Mantle Cell Lymphoma Management Updates 2018

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DISCLOSURES

• BMS – research funding (institutional), consultancy
• Genentech – research funding (in), consultancy
• Merck – research funding (in), consultancy
• Seattle Genetics - research funding (in)
• Pharmacyclics - research funding (in), consultancy
• Immune Design - research funding (in)
• KiTE Pharma - research funding (in), consultancy
Overview

- Case presentation
- Background
- Prognostic factors
- Upfront treatment
- Relapsed/refractory
- Novel therapies/clinical trials
Case presentation

- A 58-year-old male right cervical LAD
- + fever, chills, and night sweats
- PE: right cervical, bilateral axillary, and right inguinal LAD
- LABS: elevated WBC with lymphocytosis and several “unclassified” cells
- FDG-PET scan. The scan shows increased SUV uptake and discrete masses in the right cervical, bilateral axillary, retroperitoneal, and right inguinal LAD.
- LN biopsy: mantle cell lymphoma, blastoid variant type
- BM biopsy: MCL involvement.
- Flow cytometry: Monoclonal lambda-restricted CD19+, CD20+, and CD5+, CD10-, CD23-, and BCL6-negative cell population.
- This patient was diagnosed with stage IVB mantle cell lymphoma.
MCL is an aggressive B cell non-Hodgkin lymphoma and considered incurable.
4% of lymphomas in the US
Median age is ~60 years
Male disposition
~80% advanced stage disease
Splenomegaly and lymphomatous polyposis
B symptoms such as fever, chills, and night sweats are common.

Pathology

- Pathology: sheets of monomorphic lymphoid cells that are small to medium sized
- Four cytologic variants, including small cell, mantle zone, diffuse, and blastoid variant

Cyclin D1

- The pathognomonic feature of MCL is the overexpression of cyclin D1 due to chromosomal translocation t(11;14)(q13;32)
CCND1 overexpression
Clinical Prognostic Factors

- The Mantle Cell International Prognostic Index (MIPI)
  - Age, ECOG, LDH, and WBC count.
  - Low risk patients tend to do well, with a median overall survival (OS) not reached.
  - Intermediate risk patients have a median OS of 51 months.
  - High risk patients have a median OS of 29 months.

Biological Prognostic Factors

• **SOX 11**
  – SOX 11 is a transcription factor, and absence of SOX 11 has been associated with an indolent form of MCL

• **Ki-67/P53/P16**
  – High Ki-67 proliferation and p53 and p16 deletion have been shown to be associated with blastoid variant MCL and worse OS outcome.

• **Gene expression profiling (GEP)**
  – RAN, MYC, TNFRSF10B, PLE2, and SLC29A2 as predictors. Patients who had increased expression of all five genes had inferior survival.

• **Cyclin D1 truncation/MicroRNAs:**
  – Truncated cyclin D1 3’UTR as having inferior outcomes.
  – Altered mir-16-1 regulation as shown by Chen et al.

PFS according TP53

NORDIC MCL2/3

- no TP53 mut (n=136)
- TP53 mut (n=15)

Eskelund C et al, ASH 2016
Abstract 1095, Dec 5, 17:00, Room 5AB
Ki67 and Blastoid are Prognostic

Ki-67 index

- < 10%, median not reached
- 10% to < 30%, median not reached
- ≥ 30%, median = 3.4

Cytology

- Nonblastoid, median = 8.5
- Blastoid, median = 2.6

P < .001

Years From Registration

Hoster E et al. JCO 2016
Ki67 powerful even in Blastoid
MCL35: Nanostring GEP predicts survival

Scott DW et al. JCO 2016
Upfront Treatment

• Younger patients who are fit vs. Elderly patients with co-morbidities
• Aggressive induction chemotherapy followed by autologous stem cell transplantation (ASCT).
• European MCL network showed the benefit of ASCT.
  – ASCT vs. maintenance interferon
  – Improved PFS, 39 months vs. 17 months. P=0.01
• Choice of induction chemotherapy
  – R-HyperCVAD
  – Nordic Regimen (R-Maxi-CHOP alternating with R-HiDAC)
  – RCHOP
  – R-bendamustine
  – VR-CAP
  – R-CHOP/R-DHAP

R-HyperCVAD

- Romaguera et al. at MDACC
- Hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high dose cytarabine and methotrexate for 6-8 cycles.
- ORR 97%, CR 87%, 3 year FFS of 64% and OS of 82%.
- SWOG 0213 multicenter
  - ORR 86%, CR of 55%, and 3 year PFS 66%.
- 90% grade IV hematological toxicities, and 61% finished the full course of treatment.

Other Intense Regimens

- **Nordic Regimen (R-MaxiCHOP/R-HiDAC)**
  - RCHOP alternating with high dose cytarabine (without methotrexate) followed by ASCT
  - CR 54%, ORR 96%, a 6 year PFS of 66% and OS of 70%.
- **RCHOP/RDHAP**
  - 3 cycles of RCHOP followed by 3 cycles of RDHAP (rituximab, cisplatin, cytarabine, and dexamethasone) followed by ASCT.
  - CR of 57%, ORR of 93%, and 5 year OS of 75%.
- **R-bendamustine/R-HiDAC (only n = 23)**
  - 3 cycles of R-benda followed by 3 cycles of R-HiDAC
  - CR 96%, ORR 96%, No collection failures, MRD- 93%
European MCL network

Untreated pts with MCL

- Randomize

- RCHOPx 3/R-DHAP x3 Followed by ASCT
  - 248 pts

- R-CHOP (× 6 cycles) Followed by ASCT
  - 249 pts

- Primary end point: Treatment Failure Rate
## Results

<table>
<thead>
<tr>
<th>N = 51 evaluable pts</th>
<th>R-CHOP</th>
<th>RCHOP/DHAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>ORR</td>
<td>90%</td>
</tr>
<tr>
<td>CR</td>
<td>39%</td>
<td>55%</td>
</tr>
<tr>
<td>MRD negative</td>
<td>47%</td>
<td>79%</td>
</tr>
<tr>
<td>Median F/U (months)</td>
<td>6.1 years</td>
<td>6.1 years</td>
</tr>
<tr>
<td>5 year treatment failure rate</td>
<td>65%</td>
<td>40%</td>
</tr>
</tbody>
</table>
Cytarabine improves TTF

Hermine O et al Lancet Oncol 2016
Do you need CHOP? R-bendamustine plus high dose Ara-C induction

PFS at a median fu of 13 months

MRD- achieved in 77% after RB and 93% after RB-RC induction

Armand et al: BJH 2016 (173) 89-95
Less Intense Regimens

- **RCHOP**
  - ORR of 96% and CR of 48%, and a PFS 17 months.

- **VR-CAP (rituximab, bortezomib, cyclophosphamide, doxorubicin, and prednisone)**
  - Compared VR-CAP vs. RCHOP
  - Primary endpoint PFS
  - No ASCT consolidation

- **R-Bendamustine**
  - Compared R-B vs. RCHOP
  - Primary endpoint was EFS
  - No ASCT consolidation

59% improvement in PFS,

median OS was 56.3% vs. not reached in favor of VR-CAP

CR 42% vs. 53%, not stat. significant
<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>R-CHOP (N=242)</th>
<th>VR-CAP (N=240)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td>Any event</td>
<td>238 (98)</td>
<td>206 (85)</td>
</tr>
<tr>
<td>Hematologic event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>178 (74)</td>
<td>162 (67)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>46 (19)</td>
<td>14 (6)</td>
</tr>
<tr>
<td>Anemia</td>
<td>90 (37)</td>
<td>33 (14)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>93 (38)</td>
<td>71 (29)</td>
</tr>
<tr>
<td>Lymphocytopenia</td>
<td>32 (13)</td>
<td>21 (9)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>34 (14)</td>
<td>33 (14)</td>
</tr>
<tr>
<td>Gastrointestinal event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>22 (9)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Constipation</td>
<td>38 (16)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>33 (14)</td>
<td>0</td>
</tr>
<tr>
<td>Infection or infestation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>112 (46)</td>
<td>33 (14)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>15 (6)</td>
<td>11 (5)</td>
</tr>
<tr>
<td>Nervous system disorder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>69 (29)</td>
<td>10 (4)</td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>48 (20)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Other condition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>37 (15)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>47 (19)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Cough</td>
<td>20 (8)</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>23 (10)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>26 (11)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>25 (10)</td>
<td>1 (&lt;1)</td>
</tr>
</tbody>
</table>

More thrombocytopenia, diarrhea in VR-CAP

Peripheral neuropathy was similar
BR vs. R-CHOP

Untreated pts with indolent and MCL (n = 546)

BR (× 6 cycles)
Bendamustine: 90 mg/m²: day 1-2, q4w
+ Rituximab: 375 mg/m² day 1, q4w

R-CHOP (× 6 cycles)
Rituximab: 375 mg/m² day 1, q3w
+ CHOP (standard) day 1, q3w

• Primary end point: To prove a noninferiority of BR vs R-CHOP in EFS

Rummel et al. ASH 2009, ASCO 2012. StiL study
PFS: R-CHOP vs B-R in MCL

Rummel M et al Lancet 2013

Median (IQR; months)
- B-R: Not reached (22.1 to not yet reached)
- R-CHOP: 40.9 (15.2 to not yet reached)

HR 0.61 (95% CI 0.42–0.87)
p = 0.0072

N = 46
N = 48
Pre-Transplant R-Bendamustine Induces High Rates of Minimal Residual Disease in MCL Patients: Updated Results of S1106: US Intergroup Study of a Randomized Phase II Trial of R-HCVAD Vs. R-Bendamustine Followed By Autologous Stem Cell Transplants for Patients with Mantle Cell Lymphoma


US intergroup S1106: SWOG, CALGB/Alliance, ECOG
Schema

First Registration

Randomize for Induction

R-HCVAD cycle 1
R-MTX/Ara-C cycle 2

≥PR

R-HCVAD Cycle 3
Stem cell collection

<PR

OFF STUDY
Follow for survival

≥PR

R-MTX/Ara-C cycle 4

Restaging

R-Bendamustine x 4 cycles

≥PR

R-bendamustine x 2 cycles

<PR

OFF STUDY
Follow for survival

Restaging

Restaging

≥PR

R-cyclophosphamide 3 gm/m²
Stem Cell Collection

<PR

OFF STUDY
Follow for survival

Restaging

Second Registration

STEM CELL TRANSPLANT
<61 yrs: BCV, BEAM or TBI/VP16/Cy
61-65 yrs: BCV or BEAM
## Results

<table>
<thead>
<tr>
<th>N= 51 evaluable pts</th>
<th>R-HyperCVAD (N=17)</th>
<th>R-Bendamustine (N=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>94.1%</td>
<td>82.9%</td>
</tr>
<tr>
<td>CR</td>
<td>35%</td>
<td>40%</td>
</tr>
<tr>
<td>PR</td>
<td>59%</td>
<td>43%</td>
</tr>
<tr>
<td>Inadequate</td>
<td>6%</td>
<td>17%</td>
</tr>
<tr>
<td><strong>Median F/U (months)</strong></td>
<td>34 (10.0-41.0)</td>
<td>27.3 (1-39.5)</td>
</tr>
<tr>
<td><strong>Survival</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-year PFS</td>
<td>82%</td>
<td>81%</td>
</tr>
<tr>
<td>2-year OS</td>
<td>88%</td>
<td>87%</td>
</tr>
</tbody>
</table>

CT/PET not mandated
S1106: PFS

Months After Registration

<table>
<thead>
<tr>
<th>At Risk</th>
<th>Failed</th>
<th>2-year Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-Bendamustine</td>
<td>35</td>
<td>81%</td>
</tr>
<tr>
<td>R-HCVAD/MTX/Ara-C</td>
<td>17</td>
<td>82%</td>
</tr>
</tbody>
</table>
S1106:OS

Months After Registration

R-Bendamustine: PD 3, unknown 1
R-HCVAD: PD 1, suicide 1

At Risk | Deaths | 2-Year Estimate
---|---|---
R-Bendamustine | 35 | 4 | 87%
R-HCVAD/MTX/Ara-C | 17 | 2 | 88%

R-HCVAD: PD 1, suicide 1
R-Bendamustine: PD 3, unknown 1
# Safety

<table>
<thead>
<tr>
<th>Grade 3/4 Toxicities (induction phase)</th>
<th>R-HyperCVAD (N=17)</th>
<th>R-Bendamustine (N=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>59%</td>
<td>8.6%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>65%</td>
<td>34%</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>29%</td>
<td>14%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>71%</td>
<td>17%</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>29%</td>
<td>5.7%</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>24%</td>
<td>2.9%</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>12%</td>
<td>0%</td>
</tr>
<tr>
<td>ALT increased</td>
<td>5.9%</td>
<td>0%</td>
</tr>
<tr>
<td>AST increased</td>
<td>5.9%</td>
<td>0%</td>
</tr>
<tr>
<td>Catheter related infection</td>
<td>5.9%</td>
<td>2.9%</td>
</tr>
<tr>
<td>Dehydration</td>
<td>5.9%</td>
<td>0%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5.9%</td>
<td>0%</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>5.9%</td>
<td>0%</td>
</tr>
<tr>
<td>Nausea</td>
<td>5.9%</td>
<td>0%</td>
</tr>
<tr>
<td>Rash</td>
<td>5.9%</td>
<td>2.9%</td>
</tr>
<tr>
<td>Syncope</td>
<td>5.9%</td>
<td>0%</td>
</tr>
</tbody>
</table>
# Off-Treatment

<table>
<thead>
<tr>
<th>Reasons for going off-Tx or not going on to ASCT</th>
<th>R-HyperCVAD (17) 12/17</th>
<th>R-Bendamustine (35) 14/35</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure to collect stem cells</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Patient choice</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Progressive disease</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Pancytopenia</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Allergy</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Seizure</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Insurance denial</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Others</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

RH ASCT: 9 (53%), 4 off protocol
RB ASCT: 23 (66%), 2 off protocol
Conclusions

- Both R-hyperCVAD and R-bendamustine arm are active regimens with similar response rates and 2-year PFS and OS.

- R-hyperCVAD is not an ideal platform for building future multicenter trials in MCL with ASCT (marrow toxicity and inadequate stem cell mobilization).

- R-Bendamustine arm achieved a 2-year PFS of 81%, which is higher than the target of 75%. Premature study closure limits the precision around the PFS estimates.
## Safety

<table>
<thead>
<tr>
<th>Grade 3/4 Toxicities</th>
<th>RCHOP</th>
<th>RCHOP/RDHAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>8%</td>
<td>29%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>65%</td>
<td>34%</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>8%</td>
<td>17%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>9%</td>
<td>73%</td>
</tr>
<tr>
<td>Renal Toxicity</td>
<td>10%</td>
<td>43%</td>
</tr>
<tr>
<td>N/V (all grades)</td>
<td>33%</td>
<td>57%</td>
</tr>
<tr>
<td>Collection Failure</td>
<td>16%</td>
<td>34%</td>
</tr>
</tbody>
</table>
Conclusion

- Cytarabine including induction regimen can lead to higher CR, MRD negative status
- Cytarabine plus MTX or Cytarabine plus Cisplatin lead to higher adverse events, including stem cell collection failures
MRD (minimal residual disease)

- In ALL, MRD has been shown to be an independent predictive factor.
- 1) Real time quantitative PCR
  - Junctional regions of rearranged immunoglobulin heavy chain (IGH) is a highly sensitive method.
- 2) Multicolor flow cytometry
  - Bottcher et al. showed 18% of patients were negative by flow cytometry but positive for MRD by consensus IGH-PCR.
- 3) Next generation sequencing (NGS) can identify clonal B cells with high sensitivity and specificity.
  - The novel method can overcome disadvantages of PCR-based methods and avoid the need for patient-specific agents.
  - It also has the potential to operate at a higher level of sensitivity ($1 \times 10^{-6}$), which is superior to flow cytometry.
  - Incorporated into all induction trials.

MCL: Depth of Response

MRD over time in MCL patients treated with induction therapy (R-CHOP/R-DHAP, R-CHOP, or R-FC)

Pott C et al. *Blood* 2010
MCL: Molecular > clinical remission

PFS by MRD status in MCL patients at completion of induction therapy
(R-CHOP/R-DHAP, R-CHOP, or R-FC)

Pott C et al. Blood 2010
MRD status before and after ASCT

Figure 3. PFS according to results of MRD analysis.
(A) Before transplant, (B) after transplant.

Kolstad et al. Blood 2014
MRD+ in surveillance - CR patients

Pott et al. ASH 2014
MCL: MRD-based therapy?

MRD-GUIDED DE-ESCALATION OF THERAPY
MCL Intergroup Study EA4151

- Newly diagnosed MCL in first response
- Calibration successful?
- IgNGS calibration

MRD-guided therapy decision tree:
- MRD-negative CR
  - Arm A: Rituximab maintenance no ASCT
  - Arm B: ASCT + rituximab maintenance
- MRD-positive CR or PR
  - Arm C: ASCT + rituximab maintenance
  - Arm D: ASCT + rituximab maintenance

EOI restaging and PB IgNGS

Herrera AF and Armand P. JCO 2017
Elderly patients

- RCHOP/VRCAP/R-Bendamustine
  - R-lenalidomide (Ruan et al)
    - Single arm multicenter trial (38 pts)
    - Induction: 25 mg lenalidomide daily x 21 days x 12 cycles. Rituximab on weeks 1, 2, 3, 4, 13, 21, 29, 37.
    - Maintenance: 15 mg lenalidomide daily x 21 days. Rituximab once every 8 weeks.
    - Low or intermediate MIPI or high MIPI but can’t tolerate chemo
    - ORR of 92%, CR of 64%, median time to CR 11 months
    - 2 year PFS of 85%
    - 50% grade III and IV hem toxicities, 42% required dose reduction.
- Watchful waiting (Martin et al, Abrisqueta et al)
  - Asymptomatic, low MIPI, non-nodal (splenomegaly+circulating).
  - Median time to treatment was about 12 mo (35 mo in recent study)

<table>
<thead>
<tr>
<th>Regimen</th>
<th>ORR/CR</th>
<th>PFS/OS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>R-HyperCVAD (no ASCT)</strong></td>
<td>ORR 97% CR 87% ORR 86% CR 55%</td>
<td>3 yr FFS 64% 3 yr OS 82% 3 yr PFS 66%</td>
</tr>
<tr>
<td>MDACC SWOG</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>RCHOP (no ASCT)</strong></td>
<td>ORR 96% CR 48% ORR 91% CR 30%</td>
<td>Median PFS 17 months Median PFS 31 months</td>
</tr>
<tr>
<td>Dana Farber German Group</td>
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<td></td>
</tr>
<tr>
<td><strong>R-bendamustine (no ASCT)</strong></td>
<td>ORR 93% CR 40%</td>
<td>Median PFS of 70 months</td>
</tr>
<tr>
<td>German Group</td>
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</tr>
<tr>
<td><strong>RMaxiCHOP</strong></td>
<td>ORR 96% CR 54%</td>
<td>6 year PFS 66% 6 year OS 70%</td>
</tr>
<tr>
<td>Nordic</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>RCHOP/RDHAP</strong></td>
<td>ORR 93% CR 57%</td>
<td>5 year OS 75%</td>
</tr>
<tr>
<td>French Group</td>
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</tr>
<tr>
<td><strong>VR-CAP</strong></td>
<td>ORR 92% CR 53%</td>
<td>Median PFS 25 months Median OS not reached</td>
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<tr>
<td>Swiss lead multicenter</td>
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<td></td>
</tr>
<tr>
<td><strong>R-lenalidomide</strong></td>
<td>ORR 92% CR 64%</td>
<td>2 yr PFS 85% 2 yr OS 97%</td>
</tr>
<tr>
<td>Cornell Lead multicenter</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Case

• The patient in our initial case presentation received 6 cycles of R-bendamustine followed by ASCT. He also enrolled on our trial using rituximab plus bortezomib as maintenance therapy post ASCT. He is currently doing well and still in remission.
Relapsed/Refractory disease

- RICE, R-ESHAP, RDHAP, or gemcitabine-based strategies.
- R-bendamustine alone or + cytarabine (R-BAC).
- The ORR of these agents appears high (80-90%), with a CR of 60-70%
- However, grade III and IV adverse events are common, including cytopenias.

Targeted therapies – BTK inhibitors

Herrera AF and Jacobsen EJ
CCR 2014
Targeted therapies: venetoclax (BCL2 inhibition)

# Novel Therapies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of action</th>
<th>ORR/CR</th>
<th>Duration of Response</th>
<th>Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bortezomib</td>
<td>Proteosome inhibitor</td>
<td>ORR 33% CR 8%</td>
<td>DOR 9.2 months</td>
<td>13% peripheral neuropathy</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>Immunomodulator</td>
<td>ORR 35% CR 12%</td>
<td>Median PFS 9 months</td>
<td>46% grade 3-4 neutropenia, 30% grade 3-4 thrombocytopenia</td>
</tr>
<tr>
<td>Temsirolimus</td>
<td>mTOR inhibitor</td>
<td>ORR 41% CR 4%</td>
<td>MTP 6 months</td>
<td>54% grade 3-4 hem toxicities</td>
</tr>
<tr>
<td>Ibrutinib</td>
<td>BTK inhibitor</td>
<td>ORR 68% CR 21%</td>
<td>MDR 18 months</td>
<td>16% grade 3-4 hem toxicities, 44% grade 1-2 diarrhea</td>
</tr>
<tr>
<td>Idealisib</td>
<td>PI3K inhibitor</td>
<td>ORR 40% CR 5%</td>
<td>MDR 3 months</td>
<td>18% grade 3-4 diarrhea, 20% grade 3-4 AST/ALT elevation</td>
</tr>
<tr>
<td>Venetoclax</td>
<td>BCL-2 inhibitor</td>
<td>ORR 75% CR 21%</td>
<td>Median PFS 14 months</td>
<td>16% grade 3-4 anemia, 12% grade 3-4 neutropenia</td>
</tr>
</tbody>
</table>
Phase 2 Study of Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib (PCI-32765), in Relapsed or Refractory Mantle Cell Lymphoma (MCL): Durable Efficacy and Tolerability with Longer Follow-up

Michael Wang, M.D.¹, Simon A. Rule, MD*,², Peter Martin, MD³, Andre Goy, MD⁴, Rebecca Auer, MD*,⁵, Brad S. Kahl, M.D.⁶, Wojciech Jurczak⁷, Ranjana H. Advani, MD⁸, Jorge Enrique E Romaguera, MD⁹, Jesse McGreivy, MD¹⁰, Fong Clow, ScD*,¹¹, Michelle Stevens-Brogan*,¹², Lori Kunkel, MD¹⁰ and Kristie A. Blum, MD¹³

ASH 2012 abstract 904
PCI-32765 (Ibrutinib)

- Orally available inhibitor of BTK
- Once daily dosing

Wang et al, NEJM 2013
The median PFS is 13 months, DOR 17.5 months. 2-year PFS was 31%, and 2-year OS was 47%.

Wang et al, NEJM 2013
Wang et al. Blood 2016
AEs in >10% of pts

**Hematogenous AE:**
- Neutropenia
- Thrombocytopenia
- Anaemia

**Non-Hematogenous AE:**
- Diarrhoea
- Fatigue
- Nausea
- Upper respiratory tract infection
- Dyspnoea
- Oedema peripheral
- Rash
- Constipation
- Vomiting
- Decreased appetite
- Contusion
- Abdominal pain
- Cough
- Dizziness
- Myalgia
- Pyrexia
- Hyperuricaemia
- Mucosal inflammation
- Sinusitis
- Urinary tract infection
Post Ibrutinib Failure

- Median OS 2.9 months
- Median OS 5.8 months Tx

Long term follow-up of ibrutinib in relapsed/refractory MCL

- Pooled analysis of n=370
- Patients treated on 3 clinical trials
  - SPARK (required prior therapy with rituximab and bortezomib)
  - RAY
  - PCYC-1104
- 560 mg daily until progression or unacceptable toxicity
- Median f/u 3.5 years

Rule et al. ASH 2017. #151
Ibrutinib TEAE’s decrease over time

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>&gt; Year 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gr ≥ 3</td>
<td>80%</td>
<td>68%</td>
<td>48%</td>
<td>35%</td>
<td>36%</td>
<td>20%</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>7.3%</td>
<td>4.9%</td>
<td>2.2%</td>
<td>2.6%</td>
<td>2.4%</td>
<td>0%</td>
</tr>
<tr>
<td>SAE</td>
<td>62%</td>
<td>47%</td>
<td>34%</td>
<td>30%</td>
<td>25%</td>
<td>13%</td>
</tr>
</tbody>
</table>

Most common TEAE

<table>
<thead>
<tr>
<th>TEAE</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>17.0%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>12.2%</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>11.9%</td>
</tr>
<tr>
<td>Anemia</td>
<td>9.5%</td>
</tr>
<tr>
<td>A fib</td>
<td>5.9%</td>
</tr>
<tr>
<td>HTN</td>
<td>5.1%</td>
</tr>
</tbody>
</table>

Rule et al. ASH 2017. #151
Patients achieving a CR have prolonged PFS/OS

Table. PFS, OS, and Clinical Responses for MCL Pooled Analysis Including CAN3001

<table>
<thead>
<tr>
<th>End point</th>
<th>Overall (N = 370)</th>
<th>Prior LOT</th>
<th>Best Response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall (N = 370)</td>
<td>1 (n = 99)</td>
<td>&gt; 1 (n = 271)</td>
</tr>
<tr>
<td>PFS – months, median (95% CI)</td>
<td>13.0 (8.4-16.8)</td>
<td>33.6 (19.4-42.1)</td>
<td>8.4 (7.1-12.8)</td>
</tr>
<tr>
<td>OS – months, median (95% CI)</td>
<td>26.7 (22.5-38.4)</td>
<td>NE (36.0-NE)</td>
<td>22.5 (16.2-26.7)</td>
</tr>
<tr>
<td>ORR, n (%)</td>
<td>258 (69.7)</td>
<td>98 (26.5)</td>
<td>--</td>
</tr>
<tr>
<td>CR</td>
<td>98 (26.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>160 (43.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>43 (11.6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval; CR, complete response; LOT, line of treatment; MCL, mantle cell lymphoma; NE, not estimable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease.

Rule et al. ASH 2017. #151
Patients treated in second line have improved PFS

Figure. Kaplan-Meier Plot of Progression-Free Survival (A) and Overall Survival (B) by Prior Line of Therapy

Rule et al. ASH 2017. #151
Patients treated in second line have improved OS

#151
Long term follow-up of ibrutinib in MCL

- Ibrutinib related toxicities decrease over time
  - A fib 5%
  - Major bleeding 7%
- Overall response rate 70% with 26% CR
- Median PFS 13 months
  - 33 months in patients s/p 1 prior line of therapy
  - 8 months in patients s/p >1 prior line of therapy
  - In patients achieving a CR, PFS is 46 months
Acalabrutinib (ACP-196)

- Acalabrutinib is more selective for BTK with less off-target kinase inhibition compared with ibrutinib in vitro

<table>
<thead>
<tr>
<th>Kinase</th>
<th>Acalabrutinib IC50 (nM)</th>
<th>Ibrutinib IC50 (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BTK</td>
<td>5.1</td>
<td>1.5</td>
</tr>
<tr>
<td>TEC</td>
<td>126.0</td>
<td>10.0</td>
</tr>
<tr>
<td>ITK</td>
<td>&gt;1000</td>
<td>4.9</td>
</tr>
<tr>
<td>BMX</td>
<td>46.0</td>
<td>0.8</td>
</tr>
<tr>
<td>TXK</td>
<td>368.0</td>
<td>2.0</td>
</tr>
<tr>
<td>EGFR</td>
<td>&gt;1000</td>
<td>5.3</td>
</tr>
<tr>
<td>ERBB2</td>
<td>~1000</td>
<td>6.4</td>
</tr>
<tr>
<td>ERBB4</td>
<td>16</td>
<td>3.4</td>
</tr>
<tr>
<td>BLK</td>
<td>&gt;1000</td>
<td>0.1</td>
</tr>
<tr>
<td>JAK3</td>
<td>&gt;1000</td>
<td>32</td>
</tr>
</tbody>
</table>

BLK = B lymphocyte kinase; BMX = bone marrow tyrosine kinase gene in chromosome X; BTK = Bruton tyrosine kinase; EGFR = epidermal growth factor receptor; ERBB2 = erb-b2 receptor tyrosine kinase; ERBB4 = erb-b4 receptor tyrosine kinase; IC50 = inhibitory concentration of 50%; ITK = interleukin-2-inducible T-cell kinase; JAK3 = Janus kinase 3; TEC = tyrosine kinase expressed in hepatocellular carcinoma; TXK = T and X cell expressed kinase.

Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=124</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>68 (42-90)</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>99 (80)</td>
</tr>
<tr>
<td>ECOG PS ≤1, n (%)</td>
<td>115 (93)</td>
</tr>
<tr>
<td>Simplified MIPI score, n (%)(^a)</td>
<td></td>
</tr>
<tr>
<td>Low risk (0-3)</td>
<td>48 (39)</td>
</tr>
<tr>
<td>Intermediate risk (4-5)</td>
<td>54 (44)</td>
</tr>
<tr>
<td>High risk (6-11)</td>
<td>21 (17)</td>
</tr>
<tr>
<td>Ann Arbor Stage IV disease, n (%)</td>
<td>93 (75)</td>
</tr>
<tr>
<td>Tumor bulk, n (%)</td>
<td></td>
</tr>
<tr>
<td>≥5 cm</td>
<td>46 (37)</td>
</tr>
<tr>
<td>≥10 cm</td>
<td>10 (8)</td>
</tr>
<tr>
<td>Extranodal disease, n (%)</td>
<td>90 (73)</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>63 (51)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>13 (10)</td>
</tr>
<tr>
<td>Lung</td>
<td>12 (10)</td>
</tr>
</tbody>
</table>

\(^a\) Missing data, n=1 patient.

ECOG PS = Eastern Cooperative Oncology Group performance status; MIPI = Mantle Cell Lymphoma International Prognostic Index.
Most Common Adverse Events

AEs occurring in ≥15% of all patients

- **Headache**: 24 (Grade 1), 12 (Grade 2), 2 (Grade 3)
- **Diarrhea**: 17 (Grade 1), 10 (Grade 2), 3 (Grade 3)
- **Fatigue**: 19 (Grade 1), 6 (Grade 2), 1 (Grade 3)
- **Myalgia**: 15 (Grade 1), 5 (Grade 2), 1 (Grade 3)
- **Cough**: 17 (Grade 1), 2 (Grade 2)
- **Nausea**: 10 (Grade 1), 7 (Grade 2), 1 (Grade 3)
- **Pyrexia**: 11 (Grade 1), 4 (Grade 2)

Grade ≥3 AEs occurring in ≥5% of all patients

- **Anemia**: 12 (Grade 1), 8 (Grade 2), 1 (Grade 3)
- **Neutropenia**: 5 (Grade 1), 6 (Grade 2)
- **Pneumonia**: 1 (Grade 1), 5 (Grade 2)

AE = adverse event.
Serious Adverse Events

- SAEs occurred in 48 patients (39%)
  - SAEs reported in ≥2 patients:
    - Pneumonia (n=5 [4%])
    - Anemia (n=4 [3%])
    - General physical health deterioration (n=3 [2%])
    - Sepsis (n=2 [2%])
    - Tumor lysis syndrome (n=2 [2%])
    - Vomiting (n=2 [2%])
  - One Grade 3 GI hemorrhage occurred in a patient with a history of GI ulcer
  - One Grade 5 AE (aortic stenosis) occurred in a patient with a history of aortic stenosis (not treatment related)

AE = adverse event; GI = gastrointestinal; SAE = serious adverse event.
Events of Clinical Interest

• There were no cases of atrial fibrillation

• Grade 3/4 cardiac AEs (n=3):
  – Grade 3 acute coronary syndrome (n=1, treatment-related)
  – Grade 3 acute myocardial infarction (n=1, not treatment-related)
  – Grade 4 cardiorespiratory arrest (n=1, not treatment-related)

• Infections of any grade occurred in 53% of patients, with Grade 3/4 infections in 13% of patients

• Bleeding events, the most frequent being were contusion (13%) and petechiae (9%), occurred in 31% of patients and were all Grade 1/2 except for one Grade 3 GI hemorrhage (1%) in a patient with a history of GI ulcer

AE = adverse event; GI = gastrointestinal.
Response to Acalabrutinib

- The primary endpoint was investigator-assessed ORR according to the 2014 Lugano Classification

- High concordance was observed between investigator- and IRC-assessed ORR and CR (91% and 94%, respectively)

- IRC-assessed ORR by 2007 IHP criteria (exploratory endpoint) was 75% with a CR rate of 30%

<table>
<thead>
<tr>
<th>ORR using the 2014 Lugano Classification</th>
<th>N=124</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Investigator assessed n (%)</td>
</tr>
<tr>
<td>ORR (CR + PR)</td>
<td>100 (81)</td>
</tr>
<tr>
<td>Best response</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>49 (40)</td>
</tr>
<tr>
<td>PR</td>
<td>51 (41)</td>
</tr>
<tr>
<td>SD</td>
<td>11 (9)</td>
</tr>
<tr>
<td>PD</td>
<td>10 (8)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>3 (2)</td>
</tr>
</tbody>
</table>

CR = complete response; IHP = International Harmonization Project; IRC = Independent Review Committee; ORR = overall response rate; PD = progressive disease; PR = partial response; SD = stable disease.

Subgroup Analysis of ORR

- ORR was consistent across all prespecified subgroups

95% confidence interval was based on exact binomial distribution. No differences were observed by sex, race, Ann Arbor stage, tumor bulk, or prior lenalidomide exposure (data not shown).

ECOG PS = Eastern Cooperative Oncology Group Performance Status; MIPI = Mantle Cell Lymphoma International Prognostic Index; ORR = overall response rate; US = United States.
Duration of Response

• Median time to response was 1.9 months (range 1.5-4.4)
  – 92% of responders had initial response by end of cycle 2

• Median DOR has not been reached; the 12-month DOR rate was 72% (95% CI: 62%, 80%)

CR = complete response; DOR = duration of response; PR = partial response.
Progression-Free Survival and Overall Survival

- Median PFS and median OS have not been reached.

**PFS**
- 12-mo PFS rate: 67% (95% CI: 58%, 75%)

**OS**
- 12-mo OS rate: 87% (95% CI: 79%, 92%)

OS = overall survival; PFS = progression-free survival.
Conclusions

- Acalabrutinib 100 mg BID demonstrated compelling efficacy and a differentiated safety profile, thus providing an alternative therapeutic option for patients with R/R MCL
  - ORR, 81%; CR rate, 40%
  - Responses were durable
  - The most common AEs were mostly Grade 1 or Grade 2
  - There were few discontinuations due to AEs (6%)
  - No atrial fibrillation was observed and the rate of Grade ≥3 hemorrhage was low (1%)

AE = adverse event; BID = twice daily; BTK = Bruton tyrosine kinase; CR = complete response; MCL = mantle cell lymphoma; ORR = overall response rate; R/R = relapsed/refractory.
Venetoclax

- Oral BCL-2 inhibitor
- Phase I study 200 mg to 1200 mg
- No MTD established in MCL, dose moving forward is 800 mg
- ORR 75% and CR 21%
- Median PFS 14 months
- 1 year OS 87%

Davids et al. JCO 2016.
## Venetoclax in MCL

### Table 3. Objective Responses by Histology (all doses, intention to treat)

<table>
<thead>
<tr>
<th>Best Objective Response</th>
<th>All Patients (N = 106)*</th>
<th>MCL (n = 28)</th>
<th>FL (n = 29)</th>
<th>DLBCL (n = 34)*†</th>
<th>DLBCL-RT* (n = 7)</th>
<th>WM (n = 4)</th>
<th>MZL (n = 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response</td>
<td>47 (44)</td>
<td>21 (75)</td>
<td>11 (38)</td>
<td>6 (18)</td>
<td>3 (43)</td>
<td>4 (100)</td>
<td>2 (67)</td>
</tr>
<tr>
<td>CR</td>
<td>14 (13)</td>
<td>6 (21)</td>
<td>4 (14)</td>
<td>4 (12)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>33 (31)</td>
<td>15 (54)</td>
<td>7 (24)</td>
<td>2 (6)</td>
<td>3 (43)</td>
<td>4 (100)</td>
<td>2 (67)</td>
</tr>
<tr>
<td>SD</td>
<td>32 (30)</td>
<td>5 (18)</td>
<td>17 (59)</td>
<td>8 (24)</td>
<td>2 (29)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PD</td>
<td>24 (23)</td>
<td>2 (7)</td>
<td>1 (3)</td>
<td>19 (56)</td>
<td>1 (14)</td>
<td>0</td>
<td>1 (33)</td>
</tr>
</tbody>
</table>

### Duration of response

**MCL**
- Davids M et al *JCO* 2017
Auto-HCT/Allo-HCT

- **Rituximab maintenance**
  - LYSA study (randomized) shows significant PFS and OS improvement

- **Bortezomib maintenance**
  - CALGB showed consolidative bortezomib or maintenance bortezomib post ASCT improved PFS as compared to historical controls

- **Bortezomib plus rituximab**
  - COH, phase II multicenter trial.
  - Interim analysis shows a only 1/23 patients had progressed after ASCT

- **Tam et al. (RIC allo) in patients with relapsed/refractory MCL.**
  - 6 year PFS was 46% and 6 year OS was 53%.

---


Rituximab maintenance after ASCT improves PFS

mFU: 50.2m (46.4-54.2)

PFS (months) from randomization

Obs (95%CI) vs Rituximab (95%CI)
24m: 79.8% (71.5-86.0) vs 93.3% (87.1-96.6)
36m: 72.8% (63.7-79.9) vs 89.1% (82.0-93.5)
48m: 64.6% (54.6-73.0) vs 82.2% (73.2-88.4)
Rituximab maintenance after ASCT improves OS

mFU: 50.2m (46.4-54.2)

<table>
<thead>
<tr>
<th></th>
<th>Obs (95%CI)</th>
<th>OS vs</th>
<th>Rituximab (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24m</td>
<td>93.3% (87.0-96.6)</td>
<td></td>
<td>93.3% (87.1-96.6)</td>
</tr>
<tr>
<td>36m</td>
<td>85.4% (77.5-90.7)</td>
<td></td>
<td>93.3% (87.1-96.6)</td>
</tr>
<tr>
<td>48m</td>
<td>81.4% (72.3-87.7)</td>
<td></td>
<td>88.7% (80.7-93.5)</td>
</tr>
</tbody>
</table>

OS (months) from randomization
Future directions

• The median OS of MCL has been extended from 2.7 years to 4.8 years from the time period of 1975-1996 to 1996 to 2004

• Questions that remain to be answered include the following:
  – the optimal induction regimen
  – the role of ASCT in MRD-negative patients post induction
  – optimal maintenance therapy post induction and/or ASCT
  – optimal combinations of novel therapeutics

COH MCL Guidelines

• Newly Diagnosed
  – 60 < age < 75, R-Bendamustine followed by AHCT
  – Age < 60, Nordic regimen followed by AHCT
  – > 75, R-Bendamustine followed by R or R-Lenalidomide

• Relapsed/Refractory
  – Clinical Trials (Ibrutinib + venetoclax, CAR-T)
  – Ibrutinib or Acalabrutinib
  – Bortezomib or Lenalidomide-based therapy
<table>
<thead>
<tr>
<th>Studies</th>
<th>Phase</th>
<th>Sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avelumab (anti-PD-L1)/Utolimunab (4-1BB agonist) in R/R MCL</td>
<td>Phase I</td>
<td>COH IST</td>
</tr>
<tr>
<td>Consolidation with ASCT and maintenance R vs maintenance R no ASCT</td>
<td>Phase III</td>
<td>Intergroup/SWOG</td>
</tr>
<tr>
<td>Ibrutinib plus ABT 199 in patients with relapsed/refractory MCL</td>
<td>Phase I</td>
<td>Collaboration with U of Virginia multicenter IST</td>
</tr>
<tr>
<td>CAR-T cells (CD19)</td>
<td>Phase I/II</td>
<td>COH IST</td>
</tr>
<tr>
<td>Ibrutinib vs. Ibrutinib plus ABT 199 in patients with R/R MCL</td>
<td>Phase III</td>
<td>Industry</td>
</tr>
</tbody>
</table>
Thank you!