Nasopharyngeal cancer - adoptive immunotherapy and vaccines

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Disclosure slide

- Advisory boards – Roche, GSK (now Novartis), Amgen, Merck
- Educational services for Amgen
Immune control of primary and latent Epstein-Barr virus infection

Primary infection

Latency III
B blasts

Lytic cycle

Latency 0
recirculating memory B cell pool

Persistent infection

virions

O-P epithelium

EBV+ NPC Latency 2

Latency II
DC
Mo
NK

4
8
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?
Immune control of primary and latent Epstein-Barr virus infection

Primary infection

Latency III
- B blasts

Lytic cycle

Latency 0
- recirculating memory B cell pool

Persistent infection

O-P epithelium

virions

EBNA 1

LMP 1

LMP 2

DC

Mo

NK

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EBNA 1

LMP 1

LMP 2

18-21 December

Singapore

ESMO Asia
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)
27/28 continued remission
Ref refractory (21)
CR (11)
PR (2)

Remission or response

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
2-3x10⁷ / infusion
(n=14)
SD 10/14

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

Frequency CD8+ IFN-γ cells
Ex vivo T cell lines

Time to progression
Median 66.5d
Range 38-420d

Smith Can Res 2012;72:1116
A brief history of EBV-directed immunotherapy

Vaccination

1998
- Lin 2002
  - NPC n=16
  - IL4-GMCSF-TNF-DC+peptide
  - 2 PR
  - Immunogenic

2002
- Comoli 2005
  - NPC n=10
  - EBV LCL T cells
  - 2 PR, 4 SD, 4 PD

2005
- Louis 2011
  - NPC n=23
  - EBV LCL T cells
  - 5/8 continued remission
  - 5 CR, 2 PR, 2 SD, 6 PD

2010
- Chia 2011
  - NPC n=16
  - Ad-ΔLMP1-LMP2 DC
  - 9/12 DTH+, no LMP resp.
  - Median PFS 1.9m
  - 1 PR 2 SD

2011
- Smith 2012
  - NPC n=14
  - Ad-LMP-DC T cells
  - 10 SD
  - Median TTP 66.5d

2012
- 2013
- 2014

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

T cell infusion

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

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

Phase Ia, Hong Kong, remission, 3 doses of $5 \times 10^8$ pfu

<table>
<thead>
<tr>
<th>Patient 0516</th>
<th>Prevaccination</th>
<th>C2D8</th>
<th>C3D22</th>
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Hui EP, Taylor GS et al
Cancer Res. 2013;73(6):1676-88
Every patient treated at dose level 3 or higher (n=14) had a vaccine-induced EBNA1 and/or LMP2 T-cell response.

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 or low volume stable recurrence
Detailed immunogenicity
Characterise immune memory
Single arm Phase IB (n=18 NPC)
4 cycles over 20 weeks

**Phase IA Trial**
Phase IA trial

**Phase II 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)
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 $5 \times 10^8$ vaccine. Undetectable ex vivo response to vaccination. In vitro stimulation and culture and detection of IFN$\gamma$ cells by flow cytometry.
Vaccination increases immune response quality (*ex vivo* assay)

**EBNA1**
- Pre-vaccine: 0.28%
- Post-vaccine: 0.49%

**T-cells (CD4+)**
- Pre-vaccine: 0.33%
- Post-vaccine: 1.43%

**LMP2**
- Pre-vaccine: 0.33%
- Post-vaccine: 1.43%

**After Vaccination**
- Increase in response size
- Increase in polyfunctionality
Vaccination increases immune response quality (ex vivo assay)

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, 5x10^8 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

1. Tumour cell death releases tumour specific antigens
2. Dendritic cells process TSAs
3. T cells primed and activated by dendritic cells presenting TSAs
4. Trafficking of tumour-specific T cells to tumours
5. T cells recognizing tumour cells
6. Recognition of tumour cells by tumour-specific T cells
7. Killing of tumour cells by tumour-specific T cells

Infiltration of tumour-specific T cells into tumours

Therapeutic targets and strategies

1. Chemotherapy
2. Radiotherapy
3. Vaccine
4. Effector infusion
5. Block PD1, PD-L1, LAG-3 etc
6. Block CTLA-4
7. Stimulate OX40 etc

The cancer–immunity cycle

Chemotherapy
Radiotherapy
Oncolytic virus
Vaccine Adjuvant
Effector infusion
ImmTACs
Molecularly targeted treatment
Profiling the tumour micro-environment

I. Adaptive immune resistance

Antigen recognition

IFNγ

PD-1

PD-L1

II. Immune ignorance

III. Intrinsic induction

IV. Tolerance

Adapted from Teng
Can Res 2015;75:2139
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

Control regimen

ICI = immune checkpoint inhibition  
M = MVA-EL vaccine  
CT = response evaluation  
T = T cells for secondary objective
Biological profiling in phase II combination trial

The cancer–immunity cycle

- Infiltrate
- Process
- Traffic
- Release
- Prime
- Kill
- Recognise

MVA EBV vaccine

Immunogenic cell death
- Tissue
- Serum / plasma

Cancer kill
- Imaging
- Serum EBV levels

Immune checkpoint blockade

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

Circulating T cells
- Receptor expression
- Adhesion molecules
- Function

Target antigens
- Shared
- Unique
- Viral
- Epitope spreading

Circulating T cells
- Number
- Function
- Activation phenotype
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, Edwin Hui, Anthony Chan
- Cancer Research UK: Lesley McGuigan
- M. Evans
- M. Foster
- David Price
- Kristin Ladell
- T. Jones
- M. Rizawanullah
- The Kadoorie Charitable Foundation