Nasopharyngeal cancer - adoptive immunotherapy and vaccines

Dr Neil Steven

Clinical Senior Lecturer in Medical Oncology
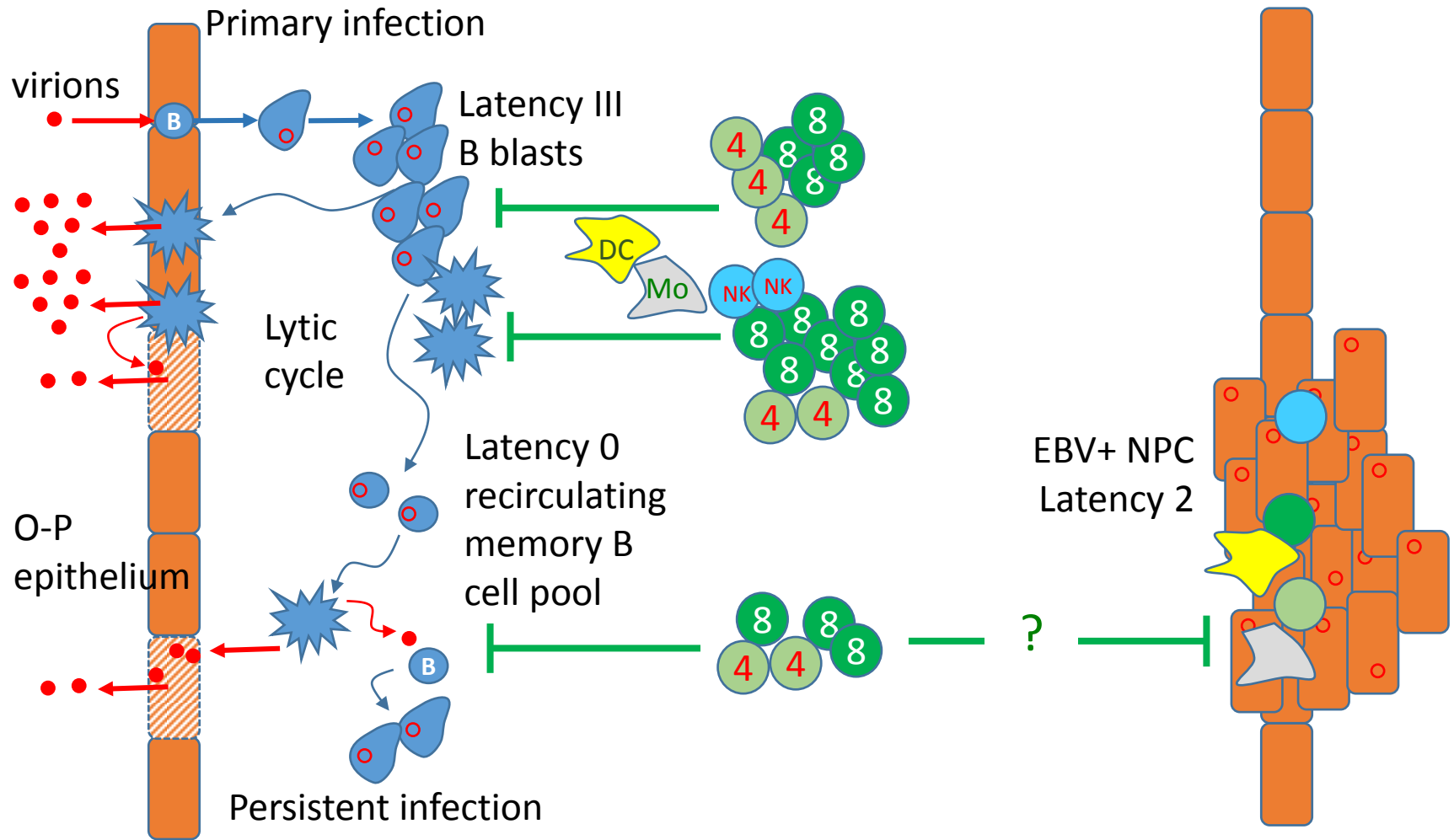
Deputy Clinical Director, Cancer Research UK Clinical Trials Unit, Birmingham
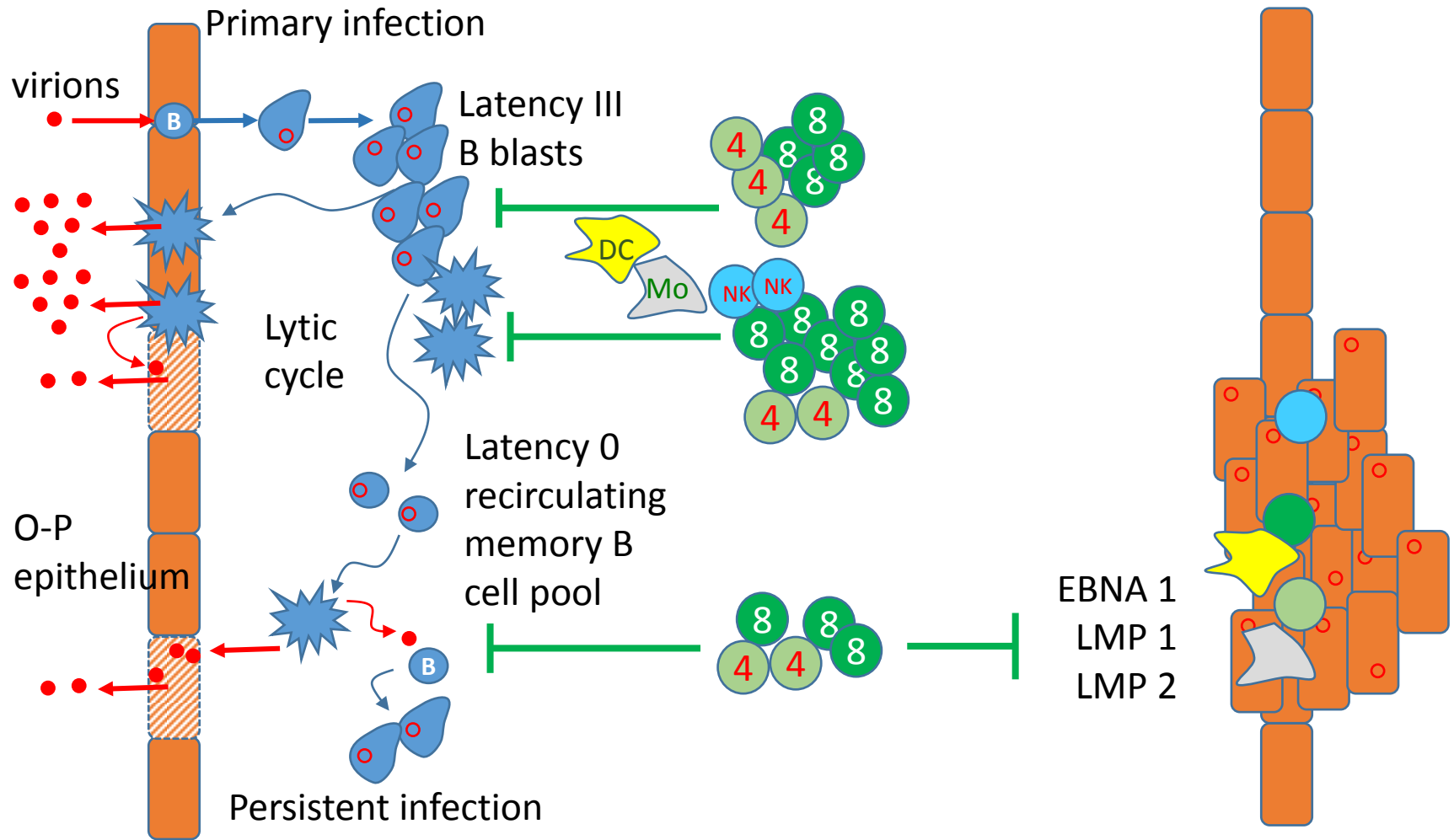
n.m.steven@bham.ac.uk

Disclosure slide

- Advisory boards – Roche, GSK (now Novartis), Amgen, Merck
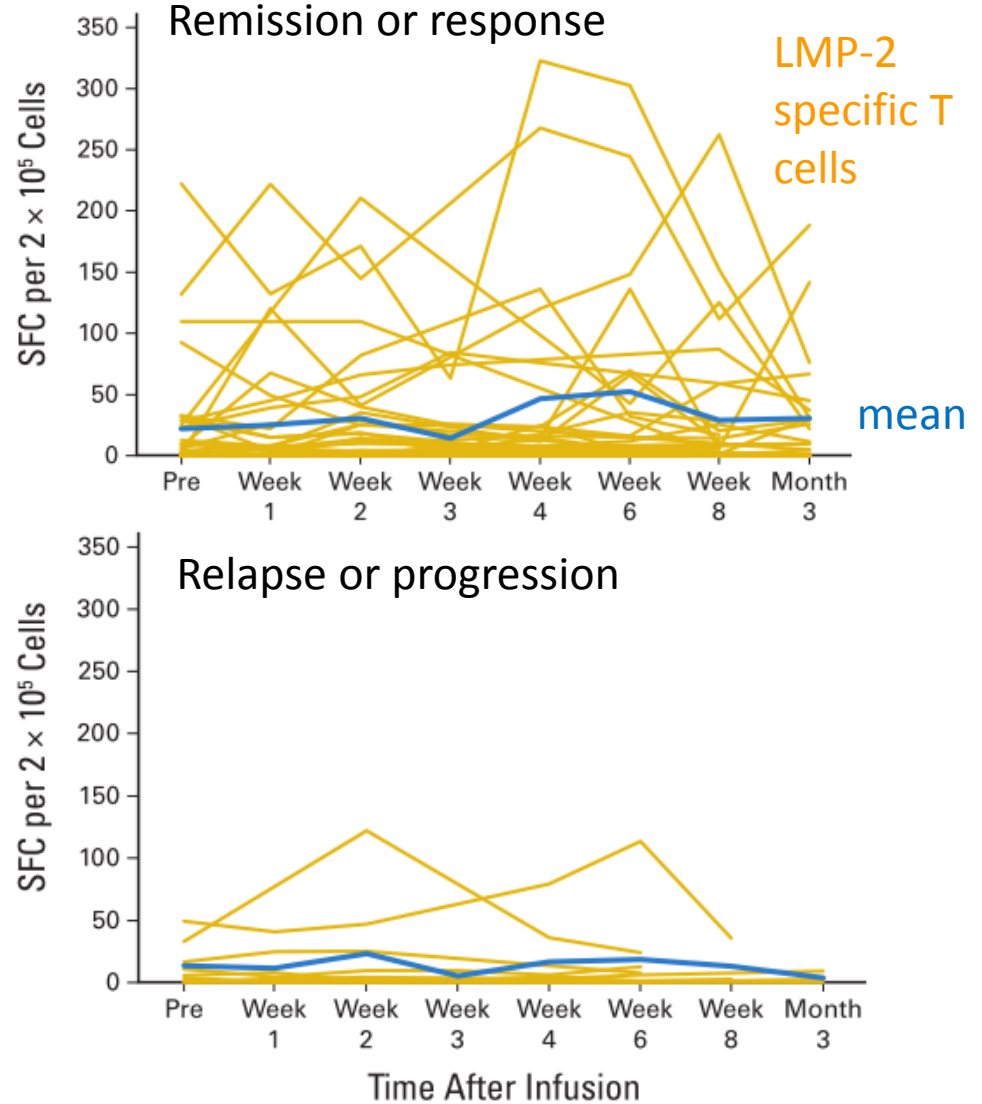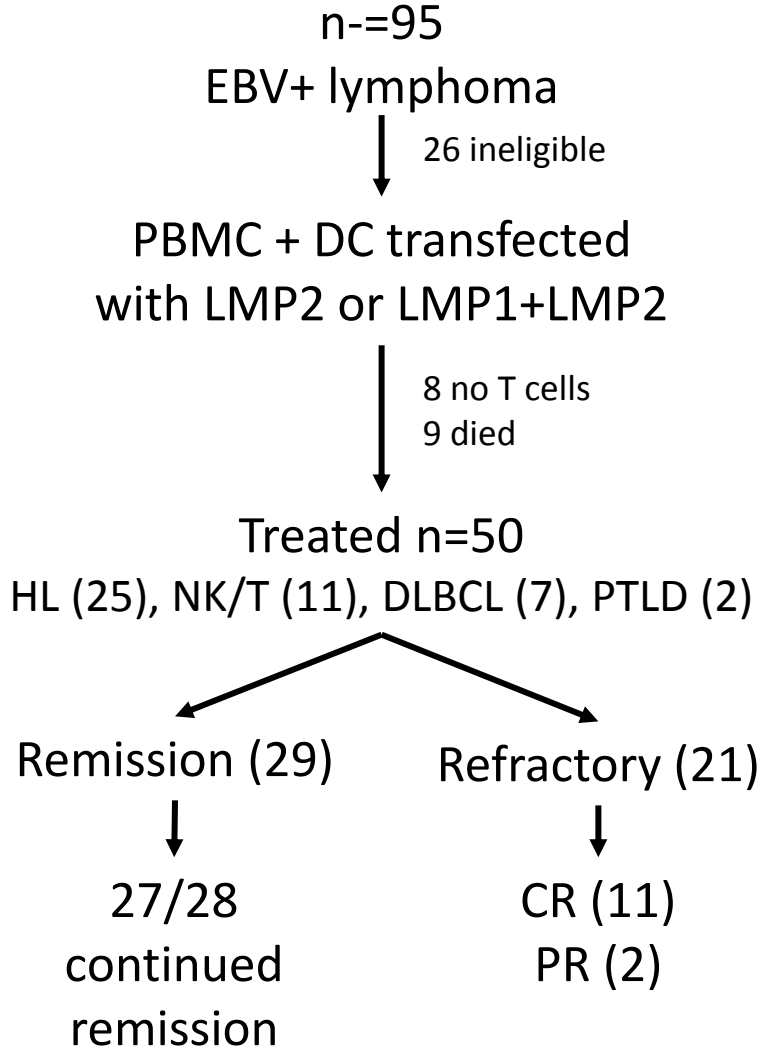- Educational services for Amgen

Immune control of primary and latent Epstein-Barr virus infection

Immune control of primary and latent Epstein-Barr virus infection

T cell therapy induces major responses

n-=95
EBV+ lymphoma

26 ineligible

PBMC + DC transfected
with LMP2 or LMP1+LMP2

8 no T cells
9 died

Treated n=50
HL (25), NK/T (11), DLBCL (7), PTLD (2)

Remission (29) → Refractory (21)

27/28
continued
remission

CR (11)
PR (2)

Remission or response

LMP-2 specific T cells

mean

Relapse or progression

Bollard JCO 2014;32:798
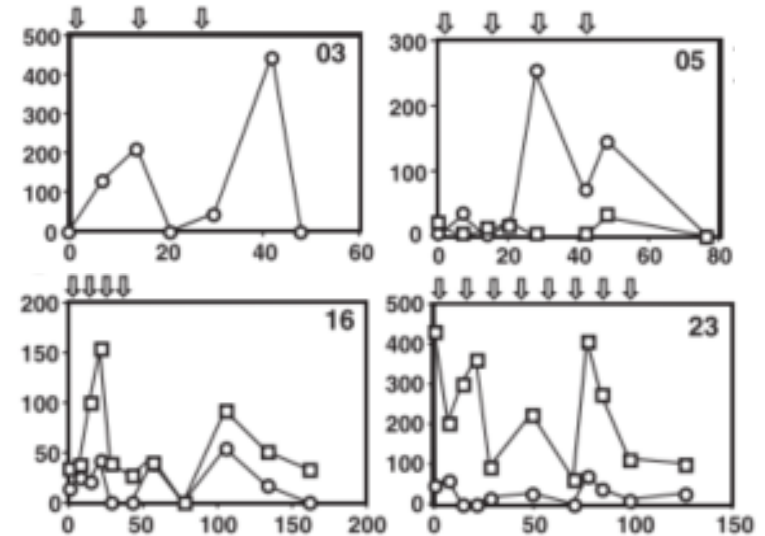
T cell therapy in NPC

n-=22
Recurrent or
metastatic UNPC

↓

PBMC + DC
transfected
LMP1+2 epitopes
+ EBNA1ΔGA
(n=16)

↓

3-8 infusions
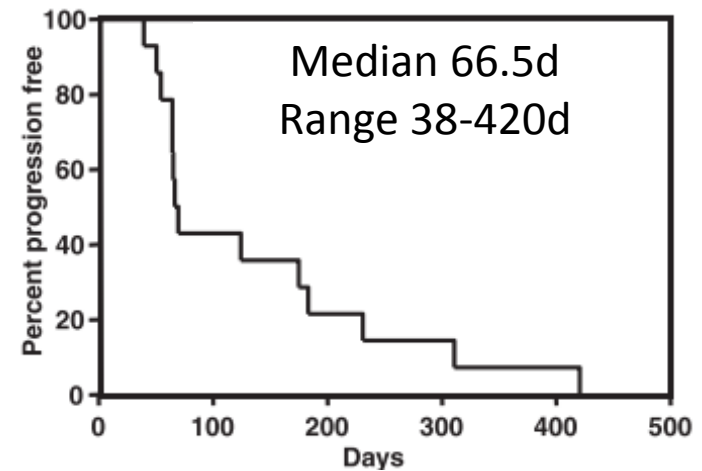2-3x10^7 / infusion
(n=14)

↓

SD 10/14

Smith Can Res 2012;72:1116

Expanded EBV-
specific T cell lines
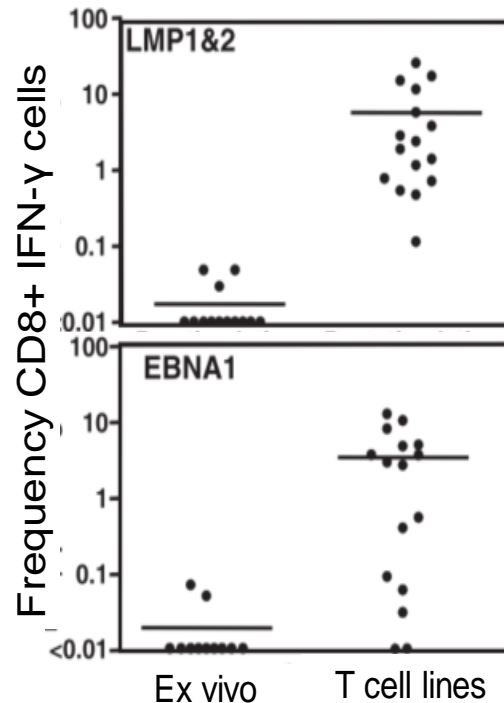
Measurable EBV-specific
effectors post-infusion

Time to progression

Median 66.5d
Range 38-420d

A brief history of EBV-directed immunotherapy

Vaccination

Lin 2002
NPC n=16
IL4-GMCSF-TNF-
DC+peptide
2PR
Immunogenic

Chia 2011
NPC n=16
Ad-ΔLMP1-LMP2 DC
9/12 DTH+, no LMP resp.
Median PFS 1.9m
1 PR 2 SD

Hui 2013, Taylor 2014
NPC n=32 adjuvant
MVA EBNA1/LMP2
Immunogenic

1998 | 2002 | 2005 | 2010 | 2011 | 2012 | 2013 | 2014

Comoli 2005
NPC n=10
EBV LCL T cells
2 PR, 4 SD, 4 PD

Louis 2011
NPC n=23
EBV LCL T cells
5/8 continued remission
5 CR, 2 PR, 2 SD, 6 PD

Smith 2012
NPC n=14
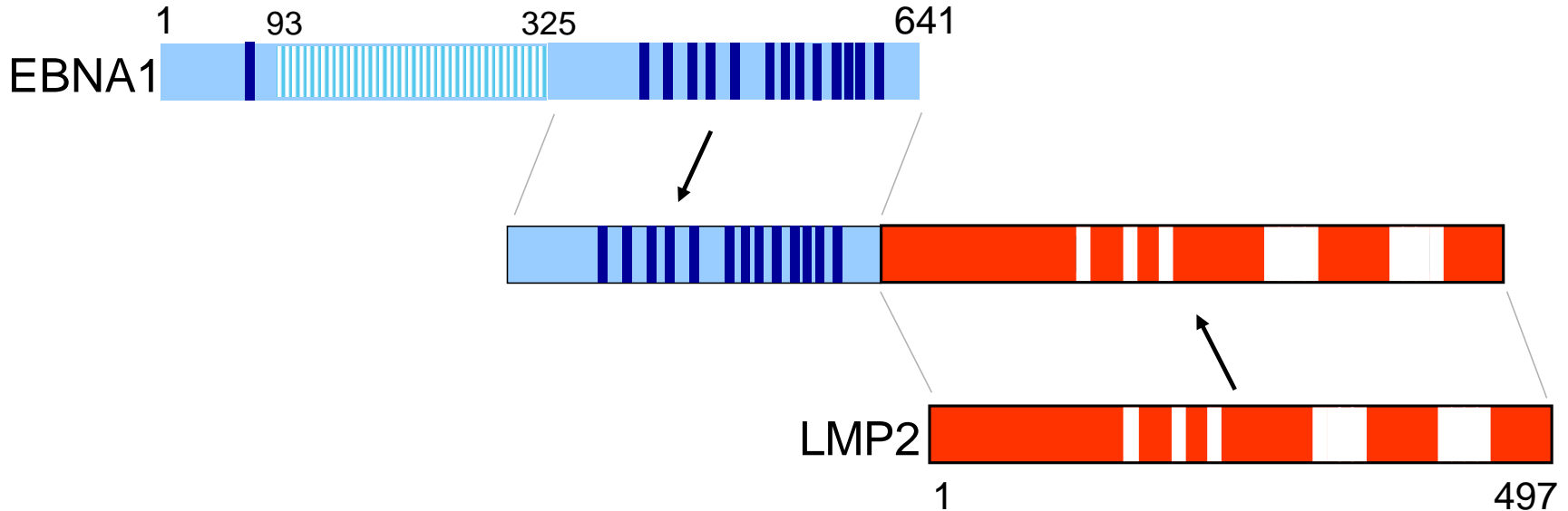Ad-LMP-DC T cells
10 SD
Median TTP 66.5d

Bollard 2014
Lymphoma n=50
21 current disease
Ad- Δ LMP1-LMP2
DC T cells
11 CR; 2PR

T cell infusion
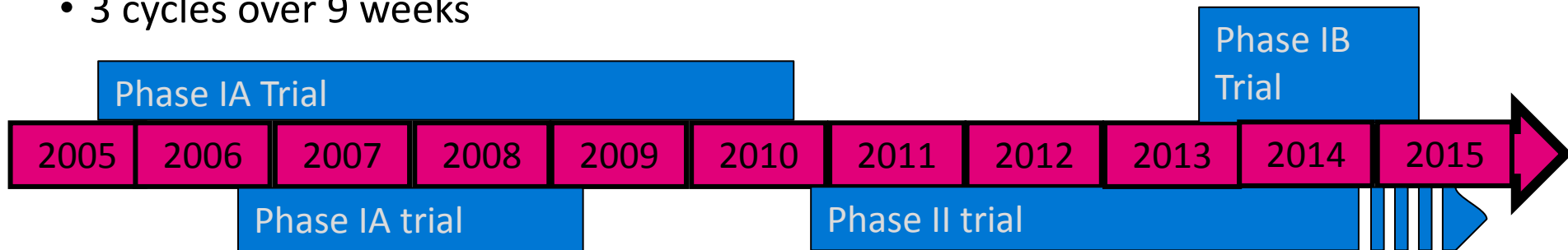
MVA-EBNA1/LMP2: A therapeutic vaccine

- Contains class I epitopes (white) and class II epitopes (blue)

- An immunogenic attenuated replication-defective vaccinia virus vector

- Fusion protein transports EBNA1 to endo/lysosomal pathway, enhancing antigen presentation

Taylor GS et al

Journal of Virology 2004; 78:768-78.

Parallel trials in UK and Hong Kong

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

2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015

Phase IA Trial

Phase IB Trial

Phase IA trial

Phase II trial

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

CANCER RESEARCH UK

The Chinese University of Hong Kong

SINGAPORE 2015 ESMO ASIA 18-21 DECEMBER SINGAPORE

Broad CD8+ and CD4+ T-cell responses to vaccination in *ex vivo* immune assays

Hui EP, Taylor GS et al
Cancer Res. 2013;73(6):1676-88
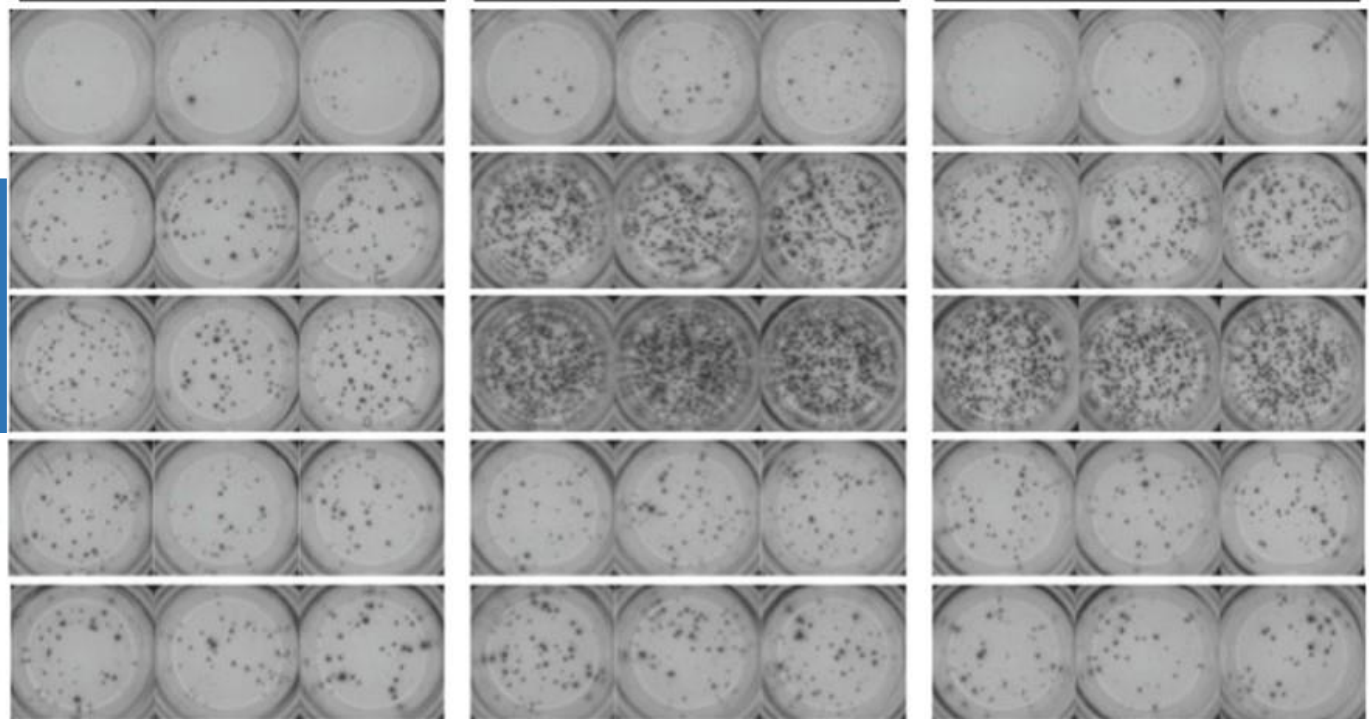
Dose selected for further study

	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 a vaccine-induced EBNA1 and/or LMP2 T-cell response.

EBNA1 T cell response
$R^2 = 0.35$
$P = 0.01$
Vaccine dose (pfu)

LMP2 T cell response
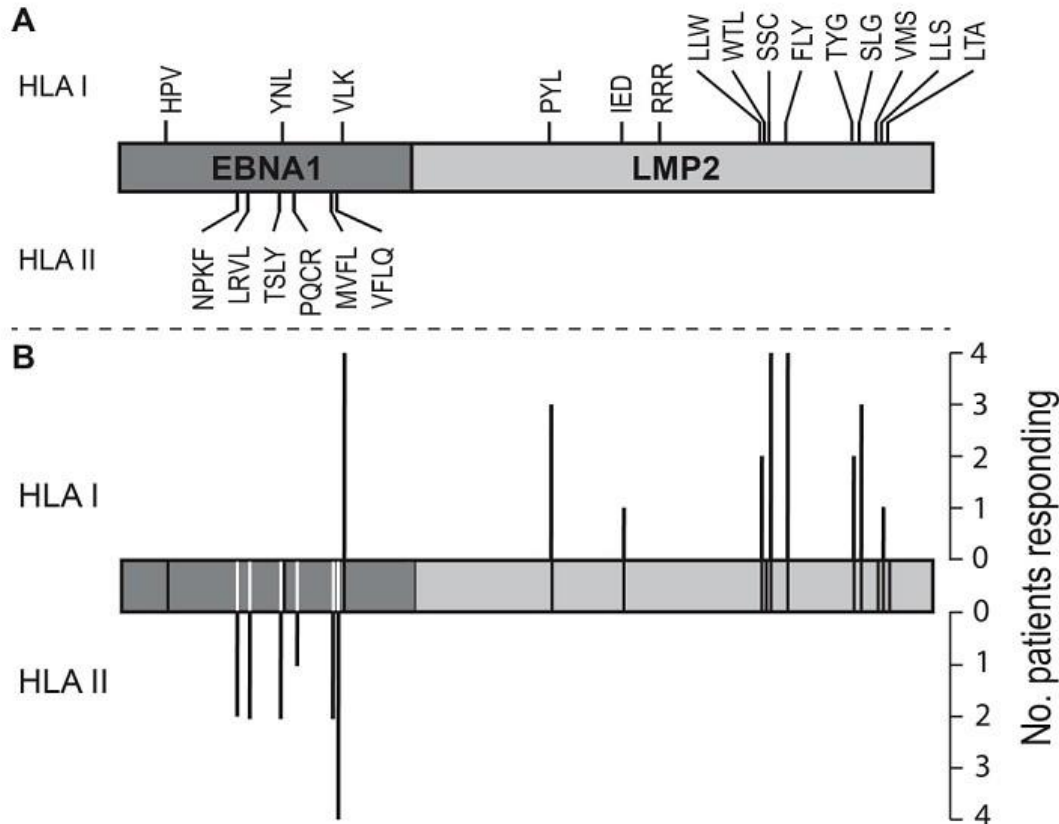$R^2 = 0.48$
$P = 0.03$
Vaccine dose (pfu)
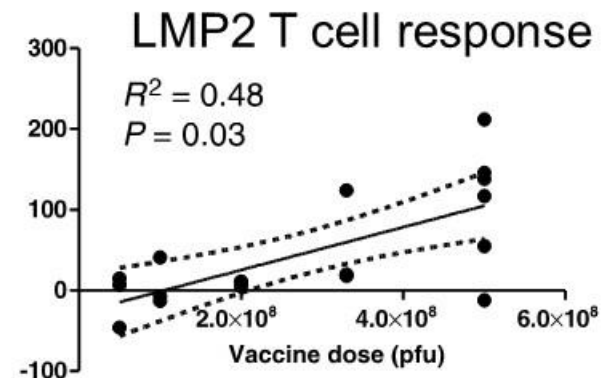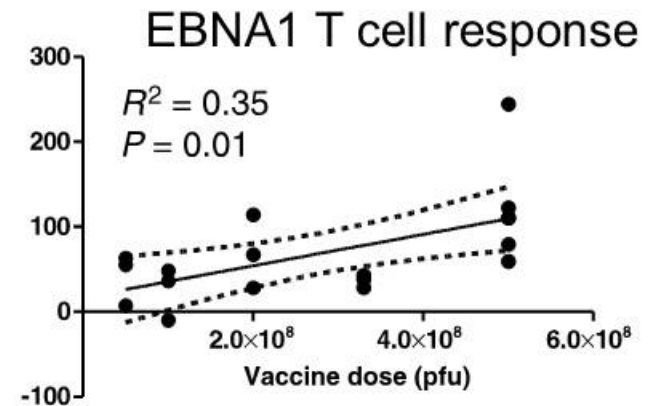
Taylor GS et al. Clin Cancer Res. 2014;20(19):5009-22

The vaccine is widely applicable

Responses in NPC patients of European or Chinese ethnicity

Responses to multiple epitopes in EBNA1 and LMP2

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.

Parallel trials in UK and Hong Kong
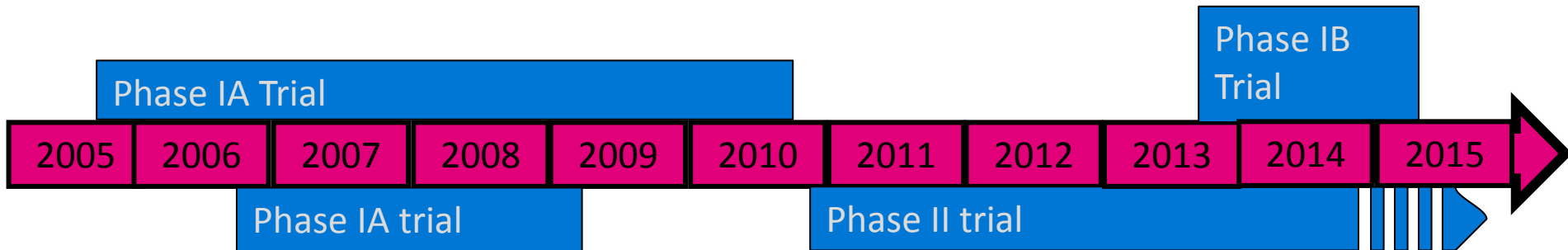
Phase IB Trial (UK)
EBV+ cancer in remission <u>or</u> low volume stable recurrence
Detailed immunogenicity
Characterise immune memory
Single arm Phase IB (n=18 NPC)
4 cycles over 20 weeks

Phase IB Trial

Phase IA Trial

| 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 |

Phase IA trial

Phase II trial

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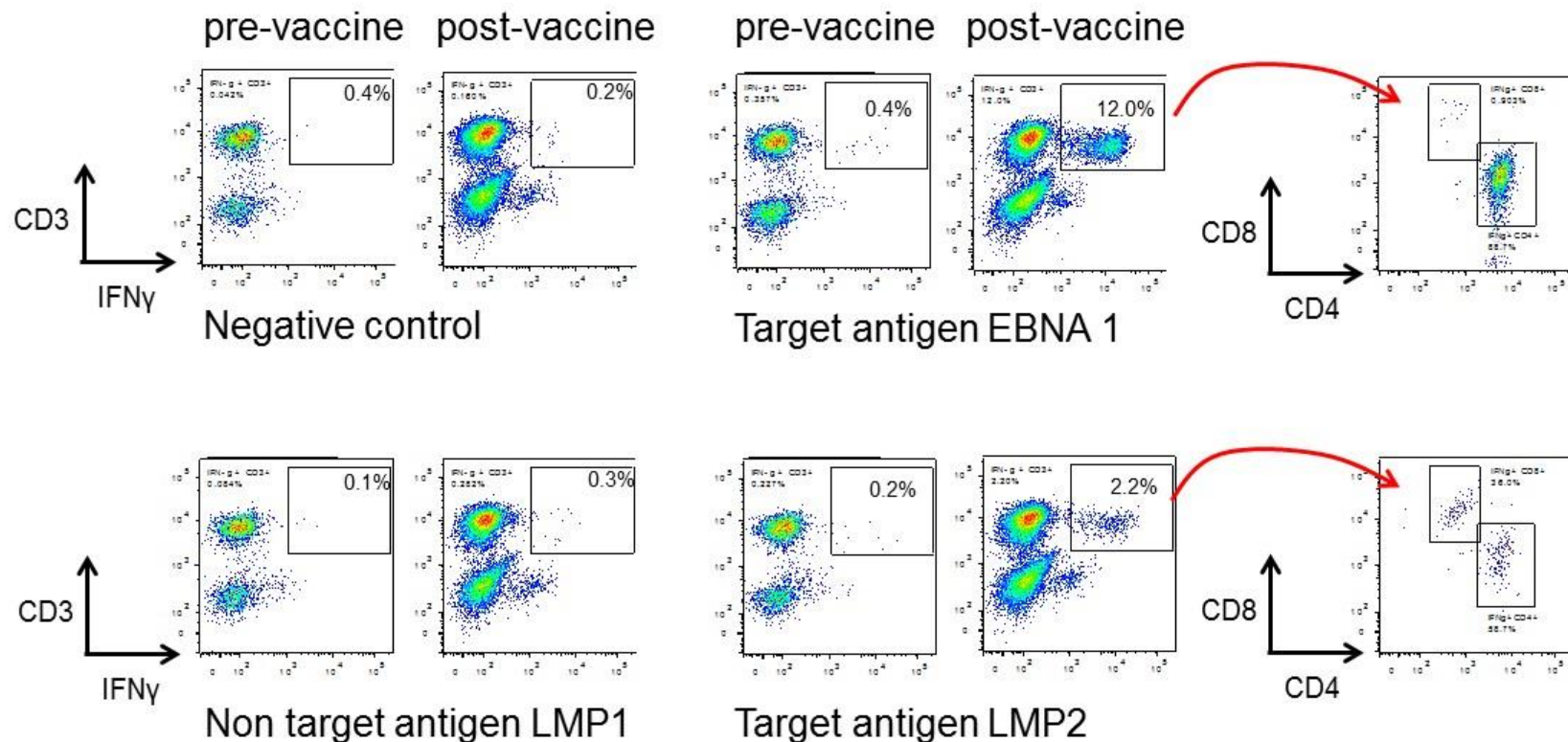n = 37; to discriminate between non progression rate of 50% (no benefit) and 70% (benefit)

CANCER RESEARCH UK

The Chinese University of Hong Kong

SINGAPORE 2015 ESMO ASIA 18-21 DECEMBER SINGAPORE

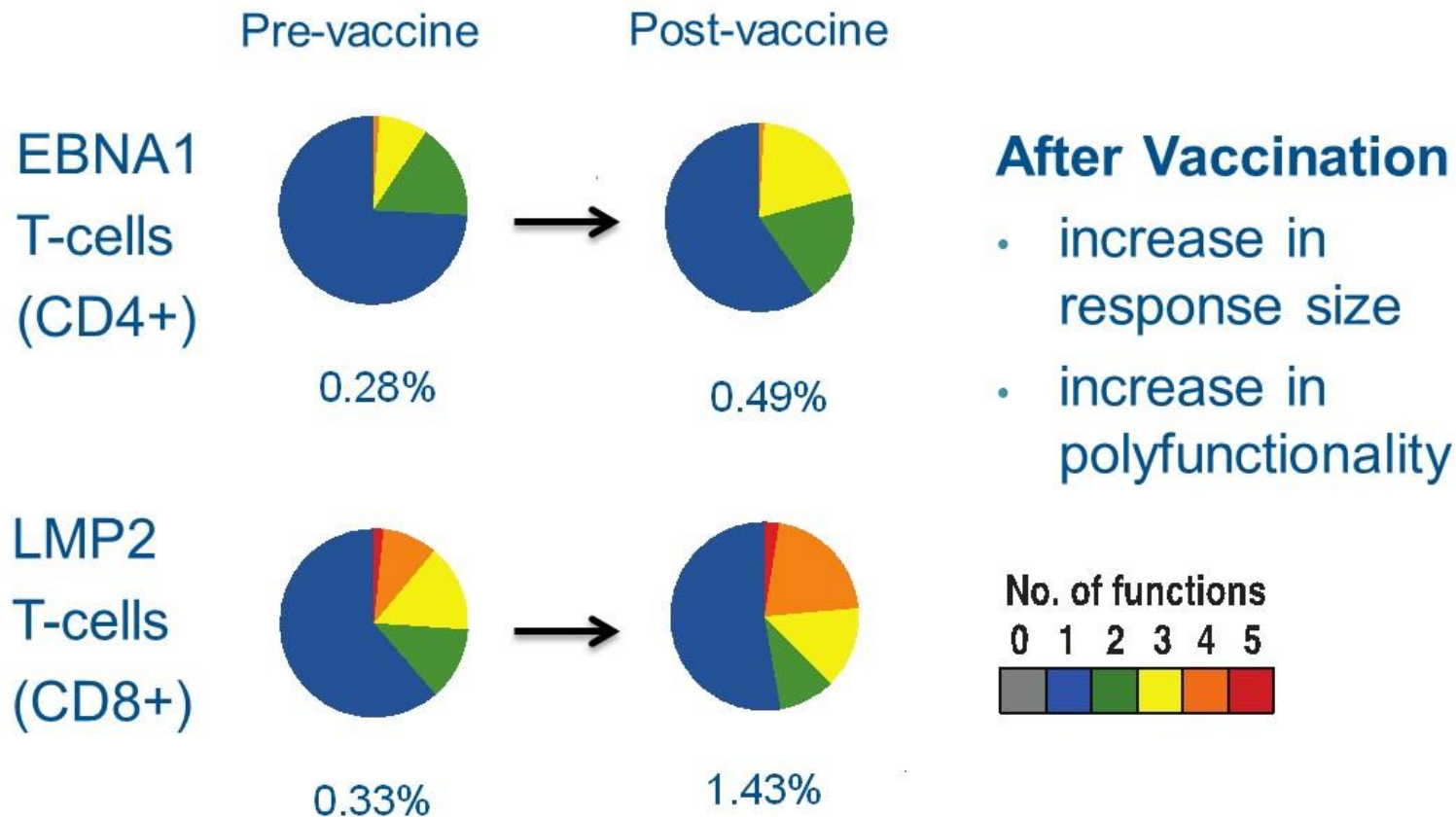# Responses after chemoradiotherapy, below limit of detection in ex vivo assays, can amplify after vaccination

UK Phase Ib trial, 80 year old patient, remission. Single dose 5×10^8 vaccine
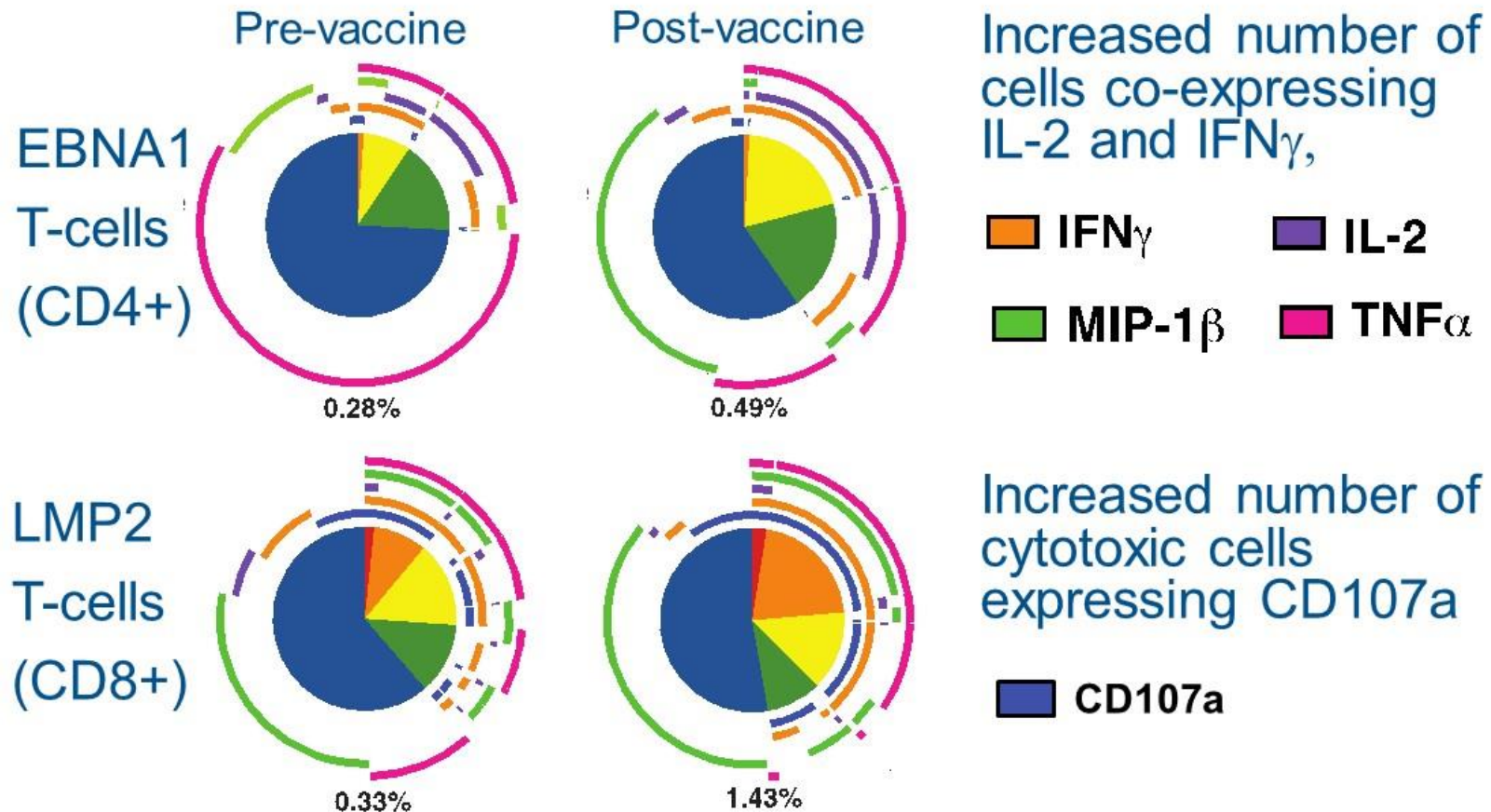
Undetectable ex vivo response to vaccination

In vitro stimulation and culture and detection of IFNγ cells by flow cytometry

Vaccination increases immune response quality (*ex vivo* assay)
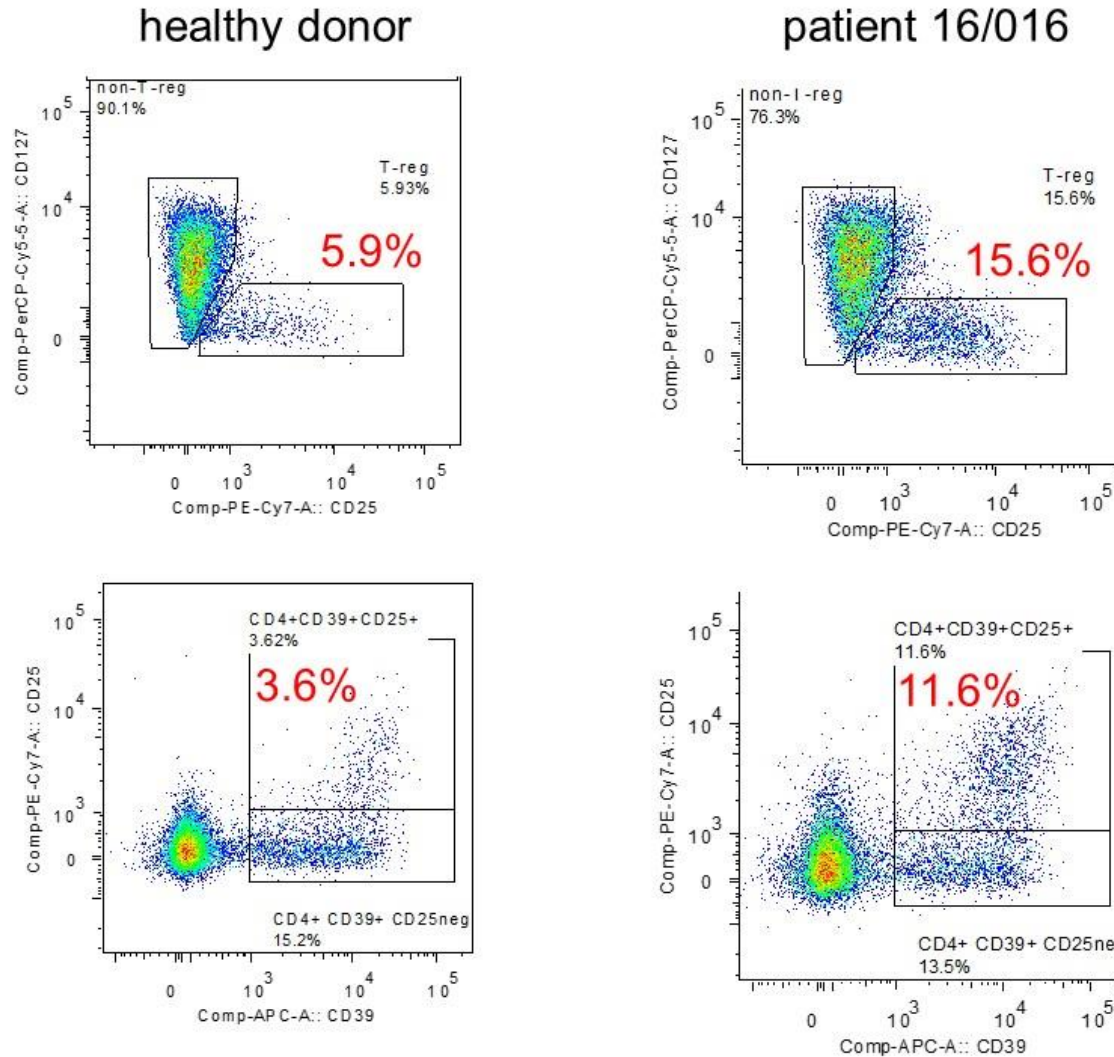

Pre-vaccine   Post-vaccine

EBNA1 T-cells (CD4+)
0.28%   0.49%

LMP2 T-cells (CD8+)
0.33%   1.43%

After Vaccination
- increase in response size
- increase in polyfunctionality

No. of functions
0 1 2 3 4 5

Vaccination increases immune response quality (*ex vivo* assay)

Pre-vaccine · Post-vaccine

EBNA1 T-cells (CD4+)

0.28% · 0.49%

LMP2 T-cells (CD8+)

0.33% · 1.43%

Increased number of cells co-expressing IL-2 and IFNγ,

IFNγ · IL-2 · MIP-1β · TNFα

Increased number of cytotoxic cells expressing CD107a

CD107a

Regulatory T-cells increased in NPC patients

healthy donor — patient 16/016

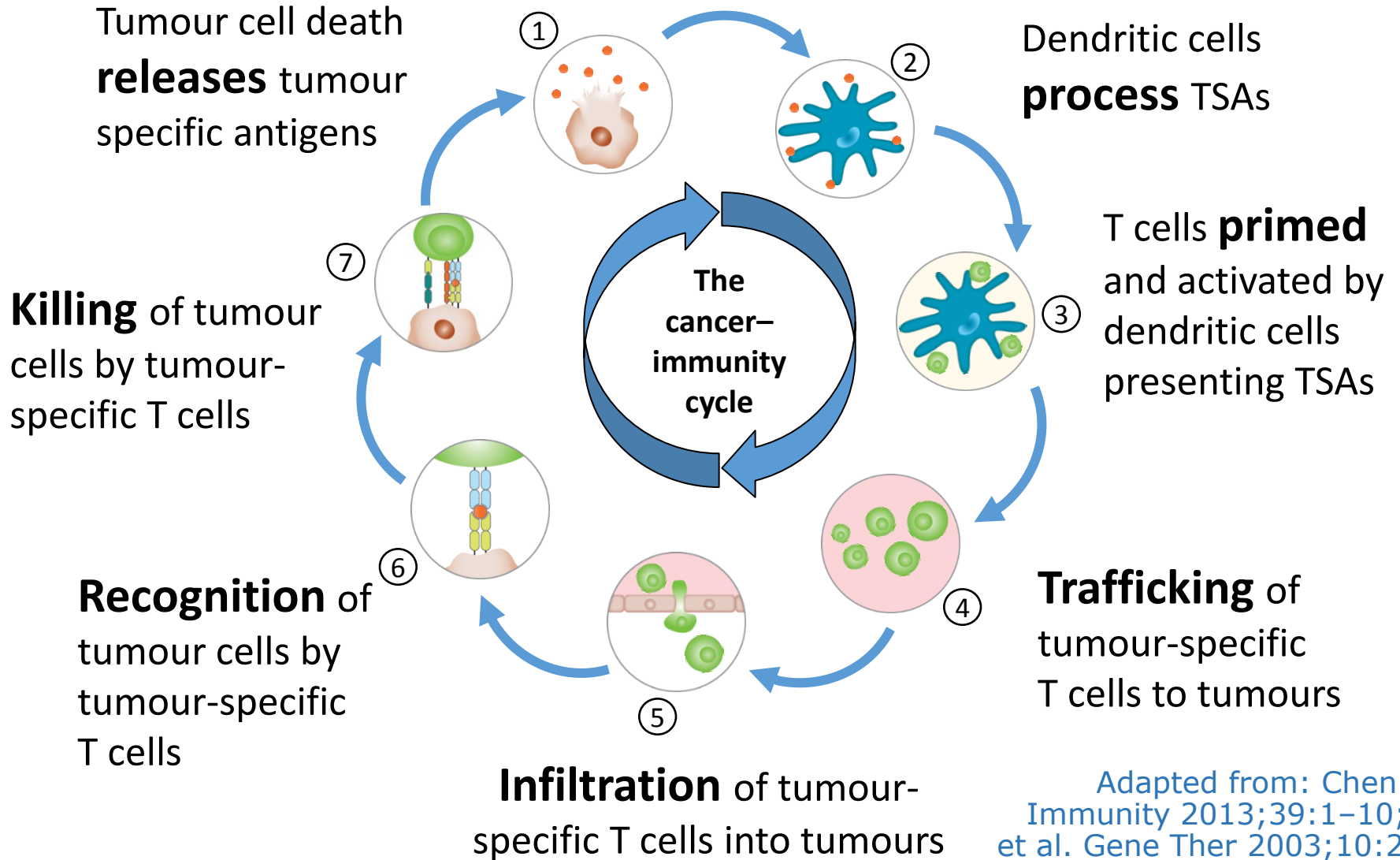# Vaccination stimulates EBNA1 and LMP2 T-cell responses despite high T-reg numbers
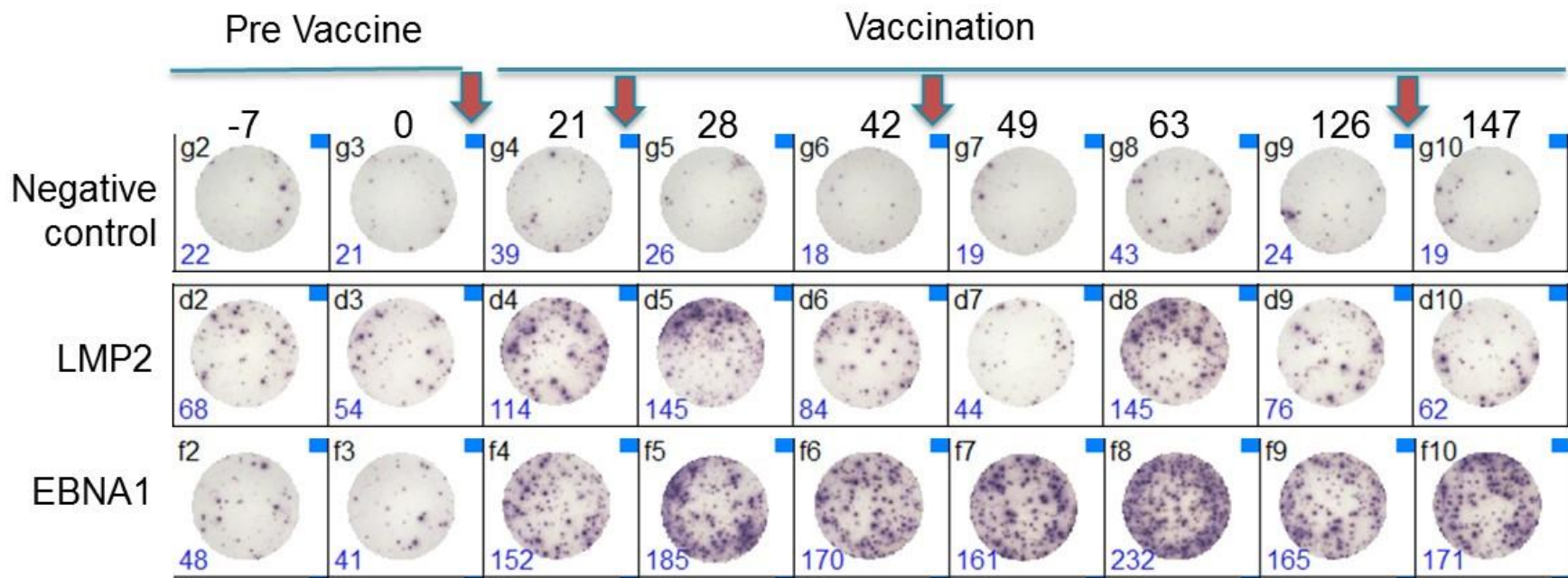
Patient 16/016 UK Phase Ib, 5×10^8 pfu, ex vivo IFN-g ELIspot assay
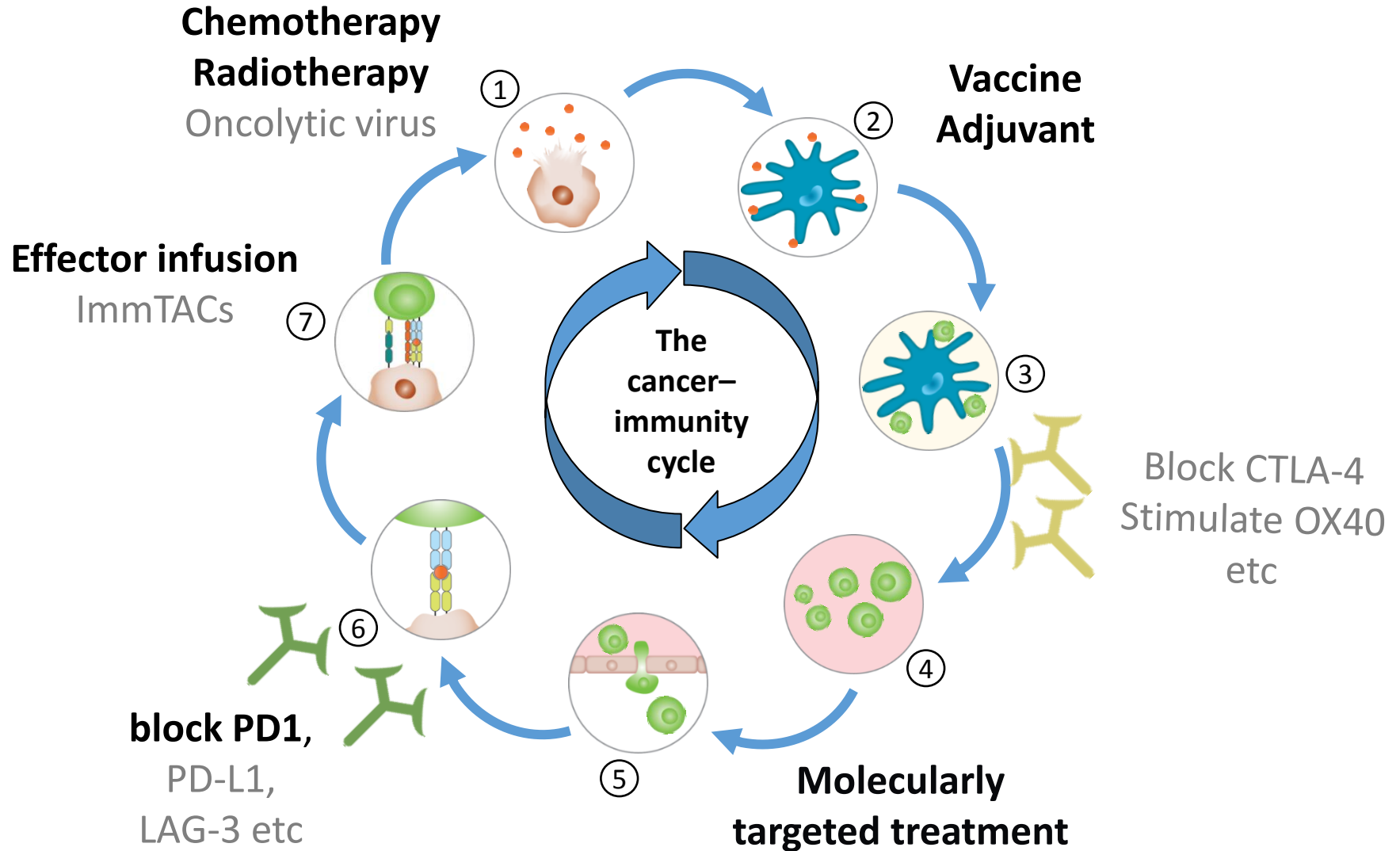
Clinical effect of blocking PD1 PD-L1 signalling

- Antitumor activity and safety of *pembrolizumab* in patients with PD-L1-positive nasopharyngeal carcinoma: Interim results from a phase 1b study.

- KEYNOTE-028 (NCT02054806) nonrandomized, multicohort phase 1b trial

- advanced (unresectable and/or metastatic) NPC, failed prior therapy, PS0-1, PD-L1 expression in ≥1% of cells in tumor nests or PD-L1[+] bands in stroma

- Pembrolizumab 10mg/kg every 2 weeks for up to 2 years

- N=27, median age 52, 63% Asian

- 1 CR, 6 PR, 14 SD

- ORR 25.9% (95% CI 11.1-46.3%)

- Median PFS 5.6 months, 12month PFS 28.6%
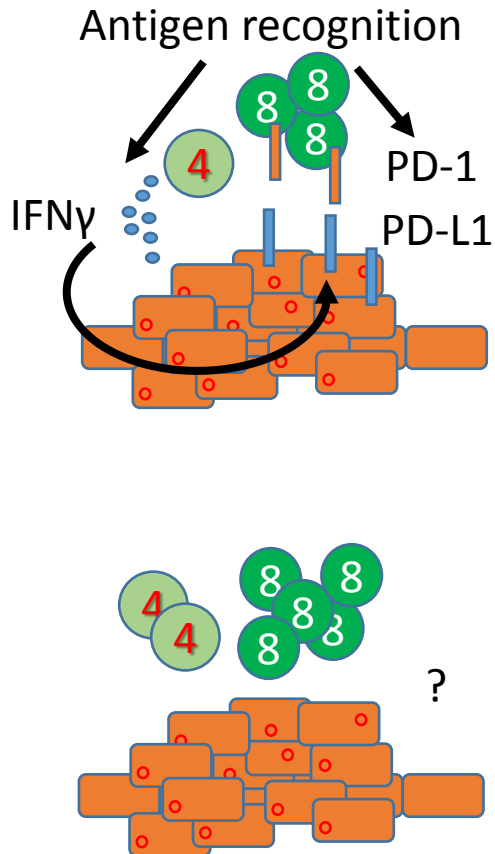
The cancer immunity cycle

Tumour cell death **releases** tumour specific antigens

Dendritic cells **process** TSAs

T cells **primed** and activated by dendritic cells presenting TSAs

Killing of tumour cells by tumour-specific T cells

Trafficking of tumour-specific T cells to tumours

Recognition of tumour cells by tumour-specific T cells

Infiltration of tumour-specific T cells into tumours

The cancer–immunity cycle

SINGAPORE 2015 ESMO ASIA
18-21 DECEMBER SINGAPORE

Therapeutic targets and strategies

Chemotherapy Radiotherapy
Oncolytic virus

Vaccine Adjuvant

Effector infusion
ImmTACs

The cancer–immunity cycle

Block CTLA-4 Stimulate OX40 etc

block PD1,
PD-L1, LAG-3 etc

Molecularly targeted treatment

Profiling the tumour micro-environment

I. Adaptive immune resistance

Antigen recognition

IFNγ

PD-1

PD-L1

II. Immune ignorance

Tumour antigens

Adapted from Teng
Can Res 2015;75:2139

IV. Tolerance

?
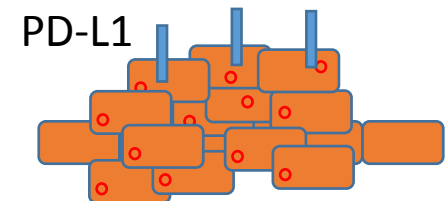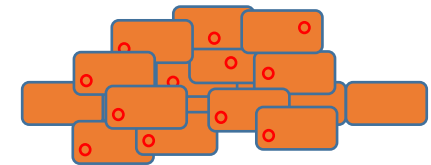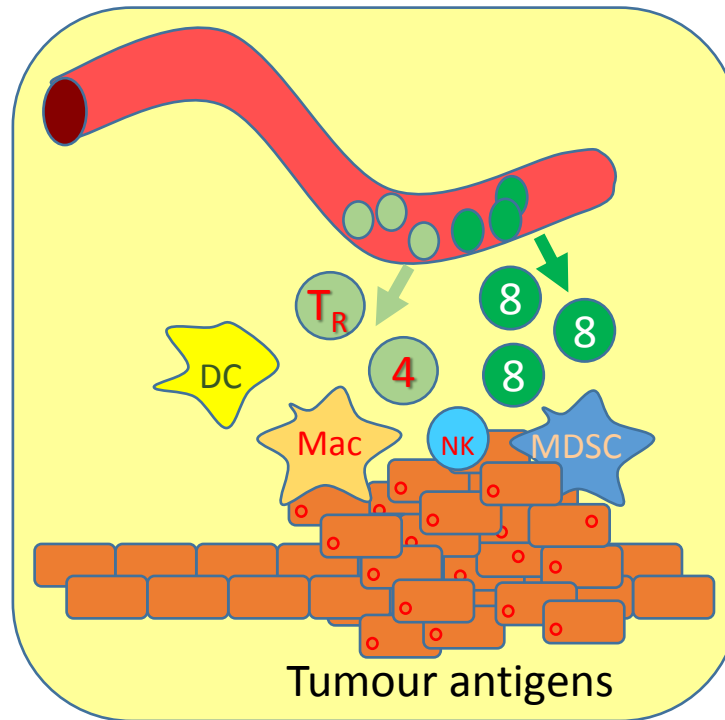
III. Intrinsic induction
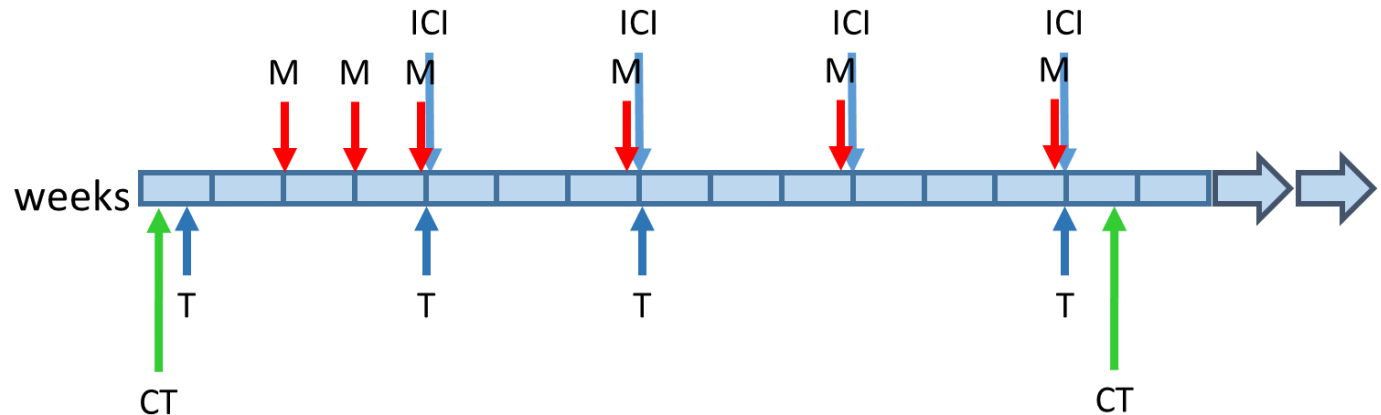
PD-L1

Phase II – combination

- Objective
  - Detect a difference between the arms in overall response rate is sufficient to justify continuation to phase III investigation

- Population
  - Patients with metastatic or refractory EBV+ cancer

- Intervention
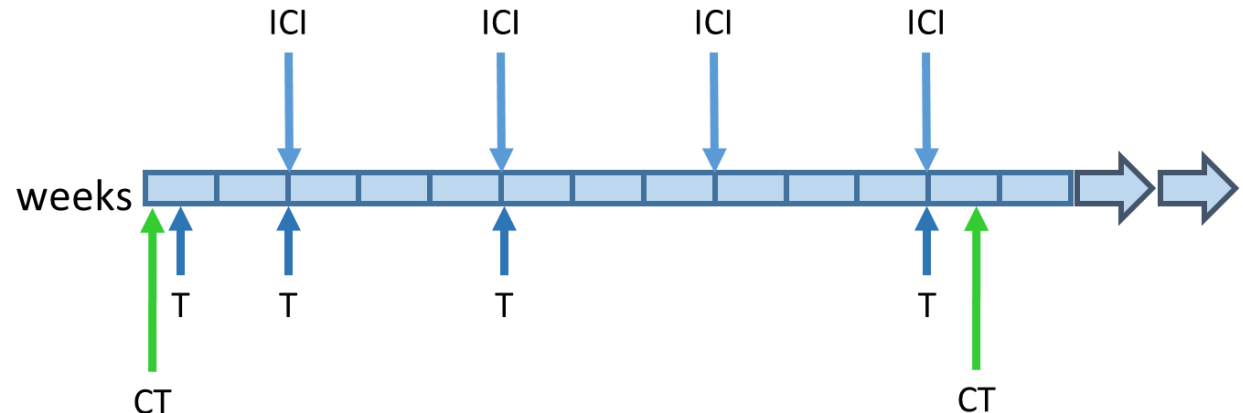 - Immune checkpoint inhibitor +/- initial accelerated vaccine schedule

Accelerated vaccination in combination

Concurrent regimen

ICI = immune checkpoint inhibition
M = MVA-EL vaccine
CT = response evaluation
T = T cells for secondary objective

Control regimen

Biological profiling in phase II combination trial

MVA EBV vaccine

Immunogenic cell death
- Tissue
- Serum / plasma

Cancer kill
- Imaging
- Serum EBV levels

Immune checkpoint blockade

Target antigens
- Shared
- Unique
- Viral
- Epitope spreading

Circulating T cells
- Number
- Function
- Activation phenotype

The cancer–immunity cycle

① Release
② Process
③ Prime
④ Traffic
⑤ Infiltrate
⑥ Recognise
⑦ Kill

Tumour micro-environment
- Micro-anatomy of infiltrates
- Profiling immune cells
- Gene expression profiling

Circulating T cells
- Receptor expression
- Adhesion molecules
- Function
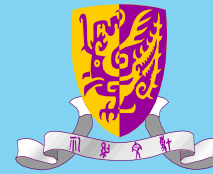
An international trials collaboration

PHASE 1 TRIALS

UNIVERSITY OF BIRMINGHAM
Graham Taylor
Alan Rickinson
Andrew Hartley
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

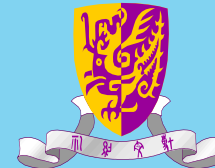**Cancer Research UK**
Ceri Edwards
Lesley McGuigan

PHASE 1b & 2

UNIVERSITY OF BIRMINGHAM
Graham Taylor
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
Lesley McGuigan
Uzma Rayani

FELINDRE NHS TRUST / VELINDRE
M. Evans

UCL
M. Foster

CARDIFF UNIVERSITY
David Price
Kristin Ladell

NHS Greater Glasgow and Clyde
M. Rizawanullah

UNIVERSITY OF LIVERPOOL
T. Jones

THE KADOORIE CHARITABLE FOUNDATION 嘉道理慈善基金會