Development of Novel Therapies for Multiple Myeloma and Waldenstrom’s Macroglobulinemia

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Historical Perspective of Multiple Myeloma Therapies

- High-dose melphalan
- Oral melphalan and prednisone
- ABMT
- VAD
- Bisphosphonates
- High-dose therapy with autologous stem cell support
- Thalidomide
- Proteasome inhibitors
- Other immunomodulatory agents. HDACs

Targeting Growth, Survival, and Drug Resistance of MM in BM Microenvironment

Cytokines:
- IL-6, VEGF
- IGF-1, SDF-1α
- BAFF, APRIL
- BSF-3

Cell surface targets:
- CD40
- FGFR3
- CS1
- BAFF-R
- VEGFR

BMSC

Adhesion
- ICAM-1
- MUC-1
- VCAM-1
- VLA-4

Hideshima T and Anderson KC. Nat Rev Cancer 2007,
Mechanisms Mediating Anti-MM Activity of Bortezomib

**ER-Stress Induction**
- Caspase-12 cleavage;
- phospo-PERK;
- GADD-153, ATF4, GRP 78, & XBP-1 splicing

**Anti-Angiogenic & Anti-Osteoclastic Activity**
- Migration, VEGF, Proangiogenic MMP-9, & Caveolin-1;
- Osteoclastogenesis via MIP1α, BAFF
- Osteoblast formation

**Apoptosis**
- JNK; Caspases & PARP cleavage;
- ROS; ▼ △Ψm
- Cyto-c & Smac release; ▼ IAPs;
- mitochondrial Ca²⁺ influx;
- Bid cleavage, Fas & FasL, BH-3 only proteins: Bim, Bik, & NOXA

**Growth & Survival**
- ▼ NF-κB, MAPK, JAK/STAT
- ▼ IGF-1/IL-6. ▲ PI3K-Akt

**Microenvironment**
- ▼ MM-BMSC’s interaction;
- ▼ ICAM, VCAM, αVβ3
- ▼ IGF-1, IL-6, BAFF, RANKL

**Heat Shock Proteins & DNA Repair**
- ▲ Heat Shock Proteins-27, -70, 90; ▼ DNA-PK

**Cell-Cycle**
- Cdk inhibitors: ▲ P21 & p27, p53
- Cyclins: D1, E1, A, B.

**Proteasome**
- Chymotrypsin- and Caspase-like proteasome activities;
- Mono-ubiquitination;
- 26S Proteasome subunits
Lenalidomide in Myeloma

MM cells

Bone Marrow Stromal Cells

IL-6
TNFα
IL-1β

Bone Marrow Vessels

NK Cells

Intercellular adhesion molecule 1 (ICAM-1)

Dendritic Cells

CD8+ T Cells

VEGF
bFGF

NFAT
PI3K

PKCζ

CD28

LeBlanc R et al. Blood 103: 1787, 2004
Integration of Novel Therapy
Into Myeloma Management
Bortezomib, Lenalidomide, Thalidomide, Doxil, Carfilzomib, Pomalidamide, Panobinostat

Target MM in the BM microenvironment to overcome conventional drug resistance in vitro and in vivo

Effective in relapsed/refractory, relapsed, induction, consolidation, and maintenance therapy

Eleven FDA approvals and median survival prolonged from 3-4 to 6-7 years, with additional prolongation from maintenance

New approaches needed to treat and ultimately prevent relapse
Chromosomes and Prognosis in Multiple Myeloma

For conventional low and high dose therapy:

Nonhyperdiploid worse prognosis than hyperdiploid
t(11;14), hyperdiploidy -standard risk
t(4;14), t(14;16), t(14;20), del(17p), del(13q14)-high risk

For novel treatments
Bortezomib, but not lenalidomide, can at least partially overcome t(4;14), del(13q14)

del(17p) p53 remains high risk
Combinations in the Upfront Treatment of MM

Stewart AK, Richardson PG, San Miguel JF Blood 2009
CALGB 100104: LEN Maintenance significantly prolonged PFS & OS vs. placebo

**PFS**

Cutoff: Oct 2011

- **Median TTP**
  - LEN: 46 months
  - PBO: 27 months

**OS**

Cutoff: Oct 2011

- **Events**
  - LEN: 35
  - PBO: 53
- **HR (P Value)**
  - LEN: 0.62 (0.03)
  - PBO: N/A

ASCT: autologous stem cell transplant; CALGB: Cancer and Leukemia Group B; HR: hazard ratio; LEN: lenalidomide; N/A: not applicable; OS: overall survival; PBO: placebo.

Increasing Stringency in Defining Complete Response

- **CR** ……………. Negative Immunofixation & < 5% PC in BM

- **Stringent CR**……Normal FLC & no clonal PC by immunohistochemistry
  (Low sensitivity $<10^{-2}$)

- **Outside BM** ……..Imaging techniques (MRI & CT-PET).

- **BM Level**………..**Immunophenotypic remission** (by multiparametric flow)
  **Molecular remission** (by sequencing) *

* Pitfalls: 1. Pattern of BM infiltration in MM is not uniform… The possibility of residual MM-PC in another territory cannot be excluded (false negative results).

2. Extramedullary relapses.
IFM/DFCI 2009 Study
Newly Diagnosed MM (N=1,000)

Induction
RVD x 3
Revlimid 18 mos
Melphalan 200mg/m²* + ASCT
CY (3g/m²)
MOBILIZATION
Goal: 5 x 10^6 cells/kg
RVD x 2

Collection
MRD
CY (3g/m²)
MOBILIZATION
Goal: 5 x 10^6 cells/kg

Consolidation
MRD
RVD x 5
Revlimid 18 mos

Maintenance
MRD
SCT at relapse

Randomize
Calibration

MRD @ CR
Current and Future Directions

1. Immune therapies

1. Targeting protein homeostasis

3. Targeting the myeloma epigenome

4. Targeting the myeloma genome

Myeloma will be a chronic illness, with sustained CR in a significant fraction of patients.
MAb Based Therapeutic Targeting of MM

Antibody-dependent Cellular Cytotoxicity (ADCC)

- Effector cells: NK cell, macrophage, neutrophil.
- ADCC

- Lucatumumab or Dacetuzumab (CD40)
- Elotuzumab (CS1)
- Daratumumab (CD38)
- XmAb®5592 (HM1.24)
- SAR650984 (CD38)

Complement-dependent Cytotoxicity (CDC)

- CDC
- C1q
- MM

- Daratumumab (CD38)
- SAR650984 (CD38)

Apoptosis/growth arrest via intracellular signaling pathways

- huN901-DM1* (CD56)
- nBT062-maytansinoid/DM4* (CD138)
- 1339 (IL-6)
- BHQ880 (DKK)
- RAP-011 (activin A)
- Daratumumab (CD38)
- SAR650984 (CD38)
- J6M0-MMAF* (BCMA)

* Ab drug conjugate

Updated from Tai & Anderson Bone Marrow Research 201
SLAMF7 (CS1) is highly and uniformly expressed at gene and protein level on patient MM cells

Elotuzumab (Elo) is a humanized monoclonal antibody targeting CS1 in preclinical models

Clinical trial of Elo in MM achieved stable disease

ADCC activity of Elo against MM enhanced by lenalidomide (len) in preclinical models (Tai et al, Blood 2008)

Phase II trial: 92% response to len dex elo in relapsed MM, PFS 32.5 months

Phase III trial of len dex elo versus len dex ongoing in relapsed MM for new drug approval

Richardson et al, ASH 2014
Daratumumab with Lenalidomide and Dexamethasone in Relapsed, or Relapsed and Refractory Multiple Myeloma

**Daratumumab**
- A human mAb that targets CD38-expressing tumor cells
- DARA+LEN enhanced killing of MM cells *in vitro* and is hypothesized to lead to synergistically higher efficacy in clinical setting

- Antibody-dependent cell-mediated cytotoxicity (ADCC)
- Antibody-dependent cellular phagocytosis (ADCP)
- Complement-dependent cytotoxicity (CDC)
- Apoptosis

Plesner et al, ASH 2014
Maximum % Change in M Protein from Baseline

- **Part 1**
  - Dose Escalation Study
  - 2-, 4-, 8- & 16 mg/kg dose
  - N=13

- **Part 2**
  - Expansion Cohort Study
  - 16 mg/kg dose
  - N=30

- Majority had >50% reduction of M protein
Tumor promoting cells

Reduction of immunosuppression

ImMIDs
Thalidomide, Lenalidomide, Pomalidomide

Checkpoint blockers
PD-L1/PD-1 inhibitors

Immune adjuvants
CpG ODNs, TLR-7/9 agonists

Vaccines
Native idiotype protein, PVX-410, CD138, MM-DC

CAR T cells
anti-Kappa, CD138, BCMA, NKG2D

Induction of anti-MM tumoral activity

Anti-tumor cellular immunity

NK cells
MDSCs
Tregs cells
pDC

DC

Cytotoxic T cells

B cells
Th cells
Cytotoxic T cells

CAR T cells

Tumor promoting cells

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NK cells
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Tregs cells
pDC

DC

Cytotoxic T cells

B cells
Th cells
Cytotoxic T cells

CAR T cells
Plasmacytoid DCs Promote Growth, Survival, and Drug-Resistance in Myeloma

Targeting PD1-PDL1 Immunologic Checkpoint in pDC-T Cell and pDC-MM Cell Interactions

Chauhan et al, Clin Cancer Res 2014
Checkpoint Blockade Induces Effector Cell Mediated MM Cytotoxicity

Effectors: Autologous effector cells (CD3T cells, NK cells)
Target: CD138+ MM cells from Rel/Ref MM-BM

Gorgon et al, Clin Cancer Res, in press
Lenalidomide Reduces PD1 and PD-L1 Expression on RR-MM Bone Marrow Cells

**CD138+ MM cells**

- Untreated
- Lenalidomide

**mMDSC**

- Untreated
- Lenalidomide

*Untreated T cells CD14+ Myeloid cells*

**PD-1**

**PD-L1**

Lenalidomide Enhances Checkpoint Blockade-Induced Immune Response in MM Bone Marrow

**Intracellular IFNγ expression**

**Effector cell mediated-MM cytotoxicity**

**Combination Trials Ongoing**

Vaccines Targeting MM Ag Specific Peptides to Delay Progression of Smoldering to Active MM

• Using immunogenic HLA-A2-specific XBP1, CD138, CS1 peptides to induce MM-specific and HLA-restricted CTL responses against several MM antigens

Polyfunctional responses: IFN-γ, cytotoxicity, proliferation, CD107a degranulation to patient MM cells and MM cell lines

Peptide-specific responses: Individual differences in specificity, more broad response to cocktail.

Clinical trial: immune responses to vaccine; lenalidomide and vaccine cohort enrolling 2014; PD-1 and vaccine cohort planned

Phase I Trial of Vaccination with DC/MM Fusions in Relapsed Refractory MM MM

- Well tolerated, no autoimmunity
- Induced tumor reactive lymphocytes in a majority of patients
- Induced humoral responses to novel antigens (SEREX analysis)
- Disease stabilization in 70% of patients

- DC/MM fusions induce anti-MM immunity in vitro and inhibit MM cell growth in vivo in xenograft models


MM/DC Vaccination following Autologous PBSCT for Myeloma


CTN Randomized trial of lenalidomide with or without vaccine posttransplant this year
Effect of Soluble NKG2D Ligands


Shedding of tumor associated NKG2D ligands

Down-regulation of NKG2D & Immune suppression

Expansion of immune suppressor cell

IL-10, TGFβ, Fas-L

Groh V, Nat Imm 2006

Dai Z, JEM 2009
NKG2D-CAR

Generation of Antitumor Responses by Genetic Modification of Primary Human T Cells with a Chimeric NKG2D Receptor

Tong Zhang, Amorette Barber, and Charles L. Sentman

Department of Microbiology and Immunology, Dartmouth Medical School, Lebanon, New Hampshire

Activating receptor on NK cells & T-cells

Sentman C, Cancer Res 2006
Targeting Ubiquitin Proteasome System

UB enzymes E1, E2 and E3-UB-Ligases

Deubiquitylating Enzymes (DUBs)

- P5091 target USP-7
- bAP15 target USP-14/UCHL5

Poly-ubiquitinated proteins (proteasome substrates)

ATPases/Cdc48

Potential Therapeutic Targets

- Bortezomib
- Carfilzomib
- Opromazib
- Ixazomib
- Marizomib: β5, β1, β2

Immunoproteasome

Potential Therapeutic Targets

- PR-924

Chauhan et al, Cancer Cell, 2012; 22(3):345
Chauhan et al, Clin Can Res., 2011; 17(16):5311
Chauhan et al, Blood, 2010; 116(23):4906
Chauhan et al, Cancer Cell, 2005; 8(5):407
Hideshima et al, Can Res, 2001; 61(7):3071
USP 7 (DUB) Inhibitor P5091 Overcomes Bortezomib Resistance in MM cells

b-AP15, a Novel USP14/UCHL5 Inhibitor, Induces Polyubiquitination Without Blocking Proteasome Catalytic Activities

Clinical Trial in R/R MM

Tian et al. Blood 2014; 123: 706-16
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>KRd (n=396)</th>
<th>Rd (n=396)</th>
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</thead>
<tbody>
<tr>
<td>Presence of neuropathy at baseline, %</td>
<td>36.4</td>
<td>34.6</td>
</tr>
<tr>
<td>Number of prior regimens, median (range)</td>
<td>2 (1–3)</td>
<td>2 (1–3)</td>
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</table>

**Prior therapies, %**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>KRd (n=396)</th>
<th>Rd (n=396)</th>
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</thead>
<tbody>
<tr>
<td>Transplant</td>
<td>54.8</td>
<td>57.8</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>65.9</td>
<td>65.7</td>
</tr>
<tr>
<td>Non-responsive to prior bortezomib*</td>
<td>15.2</td>
<td>14.6</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>19.9</td>
<td>19.7</td>
</tr>
<tr>
<td>Any IMiD</td>
<td>58.8</td>
<td>57.8</td>
</tr>
<tr>
<td>Refractory to prior IMiD in any prior regimen</td>
<td>21.5</td>
<td>22.2</td>
</tr>
<tr>
<td>Bortezomib and IMiD</td>
<td>36.9</td>
<td>35.1</td>
</tr>
<tr>
<td>Non-responsive to prior bortezomib* and refractory to prior IMiD</td>
<td>6.1</td>
<td>6.8</td>
</tr>
</tbody>
</table>

*Non-responsive is defined as less-than-minimal response to any bortezomib-containing regimen, disease progression during any bortezomib-containing regimen, or disease progression within 60 days after the completion of any bortezomib-containing regimen.
# PFS by Risk Group

<table>
<thead>
<tr>
<th>Risk Group by FISH</th>
<th>KRd (n=396)</th>
<th>Rd (n=396)</th>
<th>HR</th>
<th>P-value (one-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Median, months</td>
<td>N</td>
<td>Median, months</td>
</tr>
<tr>
<td>High</td>
<td>48</td>
<td>23.1</td>
<td>52</td>
<td>13.9</td>
</tr>
<tr>
<td>Standard</td>
<td>147</td>
<td>29.6</td>
<td>170</td>
<td>19.5</td>
</tr>
</tbody>
</table>
Phase 1/2 Study of Carfilzomib, Lenalidomide, and Dexamethasone (CRd)

Generally well tolerated and manageable side effects

Grade 3/4 adverse events in ≥10% of pts
- Hematologic: anemia, neutropenia, thrombocytopenia
- Non-hematologic: hyperglycemia, dyspnea, deep vein thrombosis/ pulmonary embolism

<table>
<thead>
<tr>
<th>Response, %</th>
<th>Overall (n=49)</th>
<th>I (n=20)</th>
<th>II/III (n=29)</th>
<th>Normal or Favorable (n=33)</th>
<th>Unfavorable (n=16)</th>
<th>Carfilzomib Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>94</td>
<td>90</td>
<td>97</td>
<td>91</td>
<td>100</td>
<td>100 100 88</td>
</tr>
<tr>
<td>VGPR</td>
<td>65</td>
<td>65</td>
<td>66</td>
<td>61</td>
<td>75</td>
<td>100 100 47</td>
</tr>
<tr>
<td>sCR, nCR, or CR</td>
<td>53</td>
<td>50</td>
<td>55</td>
<td>52</td>
<td>56</td>
<td>75 85 38</td>
</tr>
</tbody>
</table>

Weekly MLN9708 (Ixazomib) in Relapsed/Refractory MM: Phase I Study

- Single-agent oral MLN9708 MTD 2.97 mg/m² on a weekly (days 1, 8, and 15 every 28 days) schedule

- Oral MLN9708 generally well tolerated
  - hematologic and gastrointestinal events generally manageable, low rate of discontinuations
  - Infrequent PN, only 1 grade 3 PN

- Pharmacokinetic profile supports weekly oral dosing

- Relapsed and/or refractory MM patients (median 4 prior lines of therapy)
  - **ORR (≥PR)** of 18%, plus 2% MR and 30% SD, including relapse post Bortezomib

Kumar et al  ASCO 2013 Blood 2014
Best response to treatment in phase 2 patients receiving ixazomib-lenalidomide-dexamethasone induction maintenance (n=21)

- 10 (48%) patients improved their response during maintenance:
  - 2 VGPR to nCR, 5 VGPR to CR, 1 VGPR to sCR, and 2 CR to sCR

Kumar et al ASH 2014
Development of Rationally-Based Combination Therapies (HDAC and Proteasome Inhibitors)

Protein aggregates (toxic)

26S proteasome

Panobinostat, Vorinostat, ACY1215

Bortezomib, Carfilzomib, NPI0052, MLN9708, ONX 0912

HDAC6

dynein

dynein

Microtubule

Aggresome

Lysosome

Autophagy

PANORAMA 1: A Randomized, Double-Blind, Phase 3 Study of Panobinostat or Placebo Plus Bortezomib and Dexamethasone in Relapsed or Relapsed and Refractory Multiple Myeloma

Improvement in median PFS of 4 mos w/o difference in ORR or OS

Two-fold increase in nCR/CR rate (28% vs 16%)

Higher rate of Grade ¾ diarrhea (25.5% vs 8%), fatigue (23.0% vs 11.9%), thrombocytopenia (67.4% vs 31.4%), and leucopenia (34.5% vs 11.4%), discontinuation due to AE (33.6% vs 17.3%).

Confirms PAN-BTZ-Dex in BTZ-refractory pts (PANORAMA 2): ORR: 34.5%; CBR: 52.7%; median PFS: 5.4 mos; median OS: 17.5 mos

FDA approved for relapsed refractory MM exposed to bortezomib and IMiD

Need for less toxic more selective HDACi that can be given with PI to exploit synergistic cytotoxicity.

Responses for Ricolinostat in Combination with Bortezomib and Dexamethasone

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>Bortezomib Refractory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolled</td>
<td>43</td>
<td>27</td>
</tr>
<tr>
<td>Evaluable for response</td>
<td>29</td>
<td>14</td>
</tr>
<tr>
<td>Withdrew prior to C2D15</td>
<td>14</td>
<td>13</td>
</tr>
</tbody>
</table>

**Responses**

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>Bortezomib Refractory</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>VGPR</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>PR</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>MR</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>SD</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>PD</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>ORR (&gt;PR) in evaluable pts</td>
<td>45%</td>
<td>29%</td>
</tr>
<tr>
<td>ORR (&gt;PR) in all pts</td>
<td>30%</td>
<td>14%</td>
</tr>
<tr>
<td>Clinical benefit (&gt;MR) in all pts</td>
<td>34%</td>
<td>21%</td>
</tr>
</tbody>
</table>

Vogl et al ASH 2014
Responses to Ricolinostat in Combination with Lenalidomide and Dexamethasone

- 25 patients evaluable for response
- 16/25 (64%) ≥ PR
- 11/13 (85%) ≥ PR lenalidomide sensitive or naïve
- 50% ≥ PR in lenalidomide refractory
- Well tolerated on 21 d schedule

<table>
<thead>
<tr>
<th>Best response</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>sCR</td>
<td>2 (8)</td>
</tr>
<tr>
<td>VGPR</td>
<td>6 (24)</td>
</tr>
<tr>
<td>PR</td>
<td>8 (32)</td>
</tr>
<tr>
<td>MR</td>
<td>4 (16)</td>
</tr>
<tr>
<td>SD</td>
<td>5 (20)</td>
</tr>
<tr>
<td>PD</td>
<td>0</td>
</tr>
<tr>
<td>ORR (≥PR)</td>
<td>12 (64)</td>
</tr>
<tr>
<td>CLINICAL BENEFIT (≥MR)</td>
<td>20 (80)</td>
</tr>
</tbody>
</table>

Yee et al ASH 2014
Mutations in Myeloma
19 patients each with newly diagnosed and relapsed MM

- **Protein homeostasis**: 42% including FAM46C, RPL10, RPS6KA1, EIF3B, XBP1, LRRK2

- **NF-κB signaling**: 10 point mutations, 4 additional structural rearrangements affecting coding
  Confers bortezomib sensitivity

- **Histone methylating enzymes**: WHSC1, UTX, MLL

- **BRAF**: 4% activating  
  Single patient MM response

**PSMB5** β5 proteasome subunit mutation confers proteasome inhibitor resistance in laboratory, not identified in clinic

Genomic Evolution in Myeloma and Patterns of Clonal Change

No Change

Linear Evolution

Differential Clonal Response

Branching Evolution

Bolli et al, Nature Comm, 2014
YAP1 low expression correlates with poor clinical outcome in hematological patients

Cottini et al Nat Med 2014;20:599-606
YAP1 overexpression induces p73 and p73-target genes

Damaged DNA

ATM

Nuclear ABL1

Pro-apoptotic genes, cell cycle genes.

YAP1

p73

KMS-20

<table>
<thead>
<tr>
<th>Gene</th>
<th>YAP1</th>
<th>LACZ</th>
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<tbody>
<tr>
<td>YAP1</td>
<td>![Image]</td>
<td>![Image]</td>
</tr>
<tr>
<td>(TA) p73</td>
<td>![Image]</td>
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</tr>
<tr>
<td>BAX</td>
<td>![Image]</td>
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<tr>
<td>PUMA</td>
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</tr>
<tr>
<td>NOXA</td>
<td>![Image]</td>
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</tr>
<tr>
<td>p21</td>
<td>![Image]</td>
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<tr>
<td>GAPDH</td>
<td>![Image]</td>
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</tbody>
</table>
Damaged DNA

ATM

Nuclear ABL1

p73

STK4

Survival

Apoptosis

Pro-apoptotic genes, cell cycle genes.

Current and Future Directions

1. immune therapies

1. Targeting protein homeostasis

3. Targeting the myeloma epigenome

4. Targeting the myeloma genome

Myeloma will be a chronic illness, with sustained CR in a significant fraction of patients.
Waldenström’s Macroglobulinemia – first described by Jan Gosta Waldenström in 1943.
Manifestations of WM Disease

- Adenopathy, splenomegaly ≤20% (at Dx)
- Hyperviscosity Syndrome: Epistaxis, HA, Impaired vision >4.0 CP
- IgM Neuropathy (22%)
- Cryoglobulinemia (10%)
- Cold Agglutinemia (5%)
- Hepcidin ↓Fe Anemia

↓HCT, ↓PLT, ↓WBC
Advances in the Biology of Waldenstrom's Macroglobulinemia

Treatment Approach

Ixazomib
Bortezomib
Carfilzomib
Benda
GA101
CAL101
Pom
Len
RAD001

SOMEDAY, ALL THIS WILL BE YOURS.
Cyclophosphamide-Based Therapy

- Doxorubicin and Vincristine dispensable and do not appear to impact RR, PFS.
- CDR (Cyclophosphamide/Dex/Rituximab) most common regimen used in WM.
- ORR are about 70% to 90%; VGPR/CR (20-25%).
- Median PFS is about 3 years when given upfront.

• ORR 25-40%

• IgM flare: 40-60% of pts.

• Patients with IgM > 4,000 mg/dL or Symptomatic HV: Avoid Rituximab until IgM in “safe range” either by PP or CTX without Rituximab.

• IgM Neuropathy, Cryoglobulins, Cold Agglutinins: Rituximab can potentiate symptoms. Consider PP.

• Rituximab Intolerance: Very common in WM (15%). Ofatumumab can be administered. Give test dose.

Yang et al, ASH 2012; NCCN Guidelines 2013
Bendamustine in WM

- Benda-R superior to CHOP-R frontline WM (PFS 69 vs. 29 months);
- Excellent option for bulky disease;
- Modify dose for patients with extensive prior therapy, nucleoside analogues, elderly, reduced GFR;
- Shorter PFS in salvage WM (13 months);
- Caution in younger patients since long term safety remains to be established.

# Primary Therapy of WM with Rituximab-Based Options

<table>
<thead>
<tr>
<th>Regimen</th>
<th>ORR</th>
<th>VGPR/CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab x 4</td>
<td>25-30%</td>
<td>0-5%</td>
</tr>
<tr>
<td>Rituximab x 8</td>
<td>40-45%</td>
<td>5-10%</td>
</tr>
<tr>
<td>Rituximab/thalidomide</td>
<td>70%</td>
<td>10%</td>
</tr>
<tr>
<td>Rituximab/cyclophosphamide i.e. CHOP-R, CVP-R, CPR, CDR</td>
<td>70-80%</td>
<td>20-25%</td>
</tr>
<tr>
<td>Rituximab/nucleoside analogues i.e. FR, FCR, CDA-R</td>
<td>70-90%</td>
<td>20-30%</td>
</tr>
<tr>
<td>Rituximab/bortezomib i.e. BDR, VR</td>
<td>70-90%</td>
<td>30-40%</td>
</tr>
<tr>
<td>Rituximab/bendamustine</td>
<td>90%</td>
<td>30-40%</td>
</tr>
</tbody>
</table>
IMiD-Based Rituximab Therapy

- Thalidomide and Lenalidomide stimulate ADCC. May also have direct effects on WM cells.
- Can be given with rituximab (Thal-R, Len-R).
- ORR 70% (Thal-R) and 40% (Len-R).
- Median PFS with Thal-R is 4 years.
- Peripheral neuropathy (thalidomide) and abrupt decrease in hematocrit (lenalidomide) are principal toxicities.
- Long-term risks not identified.

Bortezomib Therapy in WM

- **Primary**
  
  Bortezomib (1.3 mg/m²/biwkly)/Dexamethasone/Rituximab
  
  ORR 95%; CR 22%; TTP >4 yrs; 30% Grade 3 PN

  Bortezomib (1.6 mg/m²/wk)/Rituximab
  
  ORR 92%; CR 8%; 80% 1 Y PFS; No Grade 3 PN

- **Salvage**
  
  Bortezomib (1.6 mg/m²/wk)/Rituximab
  
  ORR 81%; CR 5%; TTP 12 months; 5% Grade 3 PN.

  Bortezomib (randomized wkly vs biwkly)/Rituximab
  
  ORR 80%; CR 0%; TTP ?; 0% Grade 3 PN.

Primary Therapy of WM with Carfilzomib, Rituximab, Dex (CaRD)

Induction Cycle 1 q21 Days
Days 1, 2, 8, 9: Carfilzomib 20 mg/m² IV; dex 20 mg IV
Days 2, 9: Rituximab 375 mg/m²

Induction Cycles 2-6 q21 Days
Days 1, 2, 8, 9: Carfilzomib 36 mg/m2 IV; dex 20 mg IV
Days 2, 9: Rituximab 375 mg/m2

Maintenance Cycles 1-8 q2 Months
Days 1, 2: Carfilzomib 36 mg/m2 IV; dex 20 mg IV
Day 2: Rituximab 375 mg/m2

Primary endpoints: ORR, TTP, neuropathy incidence

Treon et al, BLOOD 2014
CLINICAL RESPONSES TO CaRD IN WM (MEDIAN 12 CYCLES; N=31)

<table>
<thead>
<tr>
<th></th>
<th>N=</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>25</td>
<td>87.1%</td>
</tr>
<tr>
<td>≥VGPR</td>
<td>11</td>
<td>35.5%</td>
</tr>
<tr>
<td>CR*</td>
<td>1</td>
<td>3.2%</td>
</tr>
<tr>
<td>VGPR</td>
<td>10</td>
<td>32.3%</td>
</tr>
<tr>
<td>PR</td>
<td>10</td>
<td>32.3%</td>
</tr>
<tr>
<td>MR</td>
<td>6</td>
<td>19.4%</td>
</tr>
</tbody>
</table>

Median 15 (2-26) months followup; 65% without progression

* Molecular CR by AS-PCR for MYD88 L265P
MYD88 L265P Somatic Mutation

C to G at position 38186241 at 3p22.2

- Sanger sequencing (91% of WM pts, 10% IGM MGUS Have MYD88 L265P.

No difference sporadic vs. familial pts

Treon et al, ASH 2011; NEJM 2012
MYD88 L265P Signal Pathway

Yang et al, Blood 2013
Phase II Study of Ibrutinib (BTK inhibitor) in Relapsed/Refractory WM

Screening

Informed Consent and Registration

Ibrutinib 420 mg po daily

Progressive Disease or Unacceptable Toxicity

Stop Ibrutinib

Event Monitoring

SD or Response Continue x 26 cycles

Event Monitoring

Opened May 2012
DFCI, MSKCC, STANFORD
N=35; expanded to 63
<table>
<thead>
<tr>
<th></th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>63</td>
<td>44-86</td>
</tr>
<tr>
<td>Male/Female</td>
<td>48/15</td>
<td>N/A</td>
</tr>
<tr>
<td>Prior therapies</td>
<td>2</td>
<td>1-8</td>
</tr>
<tr>
<td>Hemoglobin (mg/dL)</td>
<td>10.5</td>
<td>8.2-13.8</td>
</tr>
<tr>
<td>Platelet (k/uL)</td>
<td>214</td>
<td>24-459</td>
</tr>
<tr>
<td>Serum IgM (mg/dL)</td>
<td>3,610</td>
<td>735-8,390</td>
</tr>
<tr>
<td>B2M (mg/dL)</td>
<td>3.9</td>
<td>1.3-14.2</td>
</tr>
<tr>
<td>BM Involvement (%)</td>
<td>70</td>
<td>3-95</td>
</tr>
<tr>
<td>Adenopathy &gt;1.5 cm</td>
<td>37 (58.7%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Splenomegaly &gt;15 cm</td>
<td>7 (11.1%)</td>
<td>N/A</td>
</tr>
</tbody>
</table>
### Best Clinical Responses to Ibrutinib

**Median of 12 (range 1-21) Cycles**

<table>
<thead>
<tr>
<th>Response</th>
<th>(N=)</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VGPR</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td>PR</td>
<td>35</td>
<td>56</td>
</tr>
<tr>
<td>MR</td>
<td>11</td>
<td>18</td>
</tr>
<tr>
<td>SD</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>Non-Responder</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

**ORR: 87%  Major RR (≥ PR): 69%**

Data Lock February 28, 2014, Treon et al NEJM 2015

Response criteria adapted from 3rd International Workshop on WM (Treon et al, BJH 2011)
FDA News Release
FDA expands approved use of Imbruvica for rare form of non-Hodgkin lymphoma
First drug approved to treat Waldenström’s macroglobulinemia
For Immediate Release
January 29, 2015
WHIM-like CXCR4 C-tail Mutations in WM

Warts, Hypogammaglobulinemia, Infection, and Myelokathexis.

Most common: CXCR4$^{C1013G}$ (S338X)

Somatic WHIM-CXCR4 Mutations were detected in 21/63 patients (34%) on Ibrutinib study.

Hunter et al, ASH 2012; ICML 2013; BLOOD 2014
## MYD88 and CXCR4 Mutation Status and Responses to Ibrutinib

<table>
<thead>
<tr>
<th></th>
<th>MYD88&lt;sup&gt;L265P&lt;/sup&gt; CXCR4&lt;sup&gt;WT&lt;/sup&gt;</th>
<th>MYD88&lt;sup&gt;L265P&lt;/sup&gt; CXCR4&lt;sup&gt;WHIM&lt;/sup&gt;</th>
<th>MYD88&lt;sup&gt;WT&lt;/sup&gt; CXCR4&lt;sup&gt;WT&lt;/sup&gt;</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N=</strong></td>
<td>34</td>
<td>21</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td><strong>Overall RR</strong></td>
<td>100%</td>
<td>80.9%</td>
<td>57.1%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Major RR</strong></td>
<td>88.2%</td>
<td>57.1%</td>
<td>28.6%</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Data Lock February 28, 2014
Phase II Study of Ibrutinib plus CXCR4-Antagonist in Relapsed/Refractory CXCR4\textsuperscript{WHIM} WM Patients

- Screening
- Informed Consent and Registration
- Ibrutinib 420 mg po daily + CXCR4 Inhibitor
  - Progressive Disease or Unacceptable Toxicity
    - Stop Ibrutinib/CXCR4-In
      - Event Monitoring
  - SD or Response
    - Continue x 26 cycles
      - Event Monitoring

LLS Funded Study
Summary

- MYD88 L265P is present >90% of WM patients and triggers activation of Bruton’s Tyrosine Kinase (BTK) in WM cells.
- The BTK inhibitor ibrutinib is associated with rapid reduction of serum IgM and improved HCT with an ORR of 87%, major RR of 69% in relapsed/refractory patients.
- MYD88 and CXCR4 mutations impact serum IgM and hemoglobin levels, and major response attainment to Ibrutinib.
- Inhibitors to MYD88 and CXCR4 pathways represent novel approaches to the treatment of WM, alone and in combination.
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Tom Brokaw: A Lucky Life Interrupted