Phase 1 Study of Utomilumab (PF-05082566) In Combination with Rituximab in Patients with CD20+ NHL (Study B1641001)

Aron Thall, Global Clinical Lead Utomilumab, New Therapies in Hematology, Bologna, Italy May 2016
CD137/4-1BB Mechanism of Action

• A co-stimulatory molecule induced upon TCR activation that enhances cytotoxic T cell responses

• Increases NK cell mediated killing of tumor cells targeted with IgG1 mAbs

• Utomilumab (PF-05082566) is a fully human IgG2 CD137/4-1BB agonist
Study B1641001 Treatment Schema
Rituximab Induction Followed By Utomilumab

- Range of utomilumab Doses: 0.03 to 10 mg/kg
- Rituximab induction at 375 mg/m2
Study Objectives

Primary:

• Safety and tolerability of increasing doses of utomilumab with rituximab in CD20 + B cell lymphoma

Secondary:

• Evaluate overall safety profile
• PK/ADA of utomilumab and rituximab
• Anti-tumor effect
• Explore mechanism of anti-tumor effect
Enrollment Criteria

Inclusion Criteria

• Relapsed/Refractory CD20+ Non-Hodgkin’s lymphoma
  – Now focusing on R-refractory FL and on relapsed DLBCL
• Measurable disease (Cheson 2007 criteria)
• Age ≥ 18 years or older
• ECOG performance status of ≤1
• Adequate organ function

Exclusion Criteria

• CNS primary or CNS metastases
• Monoclonal antibody within 60 days of first dose
• Prior therapy with an agent of the same mechanism
Patient Characteristics

<table>
<thead>
<tr>
<th>Patients Treated (Total = 45), n (%)</th>
<th>Male 26 (58)</th>
<th>Female 19 (42)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Prior Therapies (%)</td>
<td>1-3 25 (55.6)</td>
</tr>
<tr>
<td></td>
<td>Mean Age (range)</td>
<td>61.1 (38-84)</td>
</tr>
<tr>
<td></td>
<td>B Cell Lymphoma Subtype, n (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Follicular Lymphoma*</td>
<td>30 (66.67)</td>
</tr>
<tr>
<td></td>
<td>Mantle Cell Lymphoma</td>
<td>5 (11.1)</td>
</tr>
<tr>
<td></td>
<td>DLBCL</td>
<td>3 (6.67)</td>
</tr>
<tr>
<td></td>
<td>Small Lymphocytic Lymphoma</td>
<td>2 (4.44)</td>
</tr>
<tr>
<td></td>
<td>Marginal Zone</td>
<td>4 (8.89)</td>
</tr>
<tr>
<td></td>
<td>Nodular LPHL</td>
<td>1 (2.2)</td>
</tr>
</tbody>
</table>

*includes pts with transformation
Linear PK and Low Incidence of ADA

• Linear PK in dose range of 0.03 to 10 mg/kg

• Mean $t_{1/2}$ is ~20 days based on preliminary POPPK analysis.

• The incidence of ADA for utomilumab was ~ 8%.
The Combination Is Well Tolerated

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Rituximab (TE) Label Reference</th>
<th>Rituximab + Utomilumab (TE)</th>
<th>Rituximab + Utomilumab (Related)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades (%)</td>
<td>Grade III/IV (%)</td>
<td>All Grades n (%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>26</td>
<td>1</td>
<td>15 (33.3)</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>1</td>
<td>15 (33.3)</td>
</tr>
<tr>
<td>Infusion Related Reactions</td>
<td>77</td>
<td>3</td>
<td>9 (20.0)</td>
</tr>
<tr>
<td>Rash</td>
<td>15</td>
<td>1</td>
<td>9 (20.0)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10</td>
<td>1</td>
<td>6 (13.3)</td>
</tr>
<tr>
<td>Nausea</td>
<td>23</td>
<td>1</td>
<td>4 (8.9)</td>
</tr>
<tr>
<td>URTI</td>
<td>--</td>
<td>--</td>
<td>7 (15.6)</td>
</tr>
<tr>
<td>Headache</td>
<td>19</td>
<td>1</td>
<td>6 (13.3)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>53</td>
<td>1</td>
<td>6 (13.3)</td>
</tr>
</tbody>
</table>

No AEs > Grade 3 and Grade 3 infusion reactions were related to rituximab only
No relationship between dose of utomilumab and frequency and severity of AE's

Out of 45 patients
### Summary of response data in NHL in B1641001

<table>
<thead>
<tr>
<th></th>
<th>CR, n (%)</th>
<th>PR, n (%)</th>
<th>SD, n (%)</th>
<th>PD, n (%)</th>
<th>ORR 95% exact CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (n=43)</td>
<td>4 (9.3)</td>
<td>6 (14.0)</td>
<td>21 (48.8)</td>
<td>9 (20.9)</td>
<td>10 (23.3) (11.8, 38.6)</td>
</tr>
<tr>
<td>R-refractory* FL &amp; MCL (n=19)</td>
<td>4 (21.1)</td>
<td>4 (21.1)</td>
<td>7 (36.8)</td>
<td>4 (21.1)</td>
<td>8 (42.1) (20.3, 66.5)</td>
</tr>
<tr>
<td>FL (n= 16)</td>
<td>4 (25.0)</td>
<td>3 (18.8)</td>
<td>5 (31.3)</td>
<td>4 (25.0)</td>
<td>7 (43.8*) (19.8, 70.1)</td>
</tr>
<tr>
<td>FL Expansion Cohort 1.2 mg/kg (n=3)</td>
<td>2 (67.7)</td>
<td>1 (33.3)</td>
<td>0</td>
<td>0</td>
<td>3 (100) (29.2, 100)</td>
</tr>
<tr>
<td>Mantle Cell (n = 3)</td>
<td>0</td>
<td>1 (33.3)</td>
<td>2 (66.7)</td>
<td>0</td>
<td>1 (33.3) (0.8, 90.6)</td>
</tr>
</tbody>
</table>

*(50%) 1 R-refractory FL patient with high level response but with new lesion, on biopsy comprised mainly T cells

As of Feb 2016
Anti-Tumor Activity: All NHL Patients

Waterfall Plot for Evaluable NHL Patients in B1641001

Evaluable Patients
Best Change From Baseline (%)
-100
-75
-50
-25
-10
0
50
100
FOLLICULAR LYMPHOMA
MCL
DIFFUSE LARGE B-CELL LYMPHOMA
OTHER (nodular HL, MZL, SLL)

Evaluable Patients
As of Feb 2016
Change in Tumor Burden: All FL patients

Time from Treatment Initiation (Month)
% Change in Index Lesions from Baseline

DOSE
- <= 1.2 mg/kg
- > 1.2 mg/kg

As of Feb 2016
Response Is Generally Rapid and Durable In Patients With Rituximab-Refractory FL

Responses were confirmed.
Patient 1: CR By Week 16 (0.12 mg/kg)

Weeks:
- Baseline
- 7
- 16
- 24
- 44
- 65

Sum of Proof of Diameters (mm):
- Baseline: 1062
- 7: 430
- 16: 258
- 24: 152
- 44: 78
- 65: 56

Phases:
- RCVP
- BR
- Idelalisib
- Bexxar
- Utomilumab + R
- Rituximab

Statuses:
- CR
- PD
- PR

PET-negative:
- Original End of Treatment Period

Timeline:
- 2/09
- 3/09
- 6/09
- 7/09
- 6/10
- 11/10
- 4/11
- 8/11
- 11/11
- 6/12
- 11/12
- 6/13

Duration:
- >30 mo
Patient 2: CR by Week 16 (1.2 mg/kg)

- Original DX: 7/98
- BEXXAR: 7/98
- RITUXMAB: 11/03
- RCVP: 12/03
- FND: 9/09
- BENDAMUSTINE: 1/10
- IBRUTINIB: 6/10
- Utomilumab + R: 8/11
- CR: 1/12
- PD: 10/13
- PR: 3/15
- SD: 7/15
- PD: 12/13
- CR: 12/13
- PET-negative CR: 8/11

Sum of Prod of Diameters (mm):
- Baseline: 2859
- 8 weeks: 424
- 16 weeks: 244
- 24 weeks: 0

- PR: 1/12
- PD: 10/13
- SD: 7/15
Patient 3: CR At Month 11 (1.2 mg/kg)

Weeks

Baseline 12 21 29 37 53

Sum of Prod of Diameters (mm)

2696 992 945 791 612 510

PET-negative CR

Weeks

1/09 12/10 2/11 6/11 4/13 12/14

RCHOP + R maint ICE inotuzumab BEAM + ABMT Ibrutinib Utomilumab + R

Representative Treatment: RCHOP + R maint, ICE, inotuzumab, BEAM + ABMT, Ibrutinib, Utomilumab + R

DX CR 11/10 PD 1/11 SD 3/11 PR 9/12 PD 11/14 PD >16 mo
On-treatment Increase in Tumor Infiltrating CD8 T cells

Patient 3

Baseline

On treatment
Discussion

- R + utomilumab (PF-05082566) is well tolerated in patients with relapsed or refractory B cell NHL up to 10 mg/kg

- Preliminary ORR of 50% in R-refractory follicular lymphoma
  - Median Duration of Response at ≤1.2 mg/kg greater than 10 mo

- Tumor biomarker data are supportive of the induced expansion of anti-tumor CD8 T cells

- Expansion cohort of R-refractory FL ongoing at a dose of 1.2 mg/kg,

- DLBCL enrollment continuing in this study and in a new study with a triplet containing avelumab (anti-PD-L1)
Acknowledgments

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