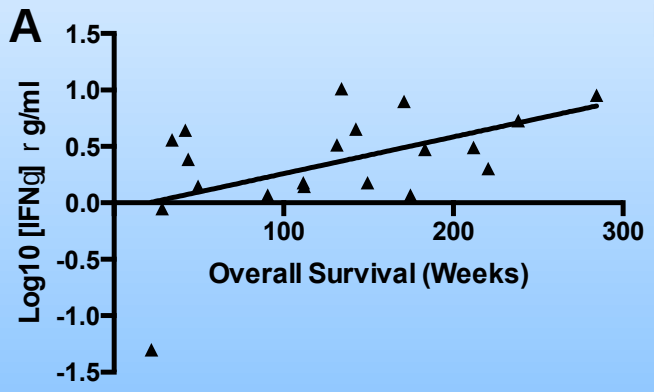


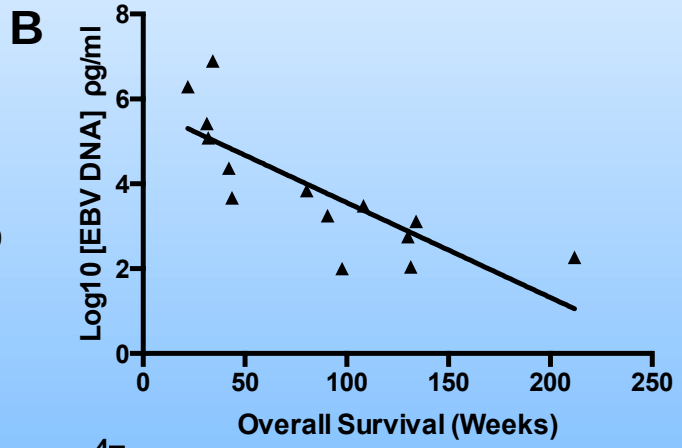
Kaplan-Meier estimated OS according to status of detectable LMP2-specific CTLs (Elispot) in infusion product

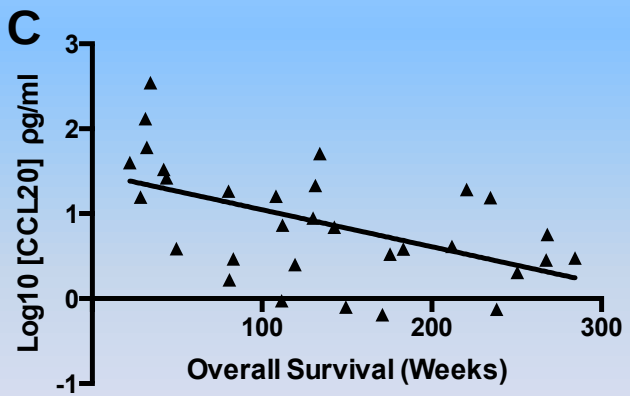
Comparison with other Clinical Trials in Metastatic NPC Patients

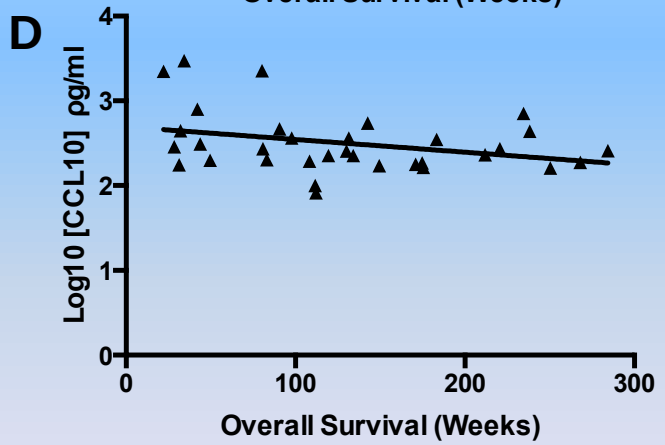
Author	Journal	Regimen	Line	*n*	ORR	PFS	Median OS	1yr OS	2yr OS
Ngan et al	Ann Oncol. 2002 Aug;13(8):1252-8	Gem 1000 Day 1,8,15 CDDP 50 Day 1,8	1st/2nd	44	73%	10.6mths	15mths	62%	*20%*
Ma BB et al	Ann Oncol. 2009 Nov;20(11):1854-9	Gem 1000 Day 1,8 Ox 20 Day 2,9	1st	42	64%	8.9mths	19.6mths	70%	*0%*
Leong 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	***unpublished***	**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 IFNγ production and Decreases in Myeloid Chemokines



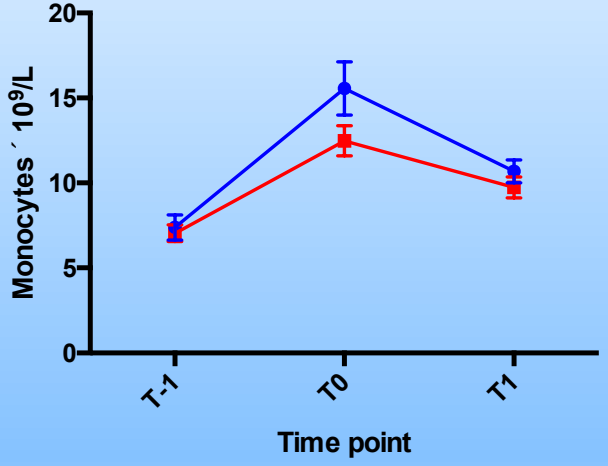


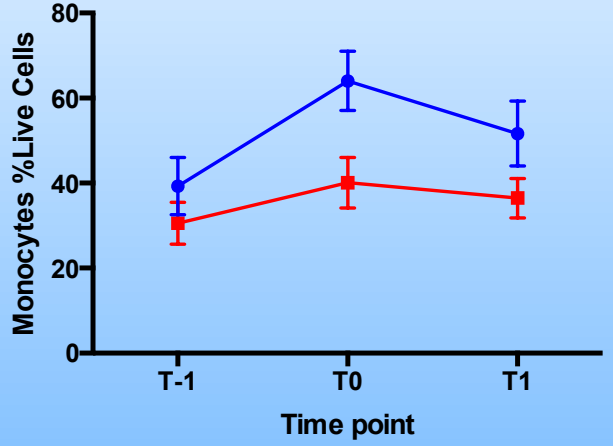


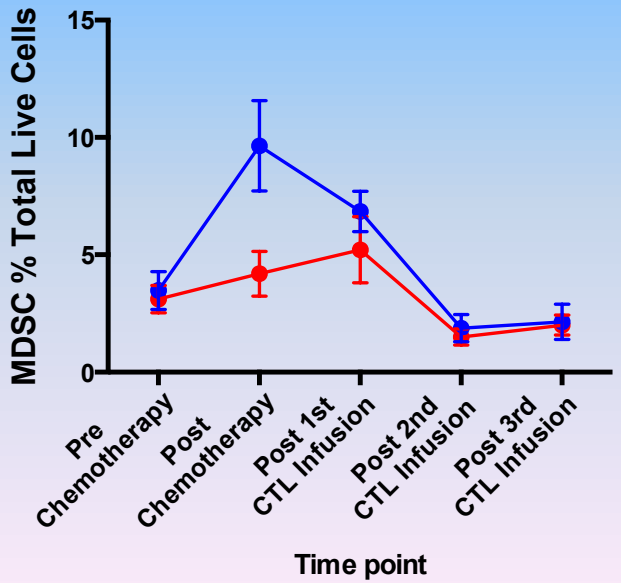


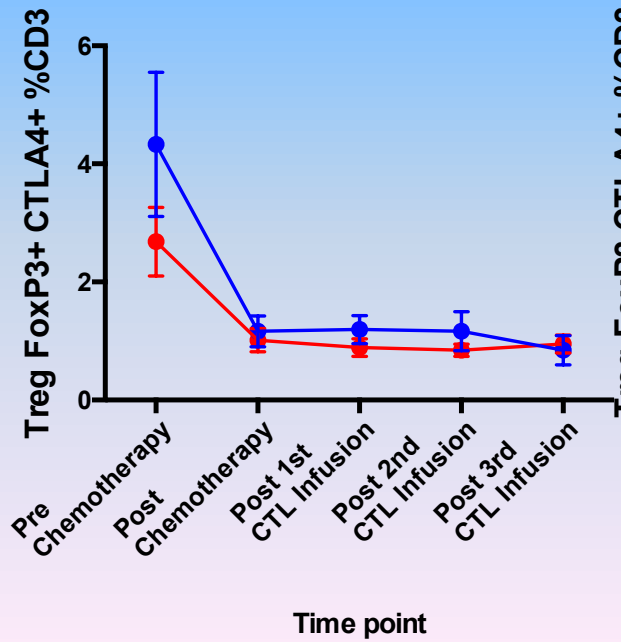
		T0	T1
IFNg	r	-0.04045	0.4637
	p	0.8511	***0.0395***
EBV DNA		-0.8818	-0.8725
	r	***0.0007***	***0.0001***
CCL20	p	-0.3951	-0.5472
		0.0339	***0.0014***
CCL10	r	-0.2425	-0.3155
	p	0.1671	0.0737

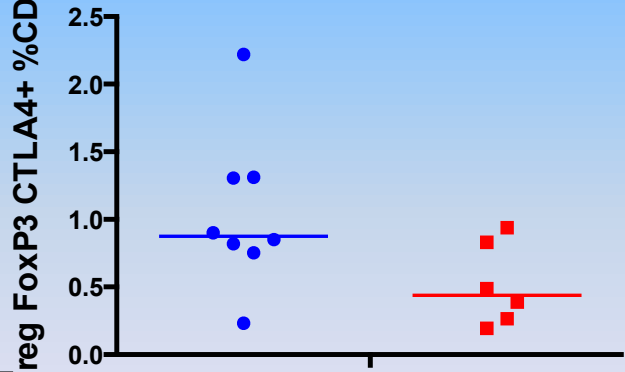
Non-Survivors Experience an Increase of Myeloid-Derived Suppressor Cells Post Chemotherapy



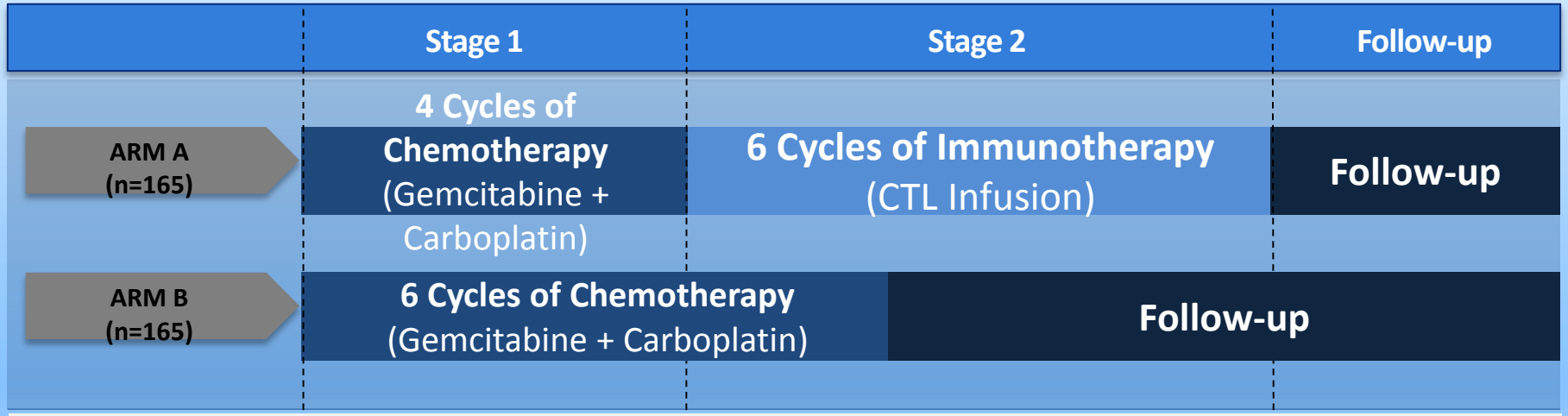








Phase III Study Design

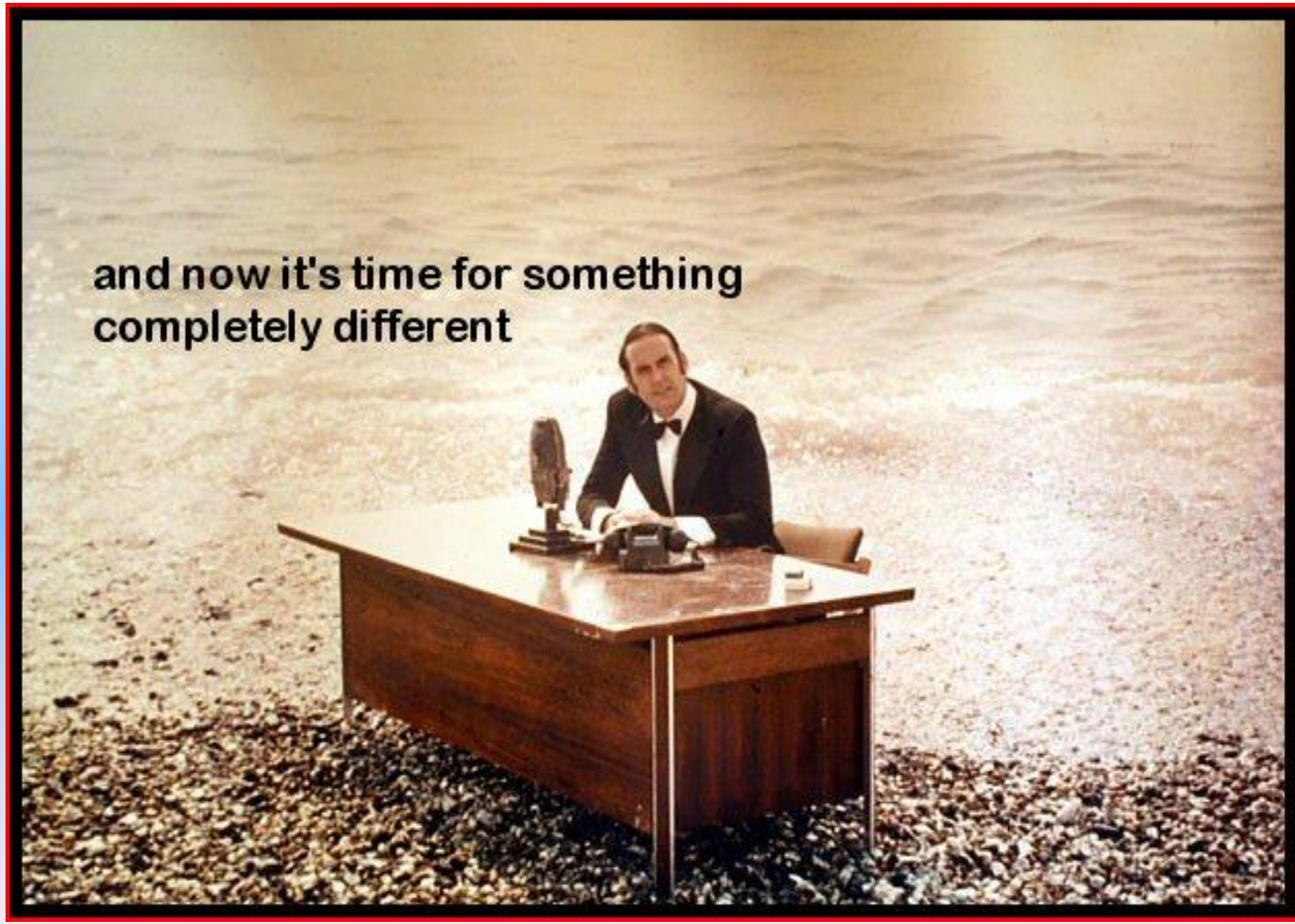


- **Chemotherapy:** Gemcitabine-Carboplatin infusions at Day 1, Day 8 and Day 15
- **Immunotherapy:** CTL infusions at Day 1 and Day 14 (Day 1 CTL Infusion - between 14 to 28 days from last chemotherapy), followed by 4 CTL

Phase III Global NPC CTL Trial:
330 Patients From 5 Countries and 25 Hospital Sites

γδ T cell Summary

- We generated *ex vivo* populations of γδ T cells that exhibit high expression levels of both effector and antigen-presentation markers
- LMP2 peptide-loaded γδ T cells are more efficient that monocyte-derived DCs in stimulating antigen-specific $CD8^+$ T cells
- In addition, these γδ T cells loaded with EBV-derived LPM2 peptides are as capable as LCL in stimulating $CD8^+$ 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

RANDOMISE

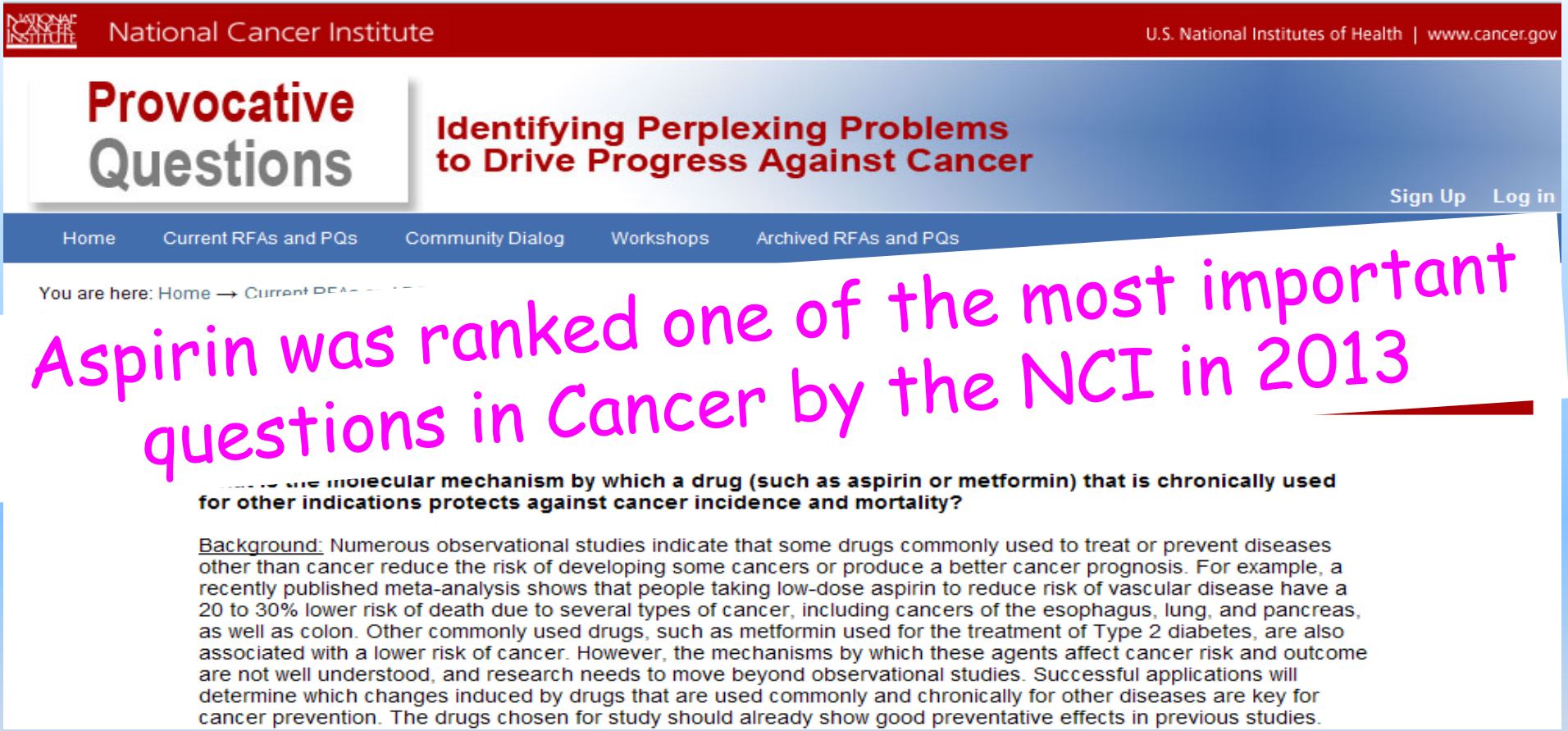
Aspirin 200mg daily (3yrs)

Placebo (3yrs)

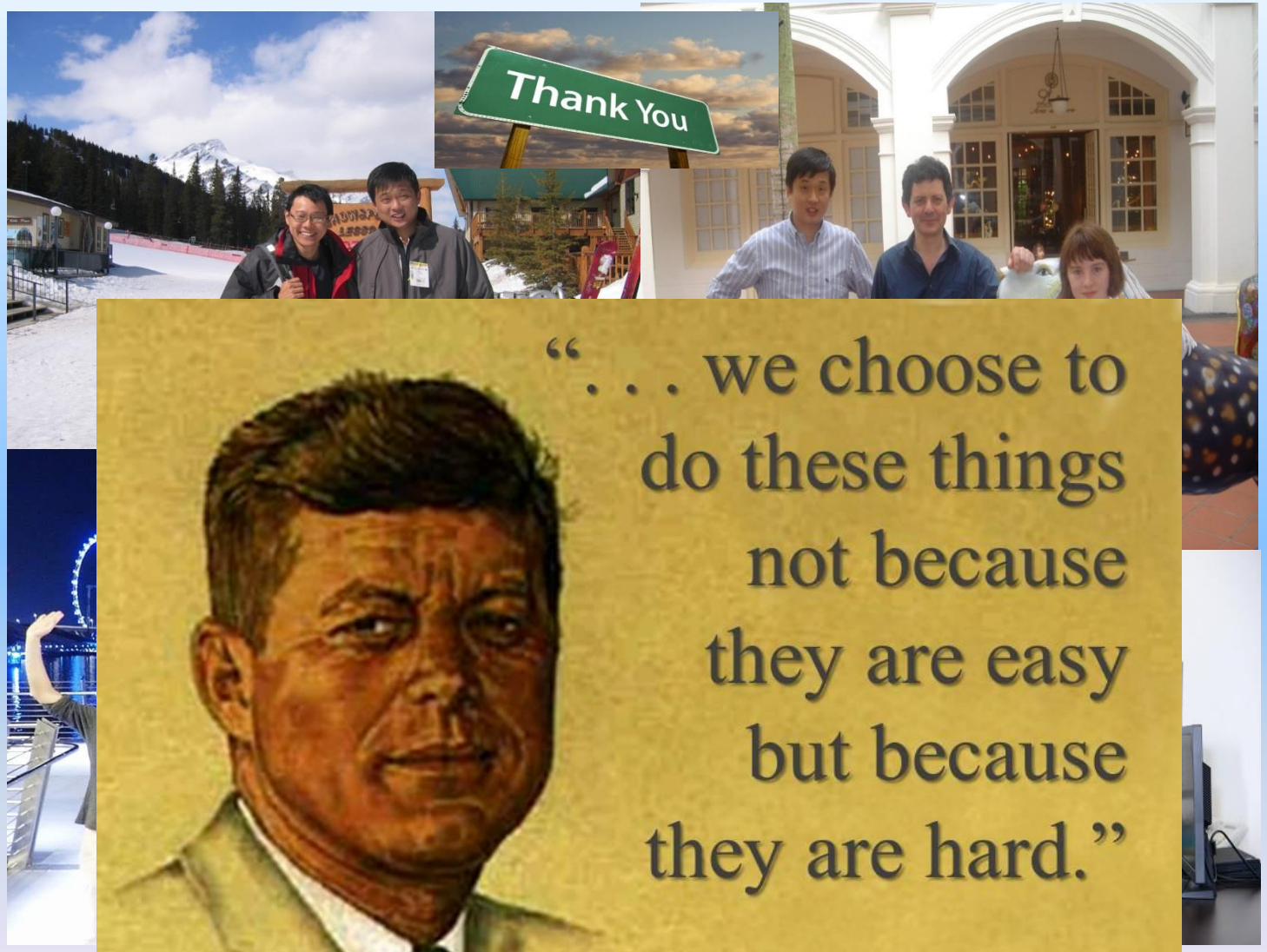
THE LARGEST CLINICAL TRIAL TO BE LED OUT OF SINGAPORE

Asia needs Large Clinical Trial Networks

Aspirin's Relevance is increasing



"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**."


Thank You
“. . . we choose to do these things not because they are easy but because they are hard.”
John F. Kennedy