Novel Therapeutic Targets for Hodgkin Lymphoma

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Hodgkin Lymphoma: Leading actors, bit actors, walkers-on & set decor

Host – Tumor - Interface
Table 3. Selected clinical studies on treatment options with novel agents in patients with relapsed/refractory cHL after ASCT

<table>
<thead>
<tr>
<th>Agent</th>
<th>No. of patients</th>
<th>Prior ASCT</th>
<th>Response, %</th>
<th>PFS</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td>Brentuximab</td>
<td>102</td>
<td>102</td>
<td>ORR, 75</td>
<td>5.6 mo</td>
<td>28</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>CR, 34</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>PR, 41</td>
<td></td>
<td></td>
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<tr>
<td>Nivolumab</td>
<td>23</td>
<td>18</td>
<td>ORR, 87</td>
<td>24-wk 86%</td>
<td>29</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>CR, 17</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>PR, 70</td>
<td></td>
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<tr>
<td>Pembrolizumab</td>
<td>15</td>
<td>10</td>
<td>ORR, 53</td>
<td>NR</td>
<td>30</td>
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<td>CR, 20</td>
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<td></td>
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<td></td>
<td>PR, 33</td>
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<tr>
<td>Lenalidomide</td>
<td>36</td>
<td>31</td>
<td>ORR, 19</td>
<td>6 mo</td>
<td>31</td>
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<td></td>
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<td></td>
<td>CR, 3</td>
<td></td>
<td>58</td>
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<td></td>
<td></td>
<td></td>
<td>PR, 16</td>
<td></td>
<td>59</td>
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<tr>
<td>Rituximab</td>
<td>22</td>
<td>18</td>
<td>ORR, 22</td>
<td>7.8 mo</td>
<td>60</td>
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<td></td>
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<td></td>
<td>CR, 4.5</td>
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<td></td>
<td></td>
<td></td>
<td>PR, 18</td>
<td></td>
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<tr>
<td>Everolimus</td>
<td>19</td>
<td>16</td>
<td>ORR, 47</td>
<td>7.2 mo</td>
<td>32</td>
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<td></td>
<td>CR, 5</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>PR, 42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vorinostat</td>
<td>25</td>
<td>11</td>
<td>ORR, 4</td>
<td>4.8 mo</td>
<td>61</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>CR, 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PR, 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Panobinostat</td>
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<td>129</td>
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<td>6.1 mo</td>
<td>33</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>PR, 23</td>
<td></td>
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</tr>
</tbody>
</table>

*Blood. 2016;127(3):287-295*
PD1 blockade in Hodgkin Lymphoma

Integrative analysis reveals selective 9p24.1 amplification, increased PD-1 ligand expression, and further induction via JAK2 in nodular sclerosing Hodgkin lymphoma and primary mediastinal large B-cell lymphoma

Michael R. Green, Stefano Monti, Scott J. Rodig, Przemyslaw Juszczynski, Treeve Currie, Evan O'Donnell, Bjorn Chapuy, Kunihiko Takeyama, Donna Neuberg, Todd R. Golub, Jeffery L. Kutok, and Margaret A. Shipp

Figure 1. Chromosome 9p24.1 amplification and increased expression of PD-1 ligands in HL and MLBCL cell lines

Blood. 2010;116(17):3268-3277
Hodgkin Lymphoma: ...Therapeutic Biology...

The 9p24.1 Amplicon Block in cHL

- 9p24.1 alterations are a typical and constant (>95% of cases) genetic trait of cHL
- The type of 9.24.1 alteration predicts intensity of PD-L1/2 expression on H-RS cells
- Amplification of 9p24.1 predicts for advanced stage and shorter PFS (ABVD)

PD1/PD-L1 signal transduction in activated T and NK cells

PD1 expression in immune cells

*PD1 is overexpressed in ‘exhausted’ T-cells*

---

A diagram illustrating the immune response and the expression of PD1 in various immune cell types.
Hodgkin Lymphoma: ...Therapeutic Biology...

- CD8+ T Cell infiltration is associated to tumor response in melanoma
- Loss of surface HLA-Class I expression by β2M mutation is a mechanism of acquired resistance to Pembrolizumab in melanoma

Hodgkin Lymphoma: ...Therapeutic Biology...

- **H-RS cells display a ‘structurally’ deficient expression of HLA expression**
  - *HLA Class I deficit*
    - 63% to 79% of cases
  - *HLA Class II deficit*
    - 41% to 67% of cases
  - *Both Class I and II deficit*
    - 46% of cases
  - *Normal expression: 12% of cases*

- **Genetic alterations (mutations, breaks, translocations, etc.)**
  - β2 microglobulin, CIITA, etc.

- **Low abundance of CD8+ (PD1+) cytotoxic T cells in HL microenvironment**
  - PD1 blockade: how it works ????
  - Mediated by cytotoxic T-cells
  - Requires intact Ag presentation by HLA

Diepstra et al. *JCO* 2007
The majority of PD-L1 in the TME is expressed by the abundant PD-L1+ TAMs which physically co-localize with PD-L1+ HRS cells in a microenvironmental niche.
Nivolumab & Pembrolizumab Target PD1

- HRS cells do not express PD1 (indirect tumor targeting)

- Potential PD1 expressing-cells in the HL microenvironment:
  - CD8+ T cells (like in solid tumors ?)
  - CD4+ T cells (regulatory function ?)
  - γ/δ T cells
  - Macrophages
  - NK cells
  - Other cells ?

- PD1-blocking antibodies unleash all these cell types from PD-L1-mediated functional inhibition

- One or more of these ‘unleashed’ PD1+ cell populations act as the effector(s) of antitumor efficacy
Brentuximab Vedotin in the Overall Treatment Strategy for HL

**PFS by best response**

<table>
<thead>
<tr>
<th>Response</th>
<th>N</th>
<th>Events</th>
<th>Median (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>34</td>
<td>15</td>
<td>NR</td>
</tr>
<tr>
<td>PR</td>
<td>39</td>
<td>34</td>
<td>6.9</td>
</tr>
<tr>
<td>SD</td>
<td>28</td>
<td>20</td>
<td>5.8</td>
</tr>
</tbody>
</table>

Chen et al., Blood 2016

**PFS in CheckMate 205**

- CR: 22 (19, NE) months
- PR: 15 (11, 19) months
- SD: 11 (6, 18) months
- PD: 2 (2, 2) months

Median (range) follow-up: 18 (1, 27) months

Fanale et al. ICML 2017 [Oral 125]
Brentuximab Vedotin-based combinations for RR-HL

Interim results of brentuximab vedotin in combination with nivolumab in patients with relapsed or refractory Hodgkin lymphoma

Table 1. Baseline demographics and disease characteristics

<table>
<thead>
<tr>
<th></th>
<th>n = 62</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y), median (range)</td>
<td>36 (18–69)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>30 (48)</td>
</tr>
<tr>
<td>Female</td>
<td>32 (52)</td>
</tr>
<tr>
<td>Disease stage at initial diagnosis, n (%)</td>
<td></td>
</tr>
<tr>
<td>I/II</td>
<td>37 (60)</td>
</tr>
<tr>
<td>III/IV</td>
<td>24 (39)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

CR rate: 61%,
ORR: 82%
6-mo.s PFS: 86%
Anti-PD1 Antibodies as Platform Agents for Novel Strategies in HL...
... Anti-PD1 Antibodies as Platform Agents for Novel Strategies in HL ...
Vorinostat: biologic & clinical activity in RR-HL

<table>
<thead>
<tr>
<th>Drug</th>
<th>Author</th>
<th>ORR% (CR%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDAC Inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Panobinostat n=13</td>
<td>Dickinson</td>
<td>58(0)</td>
</tr>
<tr>
<td>Panobinostat n=129</td>
<td>Sureda</td>
<td>26(3)</td>
</tr>
<tr>
<td>Vorinostat n=25</td>
<td>Kirshbaum</td>
<td>4(0)</td>
</tr>
<tr>
<td>Mocetinostat n=51</td>
<td>Younes</td>
<td>30(9.5)</td>
</tr>
<tr>
<td>Resminostat n=37</td>
<td>Walewsky</td>
<td>35 (NR)</td>
</tr>
</tbody>
</table>

Budde et al., BJ H2013, 161, 183–191
RR-HL: Effect of Pre-Transplant (ASCT) PET assessment

1. Works

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No.</th>
<th>CR (%)</th>
<th>PR (%)</th>
<th>ORR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response (all pts)</td>
<td>36</td>
<td>12(33)</td>
<td>7(19)</td>
<td>19(53)</td>
</tr>
<tr>
<td>Response to last Rx</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitive</td>
<td>16</td>
<td>9 (56)</td>
<td>2 (13)</td>
<td>11(69)</td>
</tr>
<tr>
<td>Resistant</td>
<td>18</td>
<td>3 (17)</td>
<td>5 (28)</td>
<td>8 (45)</td>
</tr>
</tbody>
</table>

2. Works rapidly

2-4 courses to best resp.

3. Synergizes with BV

Reference

- Corazzelli 41: 90-120 mg/m², days 1 & 2, every 3-4 wks, ORR 58%, CR 31%
- Ghesquieres 28: 90-120 mg/m², days 1 & 2, every 4 wks, ORR 50%, CR 29%
- Anastasia 67: 90-120 mg/m², days 1 & 2, every 4 wks, ORR 57%, CR 25%
- Zinzani 27: 90 mg/m², days 1 & 2, every 4 wks, ORR 56%, CR 37%

All received prior BV, 56% refractory to BV

67% failed auto SCT, 33% failed allo SCT

De Filippi et al. ASH 2015
Leoni et al. ASH 2003

Tinostamustine (EDO-S101)

DNA Alkylation Moiety

Purine-like Benzimidazole ring

Butyric acid group

Vorinostat HDAC Moiety
Tinostamustine (EDO-S101): Preclinical evidences in HL

- EDO-S101 Inhibits HL Cell Growth @ IC50s ~10-fold lower than Bendamustine
- EDO-S101 exerts a potent antiproliferative effects on Bendamustine-resistant HL cells
- EDO-S101 is synergic with Brentuximab vedotin

De Filippi R, et al. ASH 2015
Tinostamustine (EDO-S101): DNA damage response in HL cells

EDO-S101 triggers DNA damage response in HL cells sensitive or resistant to BDM
Extended exposure to BDM of HL cells: CD30 upregulation

- L1236 48 Hrs IC50 = 3.16
- L1236 72 Hrs IC50 = 3.87
- R100 48 Hrs IC50 = 0.21
- R100 72 Hrs IC50 = 0.19

Extended exposure and resistance to Bendamustine in HL cells is associated to a stable upregulation of CD30 and increased sensitivity to Brentuximab Vedotin
Tinostamustine (EDO-S101): Effects of HL cells proliferation

EDO-S101 is synergic with Brentuximab Vedotin at sub-IC concentrations allows low doses of Brentuximab Vedotin (10-fold lower than IC50) to exert a striking cytotoxic effect on BDM-resistant L1236 R100 cells which overexpress CD30.

Differently from Vorinostat, EDO-S101 does not downregulate CD30.
Tinostamustine (EDO-S101): Effects on NOD-SCID-gammac-/- mice

- **L-540**
  - Vehicle
  - Bendamustine 15 mg Kg\(^{-1}\)
  - Vorinostat 100 mg Kg\(^{-1}\)
  - Benda/Vorinostat
  - EDO 60 mg Kg\(^{-1}\)

**Tumor Volume (mm\(^3\))**

**Days after tumor inoculation**

Day 17, 24, 31, 38, 45
Study of EDO-S101, A First-in-Class Alkylating HDACi Fusion Molecule, in Relapsed/Refractory Hematologic Malignancies

ClinicalTrials.gov Identifier: NCT02576496
First received: October 12, 2015
Last updated: April 21, 2016
Last verified: March 2016

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Principal Investigator: Luigi Zinzani, MD

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Kantonsspital St.Gallen
St.Gallen, Switzerland, 9007
Principal Investigator: Christoph Driessen, MD
Tinostamustine (EDO-S101): First-in-Humans study

A Phase 1 Study to Investigate the Safety, Pharmacokinetic Profiles and the Efficacy of EDO-S101, a First-in-Class Alkylation Histone Deacetylase Inhibition (HDACi) Fusion Molecule, in Relapsed/Refractory Hematologic Malignancies

3+3 Escalation
N= 12-18

Patient Definition
r/r Hem Malignancies
Inclusion/Exclusion

Duration 12-18 months

MTD

Expansion
N= 12 per group

Group 1 - r/r HL
Group 2 - r/r B ref
Group 3 - r/r MM
Group 4 - r/r PTCL/TPLL

5 centers actively recruiting: US (3), CH (1), IT (2)
Clinical trial applications underway: ES (1), F (3)
26 patients recruited up to date
Number of cycles: 1-8
Efficacy observations: SD, PR, CR

Key Objectives:
- Safety
- MTD & RP2D
- PK - /PK-PD
- Optimal infusion time
- Signals of efficacy
- Tumor samples for genetic testing
Tinostamustine (EDO-S101): First-in-Humans study

A Phase 1 Study to Investigate the Safety, Pharmacokinetic Profiles and the Efficacy of EDO-S101, a First-in-Class Alkylation Histone Deacetylase Inhibition (HDACi) Fusion Molecule, in Relapsed/Refractory Hematologic Malignancies

<table>
<thead>
<tr>
<th>Disease Type</th>
<th>Pts No</th>
<th>20/1h</th>
<th>40/1h</th>
<th>60/1h</th>
<th>80/1h</th>
<th>100/1h</th>
<th>120/1h</th>
<th>80/45m'</th>
<th>60/30m'</th>
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<td>7</td>
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<td>NHL</td>
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<td>4</td>
<td>2</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>46</strong></td>
<td><strong>3</strong></td>
<td><strong>3</strong></td>
<td><strong>3</strong></td>
<td><strong>3</strong></td>
<td><strong>8</strong></td>
<td><strong>6</strong></td>
<td><strong>10</strong></td>
<td><strong>9</strong></td>
<td><strong>1</strong></td>
</tr>
</tbody>
</table>
EDO-S101 for primary refractory HL (case # 1)

- 42-year-old female
- cHL diagnosed 2014

- ABVD x 4 PD
- EscBEACOPP x 2 PD
- IGEV x 1 PD
- Brentuximab vedotin x 4 PD
- Pembrolizumab x 15 SD
  stop due to lung toxicity
  3 mo.s afterwards PD

- **EDO-S101 120 mg/m2 q21 days**
  - 4 courses delivered
  - DLT G4 thrombocytopenia
  - Best clinical response:
    - ‘conservative’ PR
    - DOR: 5 mo.s

17.07.17 07.09.17
EDO-S101 for primary refractory HL (case # 2)

- 42-year-old female
- cHL diagnosed 2014
  - ABVD x 6 + med. RT PD
  - IGEV x 2 PD
  - Brentuximab vedotin x 6 PD
  - Nivolumab x 6 PR
    - declines ASCT
  - Nivolumab x 15 SD
  - Nivolumab x 24 PD

- **EDO-S101** 120 mg/m2 q21 days
  - 6 courses delivered
  - G3 thrombocytopenia
  - Best clinical response:
    - CR
    - DOR: continuous CR > 8 mo.s (w/o any further treatments)
    - Mobilization failure/BM hypoplasia
    - Referred for Haplo-SCT (sept. 2018)
Tinostamustine (EDO-S101): Gene expression profiling studies

- PI3K signaling
- TGF-β signaling
- CC signaling
- Unconventional Ag presentation
Tinostamustine (EDO-S101): Gene expression profiling studies

- Copanlisib is synergic with BV in CD30 overexpressing cells
- EDO-S101 is synergic with Copanlisib and BV regardless of CD30 expression levels
Tinostamustine (EDO-S101): Gene expression profiling studies

Table 2. HHLA2 protein expression in human cancers assessed by immunohistochemistry on tissue microarrays

<table>
<thead>
<tr>
<th>Cancer samples (number positive/total cores)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast (7/10)</td>
</tr>
<tr>
<td>Malignant melanoma (5/9)</td>
</tr>
<tr>
<td>Liver (4/10)</td>
</tr>
<tr>
<td>Prostate (3/9)</td>
</tr>
<tr>
<td>Endometrial (0/9)</td>
</tr>
<tr>
<td>B-cell lymphoma (0/10)</td>
</tr>
</tbody>
</table>

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Conclusions

- EDO-S101 is a potent inhibitor of HL tumor cells growth and is currently being tested in a Phase 1 study
- Activity signals have been obtained in pts. With RR-HL
- DLT has been determined and expansion cohorts are recruiting

- EDO-S101 activates a unique gene expression program encompassing regulatory pathways involved in:
  - PI3K signaling
  - TGF-β signaling,
  - CC signaling
  - Unconventional Ag presentation

- This can guide identification of potential partners for EDO-S101-based combination therapy for HL
  - PI3k inhibitors
  - Brentuximab vedotin
Hodgkin Lymphoma: Future Directions

**Strategy A**
- Chemo therapy
- Brentuximab vedotin
- PD1/PDL1 antibodies
- PI3Ki mTORI
- HDACi

**Strategy B**
- Chemo therapy
- PI3Ki mTORI
- Brentuximab vedotin + PD1/PDL1 antibody
- HDACi
...No man is an island...
**Brentuximab Vedotin in the Overall Treatment Strategy for HL**

- **Pre ASCT**
  - Boost Salvage Strategy
  - Boost Conditioning

- **Post ASCT**
  - Prevent Recurrence
  - Consolidation
  - Optimize Treatment of Failures

- **Pts @ risk**
- **Pts with suboptimal response to salvage**
- **All Pts ?**

- **Develop more effective combinations to achieve a PET negative status @ Transplant**
- **Brentuximab vedotin**
- **Improve results of 1st line Programs**

- **Pts @ risk**
- **Pts with suboptimal response to salvage**
- **All Pts ?**

- **Improve Survival & QoL**
- **Long Term Survival**
- **Bridge to Allo those eligible**

- **Approved indication**
- **Advanced clinical testing**
• Usually 6 courses are given
• CE-CT scan is preferred to CT/PET unless familiar with drug & LyRiC
• Treatment is stopped if PR0 is confirmed at 2 separate evaluations six weeks apart
**Brentuximab Vedotin in the Overall Treatment Strategy for HL**

**Pre ASCT**
- Boost Salvage Strategy
- Boost Conditioning

**Post ASCT**
- Prevent Recurrence
- Consolidation
- Optimize Treatment of Failures

**Pts @ risk**
- Pts with suboptimal response to salvage
- All Pts?

**Pts @ risk**
- Improve results of 1st line Programs

**Develop more effective combinations to achieve a PET negative status @ Transplant**

**Nivolumab**
- Improve Survival & QoL
- Long Term Survival
- Bridge to Allo those eligible

**Brentuximab vedotin**
- Approved indication

**Advanced clinical testing**

**Pembrolizumab**
- Improve results of 1st line Programs

**Approved indication**