Immunotherapy in Treating Nasopharyngeal Carcinoma

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Disclosure

- Received honorarium from Merck Sharp & Dohme (MSD) and Bristol-Myers Squibb Pharma (HK) Ltd.
- Advisor for Atara.
- Hold shares in Pfizer.

Disclaimer

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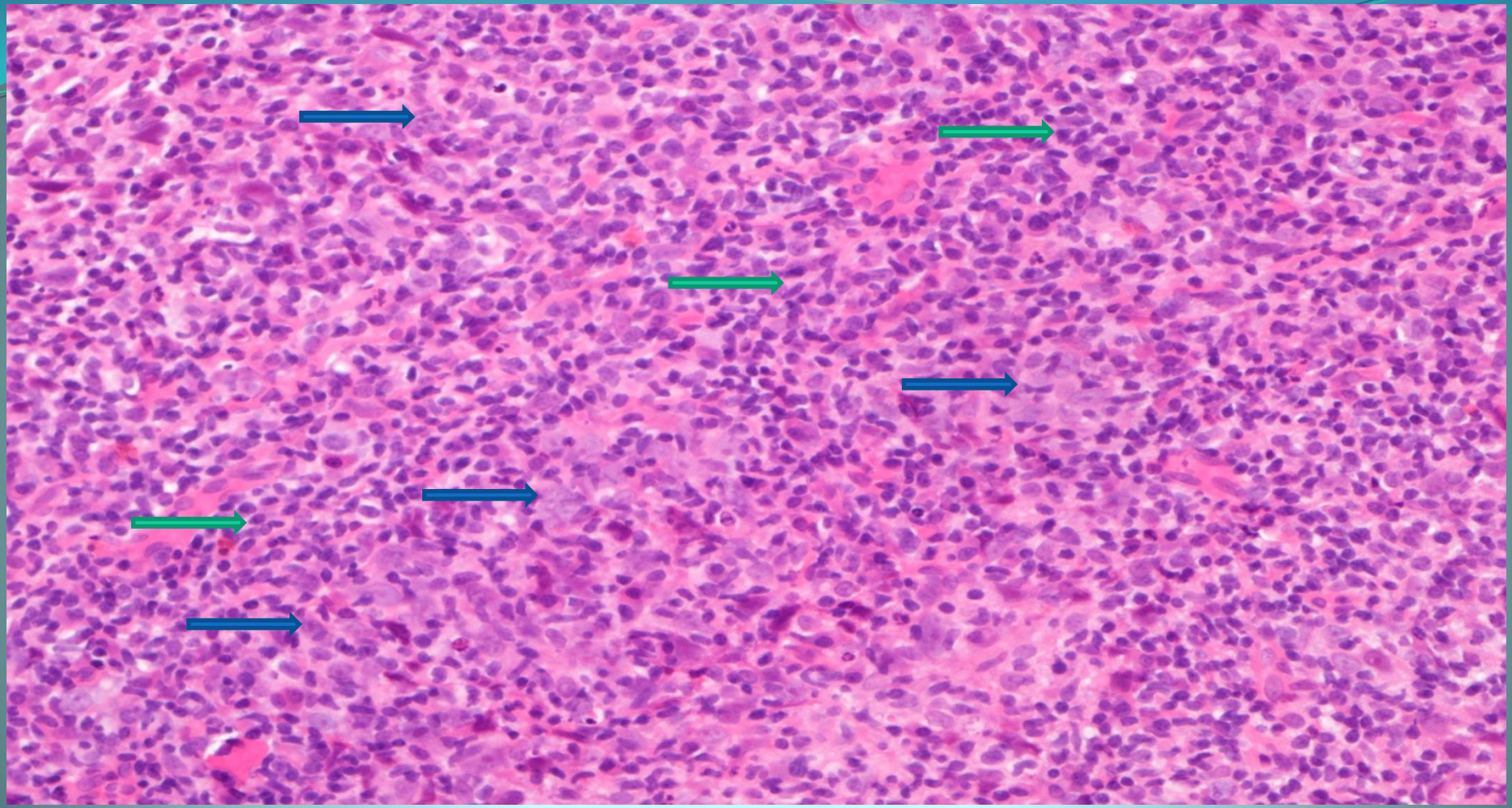
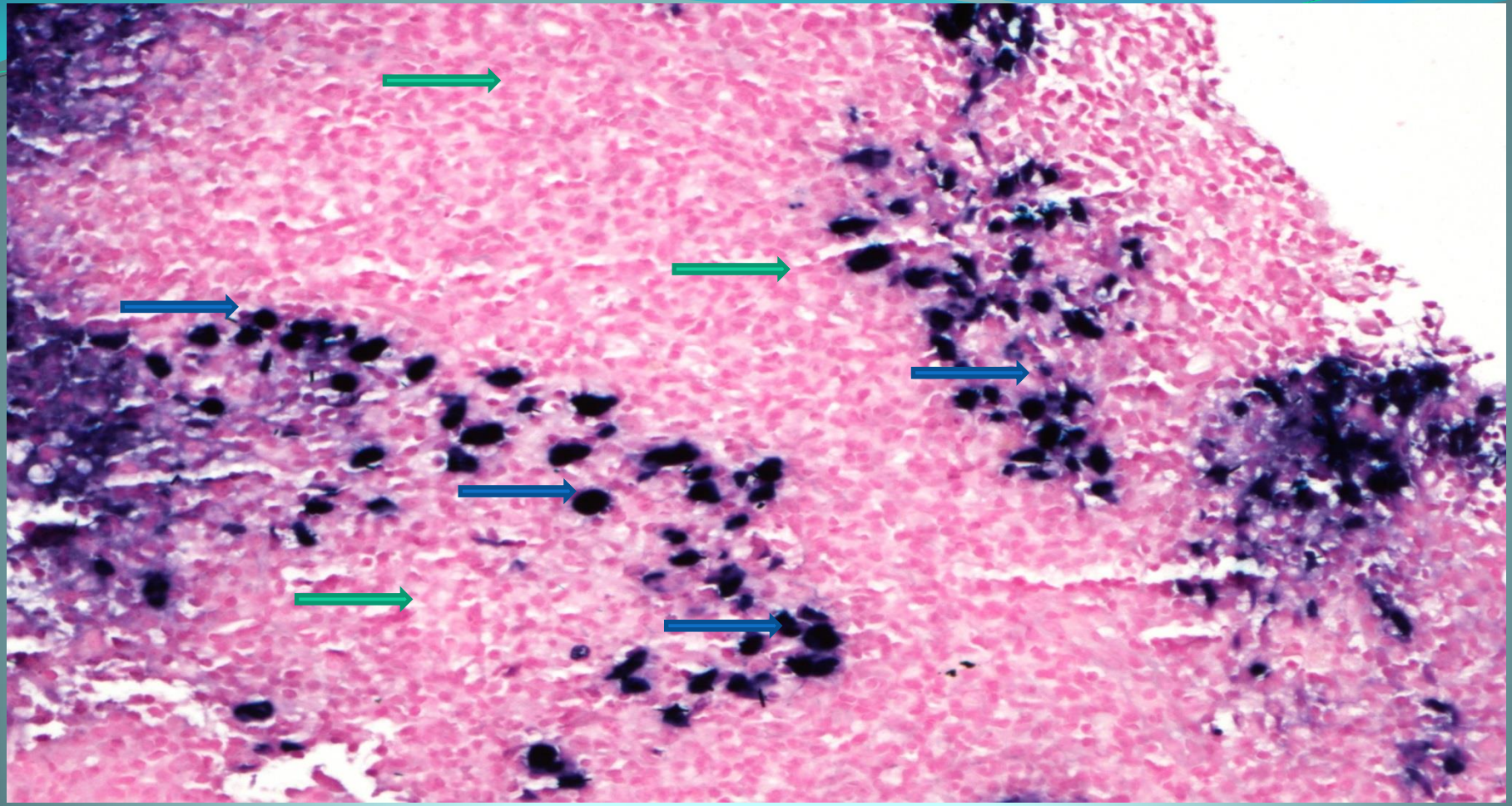
Nasopharyngeal Carcinoma (NPC)

- Endemic in Southern China, SE Asia: poorly differentiated and undifferentiated non-keratinizing NPC (WHO type II and III).
- Virtually all endemic NPCs are associated with Epstein-Barr virus (EBV) infection.
- The EBV viral antigens expressed by the NPC tumour cells are surrogate tumor antigens
- There is heavy lymphocytes infiltration





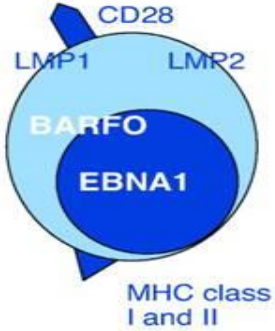
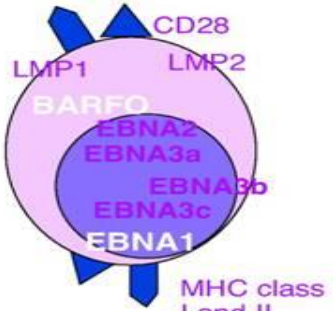
Immunotherapy approach for NPC

- Targeting Epstein-Barr Virus (EBV)
  - T cell therapy
  - Vaccine
- Non-EBV specific
  - Immune checkpoint inhibitors

Background

- NPC is an attractive candidate for cellular immunotherapy targeted against tumour-associated viral antigen
  - EBV specific cytotoxic T-cell (CTLs) lines can be expanded in vitro.
  - Previous immunotherapy is mainly based on LCL mainly target EBNA 3-6 antigens, good for PTLD
  - Viral antigen expressed in NPC
    - Nuclear antigen EBNA1
    - The latent membrane proteins LMP2 & (in some cases)LMP1
  - AdE1-LMP poly vector based stimulation will preferentially expand T cells against EBNA1 and LMP

EBV antigen expression in different tumor types

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

Straathof, K. et al. Oncologist 2003;8:83-98

Adoptive Immunotherapy for Epstein-Barr Virus-associated NPC

A joint collaboration of

The University of Hong Kong

&

The Queensland Institute of Medical Research

Study Endpoints

- Primary endpoints:
  - To determine the tolerability & safety of administering autologous LMP/EBNA-1 specific CTL
- Secondary endpoints:
  - To monitor clinical and radiological response
  - To monitor patients' blood samples with regard to any effect of LMP/EBNA1 CTL therapy on different parameters of EBV immunity, esp. EBV DNA levels

Concept of EBV adoptive immunotherapy

Patient PBMC

+ EBV stimulation
(EBV epitopes from LMP1&2 and EBNA1 encoded in Adenovirus)

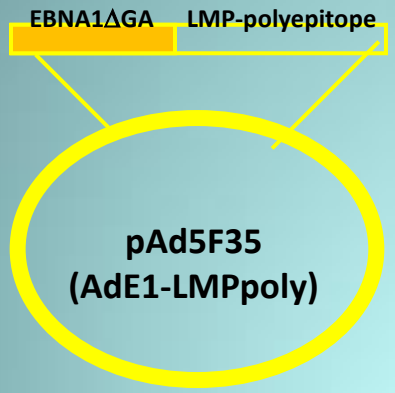
→

Expand CTL in vitro

→

Adoptive transfer to patient

Multi-epitope Technology:E1-LMPpoly™



Adenochimera™
E1-LMPpoly

Epitope Sequence	Antigen	HLA Restriction
PYLFWLAA	LMP2A	A23, A24, A30
SSCSSCPLSKI	LMP2A	A11
TYGPVFMCL	LMP2A	A24
RRRWRRLTV	LMP2A	B27
LLSAWILTA	LMP2A	A2.03
LTAGFLIFL	LMP2A	A2.06
CLGGLLTMV	LMP2A	A2.01
VMSNTLLSAW	LMP2A	A25
IEDPPFNSL	LMP2A	B40
YLLEMLWRL	LMP1	A2.01, A68, A69
YLQQNWWTL	LMP1	A2.01
ALLVLYSFA	LMP1	A2
IALYLQQNW	LMP1	B57, B58
FLYALALLL	LMP2A	A2.01
WTLVLLI	LMP2A	B63
CPLSKILL	LMP2A	B8

Methodology

Recurrent or metastatic NPC (Active disease)

No/minimal residual disease (in remission)

↓

Tumour biopsy confirmed EBV-encoded RNA (EBER) positive or WHO III histology Where staining unavailable

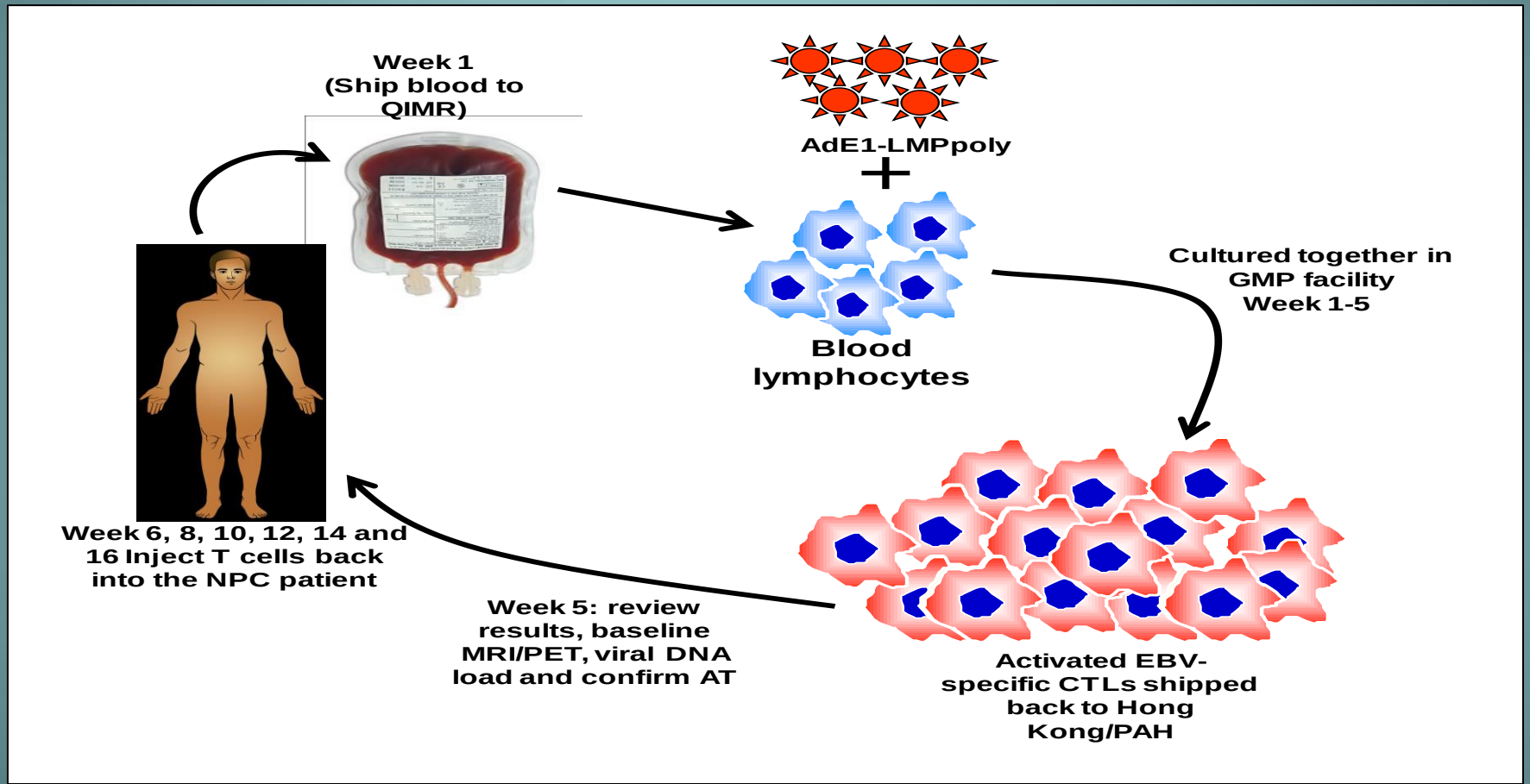
↓

MHC Class I HLA type appropriate for the study

↓

Transport fresh peripheral blood samples from HK to QIMR Brisbane

NPC Adoptive Immunotherapy Therapy: Production Process



Treatment Timeline

- Week 6 onwards (Adoptive Immunotherapy)
  - Adoptive immunotherapy up to 8 transfers (Wk 6, 8, 10, 12, 14, 16), every 2-weekly
  - Monitoring of bloods (CBP, L/RFT), EBV DNA load
  - Radiological assessment with imaging at 1,2,3,4,6 months after T cell infusion and then every 3 months

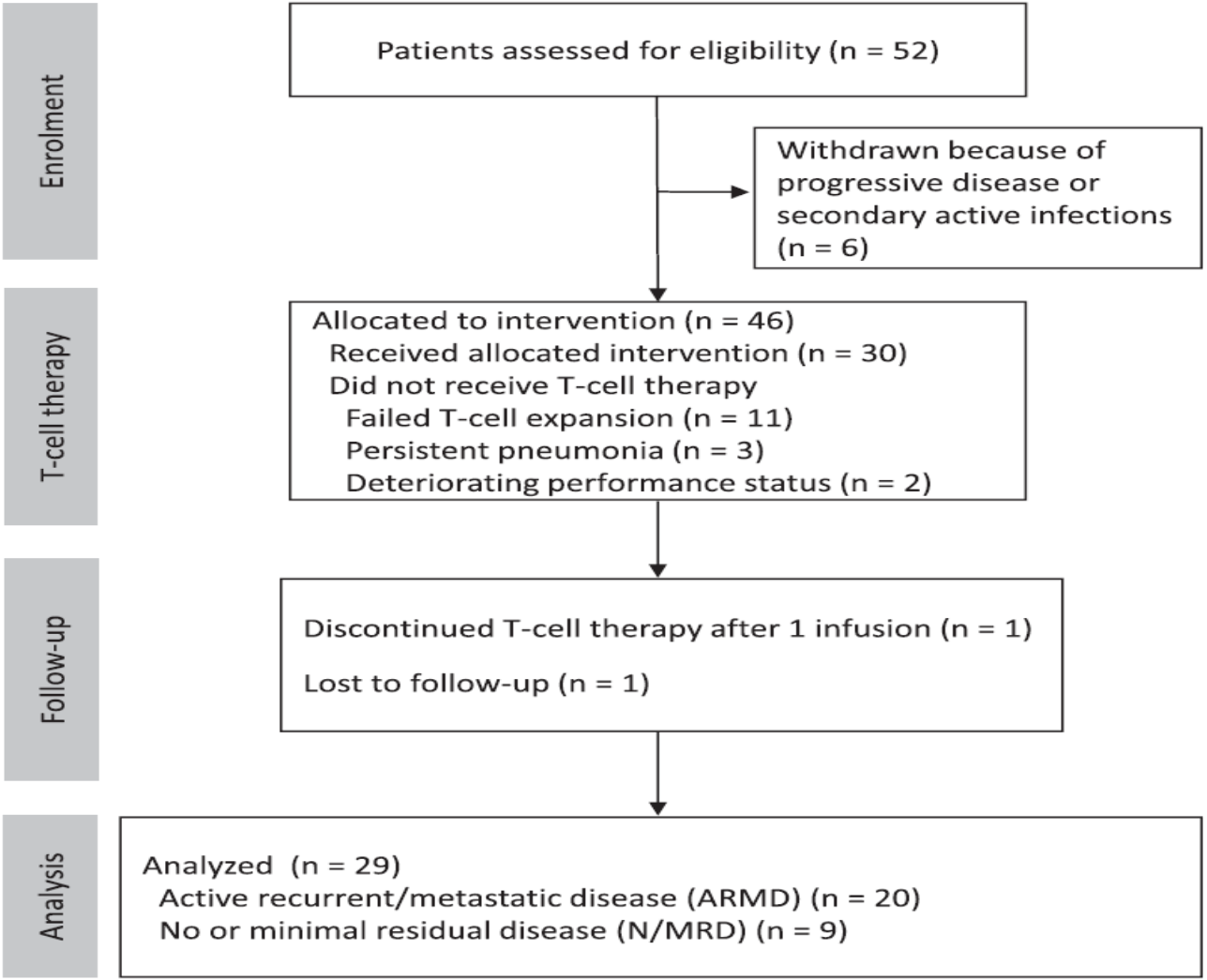

Enrolment
Patients assessed for eligibility (n = 52)
Withdrawn because of progressive disease or secondary active infections (n = 6)
T-cell therapy
Allocated to intervention (n = 46)
Received allocated intervention (n = 30)
Did not receive T-cell therapy
Failed T-cell expansion (n = 11)
Persistent pneumonia (n = 3)
Deteriorating performance status (n = 2)
Follow-up
Discontinued T-cell therapy after 1 infusion (n = 1)
Lost to follow-up (n = 1)
Analysis
Analyzed (n = 29)
Active recurrent/metastatic disease (ARMD) (n = 20)
No or minimal residual disease (N/MRD) (n = 9)

Table 1. Clinical characteristics of NPC patients treated with AdE1-LMPpoly T-cells.

	ARMD (n = 21)	N/MRD (n = 9)
Median age in years (range)	46 (34–68)	49 (22–66)
Sex		
Male	18	8
Female	2	1
Stage on diagnosis		
I	2	2
II	2	1
III	7	4
IVA	7	1
IVB	1	1
IVC	2	0
Median number of lines of chemotherapy before T-cell therapy (range)	3 (1 to 5)	2 (1 to 4)
History of recurrent NPC	21	7
Disease status at first T-cell infusion		
No radiological disease	0	9
Local recurrence	11	0
Regional nodal recurrence	6	0
Lung metastasis	9	0
Liver metastasis	5	0
Bone metastasis	5	0
Distant nodal metastasis	4	0
Median plasma EBV DNA copies/mL before T-cell therapy (range)	2.3×10^3 (0 to 6.3×10^6)	0 (0)

Outcomes

One patient with local recurrence died after 1st infusion due to severe epistaxis, probably due to disease progression. Excluded from efficacy analysis but included in safety analysis. 29 patients received at last 2 doses of CTL

ARMD (20 patients)

- 12 patients (60%) achieved SD, no PR or CR
- median PFS: 3.2m, OS: 15.7m

N/MRD (9 patients)

- 6 remains in continuous remission, median PFS and OS not reached

AE: mostly grade 1/2. 2 patients died of lung abscess during treatment, probably due to disease progression.

Table 2. Safety profiles after T-cell therapy.

Adverse events	n = 30 (%)
Grade 1	10 (33.3%)
Fatigue	1 (3.3%)
Dry cough	1 (3.3%)
Fever	3 (10%)
Chills	1 (3.3%)
Chest pain	1 (3.3%)
Sore throat	1 (3.3%)
Hyperbilirubinemia	1 (3.3%)
Altered hearing ability	1 (3.3%)
Grade 2	6 (20%)
Fatigue	2 (6.7%)
Fever	1 (3.3%)
Dyspnea	1 (3.3%)
Headache	1 (3.3%)
Vomiting	1 (3.3%)
Grade 3	2 (6.7%)
Lung abscess	2 (6.7%)

Post EBV-specific T cell therapy and clinical outcome

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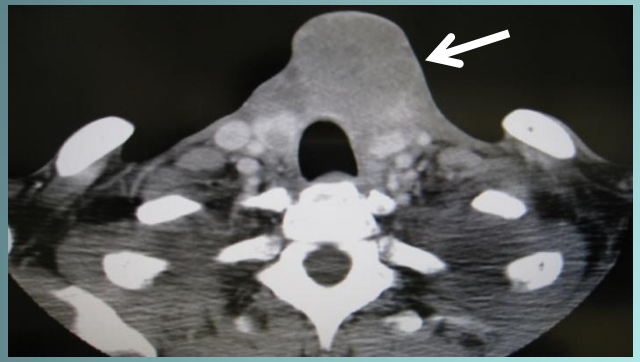
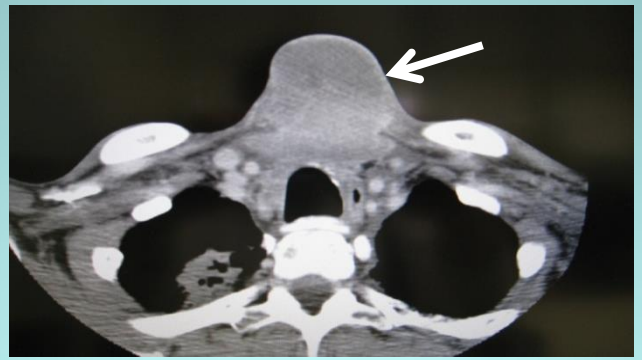
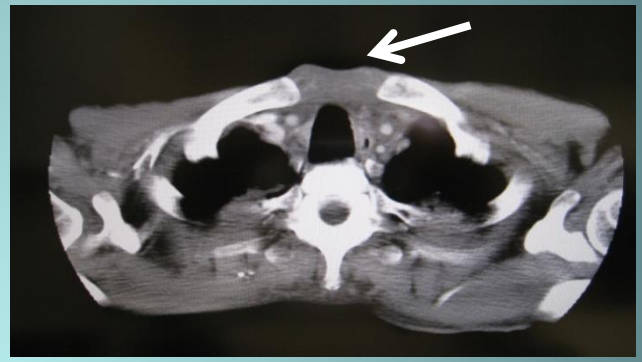


1 wk before immunotherapy, this patient suffered from advanced recurrence with tumor spreading to neck and chest, part of the tumor was fungating through the anterior surface of the lower neck

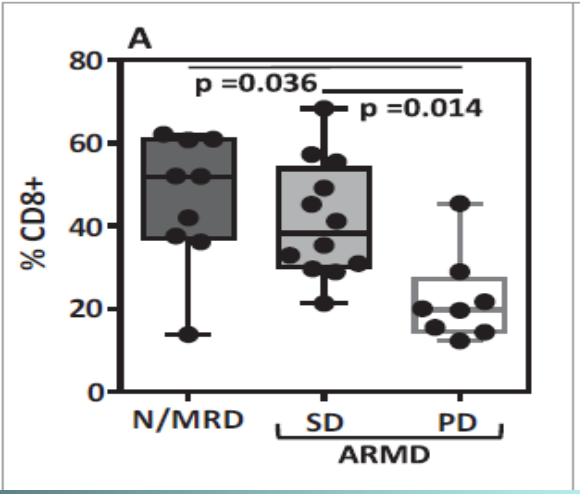


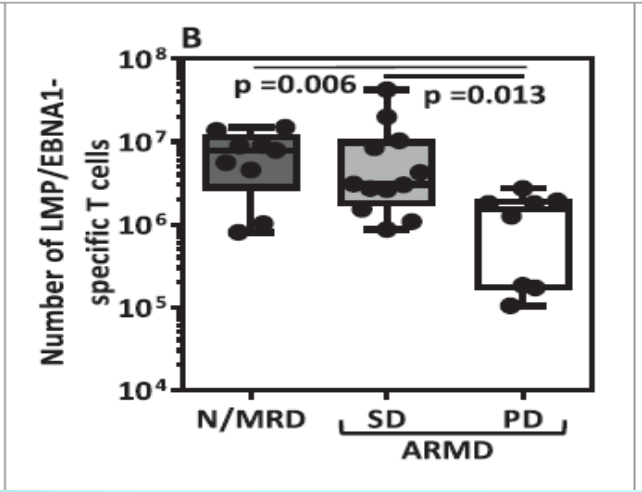
4 wks after immunotherapy, tumor appears to be static with no significant regression

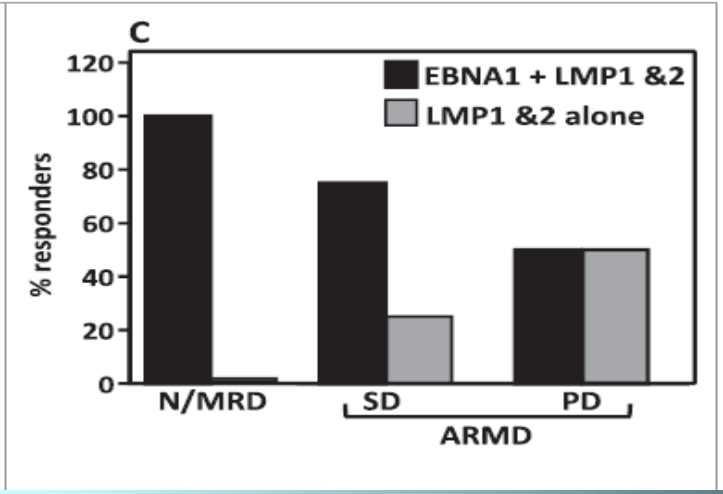


12 wks after immunotherapy and 1 cycle of chemotherapy, dramatic shrinkage of tumor was noted

Quantitative difference in EBV-specific T cells and clinical outcome







Conclusions

- The adoptive transfer of autologous LMP/EBNA1-specific CTL is generally well tolerated with mild G1 side effects.
- The SAE that occurred was probably related to clinical progressive disease.

Conclusions

- As part of the secondary objectives, clinical follow-up analyses of the patients showed that adoptive transfer of LMP/EBNA1-specific T cells was coincident with disease stabilization.

- There seems to be no correlation between the number of CTL infused and the disease response or TTP

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Microenvironment and Immunology

Cancer Research

Effective Treatment of Metastatic Forms of Epstein-Barr Virus–Associated Nasopharyngeal Carcinoma with a Novel Adenovirus-Based Adoptive Immunotherapy

Corey Smith[1], Janice Tsang[3], Leone Beagley[1], Daniel Chua[5], Victor Lee[3], Vivian Li[3], Denis J. Moss[1], William Coman[2], Kwok H. Chan[3], John Nicholls[4], Dora Kwong[3], and Rajiv Khanna[1]

Abstract

Nasopharyngeal carcinoma (NPC) is endemic in China and Southeast Asia where it is tightly associated with infections by Epstein-Barr virus (EBV). The role of tumor-associated viral antigens in NPC renders it an appealing candidate for cellular immunotherapy. In earlier preclinical studies, a novel adenoviral vector–based vaccine termed AdE1-LMPpoly has been generated that encodes EBV nuclear antigen-1 (EBNA1) fused to multiple $CD8^+$ T-cell epitopes from the EBV latent membrane proteins, LMP1 and LMP2. Here, we report the findings of a formal clinical assessment of AdE1-LMPpoly as an immunotherapeutic tool for EBV-associated recurrent and metastatic NPC. From a total of 24 patients with NPC, EBV-specific T cells were successfully expanded from 16 patients with NPC (72.7%), whereas six patients with NPC (27.3%) showed minimal or no expansion of virus-specific T cells. Transient increase in the frequencies of LMP1&2- and EBNA1-specific T-cell responses was observed after adoptive transfer to be associated with grade I flu-like symptoms and malaise. The time to progression in these patients ranged from 38 to 420 days with a mean time to progression of 136 days. Compared with patients who did not receive T cells, the median overall survival increased from 220 to 523 days. Taken together, our findings show that adoptive immunotherapy with AdE1-LMPpoly vaccine is safe and well tolerated and may offer clinical benefit to patients with NPC. *Cancer Res; 72(5); 1116–25.* ©2012 AACR.

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ORIGINAL RESEARCH

OPEN ACCESS

Pre-emptive and therapeutic adoptive immunotherapy for nasopharyngeal carcinoma: Phenotype and effector function of T cells impact on clinical response

Corey Smith[a,*], Victor Lee[b,*], Andrea Schuessler[a], Leone Beagley[a], Sweera Rehan[a], Janice Tsang[b], Vivian Li[b], Randal Tiu[b], David Smith[a], Michelle A. Neller[a], Katherine K. Matthews[a], Emma Gostick[c], David A. Price[c,d], Jacqueline Burrows[a], Glen M. Boyle[a], Daniel Chua[e], Benedict Panizza[f], Sandro V. Porceddu[f], John Nicholls[g], Dora Kwong[b], and Rajiv Khanna[a]

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ABSTRACT

Adoptive T cell therapy has emerged as a powerful strategy to treat human cancers especially haematological malignancies. Extension of these therapies to solid cancers remains a significant challenge especially in the context of defining immunological correlates of clinical responses. Here we describe results from a clinical study investigating autologous Epstein-Barr virus (EBV)-specific T cells generated using a novel AdE1-LMPpoly vector to treat patients with nasopharyngeal carcinoma (NPC) either pre-emptively in at-risk patients with no or minimal residual disease (N/MRD) or therapeutically in patients with active recurrent/metastatic disease (ARMD). Tolerability, safety and efficacy, including progression-free survival (PFS) and overall survival (OS), were evaluated following adoptive T-cell immunotherapy. Twenty-nine patients, including 20 with ARMD and nine with N/MRD, successfully completed T-cell therapy. After a median follow-up of 18.5 months, the median PFS was 5.5 months (95% CI 2.1 to 9.0 months) and the median OS was 38.1 months (95% CI 17.2 months to not reached). Post-immunotherapy analyses revealed that disease stabilization in ARMD patients was significantly associated with the functional and phenotypic composition of *in vitro*-expanded T cell immunotherapy. These included a higher proportion of effector $CD8^+$ T-cells and an increased number of EBV-specific T-cells with broader antigen specificity. These observations indicate that adoptive immunotherapy with AdE1-LMPpoly-expanded T cells stabilizes relapsed, refractory NPC without significant toxicity. Promising clinical outcomes in N/MRD patients further suggest a potential role for this approach as a consolidation treatment following first-line chemotherapy.

ARTICLE HISTORY
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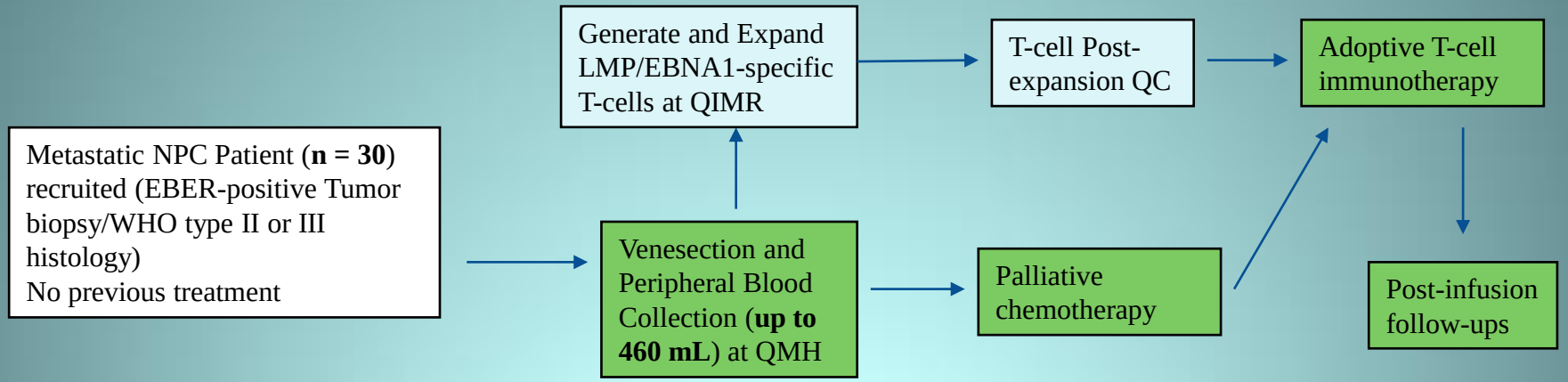
KEYWORDS
Adoptive immunotherapy; Epstein-Barr virus; T cells; safety; nasopharyngeal carcinoma

Phase II open-label clinical trial of autologous Epstein-Barr virus-specific T cell therapy as consolidative treatment following chemotherapy for metastatic EBV-associated nasopharyngeal carcinoma (NPC)



Palliative Chemotherapy Regimen (Not a part of trial):

Drug	Dosage/Route	Duration	Remarks
*Cisplatin	50 mg/m2, IV	Every 4 weeks, Day 1 and 8; up to 6 cycles	* Switch to Carboplatin (AUC = 5) in case of inadequate renal function
Gemcitabine	1000 mg/m2, IV	Every 4 weeks, Day 1, 8 and 15; up to 6 cycles	

Targeting the PD-1 Pathway Involved in Tumor Immunosuppression

- PD-1 receptors are normally expressed on various immune cells, including inactivated T cells[1]
- Activated (primed) T cells upregulate PD-L1[1]
- Tumor cells can express the PD-1 ligands, PD-L1 and PD-L2[1]
- PD-L1 and PD-L2 bind to the PD-1 receptors to inhibit the activated T cells and allow tumor cells to evade the immune response[1]
- Studies have demonstrated significant correlations between impaired survival and tumor expression of PD-L1 and PD-L2[2]
- Anti–PD-1 antibodies block PD-L1 and PD-L2 from binding to PD-1 in the tumor microenvironment[3]

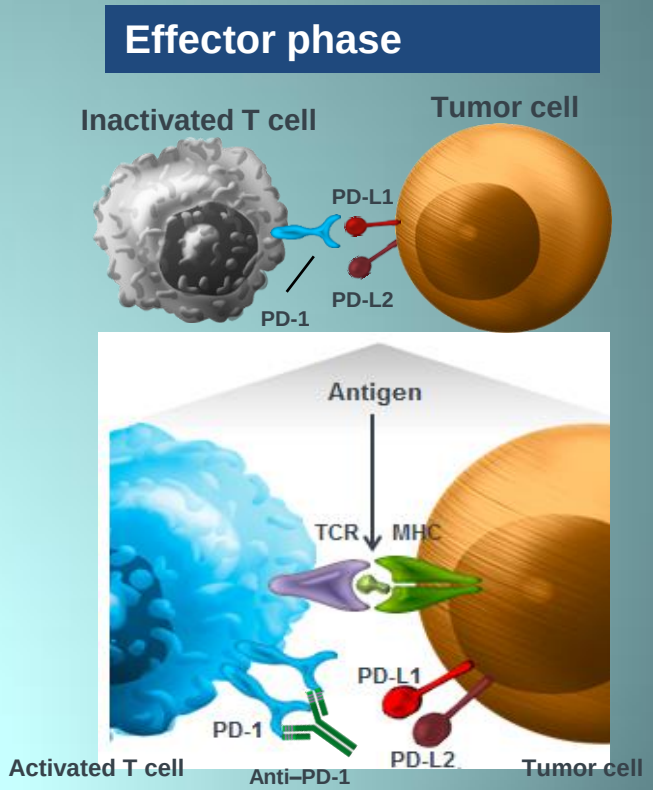


Image adapted from Pardoll DM. *Nat Rev Cancer*. 2012;12(4):252–264.

PD-1 = programmed death receptor-1; PD-L1 = programmed death ligand 1; PD-L2 = programmed death ligand 2; MHC = major histocompatibility complex; TCR = T-cell receptor.

1. Pardoll DM. *Nat Rev Cancer*. 2012;12(4):252–264. 2. Khan H et al. *J Oncol*. 2015;2015:847383. 3. McDermott DF, Atkins MB. *Cancer Med*. 2013;2(5):662–673.

Keynote-028: Phase 1b Multicohort Study of Pembrolizumab for PD-L1+ Advanced Solid Tumors

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Safety and Antitumor Activity of Pembrolizumab in Patients With Programmed Death-Ligand 1–Positive Nasopharyngeal Carcinoma: Results of the KEYNOTE-028 Study

Chiun Hsu, Se-Hoon Lee, Samuel Ejadi, Caroline Even, Roger B. Cohen, Christophe Le Tourneau, Janice M. Mehnert, Alain Algazi, Emilie M.J. van Brummelen, Sanatan Saraf, Pradeep Thanigaimani, Jonathan D. Cheng, and Aaron R. Hansen

Author affiliations and support information (if applicable) appear at the end of this article.

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Clinical trial information: NCT02054806.

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0732-183X/17/3536w-4050w/$20.00

A B S T R A C T

Purpose

To establish the safety profile and antitumor activity of the anti–programmed death 1 receptor monoclonal antibody, pembrolizumab, in patients with recurrent or metastatic nasopharyngeal carcinoma (RM-NPC) that expressed programmed death-ligand 1 (PD-L1).

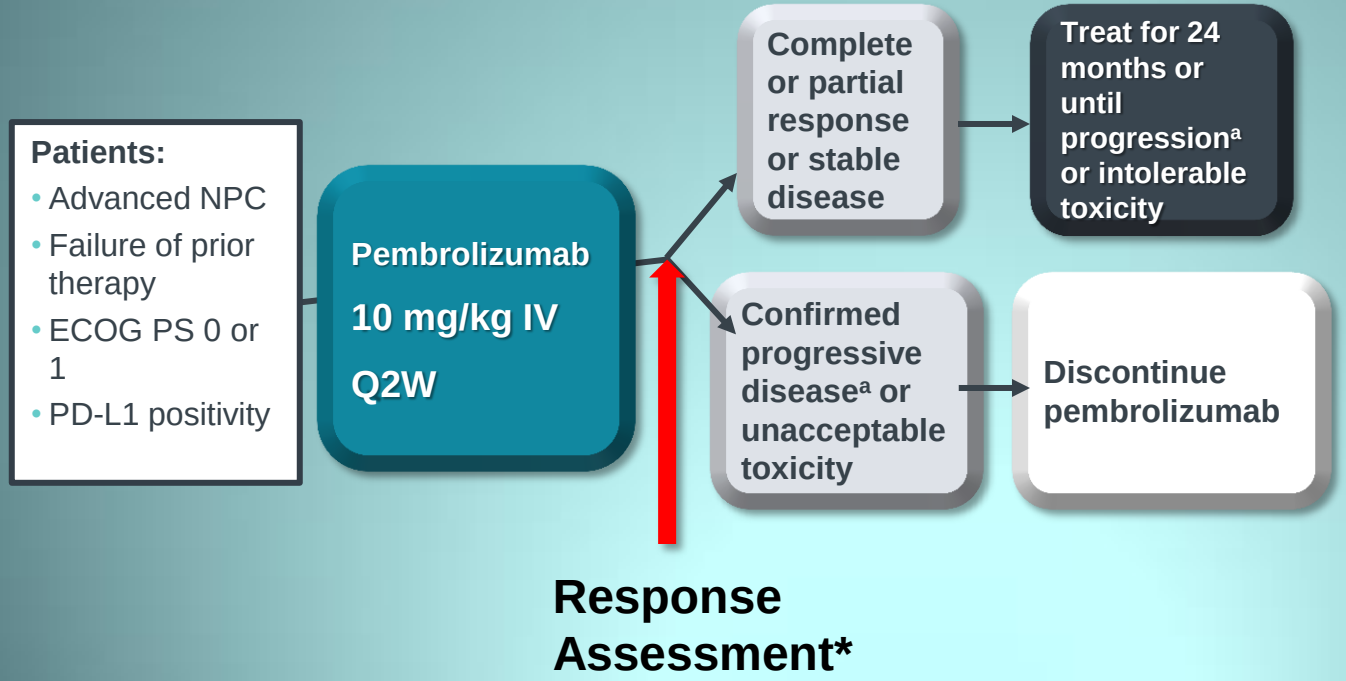
Patients and Methods

KEYNOTE-028 (NCT02054806) is a nonrandomized, multicohort, phase Ib trial of pembrolizumab in patients with PD-L1–positive advanced solid tumors. Key eligibility criteria for the NPC cohort included unresectable or metastatic disease, failure on prior standard therapy, and PD-L1 expression in 1% or more of tumor cells or tumor-infiltrating lymphocytes. Patients received pembrolizumab 10 mg/kg every 2 weeks up to 2 years or until disease progression or unacceptable toxicity. Primary end point was objective response rate (ORR) per investigator review. Tumor response was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1) every 8 weeks for the first 6 months and every 12 weeks thereafter.

Hsu C et al. *J Clin Oncol*. 2017;35:4050–4056.

Pembrolizumab is not approved for NPC in HK

Keynote-028: Phase 1b Multicohort Study of Pembrolizumab for PD-L1+ Advanced Solid Tumors



- ***Response assessment**: Every 8 weeks for the first 6 months; every 12 weeks thereafter
- **Primary end point:** ORR per RECIST v1.1
- **Secondary end points:** PFS, OS, duration of response, and safety

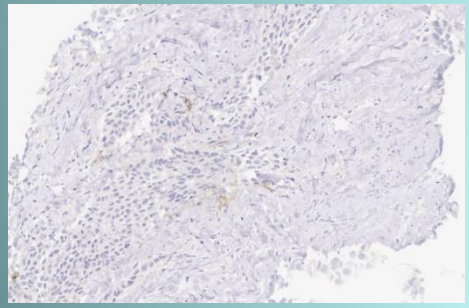
[a]If clinically stable, patients are to remain on pembrolizumab until progressive disease is confirmed on a second scan performed ≥4 weeks later. Patients who experience progression may be eligible for up to 1 year of additional pembrolizumab if no other anticancer therapy is received.

Hsu C et al. *J Clin Oncol*. 2017;35:4050–4056.

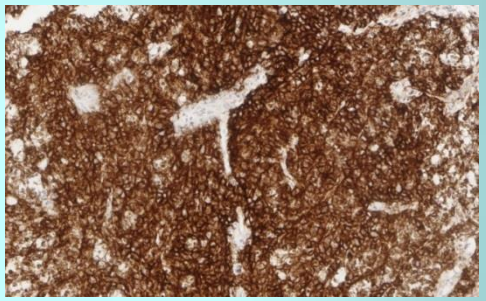
Pembrolizumab is not approved for NPC in HK

Keynote-028: Analysis of PD-L1 Expression

- Tumor samples: archival or newly obtained core or excisional biopsy of non-irradiated lesion
- Immunohistochemistry: assessed at a central laboratory using a prototype assay (QualTek) and 22C3 antibody clone (Merck)
- Positivity: membranous PD-L1 expression in ≥1% of cells in tumor and stroma
- 41 of 44 (93.2%) patients with nasopharyngeal carcinoma who provided tissue had PD-L1–positive tumors



PD-L1 Negative



PD-L1 Positive

Hsu C et al. Presented at ECCO ESMO 2015..

Keynote-028: Baseline Characteristics

Characteristic	Value (N = 27)
Age, median (range), years	52 (18-68)
Sex	
Male	21 (77.8)
Female	6 (22.2)
Race	
Asian	17 (63.0)
White	6 (22.2)
Black or African American	2 (7.4)
American Indian or Alaskan native	1 (3.7)
Not specified	1 (3.7)
ECOG performance status	
0	7 (25.9)
1	20 (74.1)
Histology at baseline	
WHO class 1	6 (22.2)
WHO class II and III	18 (66.7)
Other	3 (11.1)

Characteristic	Value (N = 27)
Prior adjuvant or neoadjuvant systemic therapy	8 (29.6)
Prior lines of therapy for advanced disease	
0†	2 (7.4)
1	3 (11.1)
2	3 (11.1)
3	8 (29.6)
4	2 (7.4)
≥ 5	9 (33.3)
Patients with prior therapies	
Cisplatin	25 (92.6)
Fluorouracil	22 (81.5)
Gemcitabine	14 (51.9)
Carboplatin	11 (40.7)
Docetaxel	10 (37.0)
Cyclophosphamide	7 (25.9)
Paclitaxel	6 (22.2)
Capecitabine	5 (18.5)

†Both patients had previously received adjuvant and/or neoadjuvant chemotherapy

Hsu C et al. *J Clin Oncol*. 2017;35:4050–4056.

Keynote-028: Antitumor Activity

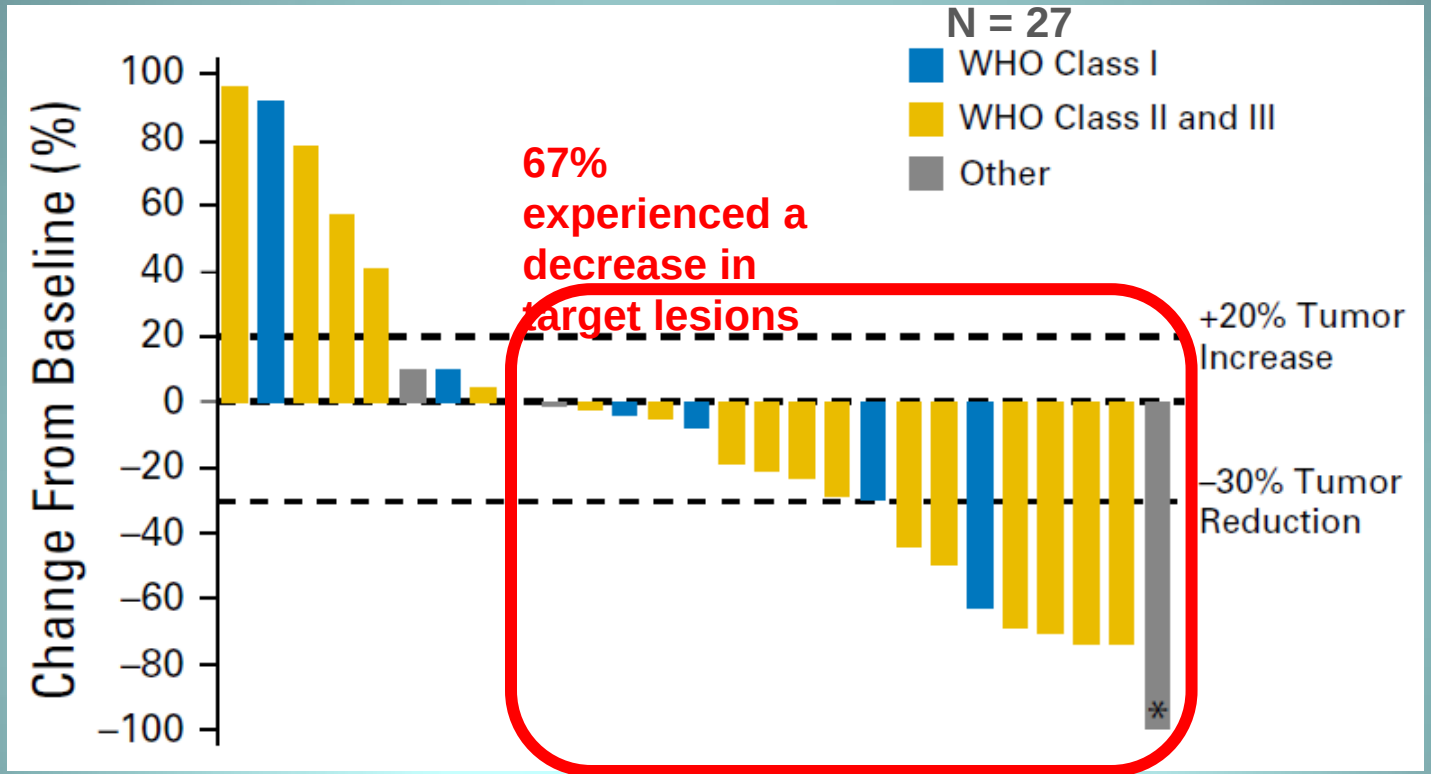
Confirmed Antitumor Activity
Full analysis set per investigator and central review, RECIST v1.1

Response Evaluation	Per Investigator Review (N = 27)	Per Central Review (n = 19)
ORR (CR + PR), No.; % (95% CI)	7; 25.9 (11.1 to 46.3)	5; 26.3 (9.1 to 51.2)
CR, No.; % (95% CI)	0; 0 (0 to 12.8)	0; 0.0 (0.0 to 17.6)
PR, No.; % (95% CI)	7; 25.9 (11.1 to 46.3)	5; 26.3 (9.1 to 51.2)
SD, No.; % (95% CI)	14; 51.9 (31.9 to 71.3)	8; 42.1 (20.3 to 66.5)
PD, No.; % (95% CI)	6; 22.2 (8.6 to 42.3)	6; 31.6 (12.6 to 56.6)
DCR (CR + PR + SD ≥ 6 months), No.; % (95% CI)	10; 37.0 (19.4 to 57.6)	5; 26.3 (9.1 to 51.2)
DCR regardless of SD duration, No. (%)	21 (77.8)	13 (68.4)
Median DOR, No.; months (range)	7; 17.1 (4.8 to ≥ 22.1+)	5; 10.8 (1.0 to ≥ 20.9+)
Median duration of SD, No.; months (range)	14; 5.6 (≥ 1.7+ to ≥ 12.9+)	8; 3.8 (≥ 1.7+ to ≥ 5.6+)

Abbreviations: CR, complete response; DCR, disease control rate; DOR, duration of response; ORR, objective response rate; PFS, progression-free survival; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

Hsu C et al. *J Clin Oncol*. 2017;35:4050–4056.

Keynote-028: Change from Baseline in Tumor Size



Hsu C et al. *J Clin Oncol*. 2017;35:4050–4056.

Keynote-028: Treatment-related Adverse Events

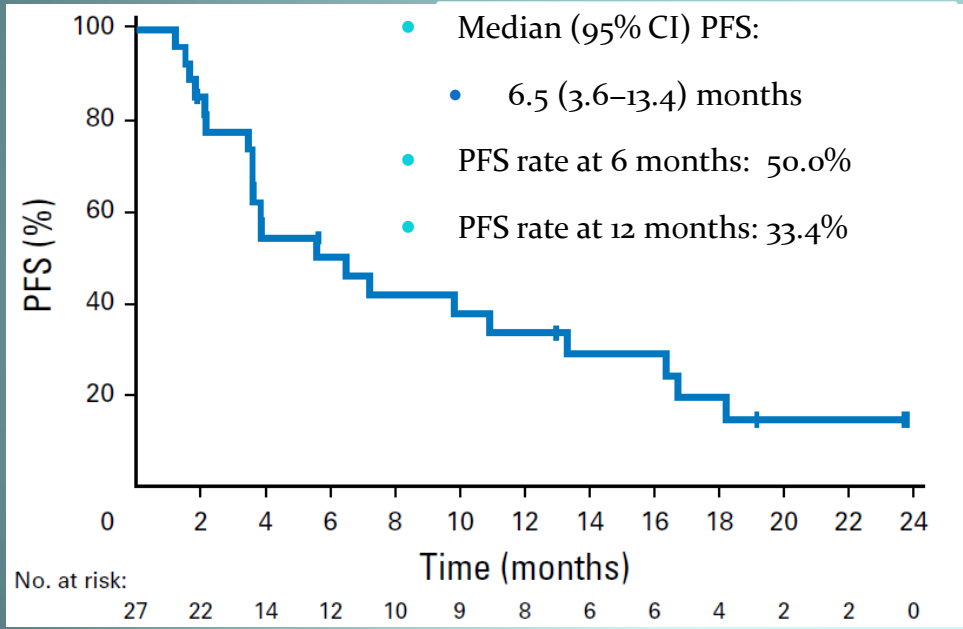
Treatment-Related Adverse Event (N = 27)	All Grades	Grade 3–5
All	20 (74.1)	8 (29.6)
Rash*	7 (25.9)	—
Pruritus	7 (25.9)	—
Pain†	6 (22.2)	1 (3.7)‡
Hypothyroidism§	5 (18.5)	—
Fatigue	5 (18.5)	—
Hepatitis§	3 (11.1)	2 (7.4)
Herpes zoster	3 (11.1)	—
Pneumonitis§	3 (11.1)	2 (7.4)
Myalgia	2 (7.4)	—
Cough	2 (7.4)	—
Diarrhea	2 (7.4)	—
Anemia	—	1 (3.7)
Sepsis	—	1 (3.7)
Blood creatine phosphokinase level increased	—	1 (3.7)
Proteinuria	—	1 (3.7)

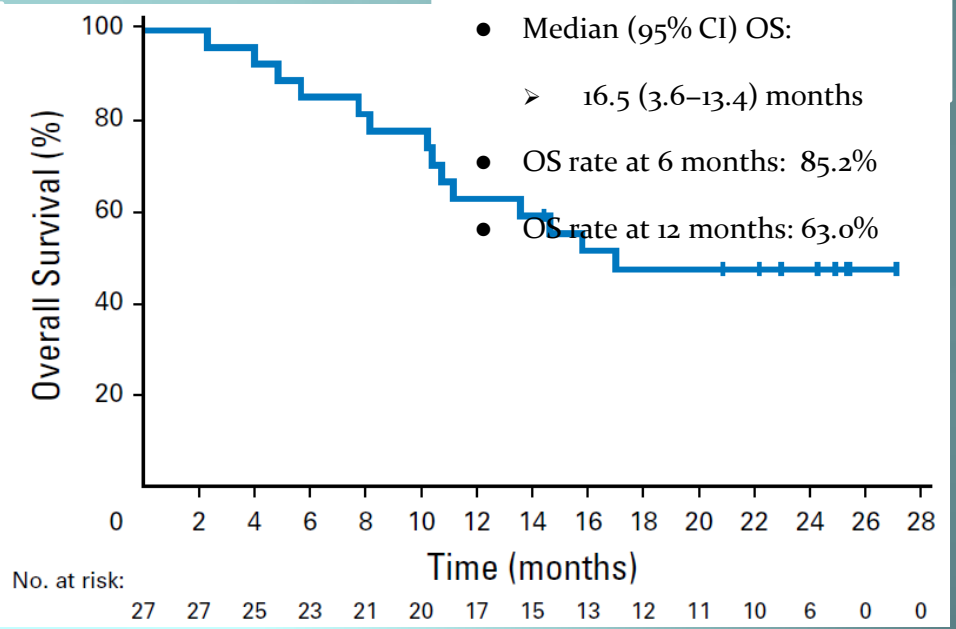
NOTE. Data are given as No. (%) unless otherwise noted.
*Includes macular (n = 1), maculopapular (n = 3), and nondescript (n = 3).
†Includes extremity (n = 1), jaw (n = 1), facial (n = 1), oropharyngeal (n = 1), abdominal (n = 1), and nondescript (n = 1).
‡Facial pain.
§Adverse event of special interest.

- One treatment-related death due to bacterial sepsis
- Five discontinuations due to treatment-related AEs: proteinuria (1), pneumonitis (1), hepatitis (1) and increased blood creatinine phosphokinase (2)

Hsu C et al. *J Clin Oncol*. 2017;35:4050–4056.

Keynote-028: Progression-free Survival and Overall Survival





Hsu C et al. *J Clin Oncol*. 2017;35:4050–4056.

Ongoing Phase 3 Trial – Keynote-122

Keynote-122 (NCT02611960): Trial Design

Phase 3, randomized, open-label study of pembrolizumab vs standard chemotherapy in patients with platinum pretreated recurrent/metastatic nasopharyngeal cancer

Patients:

- Histologically confirmed non-keratinizing differentiated NPC or undifferentiated NPC
- Metastatic disease or incurable locally recurrent disease
- Treatment with prior platinum therapy
- Tumor tissue available for PD-L1 testing
- Measurable disease based on RECIST v1.1
- ECOG PS of 0 or 1
- Adequate organ function
- Life expectancy of >3 months

RANDOMIZATION

1:1
n=230

Pembrolizumab
200 mg Day 1
Q3W x 35 cycles

Capecitabine 1,250 mg/m^2 BID on Days 1–14, Q3W x 35 cycles
or
Gemcitabine 1,000 mg/m^2 IV on Days 1 and 8, Q3W x 35 cycles
or
Docetaxel 75 mg/m^2 IV on Day 1, Q3W x 35 cycles

- **Primary end points**: PFS per RECIST v1.1, OS
- **Secondary end points**: ORR (RECIST v1.1), AEs, discontinuations due to AEs

AEs = adverse events; BID = twice daily; ECOG PS = Eastern Cooperative Oncology Group performance status; IV, intravenously; NPC = nasopharyngeal cancer ; PD-L1 = programmed death ligand 1;
Q3W = every 3 weeks; RECIST v1.1= Response Evaluation Criteria in Solid Tumors version 1.1.
ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02611960. Accessed August 17, 2018.

Pembrolizumab is not approved for NPC in HK

NCI-9742: Multicentre study of Nivolumab in recurrent and Metastatic NPC

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ORIGINAL REPORT

Antitumor Activity of Nivolumab in Recurrent and Metastatic Nasopharyngeal Carcinoma: An International, Multicenter Study of the Mayo Clinic Phase 2 Consortium (NCI-9742)

Brigette B.Y. Ma, Wan-Teck Lim, Boon-Cher Goh, Edwin P. Hui, Kwok-Wai Lo, Adam Pettinger, Nathan R. Foster, Jonathan W. Riess, Mark Agulnik, Alex Y.C. Chang, Akhil Chopra, Julie A. Kish, Christine H. Chung, Douglas R. Adkins, Kevin J. Cullen, Barbara J. Gitlitz, Dean W. Lim, Ka-Fai To, K.C. Allen Chan, Y.M. Dennis Lo, Ann D. King, Charles Erlichman, Jun Yin, Brian A. Costello, and Anthony T.C. Chan

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J.Y., B.A.C., and A.T.C.C. are joint senior authors.

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0732-183X/18/3614w-1412w/$20.00

A B S T R A C T

Purpose
This multinational study evaluated the antitumor activity of nivolumab in nasopharyngeal carcinoma (NPC). Tumor and plasma-based biomarkers were investigated in an exploratory analysis.

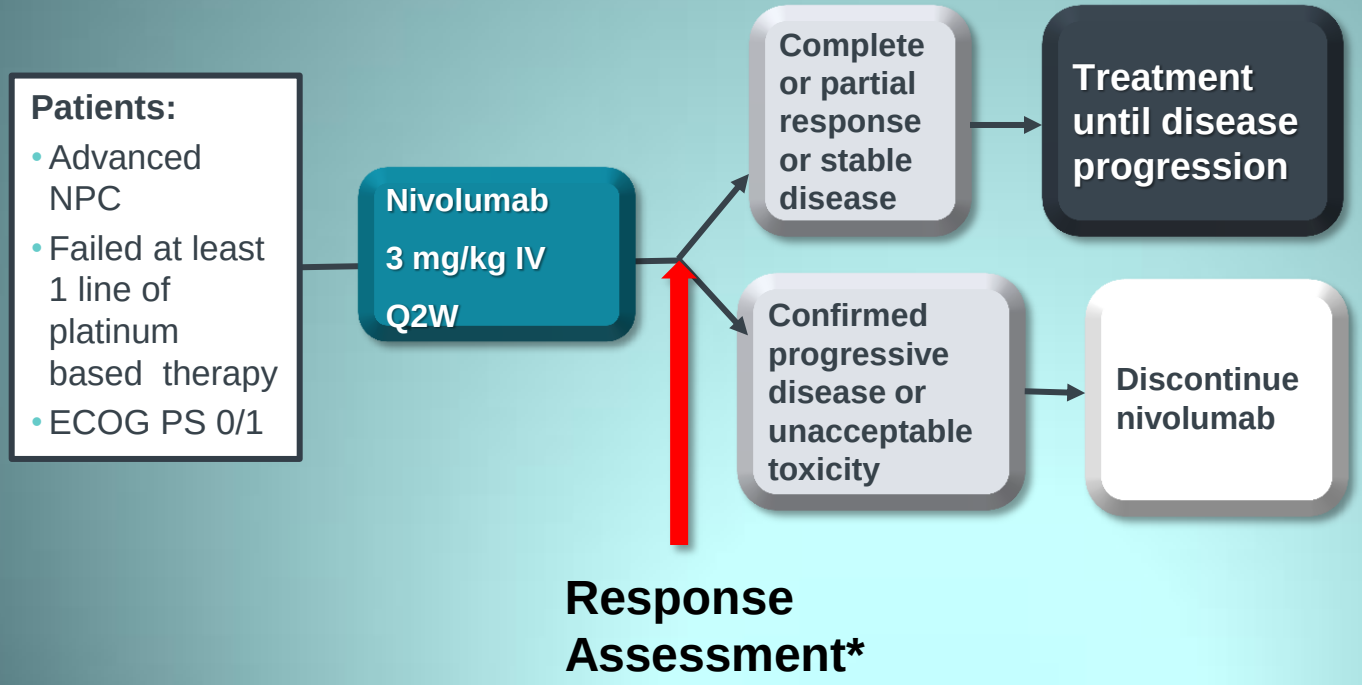
Patients and Methods
Patients with multiply pretreated recurrent or metastatic NPC were treated with nivolumab until disease progression. The primary end point was objective response rate (ORR) and secondary end points included survival and toxicity. The expression of programmed death-ligand 1 (PD-L1) and human leukocyte antigens A and B in archived tumors and plasma clearance of Epstein-Barr virus DNA were correlated with ORR and survival.

Results
A total of 44 patients were evaluated and the overall ORR was 20.5% (complete response, n = 1; partial response, n = 8). Nine patients received nivolumab for > 12 months (20%). The 1-year overall survival rate was 59% (95% CI, 44.3% to 78.5%) and 1-year progression-free survival (PFS) rate was 19.3% (95% CI, 10.1% to 37.2%). There was no statistical correlation between ORR and the biomarkers; however, a descriptive analysis showed that the proportion of patients who responded was higher among those with PD-L1 positive tumors (> 1% expression) than those with PD-L1-negative tumors. The loss of expression of one or both human leukocyte antigen class 1 proteins was associated with better PFS than when both proteins were expressed (1-year PFS, 30.9% *v* 5.6%; log-rank $P = .01$). There was no association between survival and PD-L1 expression or plasma Epstein-Barr virus DNA clearance. There was no unexpected toxicity to nivolumab.

Conclusion
Nivolumab has promising activity in NPC and the 1-year overall survival rate compares favorably with historic data in similar populations. Additional evaluation in a randomized setting is warranted. The biomarker results were hypothesis generating and validation in larger cohorts is needed.

J Clin Oncol 36:1412-1418. © 2018 by American Society of Clinical Oncology

NCI-9742: Multicentre study of Nivolumab in recurrent and Metastatic NPC



- ***Response assessment**: Every 8 weeks for the first 6 months; every 12 weeks thereafter
- EBV DNA
- **Primary end point:** ORR per RECIST v1.1
- **Secondary end points:** PFS, OS, duration of response, and safety

BB Ma et al. JCO 36: 1412-1418; 2018

NCI-9742: Multicentre study of Nivolumab in recurrent and Metastatic NPC

Table 1. Patient Characteristics

Characteristic	Data (%)
No. of patients	45
Median age, years (range)	57.0 (37.0-76.0)
Sex	
Male	35 (77.8)
Female	10 (22.7)
Race	
Asian	37 (82.2)
African American	1 (2.2)
Native Hawaiian/other Pacific Islander	1 (2.2)
White	4 (8.9)
Unknown/not reported	2 (4.4)
ECOG PS	
0	17 (37.8)
1	27 (60)
2	1 (2.2)
Histology (WHO)	
Undifferentiated NPC	25 (55.6)
Poorly differentiated NPC	12 (26.6)
NPC (not otherwise specified)	8 (17.8)
Most common sites of recurrent disease	
Lung	42 (95.5)
Liver	42 (95.5)
Bone	16 (36.4)
Lymph nodes	35 (79.5)
Nasopharynx	13 (29.5)
No. of prior lines of chemotherapy, median (range)	
Median (range)	3 (1-9)
1-2	17 (38.6)
3-4	16 (36.4)
> 5	11 (25)
Response to the last line of chemotherapy before study enrollment	
Responders to nivolumab (n = 9):	
CR or PR to last chemotherapy	3 (33.3)
SD or PD to last chemotherapy	6 (66.7)
Nonresponders to nivolumab (n = 35)	
CR or PR to last chemotherapy	6 (17.1)
SD or PD to last chemotherapy	29 (82.9)
Prior radical radiotherapy*	
Yes	37 (82.2)
No	8 (17.8)
No. of nivolumab cycles, median (range)	3 (1-24)
Follow-up for 44 evaluable patients	
Progression	35 (79.5)
No progression	9 (20.5)
Alive	28 (63.6)
Dead	16 (36.4)
Reasons for withdrawal from study for the 44 evaluable patients	
Still receiving treatment	5 (11.1)
Adverse events/ toxicity	4 (10.3)
Intercurrent illness	1 (2.6)
Death	1 (2.6)
Disease progression	27 (69.2)
Patient refusal	3 (7.7)
Reasons not specified	3 (7.7)

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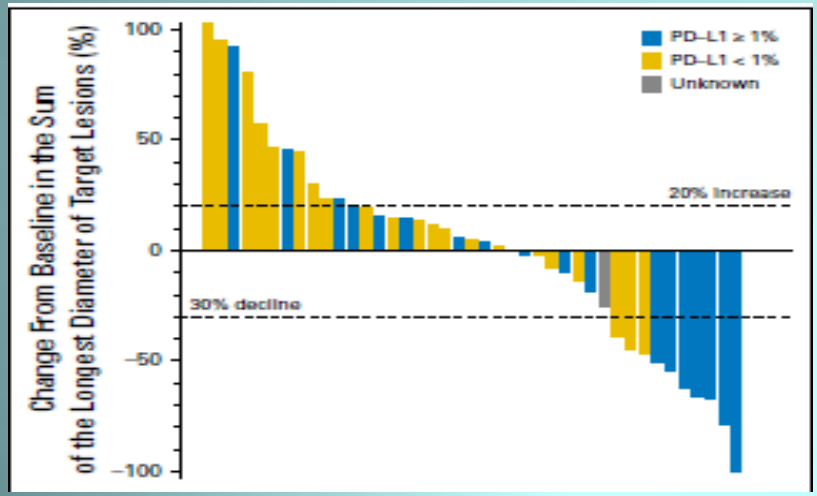
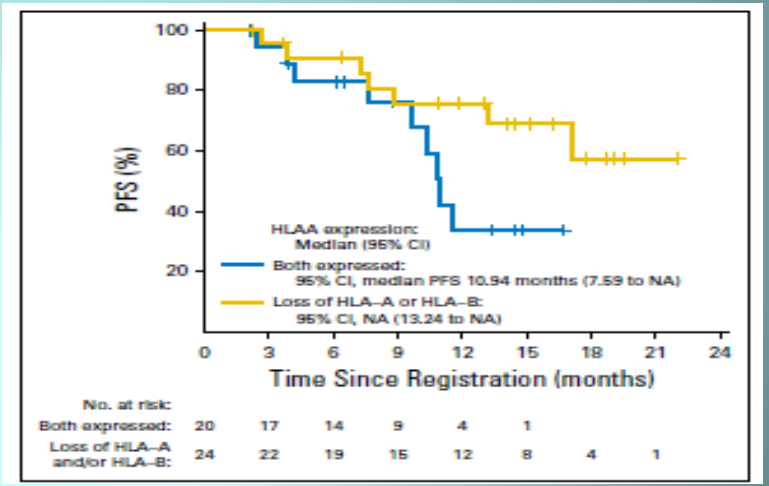
NCI-9742: Multicentre study of Nivolumab in recurrent and Metastatic NPC

44 patients evaluable, ORR: 20.5% (CR 1, PR 8). 1y OS: 59%, 1yr PFS: 19.3%
PD-L1 positive (>1% expression): higher RR
Loss of HLA class 1 protein expression associated with better PFS
Rate of EBV DNA clearance did not predict for response





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Future direction for IO treatment

- Combination treatment
  - Chemotherapy +IO
  - Radiotherapy + IO
  - T cell therapy +IO
  - Combination of IO
  - Combination of target +IO

- Biomarker research