Pixantrone in relapsed and refractory NHL

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St George’s University of London
DOX → topo IIα inhibition → p53 → APOPTOSIS

MITOX

cell cycle-dependent
PIX works by different mechanisms.

6. Cell death by pixantrone as a result of multiple aberrant cell divisions.
Pixantrone induced chromosome bridges and micro- and multi-nucleation

Beeharry et al.
2013-2015
Lack of juxtaposed quinone-hydroquinone may be a factor of reduced interactions with topoisomerase 2α.
The Novel Anthracenedione, Pixantrone, Lacks Redox Activity and Inhibits Doxorubicinol Formation in Human Myocardium: Insight to Explain the Cardiac Safety of Pixantrone in Doxorubicin-Treated Patients

Emanuela Salvatorelli, Pierantonio Menna, Odalys Gonzalez Paz, Massimo Chello, Elvio Covino, Jack W. Singer, and Giorgio Minotti

Drug Sciences (E.S., P.M., O.G.P., G.M.) and Cardiac Surgery (M.C., E.C.), Center for Integrated Research, University Campus Bio-Medico, Rome, Italy; and Cell Therapeutics Inc., Seattle, Washington (J.W.S.)
PIX does not target newly identified target, top2β

PIX - top2β crystallization

PIX - top2β ICE assay

CTI data on file

B. Hasinoff, AACR 2015
PSUR submitted in January 2015

Reversible, asymptomatic, dose-independent LVEF decreases

investigations
CHF
HF
tachycardia
RV dysfunction
LV dysfunction
cardiac arrest

cumulative number of events
Data from R-CPOP vs R-CHOP

<table>
<thead>
<tr>
<th></th>
<th>CPOP-R n = 59</th>
<th>CHOP-R n = 63</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical CHF</td>
<td>0</td>
<td>5 (7.9%)</td>
<td>0.03</td>
</tr>
<tr>
<td>LVEF decline &gt;20%</td>
<td>1 (1.7%)</td>
<td>8 (12.7%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Troponin T Elevation</td>
<td>2/42 (4.8%)</td>
<td>15/46 (32.6%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Mean Decline in LVEF at 12 months</td>
<td>-1.1%</td>
<td>-7.0%</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Herbrecht et al., 2013
PIX301: Study design

≥ 3rd-line treatment of relapsed aggressive NHL n = 140

Randomise 1:1

Pixantrone base
(50 mg/m² Days 1,8,15)**

Comparator
(physician’s choice)*

Treatment
(28 days/cycle, ≤ 6 cycles)

Follow-up
(18 months)

Inclusion criteria
- Histologically-confirmed aggressive NHL
- Response to anthracycline regimen ≥ 24 weeks
- ECOG PS 0–2
- Baseline LVEF ≥ 50%
- No clinically significant CV abnormalities

Exclusion criteria
- Prior exposure to doxorubicin > 450 mg/m²
- Myocardial infarction within previous 6 months

*Choice of comparators included vinorelbine, oxaliplatin, ifosfamide, etoposide, mitoxantrone, gemcitabine or rituximab

**Clinical trials were based on pixantrone dimaleate 85 mg/m², equivalent to 50 mg/m² pixantrone base, the EU approved dose

Phase III PIX301: response in histologically confirmed aggressive B-cell (+ prior rituximab)

Post-hoc analysis: RR at EOS in prior Rituximab treated aggressive B NHL (central review)

Primary analysis: RR at EOS (central review)

Patients (%)

<table>
<thead>
<tr>
<th></th>
<th>CR / CRu</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>3rd/4th line</td>
<td>5.6</td>
<td>11.1</td>
</tr>
<tr>
<td>All lines</td>
<td>7.1</td>
<td>24.3</td>
</tr>
</tbody>
</table>

3rd/4th line (Pix: n = 20; comp: n = 18)

CR / CRu: n = 70; ORR: n = 70

Post-hoc analysis: RR at EOS in prior Rituximab treated aggressive B NHL (central review)

Primary analysis: RR at EOS (central review)

CR / CRu

CR / CRu: n = 70; ORR: n = 70

Post-hoc analysis: RR at EOS in prior Rituximab treated aggressive B NHL (central review)

Primary analysis: RR at EOS (central review)

CR / CRu

CR / CRu: n = 70; ORR: n = 70

Pettengell et al. EHA 2013. P310
PIX301 Responders by Response to Last Therapy

Patients with CR/CRu During PIX301

<table>
<thead>
<tr>
<th>Response to last Chemotherapy</th>
<th>Response to pixantrone (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/CRu</td>
<td>3 (4.3%)</td>
</tr>
<tr>
<td>PR</td>
<td>8 (11.4%)</td>
</tr>
<tr>
<td>SD</td>
<td>3 (4.3%)</td>
</tr>
<tr>
<td>PD</td>
<td>3 (4.3%)</td>
</tr>
</tbody>
</table>

Last therapy regimens (n): +/- rituximab
- CHOP (4)
- ESHAP (2)
- CVP (2)
- DHAP (3)
- ICE (2)
- Other multi-agent regimens (4)

SD = Stable Disease
PD = Progressive Disease

- Single agent pixantrone achieved CR/CRu’s in patients that had PR, SD, PD from prior intensive salvage therapies
- **82% (14 of 17)** of the pixantrone CR/CRu had a sub-optimal response to these prior therapies yet went on to achieve a CR with single agent pixantrone

Cell Therapeutics Inc. Data on File
Phase III PIX301: PFS in histologically confirmed aggressive B-cell (3rd/4th line, + prior rituximab)

HR = 0.60 (95% CI: 0.42, 0.86)

Pettengell et al. EHA 2013. P310
Phase III PIX301: significance of CR / CRu

Duration of CR/CRu (months)  OS in patients with and without a CR/CRu

CR/CRu was a significant predictor of survival (HR = 0.35, 95% CI 0.18–0.68)

Cell Therapeutics Inc. Data on File.
**Phase III PIX301: adverse events ≥ 5%**

<table>
<thead>
<tr>
<th></th>
<th>Grades 3 or 4</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Pixantrone (n = 68)</td>
<td>Comparator (n = 67)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td><strong>Haematological</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>4 (5.9)</td>
<td>9 (13.4)</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>28 (41.2)</td>
<td>13 (19.4)</td>
<td></td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>5 (7.4)</td>
<td>2 (3.0)</td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td>16 (23.5)</td>
<td>5 (7.5)</td>
<td></td>
</tr>
<tr>
<td><strong>Non-haematological</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>5 (7.4)</td>
<td>3 (4.5)</td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>3 (4.4)</td>
<td>6 (9.0)</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>4 (5.9)</td>
<td>3 (4.5)</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>4 (5.9)</td>
<td>3 (4.5)</td>
<td></td>
</tr>
</tbody>
</table>

## Activity of single agents in R/R DLBCL

<table>
<thead>
<tr>
<th>Agent</th>
<th>n</th>
<th>Number of prior chemo regimens</th>
<th>RR (CR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vincristine(^1)</td>
<td>15</td>
<td>≥ 1</td>
<td>40%</td>
</tr>
<tr>
<td>Etoposide(^1)</td>
<td>10</td>
<td>≥ 1</td>
<td>50%</td>
</tr>
<tr>
<td>Gemcitabine(^2)</td>
<td>30</td>
<td>1-3</td>
<td>20% (5%)</td>
</tr>
<tr>
<td>Rituximab(^3)</td>
<td>21</td>
<td>≥ 1</td>
<td>38%</td>
</tr>
<tr>
<td>Inotuzumab(^4)</td>
<td>10</td>
<td></td>
<td>90%</td>
</tr>
<tr>
<td>Lenalidomide(^5)</td>
<td>108</td>
<td>4 (median)</td>
<td>27% (7%)</td>
</tr>
<tr>
<td>Bendamustine(^6)</td>
<td>18</td>
<td>≥ 1</td>
<td>44% (17%)</td>
</tr>
<tr>
<td>Ibrutinib (ABC)(^7)</td>
<td>29</td>
<td>3</td>
<td>32% (6%)</td>
</tr>
<tr>
<td>Pixantrone(^8)</td>
<td>70</td>
<td>3</td>
<td>45% (30%)</td>
</tr>
</tbody>
</table>

PIX306 (PIX-R): phase III trial in R/R aggressive B-cell NHL non-SCT eligible

**Relapsed/refractory NHL or follicular grade 3 lymphoma**

Estimated enrolment n = 260

**Randomise 1:1**

- **Pixantrone**
  - (50 mg/m² Days 1,8,15)
  - + rituximab
    - (375 mg/m² Day 1)

- **Gemcitabine**
  - (1000 mg/m² Days 1,8,15)
  - + rituximab
    - (375 mg/m² Day 1)

**Treatment**
- (28 days/cycle, ≤ 6 cycles)

**Primary endpoint**
- OS

**Secondary endpoints**
- PFS
- CRR
- ORR
- Safety

**Inclusion criteria**
- De novo DLBCL or follicular lymphoma: 1–3 previous treatment regimens
- DLBCL transformed from indolent lymphoma: 1–4 treatment regimens
- Received rituximab-containing multiagent therapy
- Not eligible for high-dose chemotherapy and stem cell transplant

**Exclusion criteria**
- 1. Prior exposure to doxorubicin > 450 mg/m²
Activity and Synergism of PIX in both GC and ABC cell lines
Chk-1 inhibition enhances PIX activity

Beeharry et al.
AACR – EORTC 2013
# Current Pixantrone Clinical IST Program

<table>
<thead>
<tr>
<th>PI</th>
<th>Site</th>
<th>Title</th>
<th>Disease</th>
<th>Treatment</th>
<th>Enrollment status</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heß</td>
<td>Univ Mainz</td>
<td>Rescue Treatment With The Monoclonal Anti Cd20-antibody Obinotuzumab (GA101) In Combination With Pixantrone (Plus Dexamethasone) For The Treatment Of Patients With Relapsed Aggressive B-cell</td>
<td>Relapsed aNHL</td>
<td>Obinutuzumab (GA101) + PIX</td>
<td>17/64</td>
<td>In discussion for next agent: BCL2i</td>
</tr>
<tr>
<td>Marks</td>
<td>Univ Med Clinic Freiburg</td>
<td>R-CPOP as first line therapy for elderly patients with DLBCL and for patients with limited cardiac function with DLBCL</td>
<td>DLBCL</td>
<td>R-CPOP</td>
<td>3/60</td>
<td></td>
</tr>
<tr>
<td>Raderer</td>
<td>Medical University Vienna</td>
<td>Lenalidomide plus pixantrone in patients with MALT lymphoma</td>
<td>MALT</td>
<td>Lenalidomide + PIX</td>
<td>0/46</td>
<td>(Not finalized)</td>
</tr>
<tr>
<td>d’Amore</td>
<td>Aarhus University Hospital</td>
<td>Pixantrone and bendamustine for relapsed non-Hodgkin lymphoma of B and T-cell phenotype. (PREBEN /Pix-Ben-Eto Trial)</td>
<td>Relapsed B/T-cell lymphoma</td>
<td>Bendamustine, etoposide, rituximab + PIX</td>
<td>0/60</td>
<td>Swedish insurance resolved. Additional country budget needed</td>
</tr>
<tr>
<td>Hübel</td>
<td>University clinic Cologne</td>
<td>A multicenter, open label, uncontrolled, phase II trial evaluating the safety and efficacy of pixantrone in combination with idelalisib and GA101 in previously treated patients with follicular lymphoma</td>
<td>Relapsed FL</td>
<td>Pixantrone GA101 Idelalisib (Gilead approved)</td>
<td>0/30-40</td>
<td>Not finalized</td>
</tr>
</tbody>
</table>
Phase I/II trial of pixantrone, rituximab [only in CD20+ tumors], etoposide, bendamustine, in pts with relapsed aggressive NHL

NORDIC LYMPHOMA GROUP

R/R aggr. B- and T-cell NHL
Estimated enrollment n = 24+60

Phase 1 ‘Fit pts’
Pixantrone (50,75 mg/m² d1+8)
Rituximab (375 mg/m² day 1)
Etoposide (100mg/m² day 1, 1+2)
Bendamustine (90 mg/m² day1, 1+2)
Q 21, max 6 cycles N=max24

Phase 2 – ‘fit’ and ‘frail’*
Pixantrone (MTD)
Rituximab (375 mg/m² day 1)
Etoposide (MTD)
Bendamustine (MTD)
Q 21, max 6 cycles N=60

Primary endpoint
• ORR [ph 2]
• MTD [ph 1]

Secondary endpoints
• PFS
• EFS
• DFS
• OS
• Safety

*Frail pts enter directly the phase II part of the trial at baseline dose level
PREBen Regimen Series

• 19 evaluable pts (10 DLBCL, 4 PTCL, 5 tFL/Ind)
• Complete metabolic responses in DLBCL (CR 40%, PR 20%) and PTCL (CR 25%, PR 50%)
• Transf indolent and primary refr to DHAP/ICE had low response rates
• Responses detectable after the 1st course (no TLS observed)
  ➢ Response durations are in the range 4-17+ mo
  ➢ Out-patient regimen
  ➢ Grade 3-4 infections in 40% of pts
PREBEn Patient Series

D’Amore et al. BSH 2016
Conclusions

✓ **Pixantrone shows unique MOAs** in tumor and cardiac cells

✓ **Pixantrone is active and safe** in patients with refractory-relapsed NHL and can bridge to other modalities

✓ **Pixantrone** is amenable to combination with potentially numerous agents