Mantle Cell Lymphoma: Paradigm Shift?

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Disclosure

- **Heterogeneity:**
  * clinical presentation
  * biological diversity
  * population: (age / comorbidities)

- **No consensus / frontline therapy** (→ 12 options NCCN)

- **Chemosresistance** over time ++ (genetic instability)

- **Significant progress:** med OS 2.5y mid 90’s to 5-7y currently (for pts in trials mostly?)

- **Progress actually relative:**
  * High-risk pts still do poorly regardless
  * Real world registry: med OS still 2 to 3y!
### Distinguish Distinct MCL “Subtypes” in the Clinic

<table>
<thead>
<tr>
<th>“Subtype MCL”</th>
<th>Features</th>
<th>Comment</th>
</tr>
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</table>
| True iMCL ≈ 10% pts      | - Non nodal presentation  
- Splenomegaly  
- High(er) WBC  
- Fewer symptoms  
- SOX11 –ve /  
- Somatic mutated  
- Distinct GEP | SLOW course (“mimics CLL”  
Likely manage differently ++  
Genetically “more stable”(ATM not mutated)→ but can transform over time (del 17p) |
| Indolent MCL @presentation ≈ 30% pts | - Low(er) MIPI /low-bulk  
- No clear (yet) biological distinctive features ++ | Med time / 1st therapy 1y  
No clear defining criteria  
No evidence they should be managed differently ++ |
| Classic MCL (cMCL) 60% pts | - All others | Manage based on “age/fit” context |
Impact of DIT-HDT Frontline (Median PFS)

- DIT/HDT
  * Typically associated with much higher CR rate (>80%)
  * which translates into median PFS well in excess of 6-7y

CR rate > 85%

CR rate > 30-35%
REAL World Impact of ASCT and Rituximab

- 167 MCL pts NCCN database frontline R-chemo - NOT on trial

3y PFS: 18% vs 58%

- 1400 pts Denmark and Sweden registry data (trials or not)

3y OS: 62% in grp 2006-2010 vs 47% before 2000-2005 (p < 0.01)

When pooling DI-HDT pts / R-CHOP >> OS (p=0.02)

Both AraC and rituximab use \(\Rightarrow\) improved outcome
Impact of DIT-HDT Frontline

- Current standard in younger pts anthracyclines / HD-AraC chemoimmunotherapy w/ (wo) HDT-ASCT consolidation

230 pts / arm

- AraC containing arm: higher % and earlier CR / molecular CR

<table>
<thead>
<tr>
<th>Resp post induction</th>
<th>R-CHOP/R-DHAP</th>
<th>R-CHOP</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR-CRu</td>
<td>55%</td>
<td>40%</td>
<td>p=0.0028</td>
</tr>
<tr>
<td>Mol CR</td>
<td>83%</td>
<td>51%</td>
<td>p &lt; 0.0001</td>
</tr>
</tbody>
</table>

R-CHOP

- CR-CRu: 55% vs 40% (p=0.0028)
- Mol CR: 83% vs 51% (p < 0.0001)

R-DHAP

- CR-CRu: 82% vs 73% (p = 0.04)
- Mol CR: 87% vs 73% (p = 0.01)

EU trial

TTF= PEP

Hermine, Lancet 2016
**Depth of Remission ie Molecular CR is Highly Predictive of Outcome**

1. **MRD –ve (molecular CR) post induction improved remission duration**
   - **Pooled** arms R-CHOP → ASCT/R-CHOP/RDHAP → ASCT
   - Also true in elderly pts group

2. Impact of MRD –ve status was independent of:
   - CR/PR
   - MIPI status
   - and regimen

3. **Impact of molecular CR (MRD –ve) confirmed outside trials (75 pts CR → ASCT)**
   - 5y OS 82% vs med OS of 3y in MRD+ve pts

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Hermine, ASH 2012 abst # 151; Lancet 2016
Pott, Blood 2010; Cowan, BBMT 2016
Remaining Challenges

- Med age at diagnosis mid to late 60’s /early 70’s

- Selection of pts for DIT/HDT approaches: age and PS

- High-risk pts still do poorly:

MIPI/NORDIC-2

Ki67

Cytology /blastoid

Geisler, Blood 2010
Hoster, April 2016
MIPI / Ki67 / p53 status

MIPI combined w/ Ki67

- L, median not reached
- LI, median = 7.8
- HI, median = 5.6
- H, median = 1.7

P < 0.001

Years From Registration

Probability

EU 2 best arms of rand trials
<65y R-CHOP/R-DHAP → ASCT
> 65y R-CHOP → Maint R

Del 17p

- not del, median = 7.0
- del, median = 3.0
p = 0.0051

Years from trial entry

Numbers At Risk

OS

R-HyperCVAD / JTCC

R-CHOP-DHAP → ASCT

TP53: experimental

EU trial – R-CHOP-DHAP → ASCT

p53 / ATM del (NGS)

Hoster, April 2016
Delfau-Larue, Blood 2015
Wang, ASH 2014
MCL: Role of Maintenance Therapy

1. Maintenance rituximab benefit 1st shown in elderly: EU trial: R-CHOP vs FCR → maint Rtx vs IFN (560 pts)

   Median remission duration
   75 ms w/ Rtx
   vs 27 ms w/ IFN

   4y OS 87% vs 63%, p = 0.005

   45% reduction progression

2. Recent data suggest maintenance Rtx also benefits younger pts post HDT

   LYM trial:
   4-R-DHAP → ASCT → Rand Maint vs Obs.

Kluin-Nelemans, NEJM Aug 2012
Le Gouill, ASH 2014 abst # 124
Maintenance Therapy – Might be REGIMEN Dependent

– MAINTAIN Trial:
  - Frontline B-R ➔ Rand maint Rtx x 2y vs Obs.
  - ORR 85% w/ 27% CR
  - Maint R had no impact

No benefit of MR post FCR in EU trial

Lymphopenia post FCR and BR (below)

Table 1. White blood cell counts before and after induction therapy

<table>
<thead>
<tr>
<th>WBC counts (n = 947)</th>
<th>Before BR Median (cells/µL)</th>
<th>After BR Median (cells/µL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocytes</td>
<td>6,600</td>
<td>3,800</td>
</tr>
<tr>
<td>Granulocytes</td>
<td>3,900</td>
<td>2,400</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>1,500</td>
<td>500</td>
</tr>
<tr>
<td>CD4+ cells</td>
<td>555</td>
<td>118</td>
</tr>
<tr>
<td>CD8+ cells</td>
<td>316</td>
<td>198</td>
</tr>
<tr>
<td>CD4+/CD8+ ratio</td>
<td>1.76</td>
<td>0.6</td>
</tr>
</tbody>
</table>

BR = bendamustine, rituximab; WBC = white blood cells

Rummel, ASCO 2016, abst # 7503
Kluin-Nelemans, NEJM 2012
Relapsed / Refractory MCL

- As in frontline NO consensus / heterogeneous population +++ (variety prior RX)

- Standard chemo (R-chemo) has (limited) benefit
  * BR 2\textsuperscript{nd} line: ORR 70-80% with $\frac{1}{2}$ CR
  * Med PFS 16-20ms

- HDT-ASCT not proven to be beneficial in r/r setting

Czuczman, Annals Hematol, 2015
Tam, Blood 2009
**R/R MCL - Allogeneic Transplantation**

**MDACC**

- OS
- CPFS

**FHCRC**

- Unrelated (n = 17)
- Related (n = 16)
- MRD
- URD

**EBMT**

- LGNHL (n = 52)
- HD (n = 52)
- MCL (n = 22)

**IBMTR**

**Only potentially curative modality**

**Issues: median age, NRM 25-35% and cGVH > 50%**

Khour, JCO 2003; Robinson, Dec 2002; Maris, Blood Dec 2004 Hamadani, BBMT, April 2013
R/R MCL – Targeted Therapies

- 3 approved new drugs in r/r MCL in the US (Bortezomib, Lenalidomide, Ibrutinib) and 3 in EU (Temsirolimus, Lenalidomide, Ibrutinib)

- Frequently used with rituximab

- Show durable responses even in chemorefractory pts

- None provides a cure – (bridge to allo? /cell therapy?)

- Provide platform to build up on current regimens
MCL – Proteasome inhibitors- Bortezomib

Several phase II: showed an ORR 30-50% in r/r MCL

- PINNACLE Ph II confirmatory trial
  - 134 pts (1-3 prior RX)
  - ORR 33%, CR 8%
  - Med DOR 10ms
  (>28 ms in pts CR-CRu)
  (off therapy / max 1y RX)

- Combinations: with B-R based regimens (B-R, BR-Dex, RIBVD)
  showed CR rate up to 75% → basis for E1411 ongoing

Ruan, JCO 2011; Till, B Jnl Hematol 2016;
Furtado, Br Jnl Haematol, 2015
Kahl, Br J Haematol Oct 2011;
Chang, Blood 2014
MCL – LYM-3002: Frontline R-CHOP vs R-CBzHP

243 pts / arm - ineligible for HDT-ASCT / 6 to 8 cycles (R-CHOP vs VR-CAP)

<table>
<thead>
<tr>
<th></th>
<th>R-CHOP</th>
<th>VR-CAP</th>
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<tbody>
<tr>
<td>ORR</td>
<td>90%</td>
<td>92%</td>
</tr>
<tr>
<td>CR rate (0.007)</td>
<td>42%</td>
<td>53%</td>
</tr>
<tr>
<td>Med DOR CR</td>
<td>18 ms</td>
<td>42 ms</td>
</tr>
</tbody>
</table>

59% improvement of PFS (PEP) (12 vs 24.7 ms) → 1st frontline novel regimen FDA approved 2014

Well tolerated / sensory NP gr ≥ 3 = 4% vs 7%

Robak, NEJM 2015
Lenalidomide in r/r MCL

Initial phase II: showed an ORR in 35-40% range in r/r MCL

EMERGE confirmatory trial:
- 134 pts / med nb prior RX 4 (2-10)
- Failed alkylating agents, anthracyclines, rituximab and bortezomib
- >½ refractory to last RX
- ORR 28% with 8% CR (IRC)
- Med TTR 2ms

Med DOR 16.6 ms

Activity across subgroups including failures to BTZ and refractory pts

Most common AE (≥ 5% grade 3/4) was myelosuppression, consistent with the known safety profile for lenalidomide in MM

Witzig, Annals Oncol July 2011
Goy, JCO Oct 2013
Witzig ASCO 2013 abst # 8533
Goy, Br J Haematol, Aug 2015
Lenalidomide in r/r MCL – Next Step

- **SPRINT Trial (EU):**
  * Len 25 mg/day vs Investig. choice)
  * in r/rMCL: ORR 40% vs 11%
  * > PFS and DOR in favor Len

- **Combination w/lenalidomide:**
  * Len+R (R2):
    - Dose esc (10 to 25 mg) D1–21/28 + R 375 x 4
    - 52 pts btw Ph I and II
    - MTD 20mg (myelotoxicity)
    - ORR 56% / 36% CR
    - Med DOR 18.9 ms

- **Other combinations:**
  - w/Dex+R, R2-Ib, Len + B-R (toxicity ++) and as maintenance post therapy
  - R-CHOP/R-HAD vs R-CHOP → 2y maint R2 / vs R
Lenalidomide + Rituximab (R2) in Frontline MCL

- **Study design:**
  * Up to 25mg post 1st cycle if tolerated
  * Treatment until POD
  * 38 pts (multicenter)
  * 1/3 each low, interm, high MIPI

- **Toxicity:**
  * 50% Gr 3-4 neutropenia
  * 29% rash
  * 11% flare

- **Impressive activity:**
  * ORR 87% / 61% CR (ITT)
  * Med time to CR 11 ms
  * 2y PFS 85%

Very promising / provides foundation to explore / build up non-chemo options in MCL
Ruan, NEJM 2015
**Ibrutinib (PCI-32765): Ph II in r/r MCL**

1\textsuperscript{st} in class BTKi  
560 mg po daily $\rightarrow$ POD or toxicity  
111 pts - med 3 prior RX (1-5)  
86\% interim / high-risk MIPI, 63 BTZ naïve / 48 BTZ failure  
45\% refractory last RX

<table>
<thead>
<tr>
<th>Efficacy, n (%)</th>
<th>No BTZ (n = 63)</th>
<th>Prior BTZ (n = 48)</th>
<th>All Patients (N = 111)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n (%)</td>
<td>43 (68)</td>
<td>32 (67)</td>
<td>75 (68)</td>
</tr>
<tr>
<td>CR, n (%)</td>
<td>12 (19%)</td>
<td>11 (23%)</td>
<td>23 (21%)</td>
</tr>
<tr>
<td>Med DOR, mo</td>
<td>15.8</td>
<td>NR</td>
<td>17.5</td>
</tr>
<tr>
<td>Med PFS, mo</td>
<td>7.4</td>
<td>16.6</td>
<td>13.9</td>
</tr>
<tr>
<td>Med OS, mo</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
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</table>

Wang, NEJM, Aug 2013
Ibrutinib (PCI-32765): Ph II in r/r MCL

Well tolerated

Transient (recirculation lymphocytosis)

- Less frequent than in CLL
- Occurs in 1/3 pts
- At mid of 8 weeks of RX
- Seems to correlate with BM involvement

Hematologic AEs*
- Neutropenia
- Thrombocytopenia
- Anemia
- Diarrhea
- Fatigue
- Nausea
- Dyspnea
- Constipation
- Upper respiratory infection
- Peripheral edema
- Vomiting
- Decreased appetite
- Cough
- Abdominal pain
- Pyrexia
- Arthralgia
- Constipation
- Rash
- Hyperuricemia
- Myalgia
- Urinary tract infection
- Back pain
- Sinusitis

Nonhematologic AEs*

<table>
<thead>
<tr>
<th>Grade 1-2</th>
<th>Grade 3-4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>Moderate</td>
<td>Minor</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Severe</td>
<td>Minor</td>
</tr>
<tr>
<td>Anemia</td>
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<td>Minor</td>
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<tr>
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<td>Moderate</td>
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<tr>
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<tr>
<td>Upper respiratory infection</td>
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<tr>
<td>Peripheral edema</td>
<td>Moderate</td>
<td>Minor</td>
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<tr>
<td>Vomiting</td>
<td>Severe</td>
<td>Minor</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>Moderate</td>
<td>Minor</td>
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<tr>
<td>Cough</td>
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<tr>
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</tr>
<tr>
<td>Sinusitis</td>
<td>Severe</td>
<td>Minor</td>
</tr>
</tbody>
</table>

*AEs were updated with an estimated median follow-up of 26.7 months.

Wang, Blood, 2015
Furtado, BJH, 2015
**Ibrutinib (PCI-32765): AFIB and Bleeding**

- **AFIB:**
  * Due to off-target inhibition of other kinases (TEC) → leading to decreased PI3K-AKT pathway in atrial and ventricular tissue
  * Occurs in 3.5% to 7% subjects (from pooled CLL, MCL, WM studies)
  * Conservative management of AFIB while holding Ibrutinib
  * Leads to interruption of RX in about 1/2 pts

- **Bleeding:**
  * Off-target effect on collagen and VWF-mediated platelet activation
  * Rare organ bleeding / subdural
  * Caution w/ anti-coagulants
  * Stop ibrutinib pre and post procedure (3-7 days depending procedure)

McMullen, Blood 2014
Leong, Blood 2016
Levade, Blood 2014
Ibrutinib (PCI-32765): Ph II in r/r MCL

Updated follow-up 26 ms

Med DOR 17.5 ms

Activity across subgroups including prior BTZ / refractory pts or del 17p / p53 +ve

Wang, Blood 2015
Ibrutinib vs Temsirolimus Ph III in r/r MCL

Ibrutinib (N = 139) 560 mg daily vs Temsirolimus (N = 141) 75 mg on Cycle 1, Days 1, 8, 15 (except 1st cycle at 175 mg)
Med nb prior RX 2.0 (1-9) / crossover after POD to Ib

2y PFS 41% versus 7%

ORR 72% vs 40%
19% CR vs 2%

PEP: PFS

Dreyling, Lancet Feb 2016
Ibrutinib (PCI-32765): Resistance / POD

- **POD post ibrutinib**
  * POD post lb CLL / “Richter transformation”
  * Series of 114 MCL pts w/ POD on lb / 15 sites
  * Med nb prior RX 3 (0-10)
  * Median time on ibrutinib 4.7 ms
  * Med OS after **POD 2.9 ms**

- **Biomarkers of resistance:**
  * **Primary resistance**: mutations affecting CAR11/NF-kB signaling or PIM1 and ERBB4 kinase genes / complex karyotypes
  * **Secondary resistance**: binding site mut. BTKC481S and downstream mut. PLCγ2 as in CLL

Martin, Blood 2016; Balasubramanian, Blood 2014
**Ibrutinib (PCI-32765): Next Steps**

- **Combination w/ R:**
  * 50 pts: Ibr + R 4 weekly then day 1/cycle
  * Med 3 prior RX
  * ORR 88% and 44% CR
  → piloted pre R-HyperCVAD++

- **Other combinations w/ ibrutinib:**
  * +R2; +bortezomib or carfilzomib
  * + BR (Ph Ib / 16/17 MCL resp 13 CR)
  * BR+/- Ib (SHINE) or BR vs Ib (UK)
  * Ib + Venetoclax +/- Obinutuzumab
  * Ib + checkpoint inhibitors

- **Triangle study**
  EU (R-CHOP-DHAP→ASCT w/w/o Ib → ASCT or Ib maint)

Wang, Lancet Oncol 2016; Maddocks, Blood 2015s
Other Novel Agents in r/r MCL

- **2nd generation PI:**
  Carfilzomib, Oprozomib, Ixazomib

- **2nd generation BTKi: (more selective)**
  ACP-196 (acalabrutinib), Ph II & BR+/−ACP196 completed, P), ONO- ONO/GS-4059, BGB-3111

- **Idelalisib (PI3Kδ inhibitor):**
  * 40 pts pts med 4 (1-14) prior RX
  * ORR 40% (16/40) / 2 CR (5%)

- **Temsirolimus:**
  * mTORC1 inhibitor (rapa derivative)
  * Original ph II ORR (33-41%) / DOR 6.9 ms
  * Ph III vs invest choice (EU) / ORR 22% vs 2%
  * Other comb ongoing w/ Temsirolimus

Kahl, Blood 2014; Wittig, JCO 2005; Hess, JCO 2009
Other Novel Agents in r/r MCL

- **Venetoclax (ABT199):**
  * ORR 75% in r/r MCL CR 21%
  * Comb ongoing:
    - VNTX + Rituximab
    - BR+ VNTX
    - Obinutuzumab + Ib + VNTX

- **Immunotherapy:**
  * BITE Ab (Blinatumomab): 5/7 pts responded
  * PD1 blockade and CPI (anecdotal so far)
  * CAR-T cells: ph I/II ZUMA-1 / anti-CD19 CAR T-cell ongoing
MCL Management Summary

- Rare disease but strong focus / clinical research (4 drugs in 10y)

- Novel therapies offering new options:
  * Durable responses in r/r pts
  * Combination with standard regimens: concomitant or as consolidation / maintenance

- Maintenance role likely to continue to increase
  (US study: rand in CR pts maint vs ASCT)

- MRD becoming a new endpoint (MRD –ve → >> outcome)
Encourage participation in trials!
Thank You!

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