A Phase Ib Proof-of-Concept study of LBH589 (LBH) and everolimus (EVE) in Advanced Solid Tumors enriched for Epstein-Barr Virus (EBV) related Cancers

Daniel SW Tan[1], Quan Sing Ng[1], Dawn QQ Chong[1], Guek Eng Lee[1], Thuan Tong Tan[2], Noan Minh Chau[1], Mei-Kim Ang[1], Liz Zhong[1], Balram Chowbay[1], John Connolly[3], Eng-Huat Tan[1], Wan-Teck Lim[1]

[1]National Cancer Centre, Singapore; [2]Singapore General Hospital, Singapore; [3]Singapore Immunology Network, Agency of Science, Technology and Research, Singapore

1. ABSTRACT

Background: Histone deacetylase and mTOR inhibition circumvent critical EBV- oncogenic pathways with preclinical studies demonstrating lytic induction in EBV infected cells, as well as immunomodulatory and antiangiogenic effects. **Methods:** Patients (Pt) with advanced solid tumors enriched for EBV–related cancers were enrolled to determine safety, tolerability, maximum tolerated dose (MTD), pharmacokinetics (PK), pharmacodynamics and preliminary antitumor activity. LBH was instituted 7-days prior to combination treatment. NPC pt received antiviral prophylaxis of either acyclovir (Ac) or valaciclovir (Vc). Serum EBV DNA levels (EBNA-1) were measured weekly and plasma cytokines profiled using a 31-plex Luminex panel. **Results:** 15 pt have been treated (M:F 13:2, median age 50, R: 38- 63) 10 NPC, 5 non-NPC (colon, RCC, breast, gastric, sarcoma) at 3 dose levels – LBH (3x/wk)-EVE (daily):10-2.5, 10-5, 15-5. Two dose limiting toxicities of G4 (grade) thrombocytopenia were observed at LBH15-RAD5. Significant adverse events (AE) (G≥3) were dysphagia (1) and thrombocytopenia (3). Common AEs (G1/2) included fatigue (80%), anorexia (60%), mucositis (53%), xerostomia (26%), dysphagia (26%). Two minor responses were seen (1 NPC, 1 breast) and 2 pt (1 NPC, 1 RCC) had prolonged stable disease (>16 weeks). Modulation of EBV DNA titres was seen only in NPC pt, with median fold-change from baseline of 10.9 (0.05-174). Pt on Ac prophylaxis (n=5) had significant increases in DNA titres (9-174 fold), while those on Vc (n=4) were less pronounced (0.05-11 fold, p<0.03), with one pt (with minor response) having persistent decline in EBV titres. In a limited pt subset (n=9, 30 timepoints), plasma cytokine profiles were consistent with a T-cell response, specifically, elevated levels of FLT3L, IFN-gamma, IL-13 and IL-17. PK and PBMC target modulation studies are being analysed. **Conclusions:** LBH-EVE results in induction of EBV DNA titres with an associated host T cell response. MTD is LBH10- EVE5 in Asian pt, majority of whom had NPC. A pre-planned expansion cohort that incorporates multi-parametric functional imaging exploring two schedules of LBH in combination with EVE5 is ongoing.

2. BACKGROUND

- EBV is closely associated with nasopharyngeal carcinoma (NPC) pathogenesis in endemic regions of the world.
- Standard treatment for metastatic NPC comprises of gemcitabine or taxane-based chemotherapy with median survival of 16.0 months.
- Lytic gene expression can be modulated by histone modifications.
- LMP1 and 2A are viral oncoproteins that signal through key survival cell signaling pathways including mTOR.
- We hypothesized that 1) LBH589 can cause EBV lytic induction in EBV positive NPC cells and consequent cell death. 2) Everolimus (EVE) inhibits mTOR activated pathways associated with LMP expression.

3. OBJECTIVES

Primary
- To determine the safety, tolerability and recommended Phase 2 dose (RP2D) of the combination of EVE and LBH589 in all solid tumors (with enrichment for EBV-driven tumors).

Secondary
- To determine the pharmacokinetic (PK) profile of EVE in combination with two schedules of LBH589.
- To assess the preliminary anti-tumor activity of EVE and LBH589.

Exploratory
- Explore the hypothesis that HDACi and mTOR inhibitors abrogate the effects of key viral proteins, and switch the virus from a latent proliferative phase to a lytic phase. Immunologic correlates will also be examined.

4. PATIENTS & STUDY DESIGN

Study Design
- 3+3 design with enrichment for EBV positive patients
- Lead in period for LBH589 (7-days), followed by EVE daily
- Weekly EBV titres
- In pt with NPC, they were commenced on antivirals at start of trial
  - Acyclovir 400 mg tds switched to valaciclovir 500 mg BD (1 g TDS if titres increase by 1 log)
- Immunologic cytokine assays evaluated at baseline, D1, D22

Patient Demographics (n=15)

Median Age	50 (38-63)
M/F	13/2
ECOG 0/1/2	9/6/0
Prior radiotherapy	9/15
Prior chemotherapy	15/15
1 line	0
2 lines	2
3 lines	2
≥ 4 lines	11
Tumor Types	
NPC	10
Breast	1
RCC	1
Sarcoma	1
Colon	1
Gastric	1
NPC patients (n=10)	
Prior chemoRT	7
Aciclovir	6
Valaciclovir	4

5. SAFETY & TOLERABILITY

Table 1: Incidence of adverse events in cycle 1.

Adverse Event	n (%) Grade 1	Grade 2	Grade 3	Grade 4	All grades (%)
Fatigue	9	2	-	-	11 (73)
Anorexia	6	3	-	-	9 (60)
Mucositis	4	3	-	-	7 (47)
Xerostomia	2	-	-	-	2 (13)
Dysphagia	2	-	1	-	3 (20)
Constipation	1	1			2 (13)
QTc prolongation	1	1	-	-	2 (13)
Voice change	2	-	-	-	2 (13)
Thrombocytopenia	1	2	3	2	8 (53)
Epistaxis	2	-	-	-	2 (13)
Haemoptysis	2	-	-	-	2 (13)
Weight loss	2	-	-	-	2 (13)

Table 2: Occurrence of adverse events by dose level.

	DL1 LBH589 10 RAD001 2.5								DL2 LBH589 10 RAD001 5								DL3 LBH589 15 RAD001 5							
No of patients	6								6								5							
Treatment period	1st cycle				Cycle 2 onwards				1st cycle				Cycle 2 onwards				1st cycle				Cycle 2 onwards			
Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Fatigue	1	1							5				1	1			3	1			2	1		
Anorexia	1	1							2	1			2	1			4	1			1			
Mucositis	1								3	1			2				2	1			3			
Xerostomia	1								1				2											
Dysphagia													1					1			2			
QTc prolongation										1							1							
Thrombocytopenia									1	1	1		1					1	2	2	1	1		
Anaemia														1										
Neutropenia																					1			
Rash			1										1											
Athralgia			1																					
Weight loss	1								1															
Epistaxis																	2							

According to dose level; worse grade per patient; DLT indicated in red

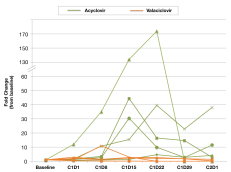
6. DLTs & RP2D

- 2 dose limiting toxicities (DLT) of Grade 4 thrombocytopenia was seen at LBH589 15 mg 3 times per week and RAD001 5 mg once daily
- The recommended phase II dose is LBH589 (10) - EVE (5)

7. PHARMACODYNAMICS

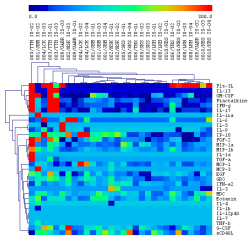
(I) Serial EBV titres

- All 5 non-NPC patients did not show increase in EBV DNA titres
- Those on valaciclovir had attenuated increment in EBV titres, despite being at higher dose levels (p<0.03)
- No significant additional toxicity



(II) Plasma cytokine profiles

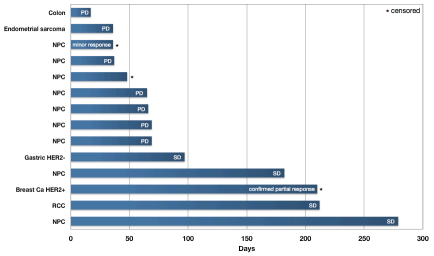
- 31-plex luminex panel (heatmap shown on right)
- 9 patients, 30 timepoints
- Elevated levels of
  - FLT3L
  - IFN-gamma
  - IL-13
  - IL-17
- Consistent with polyfunctional T cell response



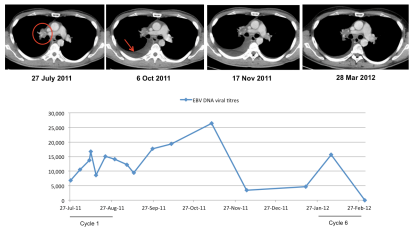
8. ANTI-TUMOR ACTIVITY

Median Progression Free Survival: **9.4 weeks 95% CI [8.7 – 10.1]**

Figure: Duration on treatment; Best RECIST response (in bars)



Pt 012: 37 year old malay man, metastatic undifferentiated NPC on LBH589 10 mg and EVE 5 mg; PFS: 9.3 months



9. CONCLUSION

- RP2D is LBH589 10 mg 3 times per week and Everolimus 5 mg OM in Asian patients; PK studies are ongoing
- Pharmacodynamic studies suggest latent-lytic switch with a concomitant T cell response observed
- Currently, trial is in dose expansion, incorporating multiparametric functional MRI to evaluate anti-angiogenic effects of LBH589-RAD001

10. ACKNOWLEDGEMENTS

We would like to acknowledge the support of Early Clinical Research Unit, Department of Medical Oncology, and Investigational Medicine Unit, Singhealth. Also, our gratitude is extended to our patients and their families for participating in this study.

Please direct any queries to Dr Daniel Tan, Department of Medical Oncology, National Cancer Centre Singapore, 11 Hospital Drive, S(169610) Email: daniel.tan.s.w@nccs.com.sg