Mantle Cell Lymphoma Management Updates 2016

Robert Chen, MD
Assistant Professor
Co-Leader Lymphoma Disease Team
City of Hope
Disclosures

I receive grant/research support from Seattle Genetics and Millennium. I am also a consultant for Seattle Genetics, Genentech and Merck. I am on the Speaker’s Bureau for Seattle Genetics, Genentech and Millennium.
Overview

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

• A 54-year-old male right cervical LAD
• + fever, chills, and night sweats
• PE: right cervical, bilateral axillary, and right inguinal LAD
• LAB: 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.
• Pathology: mantle cell lymphoma, blastoid variant type
• BM biopsy: MCL involvement.
• Flow cytometry: CD19+, CD20+, and CD51+/ CD10-, CD23-, and BCL6-negative phenotype.
• 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 [1].
• Median age is about 60 years, disposition toward male
• The majority of patients also present with advanced stage disease
• Splenomegaly and lymphomatous polyposis of the large bowel [2] can be seen.
• B symptoms such as fever, chills, and night sweats are common.
Pathology

- Pathology: sheets of monomorphic lymphoid cells that are small to medium sized [3].
- Four cytologic variants, including small cell, mantle zone, diffuse, and blastoid variant [4].
Cyclin D1

- The pathognomonic feature of MCL is the overexpression of cyclin D1 due to chromosomal translocation t(11;14)(q13;32) [4].
CCND1 overexpression
MIPI

- The Mantle Cell International Prognostic Index (6)
  - 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 [9].

• **Gene expression profiling (GEP)**
  - RAN, MYC, TNFRSF10B, PLE2, and SLC29A2 as predictors of [10]. Patients who had increased expression of all five genes had inferior survival.

• **Cyclin D1 truncation:**
  - truncated cyclin D1 3’UTR as having inferior outcomes [11].
  - altered mir-16-1 regulation as shown by Chen et al. [12].
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
  - RCHOP
  - R-bendamustine
  - VR-CAP
R-HyperCVAD

- Romaguera et al. at MDACC (14)
- Hyperfractioned 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% [15].
- 90% grade IV hematological toxicities, and 61% finished the full course of treatment.
R-HyperCVAD variants

- R-maxi-CHOP alternating with high dose cytarabine without methotrexate).
- Geisler et al. showed that this induction followed by ASCT had a 6 year PFS of 66% and OS of 70% \([16]\).
- Delarue et al. developed a regimen where patients received 3 cycles of RCHOP followed by 3 cycles of RDHAP (rituximab, cisplatin, cytarabine, and dexamethasone) followed by ASCT \([17]\).
- CR of 57%, ORR of 93%, and 5 year OS of 75%.
RCHOP/Variants

- ORR of 96% and CR of 48% [20], and a PFS 17 months.
- RCHOP has also been shown to be superior to R-FC (fludarabine, cyclophosphamide)
- 4 year OS was 65% for RCHOP vs. 50% for R-FC [21]
- VR-CAP (rituximab, bortezomib, cyclophosphamide, doxorubicin, and prednisone)
- NEJM study compared VR-CAP vs. RCHOP
- 59% improvement in PFS, median OS was 56.3% vs. not reached [22] in favor of VR-CAP
R-Bendamustine

- Rummel et al. ORR of 75% and CR of 50% and minor hematological toxicities [23].
- European R-B vs. RCHOP
- Similar ORR rates to RCHOP (93% vs. 91%) and CR rates (40% vs. 30%)
- Improved PFS (70 months vs. 31 months),
- Less hem toxicities (30% vs. 68%)
- Less infections (37% vs. 50%) [23].
Untreated pts with indolent and MCL (n = 546)

**Primary end point:** To prove a noninferiority of BR vs R-CHOP in EFS (defined as a difference of less than 10% in EFS after 3 years)

**Randomize**

**BR (× 6 cycles)**
- Bendamustine: 90 mg/m$^2$: day 1-2, q4w
- Rituximab: 375 mg/m$^2$: day 1, q4w

**R-CHOP (× 6 cycles)**
- Rituximab: 375 mg/m$^2$: day 1, q3w
- CHOP (standard): day 1, q3w

**Evaluable patients**
- 260 pts
- 253 pts

Rummel et al. ASH 2009, ASCO 2012.
Progression free survival

Hazard ratio, 0.58 (95% CI 0.44 - 0.74)

p = 0.0000148 (stratified log rank)

Median (months)

B-R 69.5
CHOP-R 31.2
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
First Registration

Randomize for Induction

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

Restaging

<PR
OFF STUDY
Follow for survival

≥PR
R-HCVAD Cycle 3
Stem cell collection

R-MTX/Ara-C cycle 4

Restaging

≥PR
R-bendamustine x 2 cycles

<PR
OFF STUDY
Follow for survival

≥PR
R-cyclophosphamide 3 gm/m²
Stem Cell Collection

Restaging

Second Registration

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

<table>
<thead>
<tr>
<th></th>
<th>R-HyperCVAD (N=17)</th>
<th>R-Bendamustine (N=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N= 51 evaluable pts</strong></td>
<td></td>
<td></td>
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<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>
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<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>
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</table>

CT/PET not mandated
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<tr>
<th>Grade 3/4 Toxicities (induction phase)</th>
<th>R-HyperCVAD (N=17)</th>
<th>R-Bendamustine (N=35)</th>
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</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>
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<tr>
<td>Hyperglycemia</td>
<td>12%</td>
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<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
S1106: PFS

Months After Registration

At Risk  Failed  2-year Estimate
R-Bendamustine: 35  8  81%
R-HCVAD/MTX/Ara-C: 17  4  82%
S1106:OS

Months After Registration

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
Conclusions

• Given the sample size, 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.
Elderly patients

- RCHOP
- VRCAP
- R-Bendamustine
- R-lenalidomide
  - Ruan et al. This single arm multicenter trial
  - ORR of 92%, CR of 64%, and a 2 year PFS of 85%
  - Patients were treated for at least 36 cycles or until disease progression on this treatment

- Watchful waiting
  - Martin et al.
  - Asymptomatic, low MIPI, or elderly MCL patients.
  - Median time to treatment was about 12 months (4-128 months) [26]
  - survival profile of the observation group appeared improved compared to the early treatment group.
<table>
<thead>
<tr>
<th>Regimen</th>
<th>ORR/CR</th>
<th>PFS/OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-HyperCVAD (no ASCT)</td>
<td>ORR97% CR 87% ORR 86% CR 55%</td>
<td>3 yr FFS 64% 3 yr OS 82% 3 yr PFS 66%</td>
</tr>
<tr>
<td></td>
<td>MDACC SWOG</td>
<td></td>
</tr>
<tr>
<td>RCHOP (no ASCT)</td>
<td>ORR 96% CR 48% ORR 91% CR 30%</td>
<td>Median PFS 17 months Median PFS 31 months</td>
</tr>
<tr>
<td></td>
<td>Dana Farber German Group</td>
<td></td>
</tr>
<tr>
<td>R-bendamustine (no ASCT)</td>
<td>ORR 93% CR 40%</td>
<td>Median PFS of 70 months</td>
</tr>
<tr>
<td></td>
<td>German Group</td>
<td></td>
</tr>
<tr>
<td>RmaxiCHOP</td>
<td>ORR 96% CR 54%</td>
<td>6 year PFS 66% 6 year OS 70%</td>
</tr>
<tr>
<td></td>
<td>Nordic</td>
<td></td>
</tr>
<tr>
<td>RCHOP/RDHAP</td>
<td>ORR 93% CR 57%</td>
<td>5 year OS 75%</td>
</tr>
<tr>
<td></td>
<td>French Group</td>
<td></td>
</tr>
<tr>
<td>VR-CAP</td>
<td>ORR 92% CR 53%</td>
<td>Median PFS 25 months Median OS not reached</td>
</tr>
<tr>
<td></td>
<td>Swiss lead multicenter</td>
<td></td>
</tr>
<tr>
<td>R-lenalidomide</td>
<td>ORR 92% CR 64%</td>
<td>2 yr PFS 85% 2 yr OS 97%</td>
</tr>
<tr>
<td></td>
<td>Cornell Lead multicenter</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% [27, 28].
- However, adverse events are common, including cytopenias.
# 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>Protesome 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 85% CR 21%</td>
<td>Median PFS 14 months</td>
<td>16% grade 3-4 anemia, 12% grade 3-4 neutropenia</td>
</tr>
</tbody>
</table>
PCI-32765 (Ibrutinib)

- Orally available inhibitor of BTK
- Once daily dosing

Advani, et al., JCO in press
Interim Results of an International, Multicenter, 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.\textsuperscript{1}, Simon A. Rule, MD\textsuperscript{*}\textsuperscript{2}, Peter Martin, MD\textsuperscript{3}, Andre Goy, MD\textsuperscript{4}, Rebecca Auer, MD\textsuperscript{*}\textsuperscript{5}, Brad S. Kahl, M.D.\textsuperscript{6}, Wojciech Jurczak\textsuperscript{7}, Ranjana H. Advani, MD\textsuperscript{8}, Jorge Enrique E Romaguera, MD\textsuperscript{9}, Jesse McGreivy, MD\textsuperscript{10}, Fong Clow, ScD\textsuperscript{*}\textsuperscript{11}, Michelle Stevens-Brogan\textsuperscript{*}\textsuperscript{12}, Lori Kunkel, MD\textsuperscript{10} and Kristie A. Blum, MD\textsuperscript{13}
# Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Bortezomib-Naïve (N=65)</th>
<th>Bortezomib-Exposed (N=50)</th>
<th>Total (N=115)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prior high intensity therapy</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Hyper CVAD</td>
<td>18 (28%)</td>
<td>15 (30%)</td>
<td>33 (29%)</td>
</tr>
<tr>
<td>Stem cell transplant</td>
<td>7 (11%)</td>
<td>4 (8%)</td>
<td>11 (10%)</td>
</tr>
<tr>
<td><strong>Prior Lenalidomide</strong></td>
<td>8 (12%)</td>
<td>19 (38%)</td>
<td>27 (23%)</td>
</tr>
<tr>
<td><strong>MIPI Score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>9 (14%)</td>
<td>6 (12%)</td>
<td>15 (13%)</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>23 (35%)</td>
<td>18 (36%)</td>
<td>41 (36%)</td>
</tr>
<tr>
<td>High risk</td>
<td>31 (48%)</td>
<td>26 (52%)</td>
<td>57 (49%)</td>
</tr>
<tr>
<td><strong>Bulky Mass (≥10 cm)</strong></td>
<td>6 (9%)</td>
<td>9 (18%)</td>
<td>15 (13%)</td>
</tr>
<tr>
<td><strong>Refractory Disease</strong></td>
<td>27 (42%)</td>
<td>25 (50%)</td>
<td>52 (45%)</td>
</tr>
</tbody>
</table>
ORR

Med DR not reached (med f/u 9.1m)
Med PFS 13.9m
Ibrutinib

- The median duration of response was 17.5 months, 2-year PFS was 31%, and 2-year OS was 47% [34].
- 16% grade III-IV hematological toxicities and 44% grade I-II diarrhea.
- The median PFS is 13 months [35]
ASCT/Allo-HCT

- **Rituximab maintenance**
  - Fred Hutchinson Cancer Center showing post transplant rituximab was associated with improved PFS (HR 0.44) and OS (HR 0.46) [38].

- **Bortezomib maintenance**
  - CALGB showed consolidative bortezomib or maintenance bortezomib post ASCT improved PFS as compared to historical controls (39)

- **Bortezomib plus rituximab**
  - COH, phase II multicenter trial.
  - Interim analysis shows a 2 year DFS of 100%, which is superior to historical controls [40].

- **Tam et al. (RIC allo) in patients with relapsed/refractory MCL [41]**.
  - 6 year PFS was 46% and 6 year OS was 53%. 
MRD (minimal residual disease)

- In ALL, MRD has been shown to be an independent predictive factor [45, 46]

- 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 [47].

- 3) Next generation sequencing (NGS) can identify clonogenic 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 x 10^-6), which is superior to flow cytometry.
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 [50].
• Questions that remain to be answered include the following:
  • 1) the optimal induction regimen,
  • 2) the role of ASCT in MRD-negative patients post induction,
  • 3) optimal maintenance therapy post induction, and
  • 4) optimal combinations of novel therapeutics
<table>
<thead>
<tr>
<th>Studies</th>
<th>Phase</th>
<th>Location</th>
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<tbody>
<tr>
<td>Maintenance bortezomib plus rituximab post ASCT in patients with MCL</td>
<td>Phase II</td>
<td>COH lead multicenter IST</td>
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<tr>
<td>Daratumamab in patients with relapsed MCL</td>
<td>Phase II</td>
<td>Pharma sponsored trial</td>
</tr>
<tr>
<td>Ibrutinib plus ABT 199 in patients with relapsed/refractory MCL</td>
<td>Phase I</td>
<td>U of Virginia lead multicenter IST</td>
</tr>
<tr>
<td>Idealisib plus Palbociclib</td>
<td>Phase I/II</td>
<td>Cornell lead multicenter IST</td>
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Acknowledgements

• Grants
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  – NCI K12, NCI CCITLA, NCI lymphoma SPORE, Tim Nesvig Lymphoma Research Foundation.

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  – Dr. Auayporn Nademanee
  – Dr. Eileen Smith
  – Dr. Amrita Krishnan
  – Dr. Myo Htut
  – Dr. Nitya Nathwani
  – Dr. Ryo Nakamura
  – Dr. John Leonard
  – Dr. Richard Furman
  – Dr. Jia Ruan
  – Dr. Tsiporah Shore

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  – Cheryl Corpus, Brianna Brophy, Jaime Bautista, Penny Lam, Annette Brown, Jennifer Simpson, Sandra Thomas, Joycelynne Palmer, Ni-Chun Tsai, Tanya Paris
References


18. Chen R, Li H, Bernstein S et al. Results 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. 13th International Conference on Malignant Lymphoma; Lugano, Switzerland:abstract #62.


