SINGAPORE 2023 ESMO ASIA

A Phase 1b/2 Study of Nanatinostat (Nstat) Plus Valganciclovir (VGCV) in EBV+ Solid Tumors and with Pembrolizumab (PEM) in Recurrent/Metastatic Nasopharyngeal Carcinoma (R/M NPC)

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DECLARATION OF INTERESTS

A. Dimitrios Colevas

Research Support:

Abbvie, AdPNP, Astra Zeneca, ATARA Biotherapeutics , BioNTech, Bristol-Squibb Pharmaceuticals, CellSight Technologies, Inc, Cue Biopharma, Inc., Cullinan, Exelixis, Forty Seven, Inc./Gilead, Incyte, Innate Pharma, National Institutes of Health, Replimune, Tessa Therapeutics , Threshold Pharmaceuticals, **Viracta**

Consulting:

Aduro Biotech, Inc, Aravive, ATARA Biotherapeutics, BeiGene, Ltd, Clarion, COTA, Inc, Cue Bipharm, Inc, Galera Therapeutics, Gilead, IQVIA RDS, Inc, KeyQuest Health, LOXO Oncology, McGivney Global Advisors, PDS Biotech, Pfizer, PRA Health Sciences

Epstein-Barr Virus (EBV): A High Global Cancer Priority

EBV+ malignancies account for ~2% of all new cancer cases globally

EBV positivity, by lymphoma subtype[1]	
Peripheral T-cell* lymphoma (PTCL)	**40-65%**
Diffuse large B-cell lymphoma (DLBCL)	**5-15%**
Post-transplant lymphoproliferative disorders (PTLD)	**60-80%**

EBV positivity, by solid tumor subtype[2]	
Nasopharyngeal carcinoma (NPC)	**75-95%**
Gastric cancer (GC)	**8-10%**

~90% of the adult population are infected with EBV

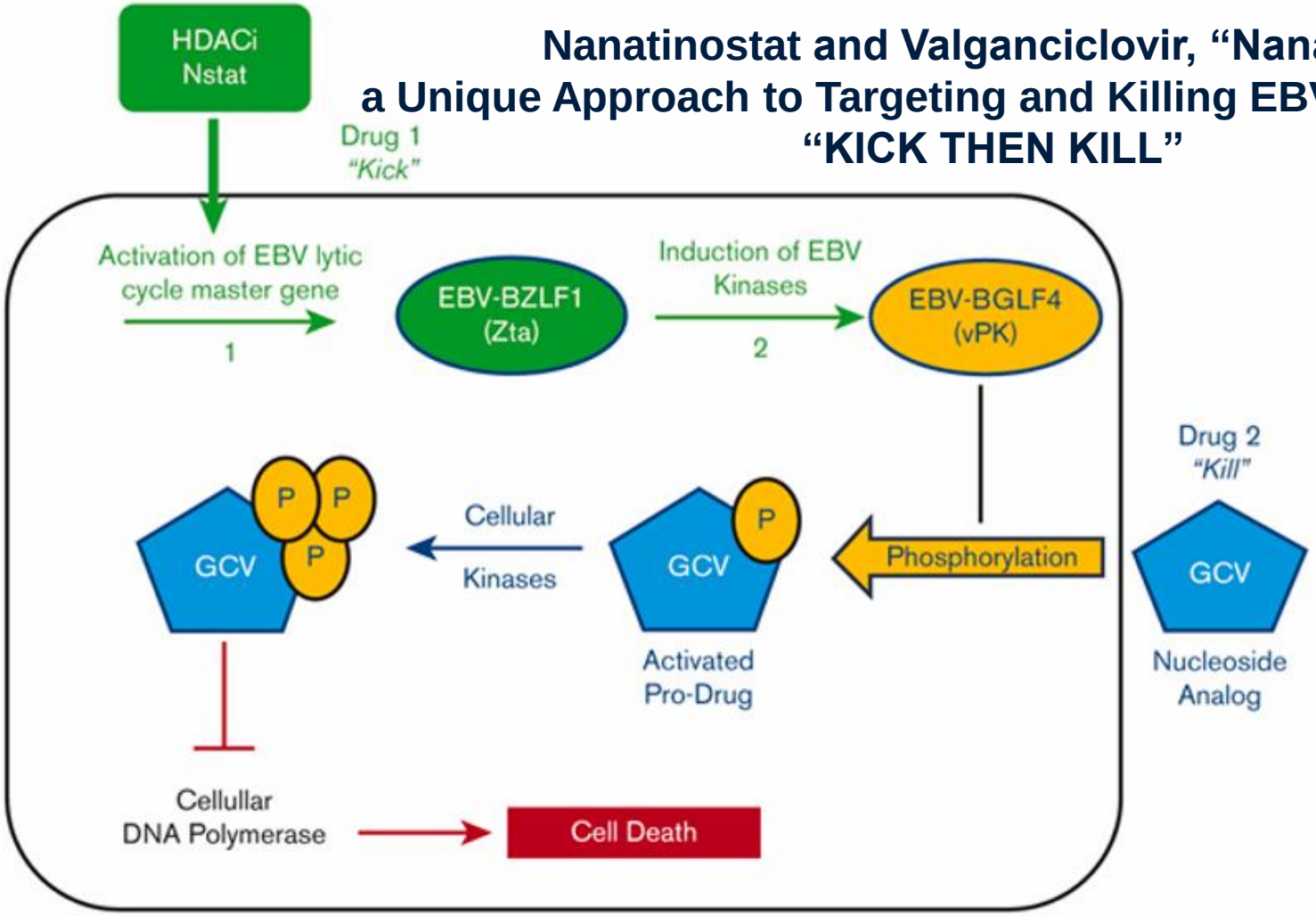
Latency confers resistance to anti-viral therapies and facilitates evasion of immune detection

>300,000 new cases/year of EBV+ lymphomas and solid tumors[2]

Responsible for **~180,000 cancer** deaths/year[2]

[1]PMID: 27943278; PMID: 16902151; WHO. (2017). WHO classification of tumours of haematopoietic and lymphoid tissues (Revised 4th ed., Vol. 2). IARC;
[2]PMID: 34705104; PMID: 29556258; PMID: 32868361

Nanatinostat and Valganciclovir, "Nana-val": a Unique Approach to Targeting and Killing EBV+ Cancer Cells "KICK THEN KILL"



Blood Adv (2023) 7 (20): 6339–6350.

Nstat not just another HDACi

Nanatinostat Unique Properties Relative to Approved HDAC Inhibitors

- Nstat specifically targets HDAC1, HDAC2 and HDAC3
- **Nstat** is an oral drug

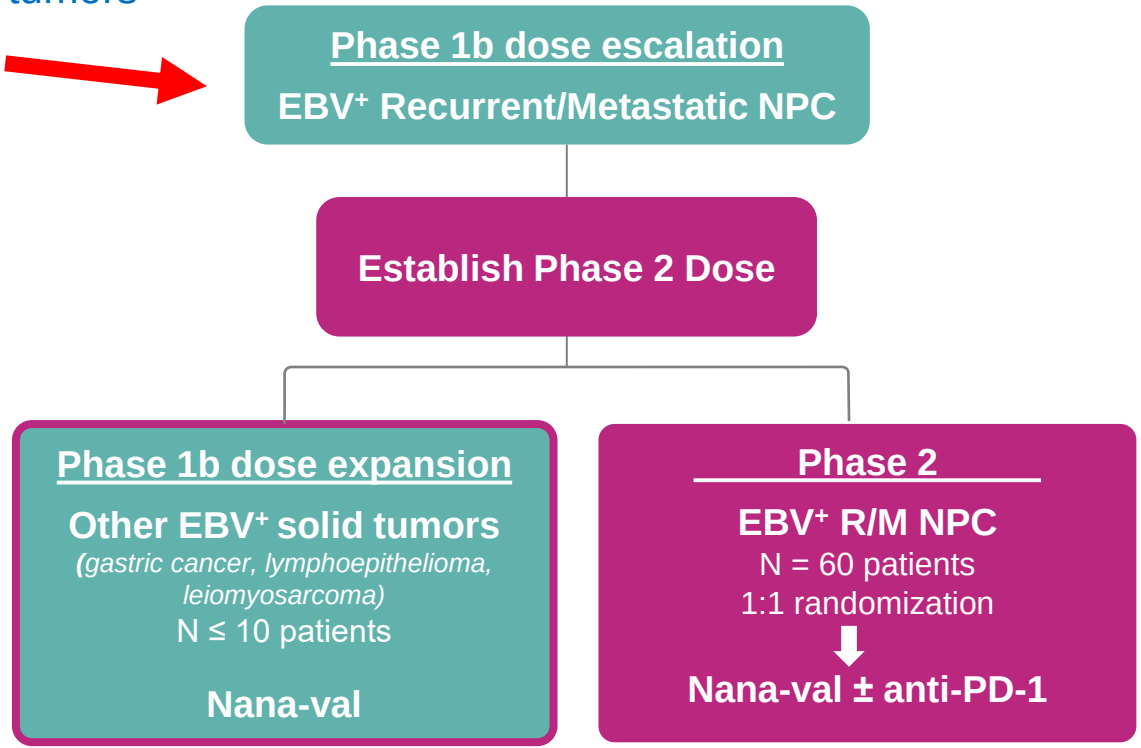
IC_{50} (nM)

Class	HDAC subtype	Nstat	FDA Approved HDACi				NaBu
			Vorinistat	Belinostat	Panobinostat	Romidepsin	
I	HDAC1	3	30	41	3	36	>10,000
	HDAC2	12	24	125	3	47	NI
	HDAC3	12	150	30	4	NI	>10,000
IIa	HDAC8	860	1524	216	248	NI	>10,000
	HDAC4	1000	101	115	12	NI	>10,000
	HDAC5	200	3000	NI	NI	NI	NI
	HDAC7	1600	104	67	14	NI	NI
	HDAC9	440	107	128	3	NI	NI
IIb	HDAC6	2100	30	82	61	>10,000	>10,000
	HDAC10	NI	63	NI	NI	NI	>10,000
III	SIRT 1-7	NI	NI	NI	NI	NI	NI
IV	HDAC11	2800	NI	NI	NI	NI	NI

NI: No Inhibition NaBu: Sodium Butyrate

Nana-val Study “301”: Phase 1b/2 Trial in Advanced EBV+ Solid Tumors

To evaluate the safety, tolerability, PK, and preliminary antitumor activity of Nanatinostat, a potent HDAC 1,2,3 selective inhibitor plus valganciclovir in patients with advanced EBV+ solid tumors



Endpoints:

- Primary:
  - Phase 1b: Incidence of dose-limiting toxicities
  - Phase 2: Overall response rate by RECIST v1.1
- Key Secondary:
  - Incidence and severity of AEs
  - Duration of response
  - Progression-free survival
  - Pharmacokinetic parameters

NCT05166577

R/M EBV+ NPC Phase 1b Dose Escalation Schedule

Dose Level	Nanatinostat Oral Dose (Days 1-4/wk)	VGCV Oral Dose	N
1	20 mg QD	900 mg QD	3
2	30 mg QD	900 mg QD	4
3	40 mg QD	900 mg QD	3
4	10 mg split dose	900 mg BID x 21 d, then QD	3
5	20 mg / 10 mg split dose	900 mg BID x 21 d, then QD	4

Nana-val has been Generally Well-Tolerated at all Dose Levels

Preliminary safety data/absence of DLTs support continued dose escalation to determine RP2D

Treatment-Related Adverse Events

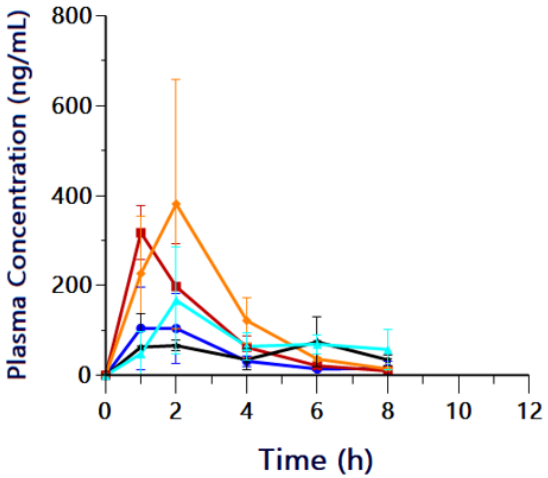
	Dose Level 1 (n=3)		Dose Level 2 (n=4)		Dose Level 3 (n=3)		Dose Level 4 (n=3)		Dose Level 5 (n=4)	
	G1-2	G3-4	G1-2	G3-4	G1-2	G3-4	G1-2	G3-4	G1-2	G3-4
Nausea	1		2		2		1		1	
Decreased appetite	1		1		1		2		2	
Creatinine increased	1		2						2	
Fatigue	1		2			1	1			
Anemia	1		1							1
Lymphopenia			1				1	1		
Vomiting					2		1			

RP2D: Recommended Phase 2 Dose; DLT: Dose-Limiting Toxicity

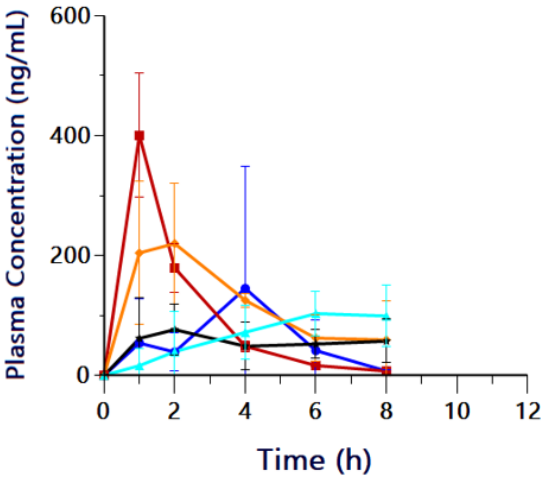
Nstat preliminary pharmacokinetics

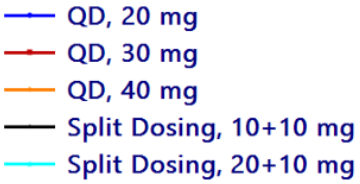
Nanatinostat Mean Plots

VRx-3996, C1D1

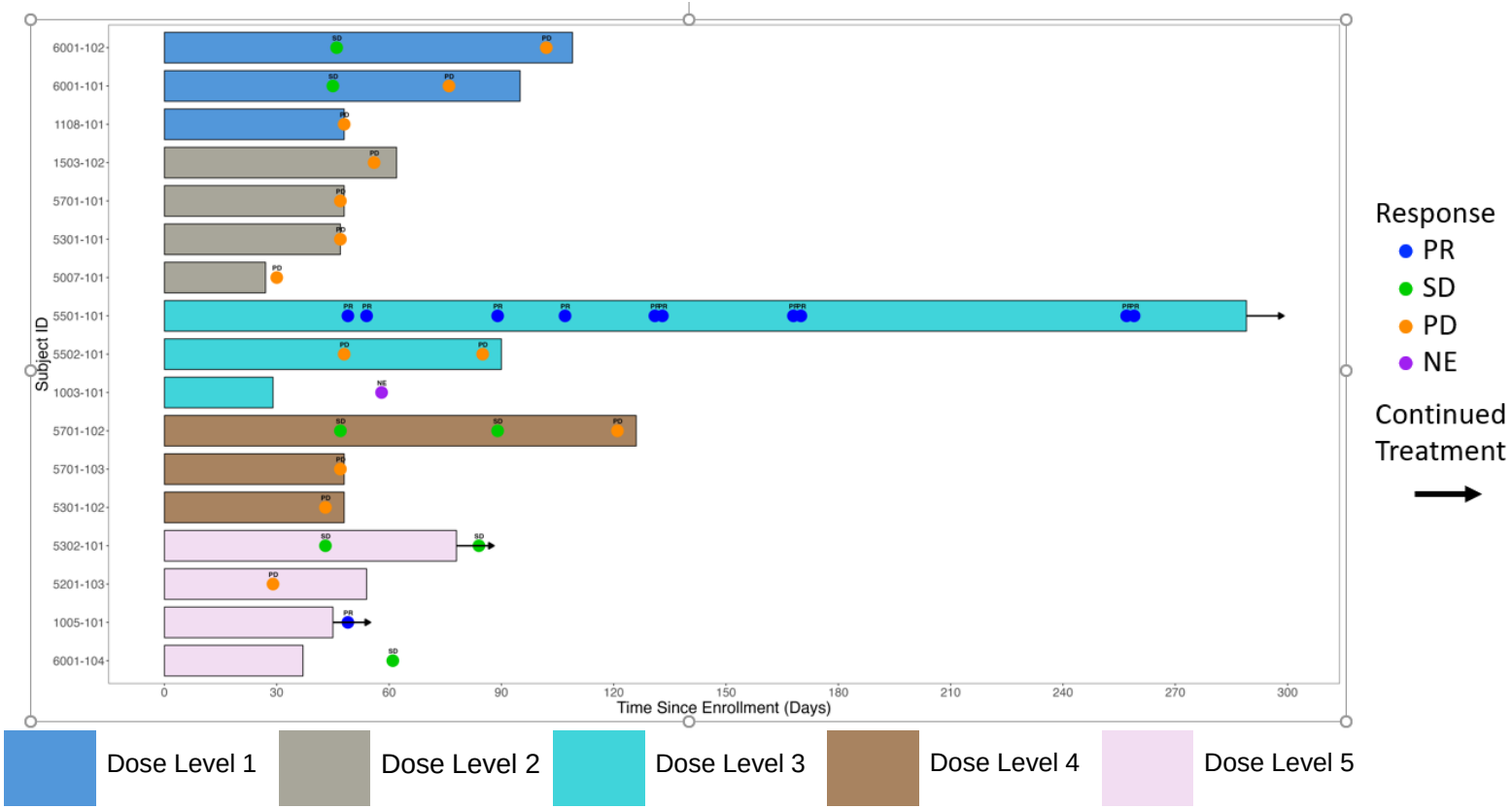


VRx-3996, C2D1





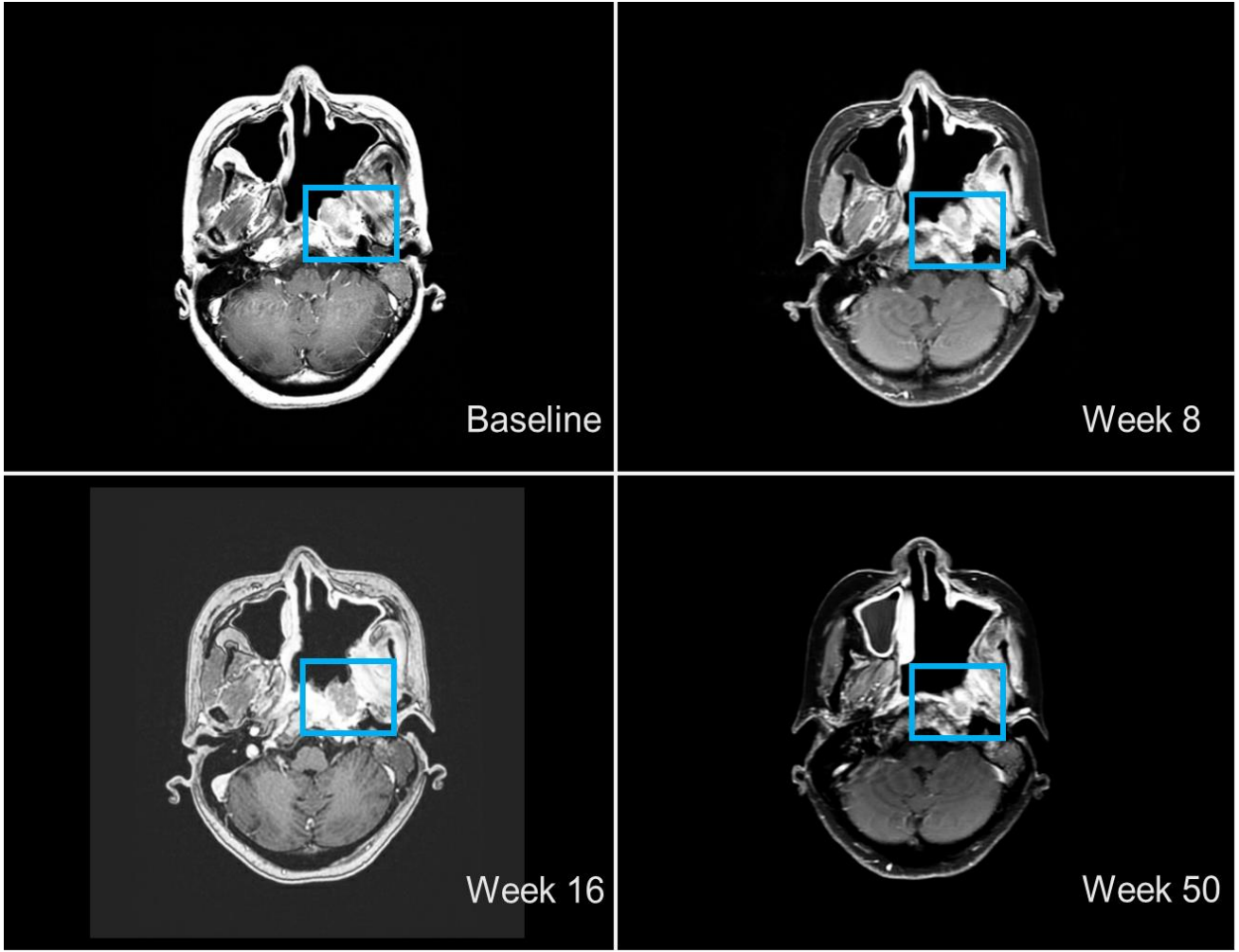
Nana-val “301” Swimmer Plot: All Dose Levels
Data Cutoff: 28-JUL-2023



Confirmed Partial Response at Dose Level 3

>50% reduction in tumor size at 8-50 weeks

- 44-year-old female with locally recurrent EBV+ NPC
- Disease previously progressed through chemoradiation therapy then combination chemotherapy
- Treated with nanatinostat 40 mg QD Days 1-4/week + VGCV 900 mg QD



Courtesy of Muh-Hwa Yang, MD, PhD and Peter Mu-Hsin Chang, MD, PhD, Taipei Veterans General Hospital

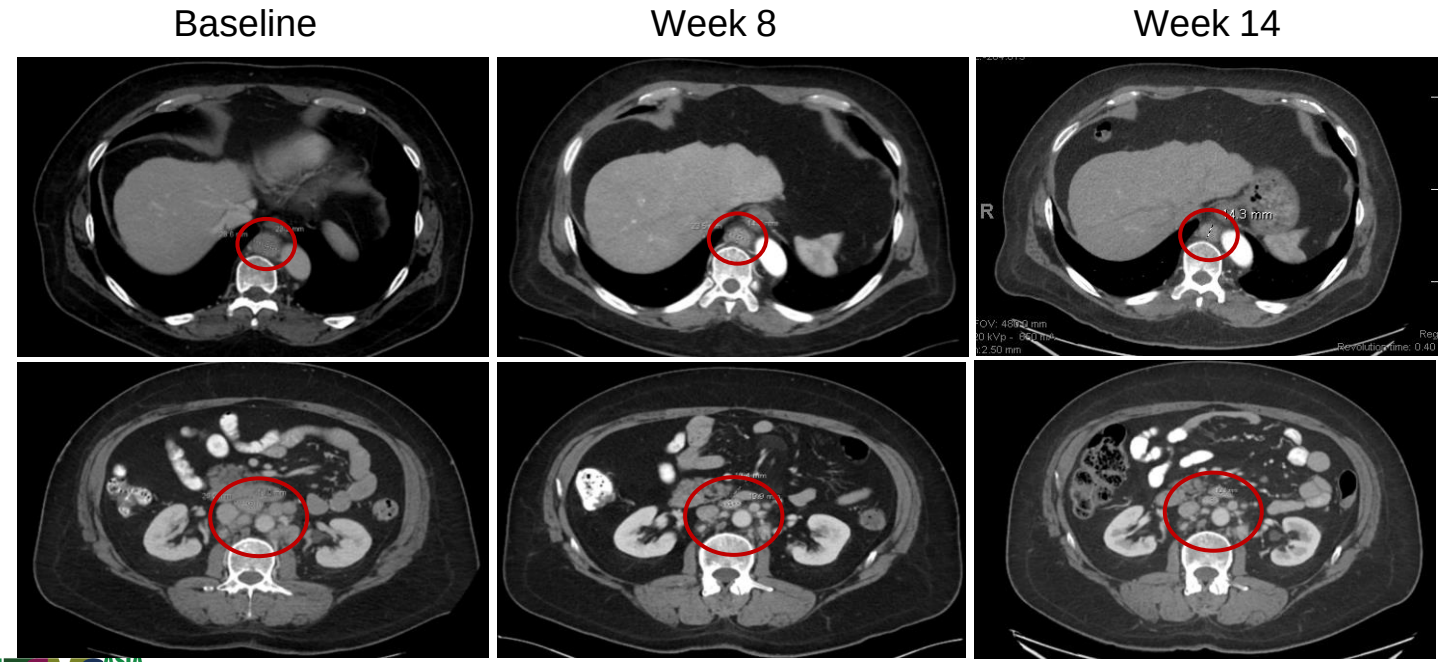
Confirmed Partial Response at Dose Level 5

~30-40% reduction in tumor size at 8-14 weeks

56-year-old male with R/M EBV$^+$ NPC

Disease previously progressed through chemoradiation therapy then chemoimmunotherapy

Treated with nanatinostat 20 mg/10 mg split dose Days 1-4/week + VGCV 900 mg BID x 21 days then 900 mg QD

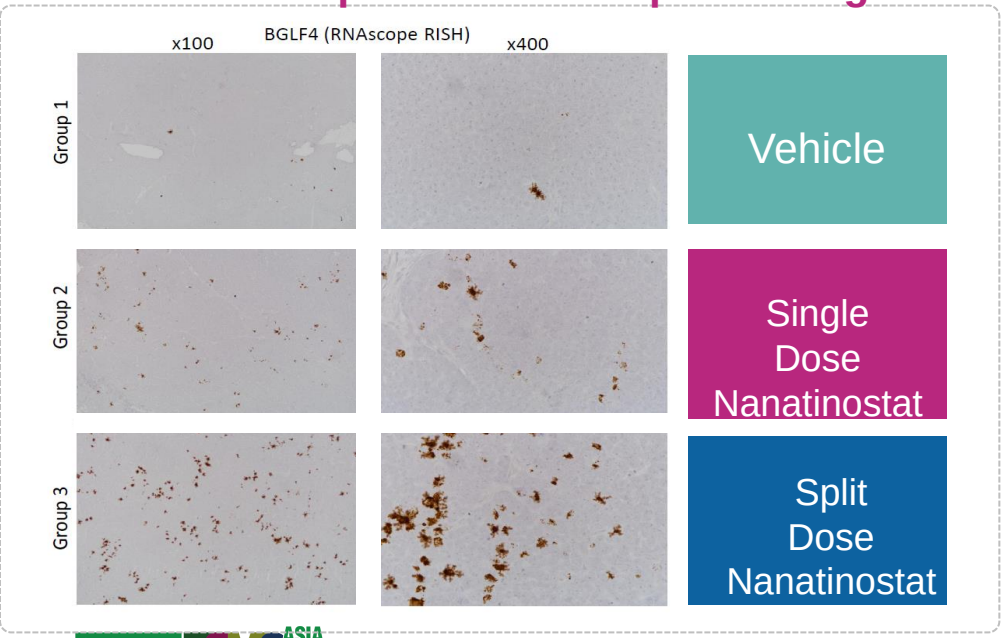


Courtesy of Dr. Renata Ferrarotto, MD Anderson Cancer Center

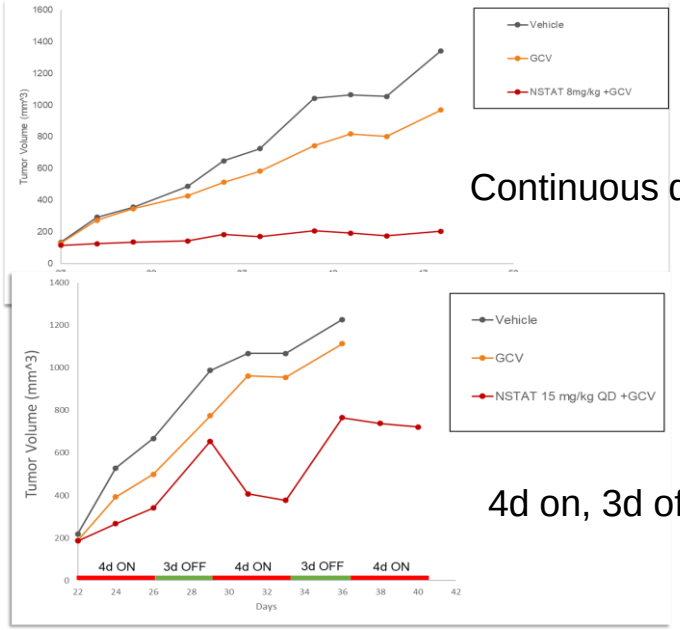
Rationale for Split Daily Dosing (SDD) of Nanatinostat in Combination with Valganciclovir

Preclinical data provides supporting evidence to evaluate a new dosing regimen (2023 AACR-KCA Joint Conference on Precision Medicine in Cancer, Abstract AK23_00556)

BGLF4 optimized with Split Dosing



Daily Dosing (vs. Intermittent Dosing)



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Planned Implementation of Split Daily Dosing (SDD) Strategy into Phase 1b

Up to 3 additional dose levels planned to determine RP2D in the absence of DLTs through Dose Level 5

Dose Level	Nstat Oral Dose	VGCV Oral Dose
8	**40 mg / 40 mg SDD**	**450 mg / 450 mg SDD**
7	**30 mg / 30 mg SDD**	**450 mg / 450 mg SDD**
6	**20 mg / 20 mg SDD**	**450 mg / 450 mg SDD**
5	20 mg / 10 mg split dose (4 days/wk)	900 mg BID x 21 d, then QD
4	10 mg split dose (4 days/wk)	900 mg BID x 21 d, then QD
3	40 mg QD (4 days/wk)	900 mg QD
2	30 mg QD (4 days/wk)	900 mg QD
1	20 mg QD (4 days/wk)	900 mg QD

QD: Once daily; BID: Twice daily

Thank You (谢谢)

The clinical investigators would like to thank ESMO Asia for selection of our abstract, the patient participants, their families, our clinical research staff and the Viracta sponsor team.

END

Backup slides

BACKUP SLIDE .NANATINOSTAT VS OTHER HDACi

Comparison to other HDACis

Lower Dose, Stronger IP, Broader Indications, Better Efficacy, Less Toxic

Brand	Nana-val	Zolinza	Beleodaq	FARYDAK	ISTODAX
Molecule	**Nanatinostat + Valgan (antiviral)**	Vorinitstat	Belinostat	Panobinostat	Romidepsin
Company	**Viracta**	Merck	Acrotech	Novartis	Celegene(BMY)
Patent Expiration	**2040**	Expired	2026	2026	Expired
Route of Administration	**Oral**	Oral	Injection	Oral	IV
Dosing	**20mg – using lowest dose (MTD 80mg)**	400mg daily (100mg Capsules)	1,000 mg/m2 30 min infusion QD on days 1-5 of a 21-day cycle	20 mg, taken orally once every other day for 3 doses per week (on Days 1, 3, 5, 8, 10, and 12) of Weeks 1 and 2 of each 21-day cycle for 8 cycles	14 mg/m2 administered intravenously (IV) over a 4-hour period on days 1, 8 and 15 of a 28-day cycle. Repeat cycles every 28 days
Indication	**EBV Malignancies (T-cell, B-cell, Solid tumor)**	Cutaneous T-cell Lymphoma (CTCL)	Peripheral T-cell lymphoma (PTCL)	Multiple Myeloma +Bortezomib +Dexamethasone	Cutaneous T-cell Lymphoma (CTCL)
Efficacy	**ORR = 40% (60% T-cell) Median dur of res 10.4 months**	ORR=24%-29% Median dur of resp 106 days	CR+PR = 25% Median dur of resp 8.4 months	ORR 59% (drug) vs 41% (PBO) PFS= 10.6mon vs 5.8 mon (PBO)	ORR = ~35% CR = 6% Median dur of resp 14-15 months
Safety Warnings	**TDB**	Thromboembolism Myelosuppression GI tox Hyperglycemia Severe Thrombocytopenia Embryo-Fetal Toxicity	Heme toxicity Infection Hepatotoxicity Tumor lysis syndrome Embro-fetal toxicity	Black Box for Severe Diarrhea and CV Tox Memorrahe Hepatotoxicity Embryo-Fetal Toxicity	QT prolongation Heme tox Embryo-Fetal Toxicity Binds to estrogen receptors. May reduce the effectiveness of estrogen-containing contraceptives

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