Combination of Oral Nanatinostat (Nstat), a Novel Histone Deacetylase Inhibitor (HDACi), and the Oral Anti-Viral, Valganciclovir (VGCV), Is Active in Relapsed/Refractory (R/R) Epstein-Barr Virus (EBV)-Positive B-Cell, T-Cell, and Hodgkin Lymphoma: Interim Safety and Efficacy Results from a Phase 1b/2a Study

Pierluigi Porcu, MD, Brad M. Haverkos, MD, MPH, MS, Onder Alpdogan, MD, Marcelo Capra, MD, PhD Tatyana A. Feldman, MD, Elizabeth Brem, MD, Anusha Vallurupalli, MD, Jonathan E. Brammer, MD, Ana Schriefer, MD, Juliana Pereira, MD, PhD, Anil Tulpule, MD, Stefan K. Barta, MD, MRCP, MS, Locke J. Bryan, MD, Richard Trauger, PhD, Sebastian Obrzut, MD, John Gutheil, MD, Afton Katkov, MSc, Robert McRae, Ivor Royston, MD and Douglas V. Faller, MD, PhD
EBV: A High Global Cancer Priority

• International Agency Research on Cancer\(^1\)
  • EBV classified as Group 1 human carcinogen

• NIH Conference 2015\(^2\)
  Recommendations:
  1. Research on pathogenesis
  2. Mouse models
  3. Biobanks and repositories
  4. Vaccine Development

• Cancer Research UK: 2016 Report\(^3\)
  Priorities
  • Eradicating EBV-related Cancers
  • Vaccine Development

High global burden of EBV-attributable cancer deaths:

• ~200,000 new cases/year of EBV-associated malignancies
• ~143,000 cancer deaths annually,
• 1.8% of all cancer deaths worldwide in 2010

\(^1\) [www.iarc.fr/research-groups-inf-icb-rationale/](http://www.iarc.fr/research-groups-inf-icb-rationale/)
\(^3\) [www.cancerresearchuk.org/](http://www.cancerresearchuk.org/)
EBV Detection and Prognostic Significance

EBV positivity is detectable by in situ hybridization for EBV encoded RNA (EBER-ISH) in B cell, T cell, and NK cell lymphomas, and Hodgkin Lymphoma

EBV positivity correlates with shortened survival in HL, PTCL, and DLBCL

Mechanistic Rationale for Nstat + VGCV Combination in EBV-associated lymphomas

Step 1: Activation of EBV Lytic Cycle Master Gene

- EBV-BZLF1 (Zta)

Step 2: Induction of EBV Kinases

- EBV-BGLF4 (vPK)

Drug 1 “Kick”

GCV

Cellular DNA Polymerase

Cell Death

Drug 2 “Kill”

GCV

Nucleoside Analogs

Until every cancer is cured

HDACi, Nstat

Tumor Cell With Latent EBV

GCV

Phosphorylation

Activated Pro-Drug

Induction of EBV Kinases

Cellular Kinases

Activated GCV

GCV

P

P

P
Clinical Proof-of-Concept Established with First Generation HDAC Inhibitor & Anti-viral

Phase 1 investigator-sponsored clinical trial (IST) in EBV+ lymphoma patients with arginine butyrate + ganciclovir

Encouraging Efficacy across lymphomas types

- Long-term survivors
- Butyrate HDACi was not commercially viable:
  - Poor drug properties, weak potency, continuous IV infusion

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENKTL N=4</td>
<td>2 CR; 1 PR; 1 NR</td>
</tr>
<tr>
<td>DLBCL, HIV N=1</td>
<td>1 PR</td>
</tr>
<tr>
<td>DLBCL N=3</td>
<td>1 CR, 1 PR, 1 NR</td>
</tr>
<tr>
<td>T cell lymphoma</td>
<td>1 PR</td>
</tr>
<tr>
<td>PTLD N=6</td>
<td>2 CR, 2 PR, 2 NR</td>
</tr>
<tr>
<td>Hodgkin’s Disease</td>
<td>1 NR</td>
</tr>
</tbody>
</table>

Study Design: R/R EBV+ Lymphoma Phase 1b/2

- Open-label study of nanatinostat/valganciclovir
- Nanatinostat = New oral Class I HDAC inhibitor
- Dose-ranging Phase 1b (N=25) → Phase 2 expansion (N=30) with RP2D
- Eligibility:
  - Relapsed/Refractory lymphoma, any histology
  - EBER-ISH positive (by local pathology)
  - ECOG 0-2; GFR >60ml/min; no CNS disease; HIV+ eligible in Phase 1, not Phase 2
- Response Assessment:
  - PET-CT, Lugano Criteria

- End-points: Safety, Response Rate, Clinical Benefit Rate, Response Duration
- Other: Change in plasma EBV DNA (pEBVd), PK
- Exploratory: Histone acetylation, EBER quantitation, CD4/CD8 ratio, EBV-specific CTLs

RP2D: Nstat 20mg po qd, days 1-4 of each week and VGCV 900 mg po qd

Phase 2 Portion of the Trial ongoing at RP2D
## Demographics and Lymphoma Subtypes in Ph1b

<table>
<thead>
<tr>
<th>Demographics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients Enrolled</td>
<td>N=25</td>
</tr>
<tr>
<td>Male/Female</td>
<td>18/7</td>
</tr>
<tr>
<td>Median Age (range, yrs)</td>
<td>58 (19-84)</td>
</tr>
<tr>
<td>ECOG 0, 1, or 2 (N)</td>
<td>8, 15, 2</td>
</tr>
<tr>
<td>Prior Therapies, median (range)</td>
<td>2 (1-9)</td>
</tr>
<tr>
<td>Radiation</td>
<td>N=6</td>
</tr>
<tr>
<td>HDAC inhibitor</td>
<td>N=3 (2 Romi, 1 Bel)</td>
</tr>
<tr>
<td>HSCT Auto, Allo, Both</td>
<td>N=9 7, 1, 1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lymphoma Subtypes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B-cell (N=12, 48%)</strong></td>
<td></td>
</tr>
<tr>
<td>DLBCL (N=5)*</td>
<td></td>
</tr>
<tr>
<td>PBL (N=2)*</td>
<td></td>
</tr>
<tr>
<td>Burkitt’s (N=1)</td>
<td></td>
</tr>
<tr>
<td>LPL (N=1)</td>
<td></td>
</tr>
<tr>
<td>PTLD (N=1)</td>
<td></td>
</tr>
<tr>
<td>Other (N=2)</td>
<td></td>
</tr>
<tr>
<td><strong>T-cell (N=8, 32%)</strong></td>
<td></td>
</tr>
<tr>
<td>AITL (N=3)</td>
<td></td>
</tr>
<tr>
<td>ENKTL (N=3)</td>
<td></td>
</tr>
<tr>
<td>CTCL (N=1)</td>
<td></td>
</tr>
<tr>
<td>PTCL-NOS (N=1)</td>
<td></td>
</tr>
<tr>
<td>Hodgkin’s (N=5, 20%)</td>
<td></td>
</tr>
<tr>
<td>* HIV-positive (N=4)</td>
<td></td>
</tr>
</tbody>
</table>

* HIV-positive
### Safety Summary to Date* - Phase 1b + Phase 2

#### Related Grade 3-4 AEs Summary

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Cohort 1 (N=7) [Nstat 20mg, VGCV 1800mg]</th>
<th>Cohort 2abc (N=13) [Nstat 10 mg, VGCV 900 mg]</th>
<th>Cohort 3 (N=5) + Phase 2 (N=8) at the RP2D [Nstat 20 mg (4/7d), VGCV 900 mg] N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>3 (43%)</td>
<td>2 (15%)</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>2 (28%)</td>
<td>2 (15%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>1 (14%)</td>
<td>1 (8%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Non-Hematologic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine Elevation</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (14%)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*As of November 6, 2019
## Summary of Ph1b Efficacy: Evaluable Patients (N=18)

<table>
<thead>
<tr>
<th>Best Response</th>
<th>All (N=18)</th>
<th>HIV-Negative (N=15)</th>
<th>Months on Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall</td>
<td>B Cell</td>
<td>T Cell</td>
</tr>
<tr>
<td>CR (Complete)</td>
<td>5</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>PR (Partial)</td>
<td>5</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Minor or Stable</td>
<td>4</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>PD (Progressive)</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>18</td>
<td>15</td>
<td>5</td>
</tr>
</tbody>
</table>

### All Patients
- ORR = 10/18 (56%)
- CR = 5/18 (28%)
- CBR = 14/18 (78%)

### HIV Negative
- ORR = 10/15 (67%)
- CR = 5/15 (33%)
- CBR = 14/15 (93%)

### Median Duration of Treatment = 6.5 mos for Responders

^ Durable Response
* Received 3 weeks Rituxan
# HIV positive
Phase 1b Patients – Swimmers Plot (N= 25)

Ordered by Lymphoma Subtype and Descending Duration

- Plasmablastic (HIV+): [1206-002 (1)]
- B-cell & CVID: [1180-001 (2b)]
- DLBCL - ABC (post-PTLD): [1194-002 (1)]
- Lymphoplasmacytic: [1206-004 (2a)]
- DLBCL - UNK: [1194-005 (2a)]
- DLBCL - GCB (post-AIAT): [1195-001 (1)]
- Gray Zone, B cell: [1075-001 (1)]
- PTLD (B cell): [1203-001 (2a)]
- DLBCL - UNK (HIV): [1203-002 (2b)]
- DLBCL - UNK: [1203-001 (2a)]
- Plasmablastic (HIV): [1206-005 (2c)]
- Burkitt's (post-PTLD)/C3P2D: [1075-003 (3)]
- ATL: [1208-001 (1)]
- Peripheral T-cell: [1195-002 (2a)]
- Cutaneous T-cell: [1208-002 (2c)]
- AITL: [1209-001 (2a)]
- AITL: [1195-003 (2b)]
- NKT cell: [1003-001 (2b)]
- NKT cell: [1009-007 (3)]
- NKT cell: [1005-003 (3)]
- HL (Hist of Lupus/C3P2D): [1195-004 (3)]
- HL: [1194-001 (1)]
- HL: [1194-006 (2a)]
- HL: [1194-002 (1)]
- HL (C3P2D): [1203-003 (3)]
- HL: [1194-003 (1)]

B-Cell

T-Cell & NK-cell

Hodgkin

^ 1206-002 unevaluable for response due to unevaluable disease at baseline.
Case History: Patient 1195-002 (58 yo man, EBV+ PTCL-NOS)

- **Front Line Therapy**
  - 6 cycles of CHOEP
  - CR but early relapse (5 months)

- **Second Line therapy:**
  - Romidepsin -> CR followed by ASCT;
  - Relapsed 13 months later

- **Third Line:**
  - Retreatment with romidepsin
  - Progression at 5 months

- **Fourth Line:**
  - Enrolls on Phase 1 Study
  - Durable PR (12.4 months)
  - Disease progression at 12.4 months

Dose level: Nstat 10 mg* + VGCV (Nstat 12.5% of MTD)
Conclusions

• The combination of oral Nstat and VGCV was well tolerated, with no unexpected G3-4 AE, in patients with R/R EBV+ lymphomas

• A safe RP2D of Nstat + VGCV identified [Nstat 20 mg (4/7d), VGCV 900 mg]

• Encouraging efficacy signal, including HDACi-refractory disease
  • CRs observed in B-cell, T/NK-cell lymphomas, and Hodgkin’s lymphoma
  • Durable responses observed, with median duration of therapy 6.5 months
  • EBV plasma DNA levels decrease with therapy in responders

• Nstat + VGCV is a compelling targeted oral therapy for R/R EBV+ lymphoma

• Phase 2 enrollment is ongoing – We are looking for new sites
Acknowledgments

Phase I Investigators
- Brad M. Haverkos, MD (U Colorado)
- Onder Alpdogan, MD (Thomas Jefferson U/SKCC)
- Marcelo Capra, MD, PhD (Porto Alegre, Brazil)
- Tatyana A. Feldman, MD (J. Theurer CC, Hackensack)
- Elizabeth Brem, MD (UC Irvine)
- Anusha Vallurupalli, MD (U. Kansas)
- Jonathan E. Brammer, MD (OSU)
- Ana Schriefer, MD (Salvador, Brazil)
- Juliana Pereira, MD, PhD (U San Paolo, Brazil)
- Anil Tulpule, MD (Norris CC, USC)
- Stefan K. Barta, MD (U Pennsylvania)
- Locke J. Bryan, MD (Georgia CC, U. Georgia)

Viracta Team & Collaborators
- Richard Trauger, PhD
- John Gutheil, MD,
- Afton Katkov, MSc,
- Robert McRae,
- Ivor Royston, MD

Patients and Families
- Douglas V. Faller, MD, PhD (BU)
- Sebastian Obrzut, MD (UCSD)