Clinical trials of MVA-EBNA1/LMP2

A therapeutic cancer vaccine designed
to treat EBV positive cancers

CANCER
RESEARCH
UK

UNIVERSITY OF
BIRMINGHAM

Disclosure Statement

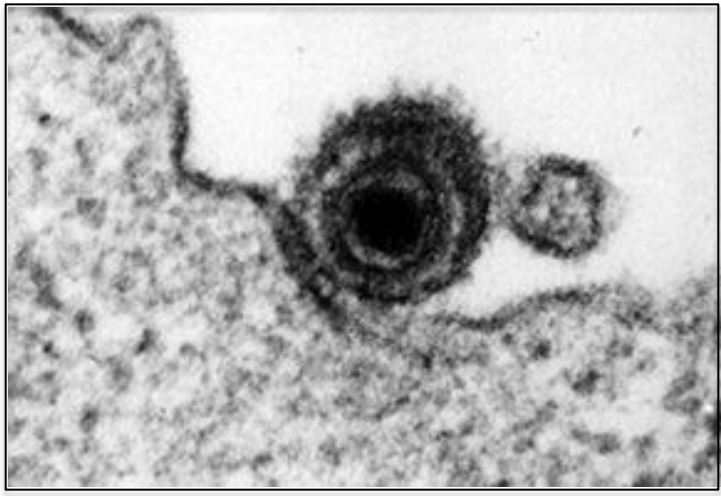
Nothing to declare.

Epstein Barr Virus

Ubiquitous Gamma Herpesvirus

>95% of adults infected, mostly asymptomatic
but infection can cause Infectious Mononucleosis

Infection persists for life in memory B cell pool



EBV associated malignancies express particular EBV proteins. Targets for Immunotherapy ?

Tumour	Post Transplant Lymphoma
EBV Latency	Latency III
EBV protein expression	EBNA1 LMP2 LMP1 EBNA 2, EBNA-LP EBNA 3A, 3B, 3C

EBV associated malignancies express particular EBV proteins. Targets for Immunotherapy ?

Tumour	Post Transplant Lymphoma
EBV Latency	Latency III
EBV protein expression	EBNA1 LMP2 LMP1 EBNA 2, EBNA-LP EBNA 3A, 3B, 3C

Lancet 1995; **345:** 9–13

Use of gene-modified virus-specific T lymphocytes to control Epstein-Barr-virus-related lymphoproliferation

Cliona M Rooney, Colton A Smith, Catherine Y C Ng, Susan Loftin, Congfen Li, Robert A Krance, Malcolm K Brenner, Helen E Heslop

EBV associated malignancies express particular EBV proteins. Targets for Immunotherapy ?

Tumour	Post Transplant Lymphoma	Nasopharyngeal Carcinoma (HL & GCa)	Burkitt Lymphoma
EBV Latency	Latency III	Latency II	Latency I
EBV protein expression	EBNA1 LMP2 LMP1 EBNA 2, EBNA-LP EBNA 3A, 3B, 3C	EBNA1 LMP2 (LMP1)	EBNA1

The scale of the problem

Table 1. EBV by the numbers. Estimated new cases of EBV-associated cancers worldwide per year (9, *10*).

Cancer	Number of cases	Number of cases attributable to EBV
Burkitt lymphoma		
Developed countries	400	100
Less-developed countries	7800	6600
Gastric carcinoma	933,900	84,050
Hodgkin lymphoma	62,400	28,600
Nasopharyngeal carcinoma	80,000	78,100
Total		197,450

ca. 200,000 cases/year = 1-2% of all cancers worldwide

Cohen et al. Sci Trans Med 2011

EBV associated malignancies express particular EBV proteins. Targets for Immunotherapy ?

Tumour	Post Transplant Lymphoma	Nasopharyngeal Carcinoma (HL & GCa)	Burkitt's Lymphoma
EBV Latency	Latency III	Latency II	Latency I
EBV protein expression	EBNA1 LMP2 LMP1 EBNA 2, EBNA-LP EBNA 3A, 3B, 3C	EBNA1 LMP2 (LMP1)	EBNA1

EBNA1 – contains many epitopes for CD4+ T cells
LMP2 – contains several T cell epitopes for CD8+ T cells

EBV associated malignancies express particular EBV proteins. Targets for Immunotherapy ?

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Sustained Complete Responses in Patients With Lymphoma Receiving Autologous Cytotoxic T Lymphocytes Targeting Epstein-Barr Virus Latent Membrane Proteins

Catherine M. Bollard, Stephen Gottschalk, Vicky Torrano, Oumar Diouf, Stephanie Ku, Yasmin Hazrat, George Carrum, Carlos Ramos, Luis Fayad, Elizabeth J. Shpall, Barbara Pro, Hao Liu, Meng-Fen Wu, Daniel Lee, Andrea M. Sheehan, Youli Zu, Adrian P. Gee, Malcolm K. Brenner, Helen E. Heslop, and Cliona M. Rooney

50 patients treated with T-cells specific for EBV **LMP2** (n=17) or **LMP1 & LMP2** (n=33).

28/29 high risk or multiple relapse patients in remission 3.1 years after CTL infusion.

11 CR 2 PR in 21 patients with relapsed or resistant disease.

Bollard et al. J Clin Oncol 2014 32:798-808.

Icheva J Clin Oncol 2013 31:39-48

EBV associated malignancies express particular EBV proteins. Targets for Immunotherapy ?

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Sustained Complete Responses in Patients With Lymphoma Receiving Autologous Cytotoxic T Lymphocytes Targeting Epstein-Barr Virus Latent Membrane Proteins

Catherine M. Bollard, Stephen Gottschalk, Vicky Torrano, Oumar Diouf, Stephanie Ku, Yasmin Hazrat, George Carrum, Carlos Ramos, Luis Fayad, Elizabeth J. Shpall, Barbara Pro, Hao Liu, Meng-Fen Wu, Daniel Lee, Andrea M. Sheehan, Youdi Zu, Adrian P. Gee, Malcolm K. Brenner, Helen E. Heslop, and Cliona M. Rooney

50 patients treated with T-cells specific for EBV **LMP2** (n=17) or **LMP1 & LMP2** (n=33).

28/29 high risk or multiple relapse patients in remission 3.1 years after CTL infusion.

11 CR 2 PR in 21 patients with relapsed or resistant disease.

Bollard et al. J Clin Oncol 2014 32:798-808.

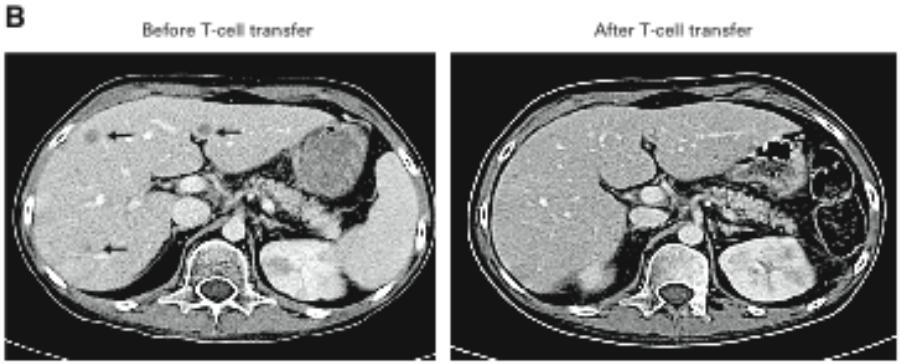
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Adoptive Transfer of Epstein-Barr Virus (EBV) Nuclear Antigen 1–Specific T Cells As Treatment for EBV Reactivation and Lymphoproliferative Disorders After Allogeneic Stem-Cell Transplantation

Vanya Icheva, Simone Kayser, Daniel Wolff, Sebastian Tuve, Christina Kyzirakos, Wolfgang Bethge, Johann Greil, Michael H. Albert, Wolfgang Schwinger, Michaela Nathrath, Michael Schumm, Stefan Stevanovic, Rupert Handgretinger, Peter Lang, and Tobias Feuchtinger

10 transplant recipients with PTLD treated with T-cells specific for **EBNA1**
(isolated from the donor)

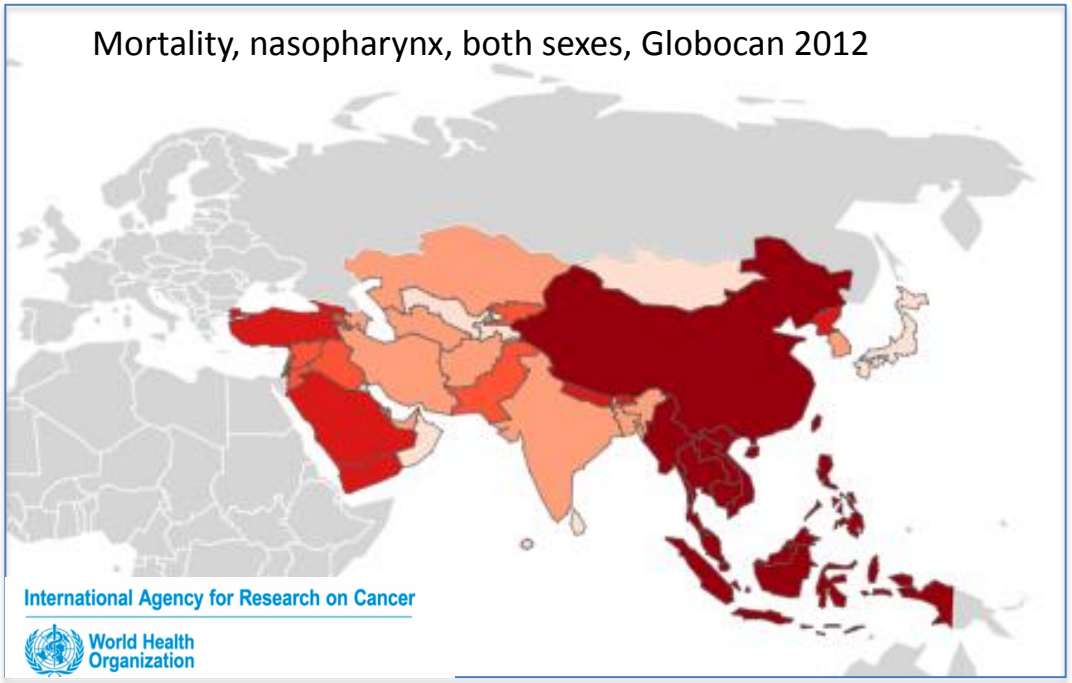
7/10 clinical responses.



Icheva J Clin Oncol 2013 31:39-48

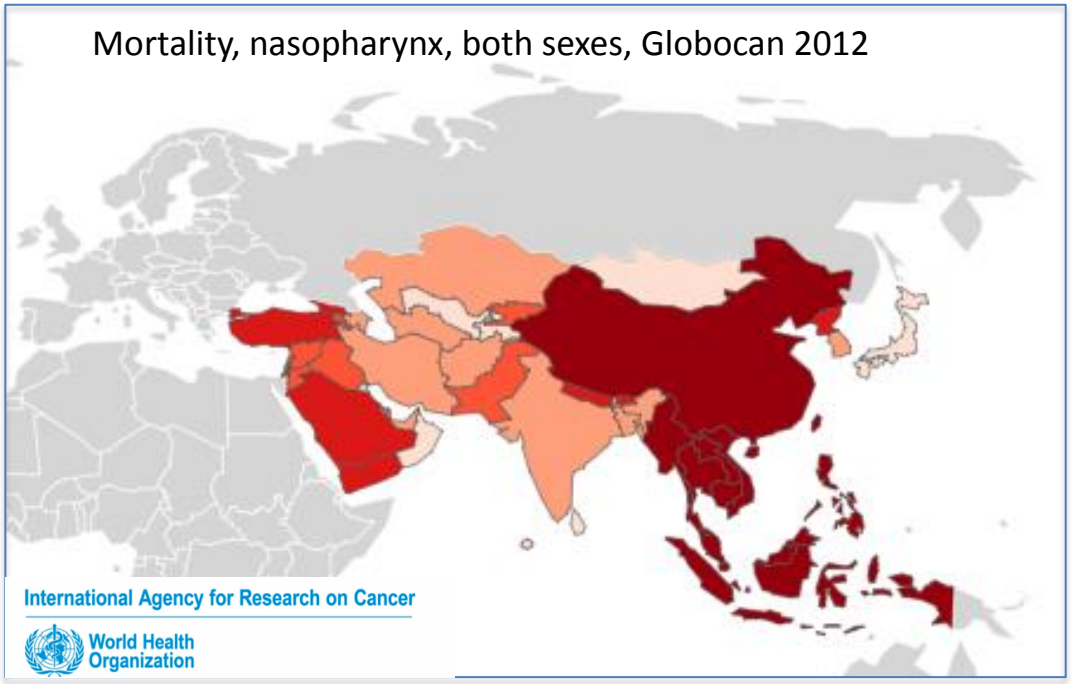
How to treat 200,000 patients every year, many in developing nations?

Rank	Country	Total health expenditure per capita PPP Int.$
1	United States	8,233
2	Luxembourg	6,712
3	Monaco	5,915
4	Norway	5,391
5	Switzerland	5,297
6	Netherlands	5,112
7	Denmark	4,467
8	Canada	4,443
9	Austria	4,398
10	Germany	4,342
11	France	3,997
12	Belgium	3,975
13	Sweden	3,760
14	Ireland	3,720
15	Australia	3,685
16	United Kingdom	3,433
80	Malaysia	645
111	China	373
131	Vietnam	216
148	Cambodia	132
152	Indonesia	123



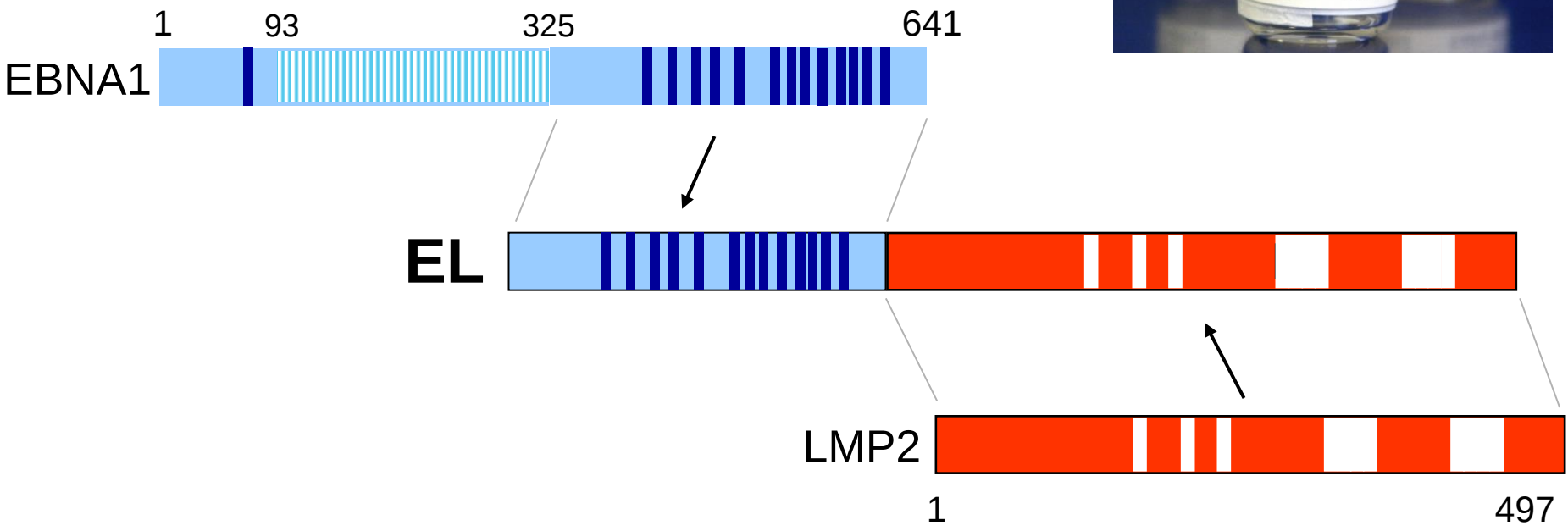
How to treat 200,000 patients every year, many in developing nations?

Rank	Country	Total health expenditure per capita PPP Int.$
1	United States	8,233
2	Luxembourg	6,712
3	Monaco	5,915
4	Norway	5,391
5	Switzerland	5,297
6	Netherlands	5,112
7	Denmark	4,467
8	Canada	4,443
9	Austria	4,398
10	Germany	4,342
11	France	3,997
12	Belgium	3,975
13	Sweden	3,760
14	Ireland	3,720
15	Australia	3,685
16	United Kingdom	3,433
80	Malaysia	645
111	China	373
131	Vietnam	216
148	Cambodia	132
152	Indonesia	123



12,000 cases of NPC each year
4th most common cancer in men

MVA-EBNA1/LMP2 : a therapeutic cancer vaccine

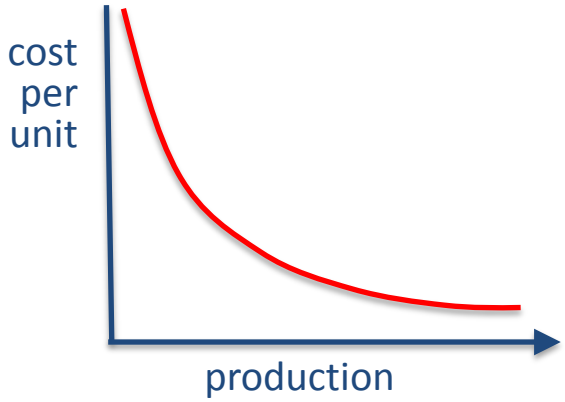


Fusion protein can stimulate both CD8 and CD4 T cells

(Taylor *et al* J. Virol 2004)

Basic economic theory

Technologies that can be mass produced and have low marginal cost benefit from **economies of scale.**

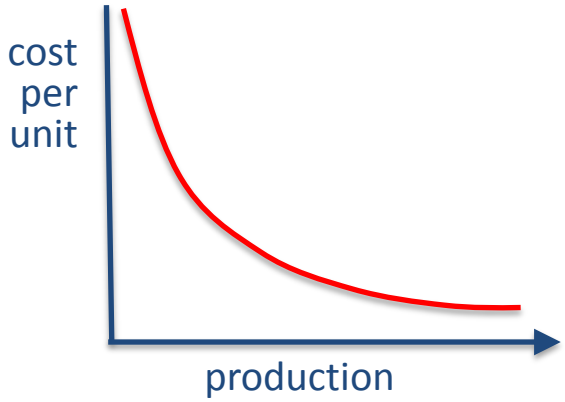


Vaccines can be **mass produced**
Single production run makes 1000s of doses

Vaccines have **low marginal cost**
Doubling the quantity of vaccine produced does not double the price.

Basic economic theory

Technologies that can be mass produced and have low marginal cost benefit from **economies of scale.**



Vaccines can be **mass produced**
Single production run makes 1000s of doses

Vaccines have **low marginal cost**
Doubling the quantity of vaccine produced does not double the price.

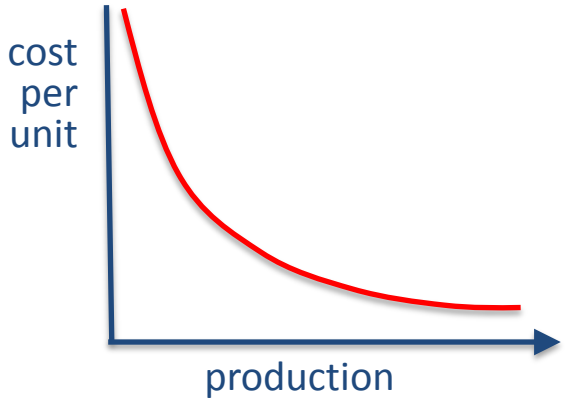
Vaccines have tremendous economies of scale

Fluvirin® (Novartis Vaccines) PoM

Injection, suspension of formaldehyde-inactivated influenza virus (surface antigen, grown in fertilised hens' eggs), net price 0.5-mL prefilled syringe = £5.55

Basic economic theory

Technologies that can be mass produced and have low marginal cost benefit from **economies of scale.**



Vaccines can be **mass produced**
Single production run makes 1000s of doses

Vaccines have **low marginal cost**
Doubling the quantity of vaccine produced does not double the price.

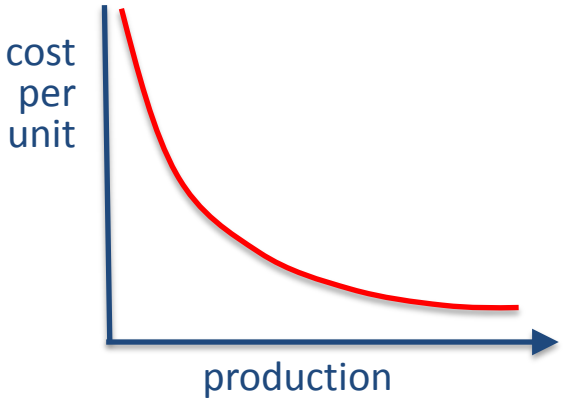
Vaccines have tremendous economies of scale

Fluvirin® (Novartis Vaccines) PoM

Injection, suspension of formaldehyde-inactivated influenza virus (surface antigen, grown in fertilised hens' eggs), net price 0.5-mL prefilled syringe = £5.55

Basic economic theory

Technologies that can be mass produced and have low marginal cost benefit from **economies of scale.**



Vaccines can be **mass produced**
Single production run makes 1000s of doses

Vaccines have **low marginal cost**
Doubling the quantity of vaccine produced does not double the price.

Vaccines have tremendous economies of scale

Fluvirin® (Novartis Vaccines) PoM
Injection, suspension of formaldehyde-inactivated influenza virus (surface antigen, grown in fertilised hens' eggs), net price 0.5-mL prefilled syringe = £5.55

Viral tumour antigens are 'ideal' targets since:

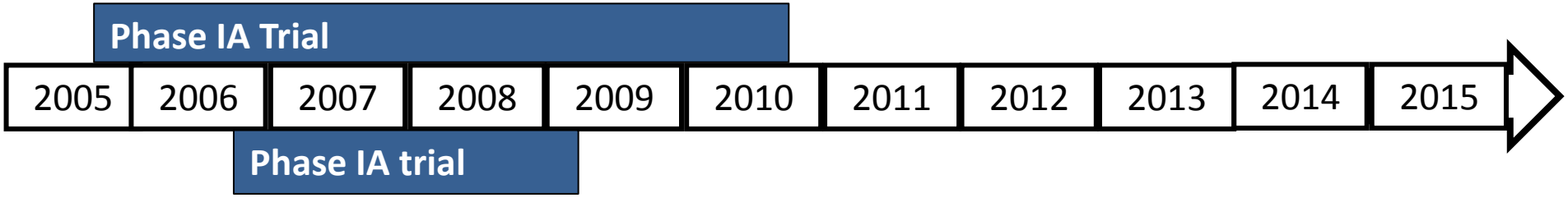
i) high avidity T-cell response that can be exploited.

ii) Antigen expression limited solely to tumour.

PARALLEL TRIALS IN UK AND CHINA

Phase IA Trial (UK)

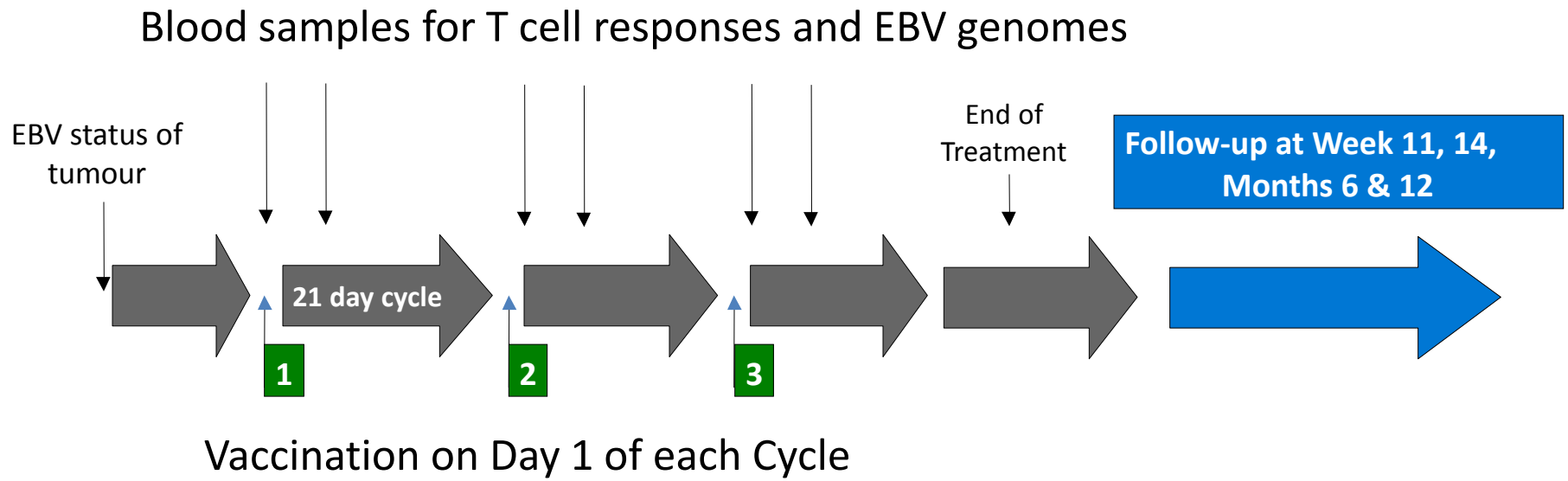
- EBV+ cancer in remission or low volume stable recurrence
- Safety, immunogenicity
- 3+3 dose escalation vaccine
- n=16/18
- 3 cycles over 9 weeks



Phase IA Trial (Hong Kong)

- EBV+ NPC in remission or low volume stable recurrence
- Safety, immunogenicity
- 3+3 dose escalation vaccine
- n=18
- 3 cycles over 9 weeks

OVERVIEW OF PHASE IA DESIGN



- Dose range: $5x10^7$,$1x10^8$, $2x10^8$ $3.3x10^8$, $5x10^8$ pfu
- Safety, tolerability
- Evidence of immunogenicity

Patient No.[a]	Age, y	Sex	Stage[b]	Radiotherapy	Chemotherapy[c]	Time since treatment, wks
0101	41	M	I (T1N0M0)	6,600 cGy in 33 fractions, (NP boost by intubation) 1,800 cGy in 4 fractions	NA	15
0102	57	F	II (T2bN0M0)	6,600 cGy in 33 fractions, (right PP boost) 1,400 cGy in 7 fractions	NA	16
0103	55	M	III (T2bN2M0)	6,600 cGy in 33 fractions, (bilateral PP boost) 1,000 cGy in 5 fractions, (left PP boost) 400 cGy in 2 fractions	Cisplatin (6 cycles)	15
0204	59	F	II (T2bN1M0)	6,600 cGy in 33 fractions, (NP boost) 800 cGy in 4 fractions	NA	22
0205	46	M	III (T2bN2M0)	6,600 cGy in 33 fractions, (NP boost) 800 cGy in 4 fractions	Cisplatin (6 cycles)	19
0206	46	M	IV (T2bN3M0)	6,600 cGy in 33 fractions, (left PP boost) 1,400 cGy in 7 fractions	Cisplatin (6 cycles)	27
0307	53	M	III (T3N2M0)	6,600 cGy in 33 fractions, (NP boost) 4 fractions 800 cGy	Cisplatin (7 cycles)	30
0308	40	M	III (T2bN2M0)	6,600 cGy in 33 fractions, (NP boost) 800 cGy in 4 fractions, (LN boost) 750 cGy in 2 fractions	Cisplatin (7 cycles)	33
0309	47	M	IV (T4N1M0)	7,000 cGy in 35 fractions	Induction carboplatin+paclitaxel (2 cycles), cisplatin (7 cycles)	22
0410	50	M	IV (T4N0M0)	7,000 cGy in 35 fractions	Induction cisplatin +gemcitabine (2 cycles), cisplatin (6 cycles)	39
0411	57	F	III (T3N0M0)	7,000 cGy in 35 fractions	Cisplatin (6 cycles)	17
0412	57	M	III (T3N0 M0)	7,000 cGy in 35 fractions	Cisplatin (4 cycles)	14
0513	62	M	II (T2bN1M0)	7,000 cGy in 35 fractions	Cisplatin (5 cycles)	14
0514	42	M	IV (T4N1M0)	7,000 cGy in 35 fractions, (LN boost) 750 cGy in 2 fractions	Cisplatin (6 cycles)	15
0515	55	M	II (T2bN1M0)	7,000 cGy in 35 fractions	Cisplatin (6 cycles)	21
0516	36	M	II (T2bN0M0)	7,000 cGy in 35 fractions	NA	18
0517	63	M	IV (T4N1M0)	7,000 cGy in 35 fractions	Cisplatin (6 cycles)	42
0518	55	M	II (T2bN1M0)	7,000 cGy in 35 fractions	Cisplatin (6 cycles)	27

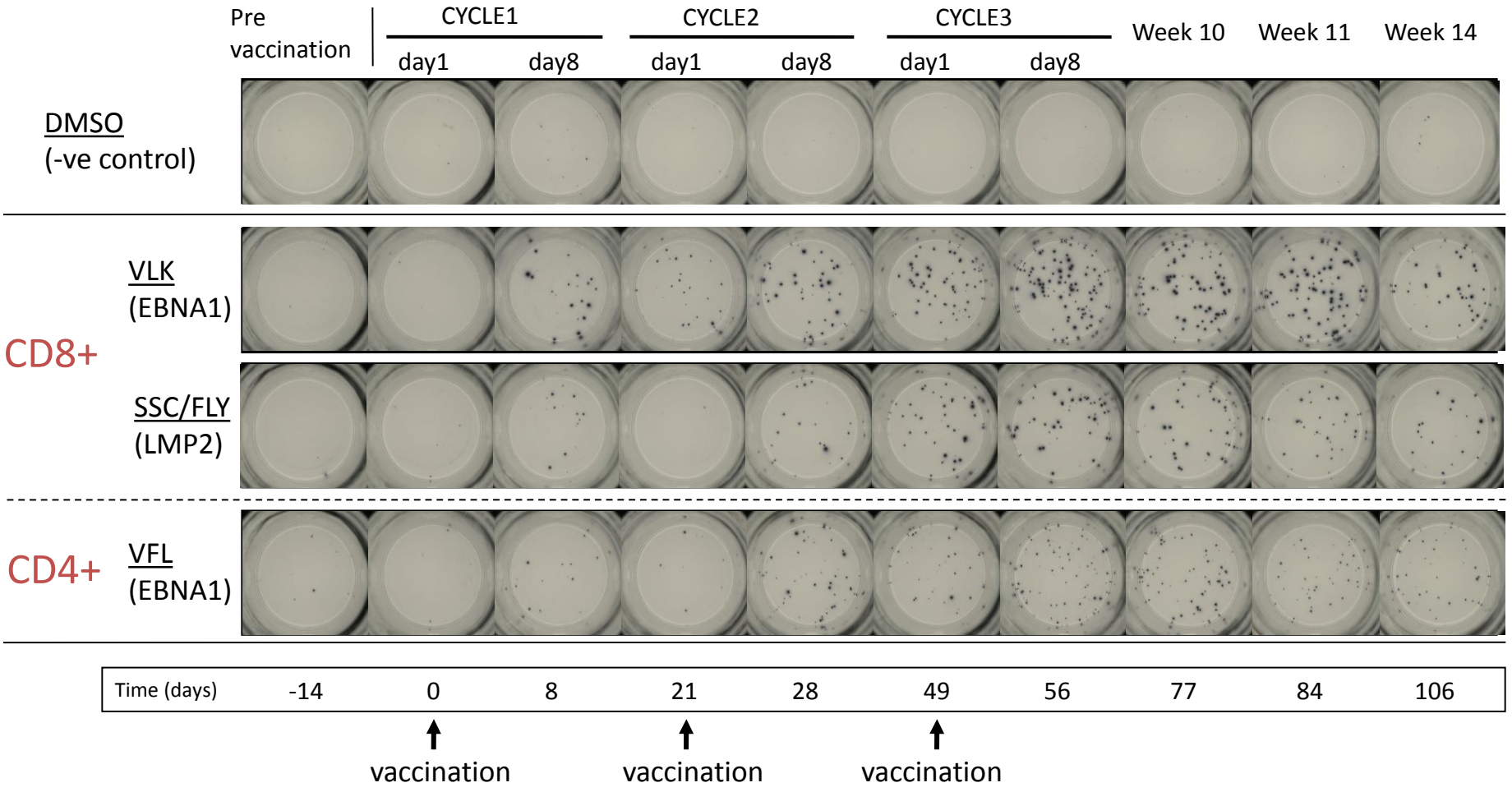
MVA-EBNA1/LMP2 is well tolerated in patients recently treated with chemo/radiotherapy

Dose level	1			2			3			4			5		
Vaccine Dose	$5x10^7$ pfu			10^8 pfu			$2x10^8$ pfu			$3.3x10^8$ pfu			$5x10^8$ pfu		
Number of patients	3			3			3			3			6		
Toxicity grade	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
Injection site reaction	2	1		3			1	1	1	3			6		
Flu-like (chills, fever)	1						2			1	1		3		
Fatigue	1	1		1	1		1			3			4	1	
Arthralgia	2	1												1	
Myalgia										2			2	1	
CNS (headaches, dizziness)	2						1						1		
Hepatotoxicity					1										

MVA-EBNA1/LMP2 is well tolerated in patients recently treated with chemo/radiotherapy

Dose level	1			2			3			4			5		
Vaccine Dose	$5x10^7$ pfu			10^8 pfu			$2x10^8$ pfu			$3.3x10^8$ pfu			$5x10^8$ pfu		
Number of patients	3			3			3			3			6		
Toxicity grade	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
Injection site reaction	2	1		3			1	1	1	3			6		
Flu-like (chills, fever)	1						2			1	1		3		
Fatigue	1	1		1	1		1			3			4	1	
Arthralgia	2	1												1	
Myalgia										2			2	1	
CNS (headaches, dizziness)	2						1						1		
Hepatotoxicity					1										

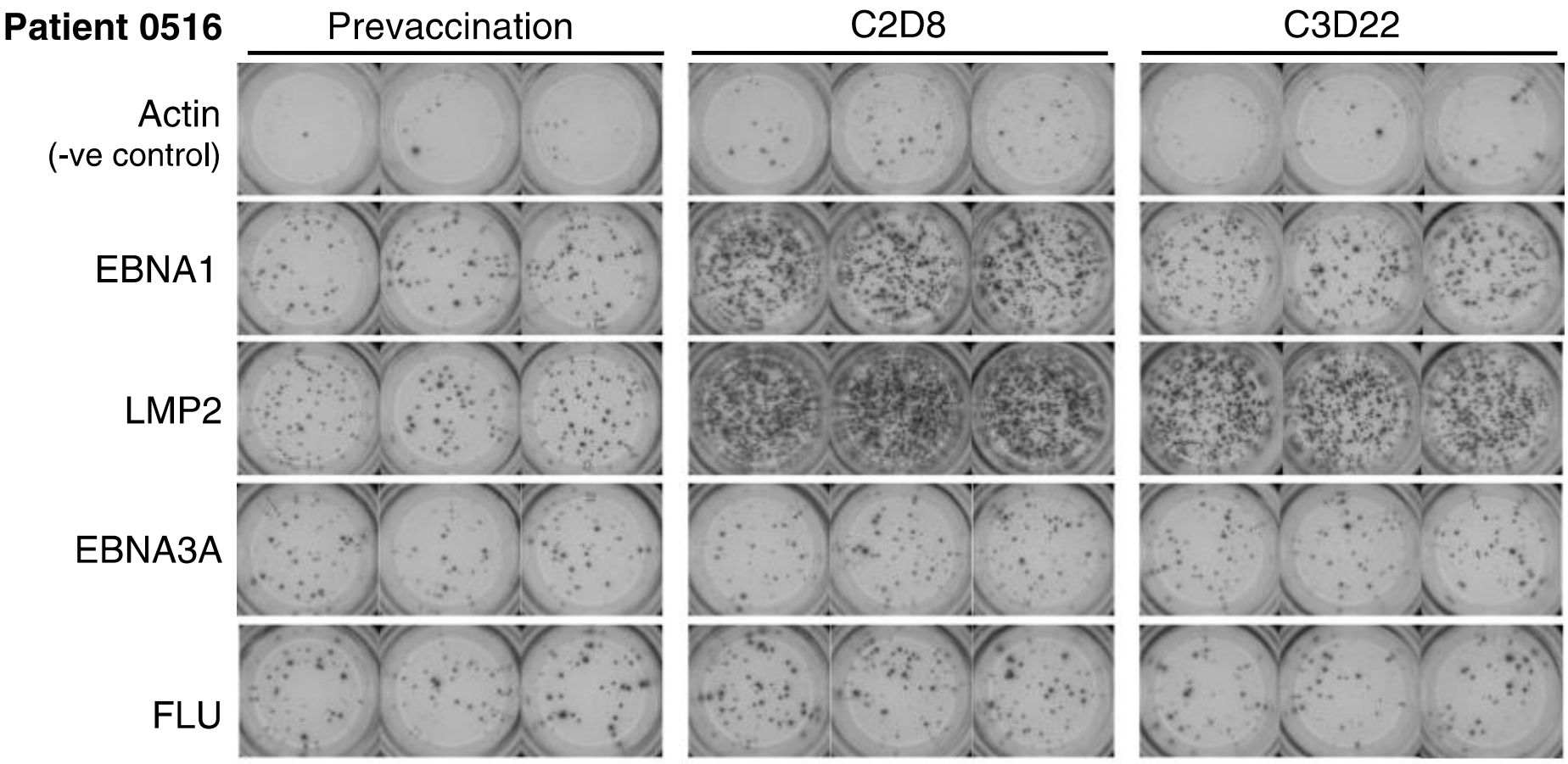
Vaccination stimulates multiple CD8+ and CD4+ T cell responses within an individual patient



Hong Kong Patient 6 Dose Level 2 ($1x10^8$ pfu X3)

Hui, Taylor *et al.* 2013 Cancer Research

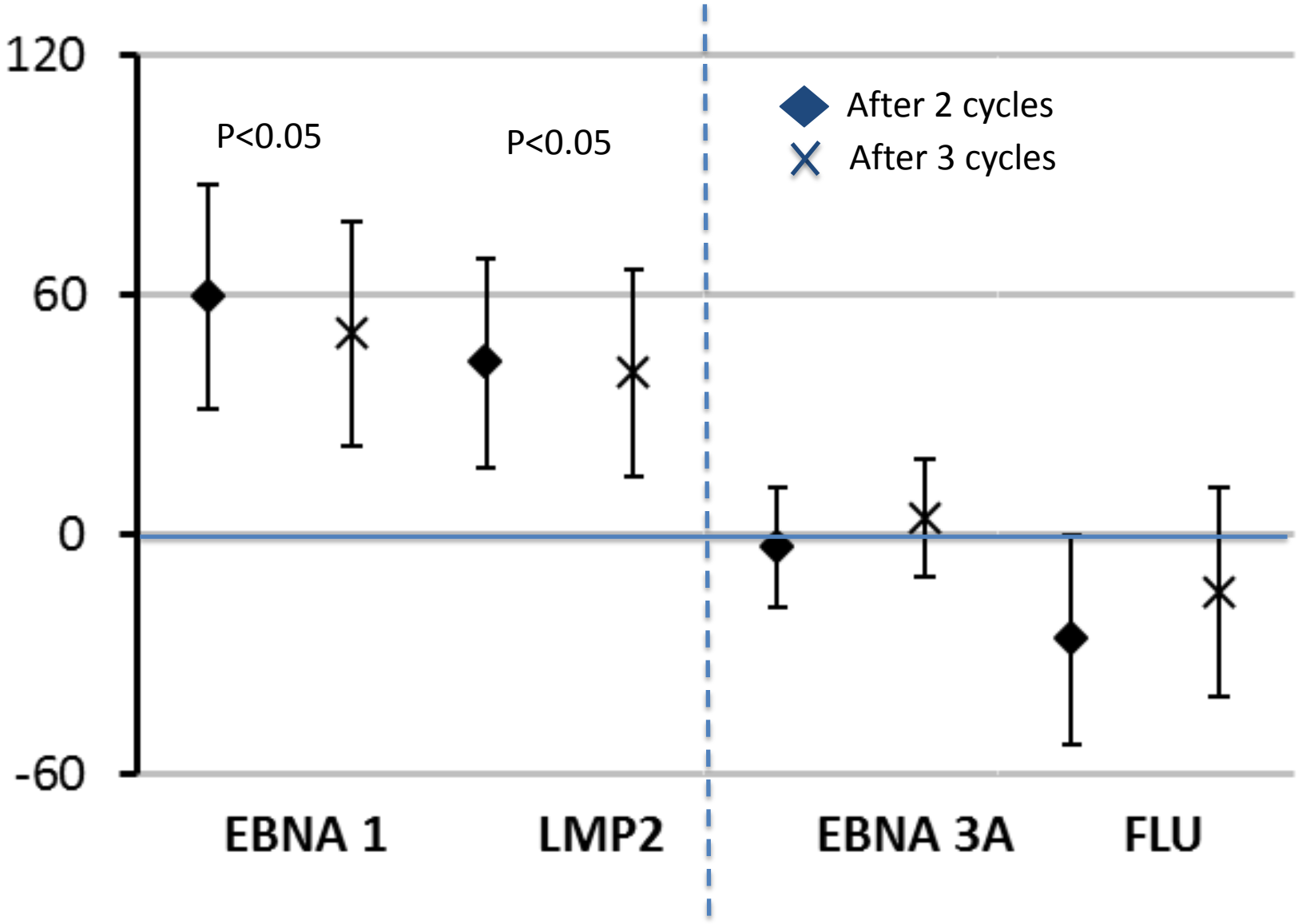
Vaccination increases frequency of EBNA1- and LMP2-specific T-cells in NPC patients



Hong Kong Patient 16 : Dose Level 5 ($5x10^8$ pfu X3)

Hui, Taylor *et al.* 2013 Cancer Research

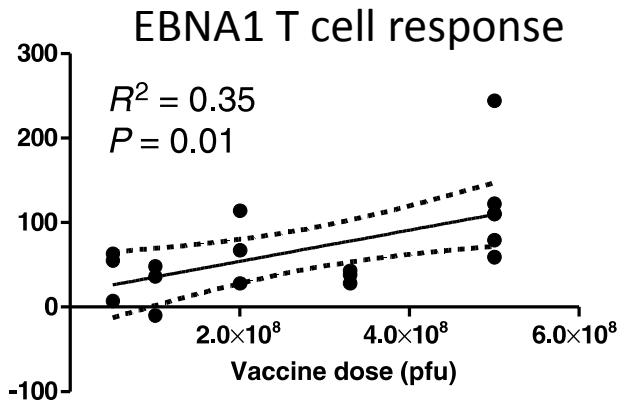
Responses to vaccine – controls versus targets

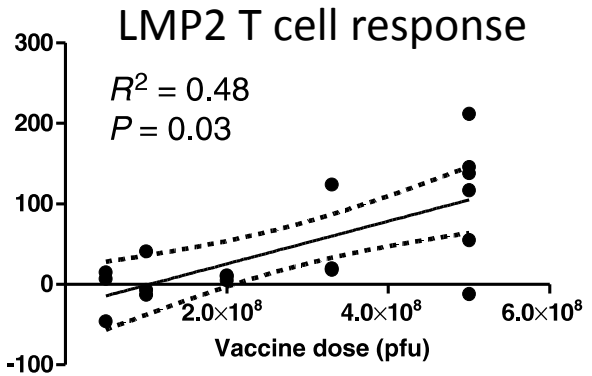


Hui, Taylor *et al.* 2013 Cancer Research

Summary of two Phase 1A trials in NPC patients (UK and Hong Kong)

	Vaccine target antigens	
	EBNA1	LMP2
Dose level 1	3/8	3/8
Dose level 2	2/5	1/5
Dose level 3	4/4	1/4
Dose level 4	3/4	2/4
Dose level 5	6/6	5/6
All patients	18/27	12/27





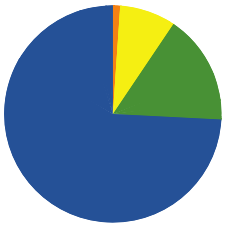
Every patient treated at dose level 3 or higher (n=14) had an increased EBNA1 and/or LMP2 T-cell response.

Hui, Taylor *et al.* 2013 Cancer Research

Vaccination increases size *and* quality of EBNA1- and LMP2-specific T cells

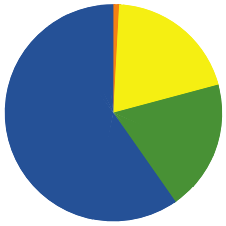
EBNA1 T-cells (CD4+)

Pre-vaccine



0.28%

Post-vaccine



0.49%

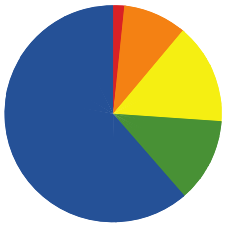
After Vaccination

increase in response size

+ increase in polyfunctionality

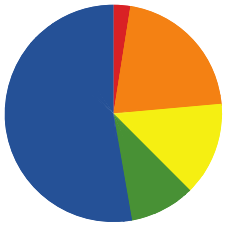
LMP2 T-cells (CD8+)

Pre-vaccine



0.33%

Post-vaccine



1.43%

After Vaccination

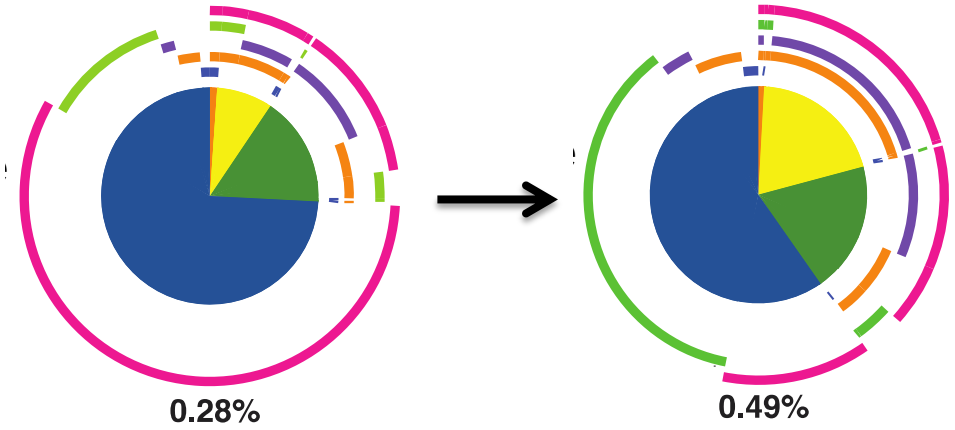
increase in response size

+ increase in polyfunctionality

Taylor *et al.* 2014 Clinical Cancer Research

Vaccination increases size *and* quality of EBNA1- and LMP2-specific T cells

EBNA1 T-cells (CD4+)



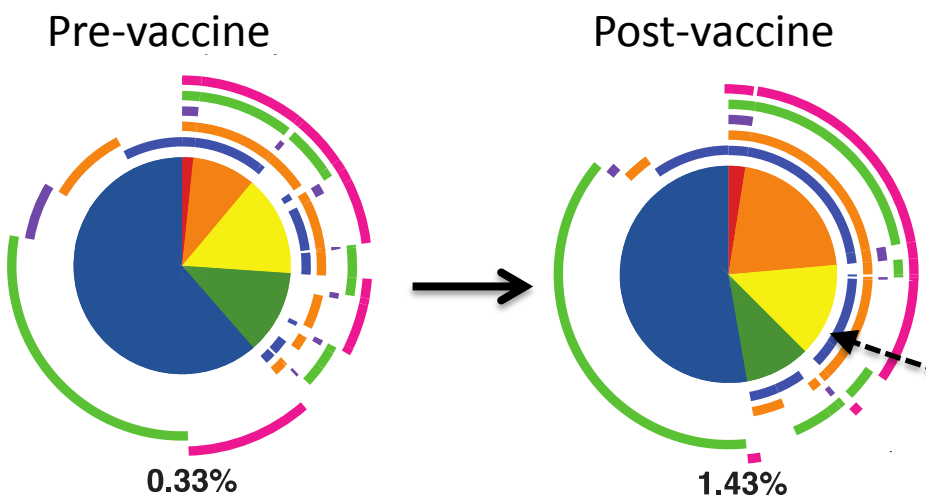
After Vaccination

increase in response size

+ increase in polyfunctionality

+ increased number of cells co-expressing IL-2, IFNγ, TNFα

LMP2 T-cells (CD8+)

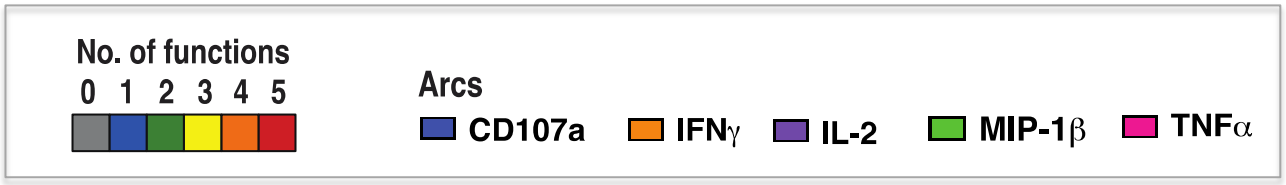


After Vaccination

increase in response size

+ increase in polyfunctionality

+ increased number of cytotoxic T cells (CD107a)

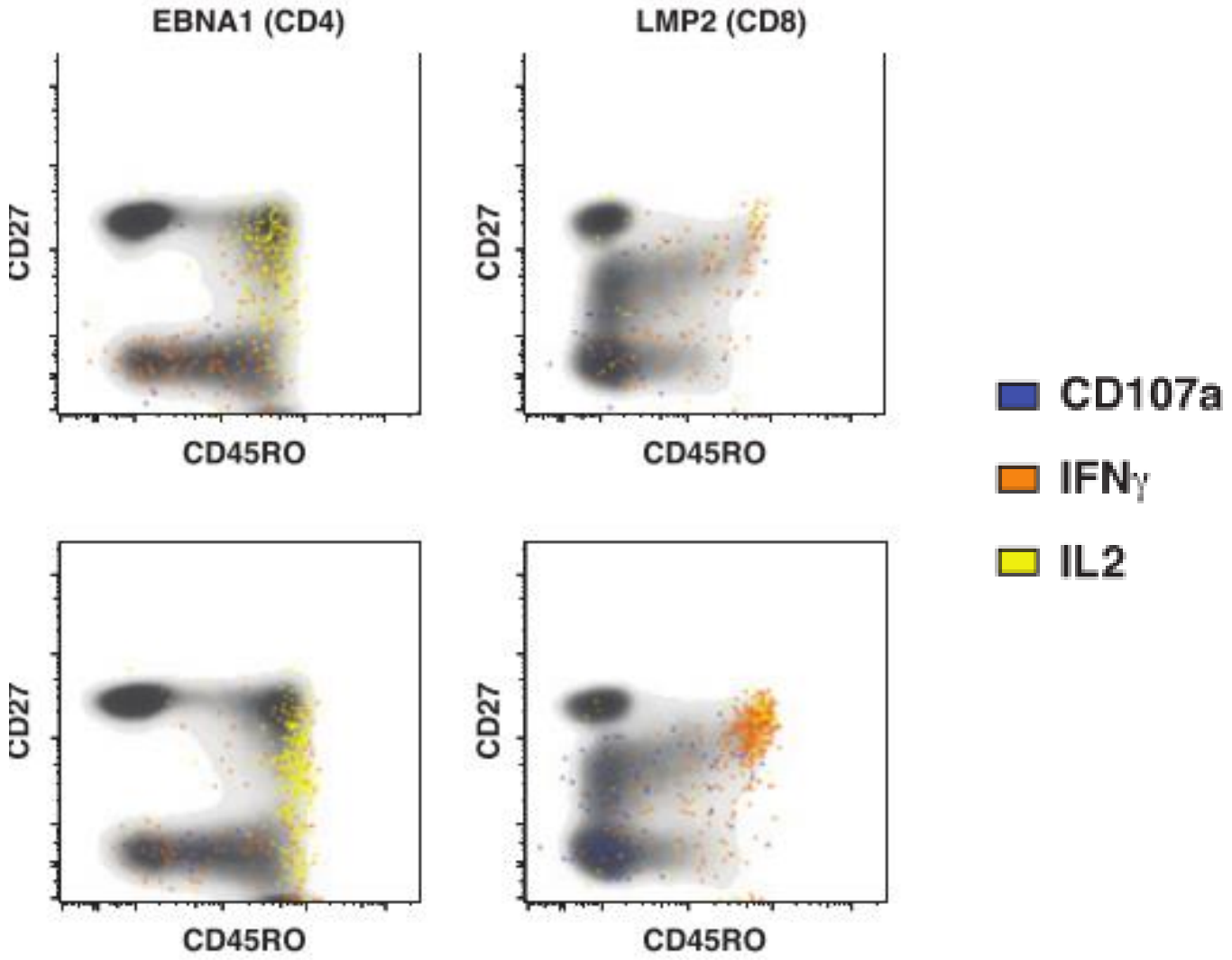


Taylor *et al.* 2014 Clinical Cancer Research

Anti-cancer effectors are not terminally differentiated post vaccination

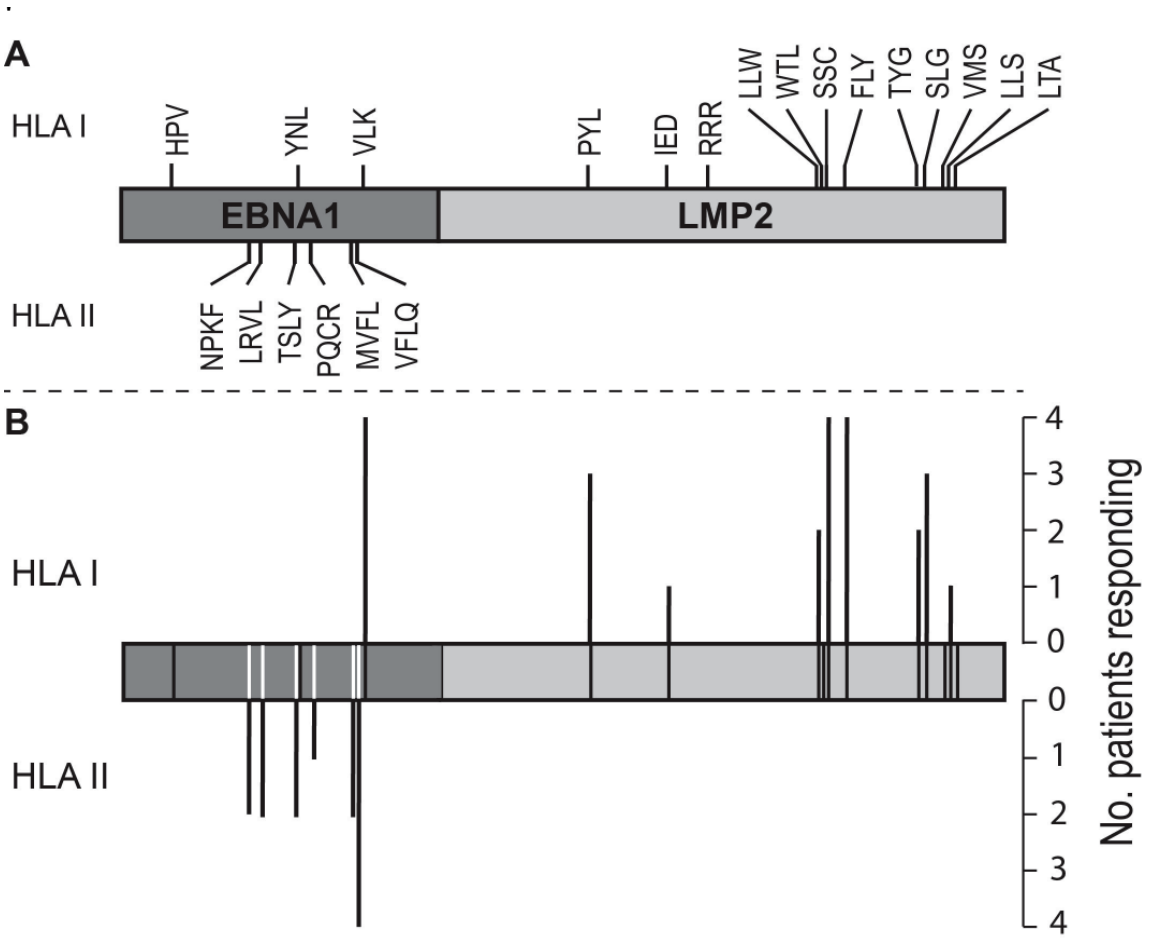
Pre-vaccination

Post-vaccination



Taylor *et al.* 2014 Clinical Cancer Research

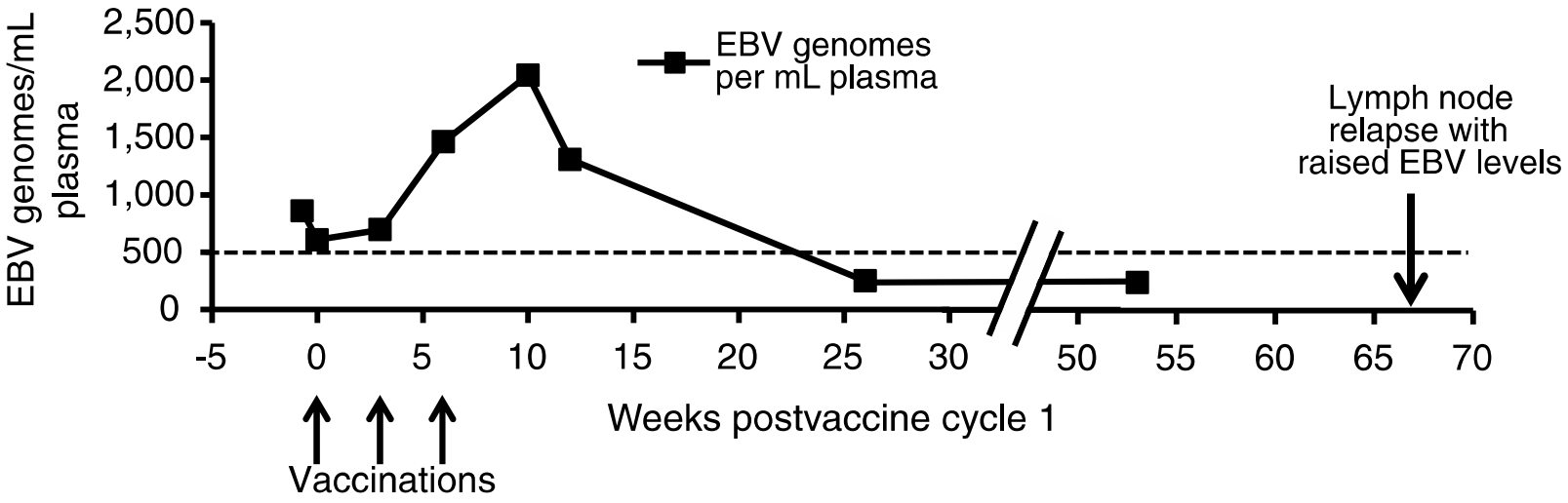
Vaccination elicits CD8 and CD4 T-cell responses to multiple epitopes in EBNA1 and LMP2



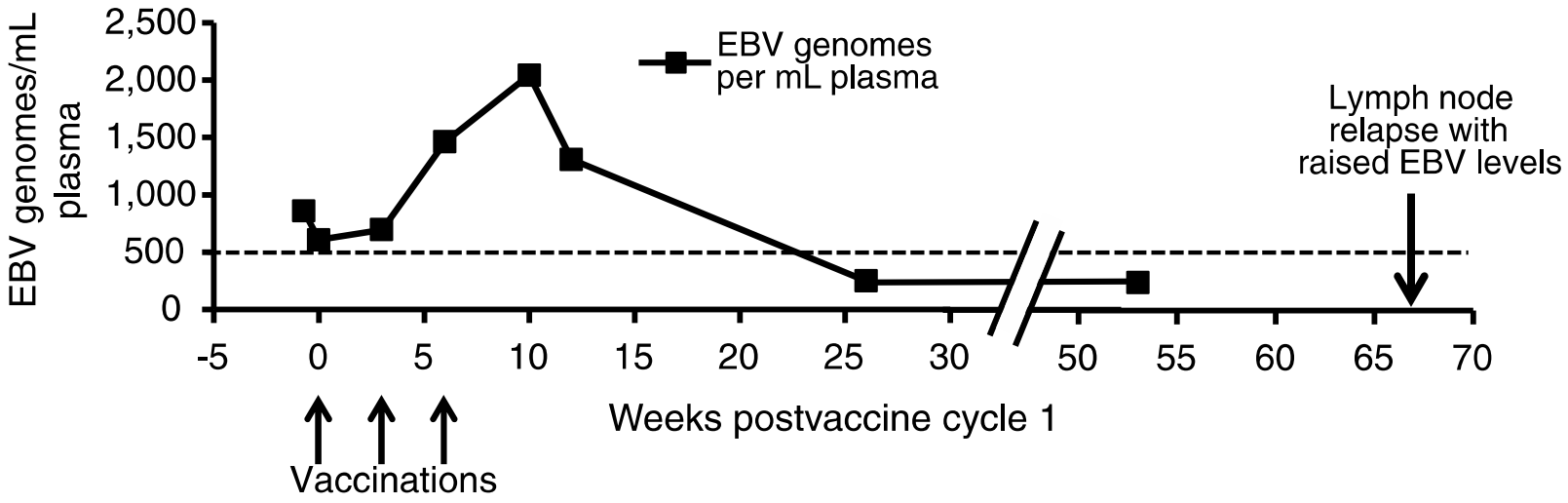
- T-cell responses achieved in NPC patients of European or Chinese ethnicity.

- T-cell responses restricted through wide range of HLA alleles:
  including common European (A*02.01) and Chinese (A*02.03, A*02.6, A*11, A*24) alleles.

Evidence of clinical response in a patient with low volume residual disease?



Evidence of clinical response in a patient with low volume residual disease?



- This patient's EBNA1 and LMP2 T-cell response declined over time.
- Some patients may require periodic re-vaccinations to maintain/boost immunity?

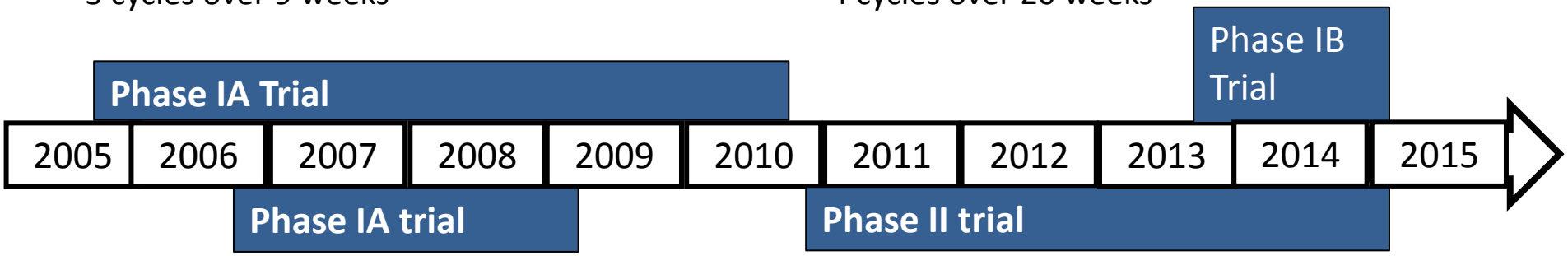
PARALLEL TRIALS IN UK AND CHINA

Phase IA Trial (UK)

- EBV+ cancer in remission or low volume stable recurrence
- Safety, immunogenicity
- 3+3 dose escalation vaccine
- n=16/18
- 3 cycles over 9 weeks

Phase IB Trial (UK)

- EBV+ cancer in remission or low volume stable recurrence or no standard therapy.
- Detailed immunogenicity
- Characterise immune memory
- Single arm Phase IB (n=18 NPC)
- 4 cycles over 20 weeks



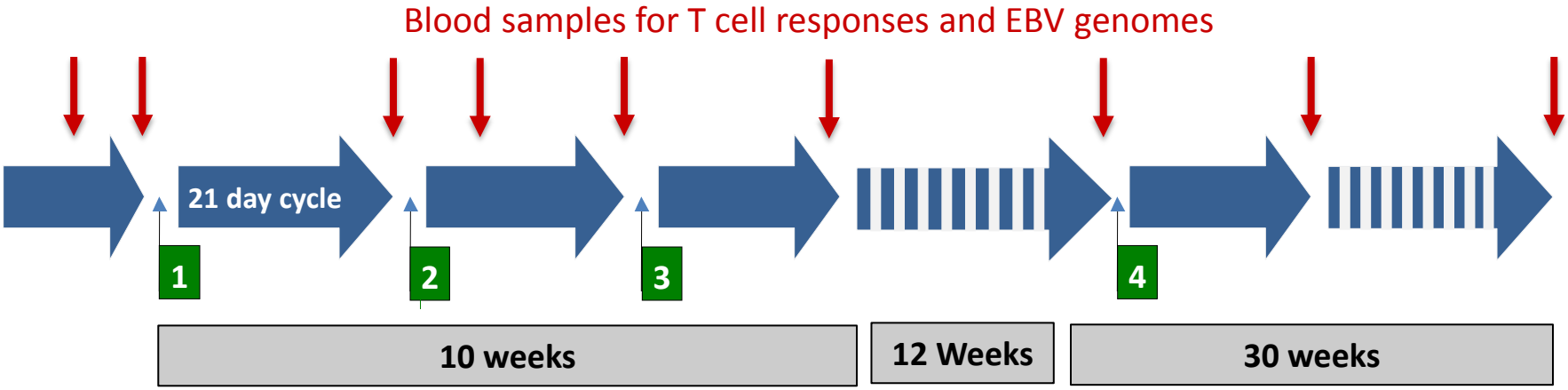
Phase IA Trial (Hong Kong)

- EBV+ NPC in remission or low volume stable recurrence
- Safety, immunogenicity
- 3+3 dose escalation vaccine
- n=18
- 3 cycles over 9 weeks

Phase II Trial (Hong Kong)

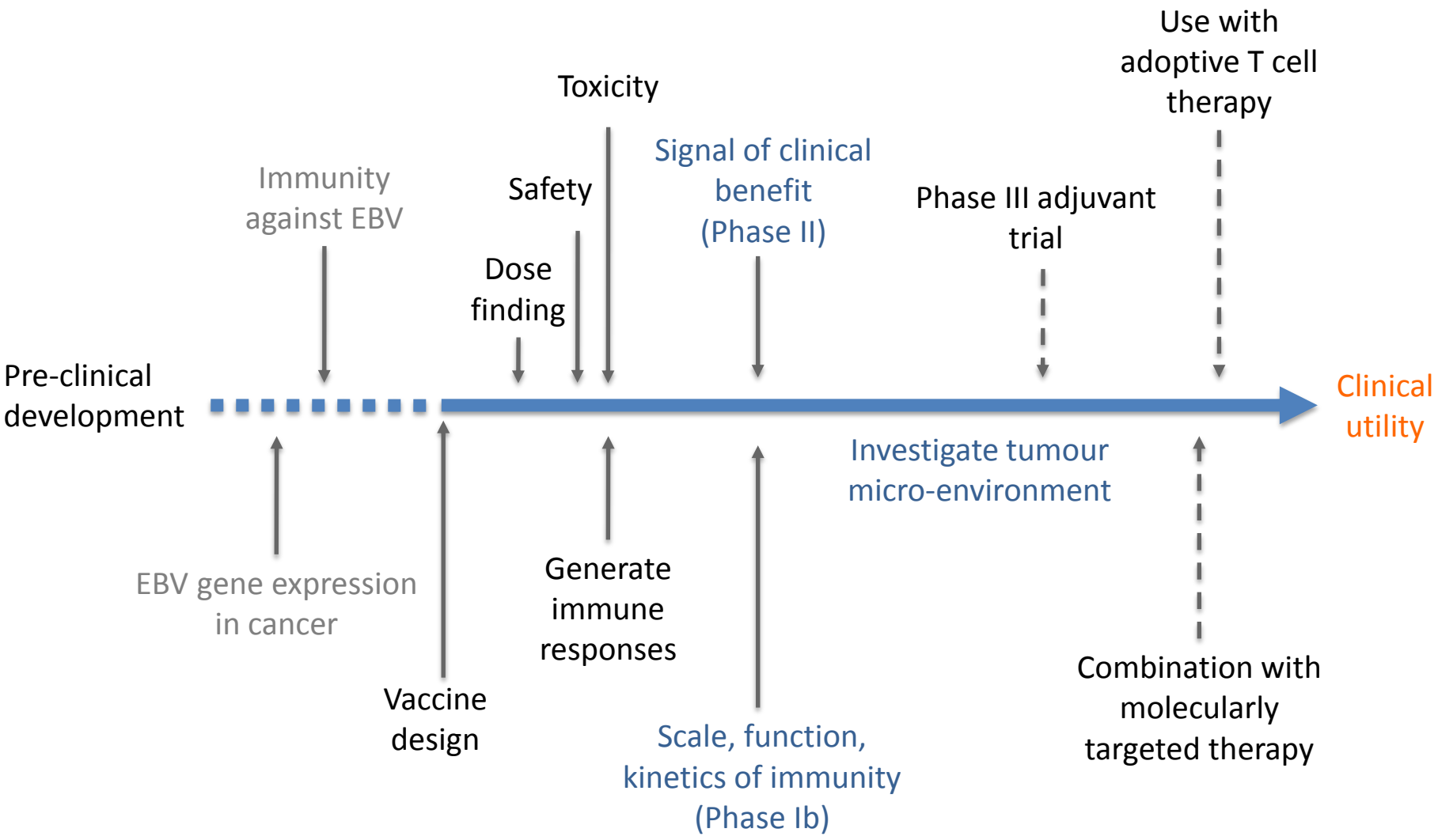
- Persistent, recurrent or metastatic EBV+ NPC
- Single arm phase II
- 6 cycles over 18 weeks
- n = 37; to discriminate between non progression rate of 50% (no benefit) and 70% (benefit)

OVERVIEW OF PHASE IB DESIGN



- Dose range: $5x10^8$ pfu.
- 4 vaccine cycles, 12 week interval between 3rd and 4th treatment.
- Blood samples taken before, during and after vaccination (up to 1 year).
- Measure EBV specific T cell responses (IFN-γ Elispot assay).
- Measure changes in the competence of EBV-specific T cells across vaccination

Development pathway



What about prophylactic vaccination to prevent EBV infection occurring?

"An ounce of prevention is worth a pound of cure"

Vaccinating against oncogenic viruses

Human papilloma virus

Nationwide vaccination programme in Australia for women aged 12-16 years between 2007-2009

High grade cervical abnormalities (women < 18 years)

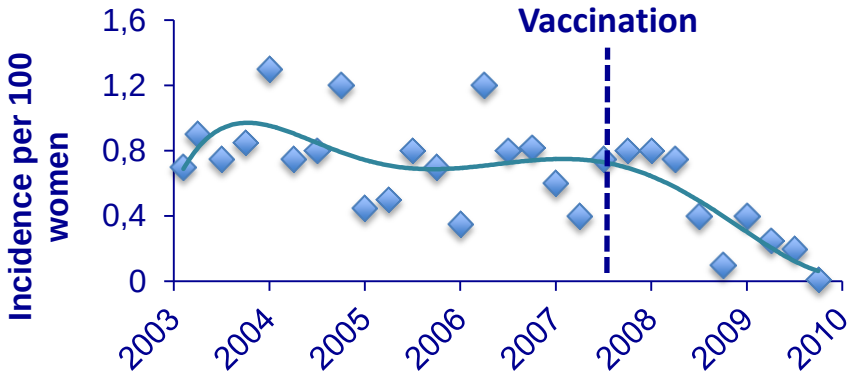


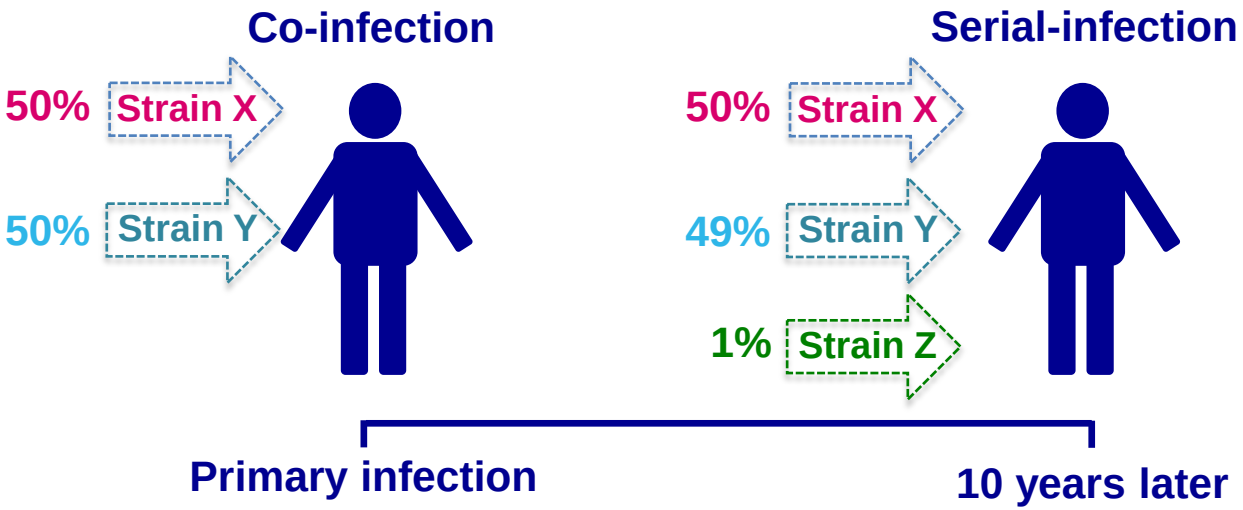
Figure adapted from: Brotherton (2011) Lancet Vol 377

Epstein Barr Virus (selected studies)

Publication	Formulation	EBV negative individuals examined	Protective effect?	Follow up
Gu 1995 Dev Biol Stand	gp220-340 Live vaccinia	9 infants vaccinated 10 infants placebo	20% of vaccinees but 100% of placebo seroconverted	16 mo
Moutschen 2007 Vaccine	gp350 Sub-unit	110 adults (no placebo)	10% seroconverted **1 report of IM**	7 mo
Sokal 2007 J Infect Dis	gp350 Sub-unit	88 adults vaccinated 90 adults placebo	15% vaccinees 20% placebo seroconverted **78% efficacy preventing IM**	18 mo

The selected results emphasize seroconversion but protection from IM in healthy individuals who receive a vaccine

Does natural immunity conferred by primary EBV infection protect against re-infection with other types or strains of EBV?



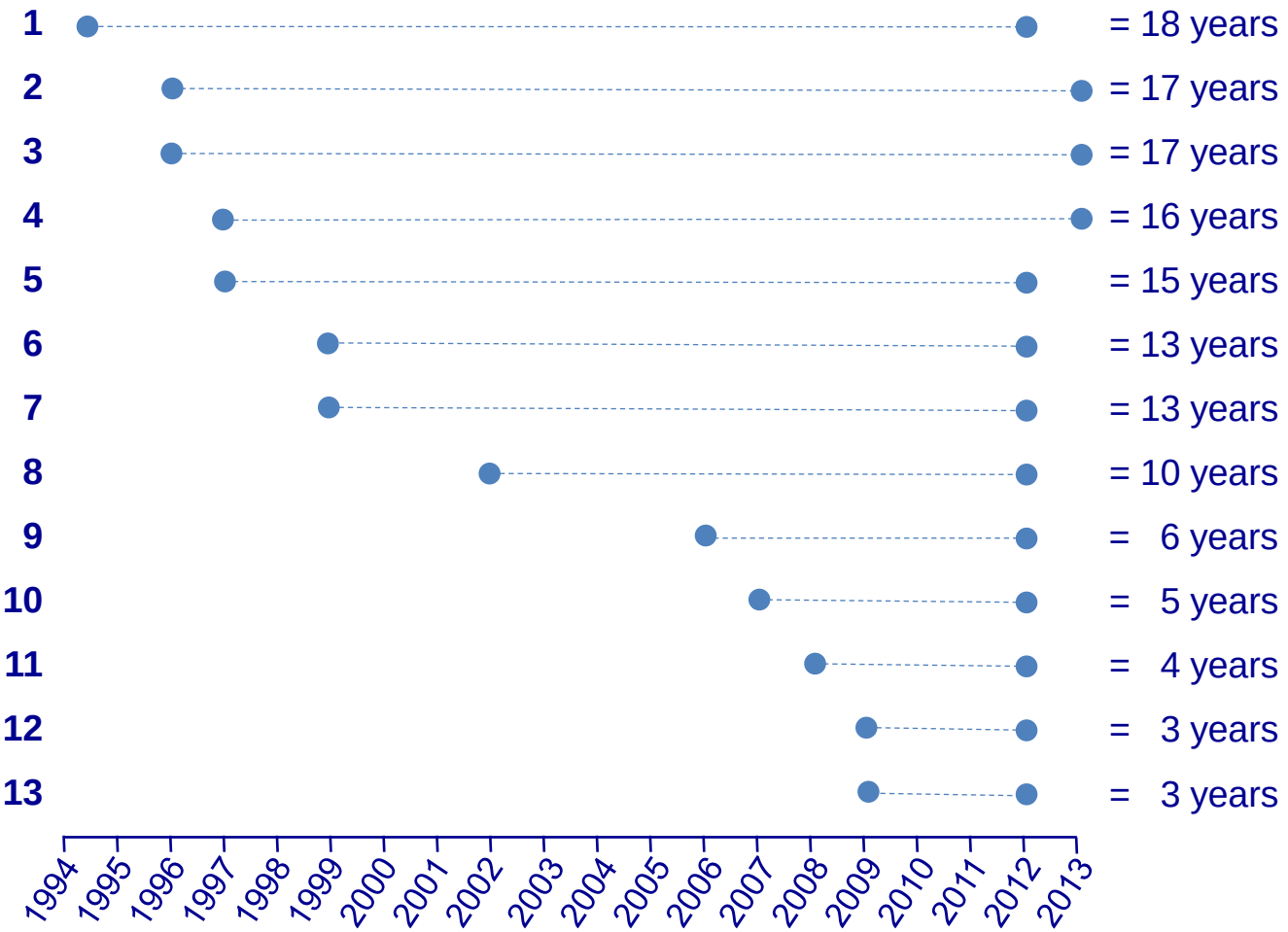
Study cohort

Donors who have had infectious mononucleosis

n = 13

Mean follow up: 11 years

= sample



PHASE 1 TRIALS

University of Birmingham
Hui Jia
Alan Rickinson
Neil Steven

The Institute of Cancer Research
Kevin Harrington

Paterson Institute for Cancer Research
Lip Wai Lee

The Chinese University of Hong Kong
Edwin Hui
Anthony Chan

Cancer Research UK
Ceri Edwards

PHASE 1b & 2

University of Birmingham
Hui Jia
Alan Rickinson
Neil Steven

The Institute of Cancer Research
Kevin Harrington

Paterson Institute for Cancer Research
Lip Wai Lee

Cancer Research UK
Ceri Edwards
Uzma Rayani

Ymddiriedolaeth GIG Felindre / Velindre NHS Trust
Mererid Evans

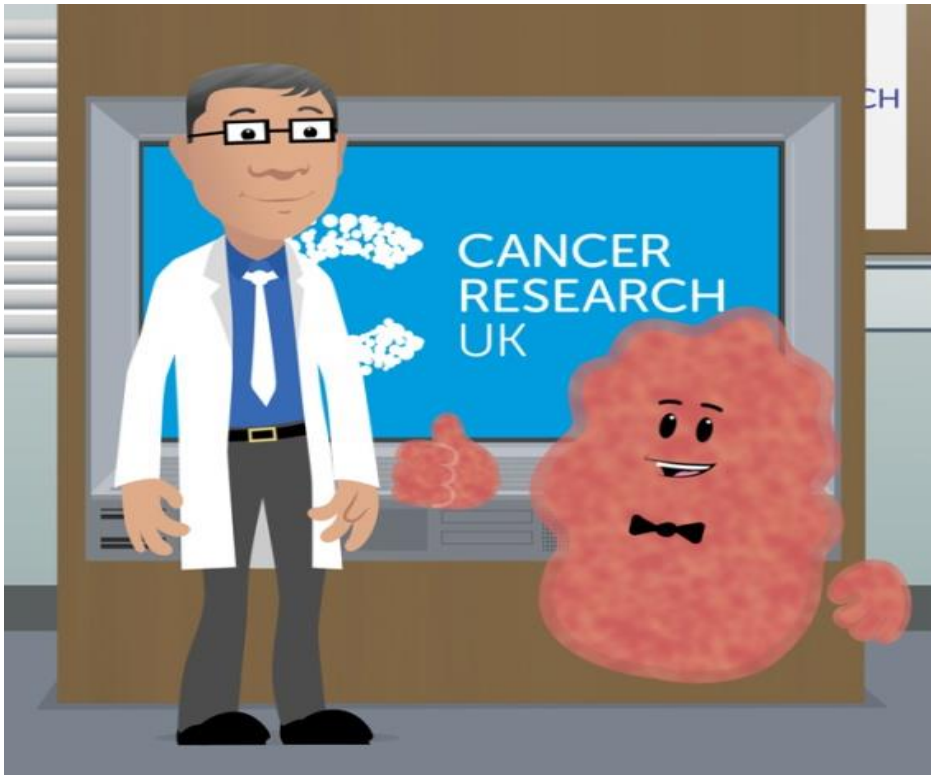
UCL
M. Foster

The Chinese University of Hong Kong
Edwin Hui
Anthony Chan

The Kadoorie Charitable Foundation 嘉道理慈善基金會

University of Liverpool
Terry Jones

NHS Greater Glasgow and Clyde
Mohammed Rizawanullah



Agent EBV: Helping the immune system fight cancer

Please support our clinical trial developing
a new treatment for cancer patients.

www.FightingEBV.org

CANCER
RESEARCH
UK