Lugano/ASH 2017 update - FL
Alvaro Alencar
Plenary Session

- Abstract 4 - Interim report from a phase 2 multicenter study of tezemetostat, an EZH2 inhibitor, in patients with refractory B-cell non-Hodgkin lymphomas

- Abstract 6 - Bendamustine followed by obinutuzumab and venetoclax in patients with chronic lymphocytic leukemia: CLL-2 bag trial of the German CELL study group (GCLLSG)
Interim report from a phase 2 multicenter study of tazemetostat, an EZH2 inhibitor, in patients with refractory B-cell non-Hodgkin lymphomas

- Preclinical and ph 1 activity in WT/mutated EZH2
- Open label, multicenter study r/r DLBCL and FL w 2+ tx lines
- Primary endpoint ORR (CR+PR)
- Interim safety data on 165 pts
  - Gr 3+ AE in 18%
- Interim efficacy data in 149 pts (median 3 tx lines)
  - ORR 40% in DLBCL w mut EZH2 (n=10)
  - ORR 18% in DLBCL w WT EZH2 (n=85)
  - ORR 63% in FL w mut EZH2 (n=8)
  - ORR 28% in FL w WT EZH2 (n=46)
  - SD 38% and 30% in mut/WT FL
Chemotherapy-free combinations

- Abstract 35 - Final results of CALGB 50803 (Alliance): a phase 2 trial of lenalidomide plus rituximab in patients with previously untreated follicular lymphoma
- Abstract 36 - L-mind: MOR208 combined with lenalidomide (LEN) in patients with relapsed or refractory diffuse large B-cell lymphoma (R-R DLBCL)—a single-arm phase II study
- Abstract 37 - A phase II LYSA study of obinutuzumab combined with lenalidomide for relapsed or refractory follicular B-cell lymphoma
- Abstract 38 - Phase IB study of CC-122 in combination with obinutuzumab (GA101): relapsed or refractory (R/R) patients with B-cell non-Hodgkin lymphomas (NHL)
Final results of CALGB 50803 (Alliance): a phase 2 trial of lenalidomide plus rituximab in patients with previously untreated follicular lymphoma

- Untreated gr 1-3a, stage 3-4, bulky stage 2, FLIPI 0-2
  - lower risk FLIPI 0-2, primarily non bulky
  - rituxan 4 weekly doses then c4, 6, 8, 10; len 20 mg 21/28 x 12 cycles
- n=65, median age 53, 68% FLIPI 0-1, 78% completed 12 cycles
- ORR 95%, CR 72% - no association of FLIPI w CR or PFS
- Gr 3+ neutropenia 21%, infection 9%
- Gr 3 TLS 2 pts, serum sickness 1 pt
- 16 progressions from CR (7), PR (8), SD (1)
- Medium f/u 5 yrs – 2 yr PFS 86%, 3 yr PFS 81%, 4 yr PFS 73%
- Confirms single center finding in multicenter study
Lenalidomide + rituximab untreated FL: Alliance 50803

Phase II single arm study evaluating lenalidomide + rituximab in untreated FL

A phase II trial of lenalidomide plus rituximab in previously untreated follicular non-Hodgkin’s lymphoma (NHL): CALGB 50803 (Alliance)

P. Martin1*, S.-H. Jung2, B. Pitcher3, N. L. Bartlett1, K. A. Blum1, T. Shea1, E. D. Hu2, J. Ruan1, S. E. Smith2, J. P. Leonard1 & B. D. Cheson8

n = 66

• Untreated FL, grade 1-3a, stage bulky II, III, IV

Lenalidomide
25 mg PO x 21 days q 28 days x 12 +
Rituximab
375 mg/m² D1, 8, 15, 22 on C1, every 8 wks x 4
Lenalidomide + rituximab untreated FL: Alliance 50803

Table 3. Response

<table>
<thead>
<tr>
<th>Best response</th>
<th>FLIPI 0–1, n = 21</th>
<th>FLIPI 2–3, n = 44*</th>
<th>Overall (N = 65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>15 (71%)</td>
<td>32 (73%)</td>
<td>47 (72%)</td>
</tr>
<tr>
<td>PR</td>
<td>5 (23%)</td>
<td>10 (23%)</td>
<td>15 (23%)</td>
</tr>
<tr>
<td>Stable</td>
<td>0</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Not evaluated: AE</td>
<td>1 (5%)</td>
<td>1 (2%)</td>
<td>2 (2%)</td>
</tr>
</tbody>
</table>
Lenalidomide + Rituximab in untreated iNHL (RELEVANCE)

Phase III randomized study comparing lenalidomide + rituximab versus rituximab + chemo in untreated indolent NHL

Study design

Patients with first-line FL (N = 1,000) → R

R² (lenalidomide + rituximab) → CR, CRu, PR

R² maintenance (lenalidomide 1 yr + rituximab 2 yrs)

R-chemo (Investigator’s choice of R-CHOP, R-CVP, or BR) → CR, CRu, PR

Rituximab maintenance (2 yrs)

6 Months → 24 Months
Celgene and LYSARC Provide Update on Phase III 'RELEVANCE' Study of REVLIMID® in Combination with Rituximab (R²) for the Treatment of Previously Untreated Patients with Follicular Lymphoma

SUMMIT, N.J.--(BUSINESS WIRE)-- Celgene Corporation (NASDAQ:CELG) and the Lymphoma Study Association (LYSA) today announced that the Lymphoma Academic Research Organisation (LYSARC) reported results from a phase III, randomized, open-label, international clinical study (RELEVANCE).

This investigational study evaluated REVLIMID plus rituximab (R²) followed by R² maintenance compared to the standard of care with rituximab plus chemotherapy (R-CHOP, R-bendamustine or R-CVP) followed by rituximab maintenance in patients with previously untreated follicular lymphoma.

The R² treatment arm did not achieve superiority in the co-primary endpoints of complete response or unconfirmed complete response (CR/CRu) at 120 weeks and progression-free survival (PFS) during the pre-planned analysis (final analysis of CR/CRu and interim analysis of PFS). Neither arm was superior for either of the co-primary endpoints. The safety findings were consistent with the known profiles of the regimens investigated. Additional analyses are ongoing and planned.

"This is the first Phase III trial to evaluate a chemotherapy-free regimen to the established standard of care in patients with previously untreated follicular lymphoma and represents a landmark study in this disease setting," said Prof. Gilles Salles, President of the Lymphoma Study Association (LYSA). "We look forward to further analyzing and presenting these important data at a future medical congress."

"We thank the patients, their families, the Co-Primary Investigators, Franck Morchhauser MD¹, PhD, and Nathan Fowler, MD² and the investigators for participating in the RELEVANCE trial," said Jay Backstrom, M.D., Chief Medical Officer and Head of Global Regulatory Affairs for Celgene. "We remain committed to advancing our broad pipeline of novel therapies to establish new standards of care for patients with lymphoma."

¹ Professor of Haematology Centre Hospitalier Régional Universitaire de Lille, Lille France
² Associate Professor, Department of Lymphoma/Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX
MAGNIFY: Design

Phase III study evaluating lenalidomide + rituximab induction followed by lenalidomide + rituximab or rituximab maintenance in R/R FL

**R²**

**Induction**
12 x 28-day cycles

- **R/R NHL**
  - FL grade 1-3b, tFL, MZL, or MCL
  - ECOG PS ≤2
  - Stage I-IV disease
  - ≥1 prior therapy

- **Lenalidomide** 20 mg/d, d1-21/28
- **Rituximab** 375 mg/m² qwk
  - c1 (d1, 8, 15, 22)
  - then d1 every other cycle (c3, 5, 7, 9, 11)

**Randomization**
CR/CRu, PR, or SD

**Maintenance**
18 x 28-day cycles up to PD

- **Arm A**
  - **Lenalidomide** 10 mg/d, d1-21/28
  - **Rituximab** 375 mg/m² d1 every other cycle (c13, 15, 17, 19, 21, 23, 25, 27, 29)

- **Arm B**
  - **Rituximab** 375 mg/m² d1 every other cycle (c13, 15, 17, 19, 21, 23, 25, 27, 29)

**Optional Lenalidomide**
10 mg/d, d1-21/28

**n = 357**
**MAGNIFY: Update Lugano 2017**

- **Interim analysis on FL**
  - \( n = 160 \), Median 2 previous lines therapy
  - Median age 65
  - 52 pts high risk (relapse 2 yrs from dx)
  - 50 pts double refractory (rituximab, alk agent)
  - ORR=66%, CR/CRu 38%
  - 1-yr PFS 70% (65% high risk, 49% double refractory)
  - Double-refractory/early relapsing gr 3/4 AE:
    - neutropenia (42%, 37%), leukopenia (8%, 10%), thrombocytopenia (8%, 4%), and lymphopenia (6%, 4%), febrile neutropenia (4%, 4%), thrombosis (2%, 0%)
A phase II LYSA study of obinutuzumab combined with lenalidomide for relapsed or refractory follicular B-cell lymphoma

- At least 1 prior tx
- Induction (87% completed)
  - Len 20 21/28
  - obinu 1000 C1 d 8,15,22, C2-6 d1
- Responders – maint (78% underwent)
  - len 10 21/28
  - obinu 1000 q 8 wks
- N=89, median age 64
- 28% POD24, median 2 lines tx, 27% ritux refractory
- median f/u 18.1 mos

<table>
<thead>
<tr>
<th>TABLE</th>
<th>All pts (N=86)</th>
<th>Early relapse pts (within 24 mo of 1st treatment line) (N=24)</th>
<th>Refractory pts (N=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IWG 1999</td>
<td>ORR, % (95%CI)</td>
<td>80.2 (70.2-88.0)</td>
<td>70.8 (48.9-87.4)</td>
</tr>
<tr>
<td></td>
<td>CR/CRu % (95%CI)</td>
<td>39.5 (29.1-50.6)</td>
<td>33.3 (15.6-55.3)</td>
</tr>
<tr>
<td>IWG 2007</td>
<td>ORR, % (95%CI)</td>
<td>74.4 (63.8-83.2)</td>
<td>66.7 (44.7-84.4)</td>
</tr>
<tr>
<td></td>
<td>CR, % (95%CI)</td>
<td>44.2 (33.5-55.3)</td>
<td>54.2 (32.8-74.4)</td>
</tr>
<tr>
<td>1-year PFS % (95%CI)</td>
<td>75.5 (64.2-83.7)</td>
<td>74.8 (52.2-87.8)</td>
<td>65.2 (42.3-80.8)</td>
</tr>
<tr>
<td>1-year OS % (95%CI)</td>
<td>88.8(79.5-94.0)</td>
<td>86.9 (64.6-95.6)</td>
<td>71.5 (47.1-86.1)</td>
</tr>
</tbody>
</table>
Novel anti-lymphoma strategies

- Abstract 76 - A Phase 1 study of pralatrexate plus romidepsin reveals marked activity in patients with relapsed or refractory (R/R) peripheral T-cell lymphoma (PTCL)

- Abstract 77 - Canadian cancer trials group (CCTG) LY.17: a randomized phase II study evaluating novel salvage therapy pre-autologous stem cell transplant (ASCT) in relapsed/refractory diffuse large B cell lymphoma (Rr-DLBCL)—outcome of ibrutinib + R-GDP

- Abstract 79 - Venetoclax (VEN), bendamustine (B), and rituximab (R) in patients (Pts) with relapsed or refractory (R/R) non-Hodgkin lymphoma (NHL): final results of a phase I study
Canadian cancer trials group (CCTG) LY.17: a randomized phase II study evaluating novel salvage therapy pre-autologous stem cell transplant (ASCT) in relapsed/refractory diffuse large B cell lymphoma (Rr-DLBCL)—outcome of ibrutinib + R-GDP

- Run in with 5 patients – increased infection
  - bid labs, antibiotic prophylaxis, and gcsf recommended
- Interim analysis with first 30 pts
- no advantage in PFS or OS
- increased infection, worse cytopenias
Session 8 - Follicular Lymphoma

- Abstract 107 - Immunochemotherapy with obinutuzumab or rituximab in previously untreated follicular lymphoma in the randomised phase III gallium study: analysis by chemotherapy regimen
- Abstract 108 - Copanlisib in Patients with relapsed or refractory indolent B-cell lymphoma (CHRONOS-1)
- Abstract 109 - High response rates with pembrolizumab in combination with rituximab in patients with relapsed follicular lymphoma: interim results of an on open-label, phase II study
CHRONOS-1 Trial: Design

Phase II single arm study evaluating copanlisib in R/R iNHL

n = 142

Previously treated iNHL (FL, MZL, CLL/SLL, WM)
At least 2 previous lines of therapy

Copanlisib 60 mg IV D1, 8, 15 q 28 d

Therapy maintained until progression or toxicity

Long-term follow-up
Copanlisib in Patients with relapsed or refractory indolent B-cell lymphoma (CHRONOS-1)

- IV PI3K inhibitor – alpha and delta – IV D1, 8, 15 q 28
- 2+ lines of tx, n=142, median tx duration 22 wks
- ORR 59.2% - 12% CR, 47.2% PR, 29.6% SD
- Median duration response 687 days
- Median PFS 340 days
- Gr 3+ hyperglycemia (40%), hypertension (23%), neutropenia (19%), diarrhea (4%), lung infection (11%), pneumonitis (1.4%), colitis (0.7%)
- 6 deaths – 3 drug related (2.1% - lung infec, resp fail, thromboemb event)
### CHRONOS-1: response

<table>
<thead>
<tr>
<th>Best response</th>
<th>N (%) [95% CI]</th>
<th>Total N = 104 / 142</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CR</strong></td>
<td>15 (14.4) 20 (14.1) [8.3-22.7]</td>
<td></td>
</tr>
<tr>
<td><strong>PR</strong></td>
<td>46 (44.2) [34.5-54.3]</td>
<td></td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td>34 (32.7) [23.8-42.6]</td>
<td></td>
</tr>
<tr>
<td><strong>Unconfirmed Sd</strong></td>
<td>1 (1.0) [0.0-5.2]</td>
<td></td>
</tr>
<tr>
<td><strong>PD</strong></td>
<td>2 (1.9) [0.23-6.8]</td>
<td></td>
</tr>
<tr>
<td><strong>N/A</strong></td>
<td>6 (5.8) [2.2-12.1]</td>
<td></td>
</tr>
<tr>
<td><strong>ORR</strong></td>
<td>61 (58.7) 83 (58.5%) [48.6-68.2]</td>
<td></td>
</tr>
</tbody>
</table>
CHRONOS-1: response

*Patient was assessed as having SD by independent review
*Patient classified by the investigator as having FL, but who was reclassified by independent assessment as having diffuse large-B-cell lymphoma, is not shown in the plot (change in lesions: increase of 250%)
SD, stable disease
Stage II (>7 cm) 
Stage III/IV FL 
(n = 611)

MAINTAIN Study: Design

Phase III trial comparing 2 vs 4 yrs of rituximab maintenance after BR

**Induction***
- Bendamustine + Rituximab 
  - 6 cycles
- Rituximab 2 cycles

**Maintenance***
- Rituximab Q2W
  - (n = 552)
- 2 yrs
- 1:1
  - (n = 350)
- Observation
  - (n = 172)
- = 4 yrs
- = 2 yrs
- Extended Maintenance
  - 2 yrs
  - 2 yrs
  - = 4 yrs

Rituximab 375 mg/m² Q2M
  - (n = 178)
MAINTAIN: PFS

Probability of PFS

HR: 0.63 (95% CI: 0.36-1.11)

Graph showing the probability of progression-free survival (PFS) over time for two groups: 4-yr rituximab maintenance (19 events; mPFS: NR) and 2-yr rituximab maintenance (29 events; mPFS: NR).
MAINTAIN: PFS vs StiL trial

**PFS**
- HR: 0.68 (95% CI: 0.47-0.87; P = .0074)
- 2-yr rituximab maintenance (MAINTAIN); mPFS: 78 mos
- Observation (NHL1-2003); mPFS: NR

**OS**
- HR: 1.01 (95% CI: 0.69-1.50; P = .9456)
- 2-yr rituximab maintenance (MAINTAIN); mOS: NR
- Observation (NHL1-2003); mOS: NR
BRIGHT: rituximab maintenance

| Table. Patient Characteristics at Baseline and Overall Response With or Without Rituximab Maintenance by Investigator Assessment |
| BR (n = 144) | R-CHOP/R-CVP (n = 144) |
| With (n = 81) | Without (n = 63) | With (n = 83) | Without (n = 61) |
| Median age (yrs) | 59 | 59 | 53 | 55 |
| ECOG >1 (n, %) | 4 (5) | 2 (3) | 3 (4) | 2 (3) |
| Ann Arbor stage III-IV (n, %) | 71 (88) | 58 (92) | 71 (86) | 57 (93) |
| B symptoms (n, %) | 31 (38) | 19 (30) | 24 (29) | 26 (43) |
| LDH >240 U/L (n, %) | 19 (23) | 20 (32) | 25 (30) | 27 (44) |
| β2-microglobulin >3 mg/L (n, %) | 15 (19) | 28 (44) | 18 (22) | 22 (36) |
| FLUPI score 0-1 (n, %) | 16 (20) | 14 (22) | 20 (24) | 8 (13) |
| FLUPI score 2 (n, %) | 36 (44) | 18 (29) | 22 (27) | 27 (44) |
| FLUPI score 3-5 (n, %) | 29 (36) | 31 (49) | 41 (49) | 26 (43) |
| Complete response (n, %) | 18 (22) | 25 (40) | 16 (19) | 13 (21) |
| Partial response (n, %) | 63 (78) | 38 (60) | 67 (81) | 48 (79) |

ECOG: Eastern Cooperative Oncology Group; FLUPI: follicular lymphoma international prognostic index.

Figure. Progression-free survival by maintenance R in patients with follicular lymphoma.

BR With vs BR Without: HR (95% CI) = 0.50 (0.26-0.94)  P = 0.0295

R-CHOP/R-CVP With vs R-CHOP/R-CVP Without: HR (95% CI) = 0.66 (0.38-1.16)  P = 0.1443
Real world data: rituximab maintenance

Figure: PFS (top row) and OS (bottom row) for patients in PR (left columns) and CR (right columns) after induction BR, who underwent observation (Obs) or rituximab maintenance (RM).
Safety and Efficacy of Atezolizumab in Combination with Obinutuzumab and Bendamustine in Patients with Previously Untreated Follicular Lymphoma: An Interim Analysis

- ph Ib/II - 6-month induction, 2-years of maintenance
- median age 57 (29-75), 93% st III/IV, 21% bulky (>7 cm), 48% BM(+), 71% gr 2-3a, FLIPI 24% low, 43% int, 33% high
- Safety n=42, 6 run-in (tx-naive= 4, prev tx= 2), 36 expansion phase (untreated)
- median f/u 5.5 months (1-15)
- ORR 85%, CR 75%, PR 10%, SD 10%
- 16 pts (+) ctDNA, negative @EOI
- gr 3/4 AE 57%, serious AE 29%. d/c 10%
  - 17% AEs of special interest – gr 1-2 infusion-related reaction (n = 3), gr 4 lipase increase (n = 3), gr 2 rash (n = 2), gr 4 myocarditis (n = 1), and gr 1 bronchiolitis (n = 1), gr 3 colitis (n=1)
  - 2 deaths: cardiac arrest (severe myocarditis and bronchiolitis), sudden death (unknown cause)
High Complete Response Rates with Pembrolizumab in Combination with Rituximab in Patients with Relapsed Follicular Lymphoma: Results of an Open-Label, Phase II Study

- ph 2, gr 1-3a FL, rituximab-sensitive, 1+tx
  - Ritux 375 mg/m2 C1 D1, 8, 15, 22, pembrolizumab C1 D2 300 mg q 3 wks x 16
- n=30, median age 64 (43-84), FLIPI low 27%, intermediate 53%, high 20%, 60% stage IV
- median follow-up 13.8 months
- ORR 67%, CR 50%
- median DOR 14.1 months, median PFS 11.4 months
  - PFS >1 year - median PFS 13.8 months, PFS <1 year - median PFS 4.1 months
- Gr 3/4 AEs – n/v (7%), diarrhea (3%), transaminitis (3%), (3%) gr 3 aseptic meningitis
  - 6 d/c immune-related AEs - gr 2/3 diarrhea (10%), gr 2 pneumonitis (7%), and gr 2 rash (3%)
- PD-L1 expression not predictor of response
Thank you

aalencar@med.miami.edu