What is New in AL Amyloidosis

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Amyloidosis

Disclosures

• Relevant Financial Relationships: None
• Off Label Usage: Yes

Learning Objectives

• Understand importance and new method of Subtyping Amyloid
• Importance of immunoglobulin light chains in evaluation and monitoring
• Role of Biomarkers and Prognostic models in selecting therapy
• Targeting the Amyloid fibrils
Amyloidosis is a protein misfolding disease

>28 different proteins can form fibrillar deposits

Primary Systemic (Light chain) Amyloidosis
Organ Involvement

Wall thickness >12 mm
Grade 1 diastolic dysfunction
Abnormal stain pattern
Troponin
NT-proBNP

Liver span >15 cm,
Alk Phos >1½ x ULN

Predominantly Albuminuria
>0.5g/day

Symmetric sensory motor PN
Autonomic dysfunction
Orthostatic hypotension
Gastric emptying disorder
Pseudo obstruction

Macroglossia
Pseudohypertrophy
Interstitial radiographic pattern
Biopsy
Constitutional symptoms
Biopsy

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Advances in AL Amyloidosis

- The field of AL amyloidosis has witnessed significant advances in diagnosis, treatment options, and response assessment methods over the past 15 years:

  - **Typing techniques**: Mass spectrometry

  - **sFLC assays**:
    - More sensitive screening test (potentiate an earlier diagnosis)
    - Better response assessment

  - **Treatment options**:
    - More use of ASCT (D’souza 2015)
    - Effective non-transplant regimens since MDex (Palladini, 2004)
    - Amyloid tissue directed therapy

- Two papers showed improved survival over the past decades (Kumar 2011; Wechalekar 2016), but without improvement in the early death rate
Amyloid subtyping workflow for FFPE specimens

Laser Capture Deposit

Heat Mediated Extraction

Reduce Cys Bridges

Digest Proteins Into Peptides

Peptide Mixture

Liquid Chromatography

Electrospray Ionization

High-Resolution Mass Spectrometry

Tandem Mass Spectra

Data Analysis

Protein Identification Profile

Assign Subtype

AL ATTR, AA LECT-2 Others

Histologic uncertainty of the amyloid subtype

λ
κ
TTR
SAP
Congo red
Evaluation and Monitoring

Free Light Chains (FLC)

Sensitivity 97%; Specificity 100%

Bradwell, Serum free light chain assay; Lachmann 2003; Katzmann 2002
## Serum Free Light Chain Assay

Diagnostic performance in AL (n = 110)

<table>
<thead>
<tr>
<th>Test</th>
<th>Abnormal</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum IF</td>
<td>76 (69%)</td>
<td>34 (31%)</td>
</tr>
<tr>
<td>Urine IF</td>
<td>86 (83%)</td>
<td>17 (17%)</td>
</tr>
<tr>
<td>Serum or Urine IF</td>
<td>104 (95%)</td>
<td>6 (5%)</td>
</tr>
<tr>
<td>Abnormal FLC ratio</td>
<td>100 (91%)</td>
<td>10 (9%)</td>
</tr>
<tr>
<td>S or U or FLC</td>
<td>109 (99%)</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

## Response Criteria for AL Amyloidosis

<table>
<thead>
<tr>
<th></th>
<th>New Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>negative serum and urine IFE normal $\kappa/\lambda$ ratio</td>
</tr>
<tr>
<td>VGPR</td>
<td>dFLC $&lt;$40 mg/L</td>
</tr>
<tr>
<td>PR</td>
<td>dFLC decrease $\geq$50%</td>
</tr>
<tr>
<td>NR</td>
<td>other</td>
</tr>
</tbody>
</table>

**Measurable disease:** dFLC $>$50 mg/L

**FLC response supersedes M-protein response**

Outcome of 300 AL Amyloidosis Patients Based on Hematologic Response at 3 months

- CR (37 patients, 1.0 deaths/100 py)
- VGPR (122 patients, 7.4 deaths/100 py)
- PR (47 patients, 19.9 deaths/100 py)
- NR (94 patients, 32.9 deaths/100 py)

High-Dose Melphalan/ASCT Versus Melphalan-Dex

56.9 mo vs 22.2 mo
HR 0.57 (95%CI 0.32-0.99)

<table>
<thead>
<tr>
<th>Ref</th>
<th>N</th>
<th>2 yr OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaccard M-Dex</td>
<td>50</td>
<td>~65%</td>
</tr>
<tr>
<td>Jaccard M-Dex</td>
<td>50</td>
<td>~49%</td>
</tr>
<tr>
<td>Skinner ASCT</td>
<td>312</td>
<td>~68%</td>
</tr>
<tr>
<td>Gertz ASCT</td>
<td>171</td>
<td>~70%</td>
</tr>
<tr>
<td>Cohen ASCT</td>
<td>45</td>
<td>~80%</td>
</tr>
<tr>
<td>Perfetti ASCT</td>
<td>22</td>
<td>~60%</td>
</tr>
</tbody>
</table>

MD (n=34) versus APBSCT (n=55)
AL Amyloidosis

$P = .02$

$P < .01$

Gertz et al, Cancer 2016;122:2197-205
## IMiD Trials in AL Amyloidosis

<table>
<thead>
<tr>
<th>Regimen</th>
<th>N</th>
<th>No prior Rx, %</th>
<th>Cardiac, %</th>
<th>Heme response / CR, %</th>
<th>Median f/u, mo</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTX/Thal/Dex</td>
<td>65</td>
<td>41</td>
<td>16</td>
<td>74 / 21</td>
<td>18</td>
<td>2-yr 77%</td>
</tr>
<tr>
<td>Mel-Dex-thal</td>
<td>22</td>
<td>86</td>
<td>100</td>
<td>36 / 5</td>
<td>28</td>
<td>1-yr 20%</td>
</tr>
<tr>
<td>Len ±Dex</td>
<td>22</td>
<td>43</td>
<td>64</td>
<td>43 / 5</td>
<td>17</td>
<td>2-yr 50%</td>
</tr>
<tr>
<td>Len ± Dex</td>
<td>69</td>
<td>6</td>
<td>45</td>
<td>47^b / 16</td>
<td>NR</td>
<td>NR^b</td>
</tr>
<tr>
<td>Len ± Dex</td>
<td>24</td>
<td>0</td>
<td>75</td>
<td>38 / 0</td>
<td>23</td>
<td>1-yr 50%</td>
</tr>
<tr>
<td>Len-Mel- Dex</td>
<td>26</td>
<td>100</td>
<td>58</td>
<td>58 / 23</td>
<td>19</td>
<td>2-yr 81%</td>
</tr>
<tr>
<td>Len-Mel- Dex</td>
<td>25</td>
<td>92</td>
<td>92</td>
<td>58 / 8</td>
<td>17</td>
<td>1-yr 58%</td>
</tr>
<tr>
<td>Len-Mel- Dex</td>
<td>16</td>
<td>69</td>
<td>69</td>
<td>43 / 7</td>
<td>34</td>
<td>3-yr 70%</td>
</tr>
<tr>
<td>Len-Cyclo-Dex</td>
<td>21</td>
<td>0</td>
<td>62</td>
<td>62 / 5</td>
<td>38</td>
<td>3-yr 50%</td>
</tr>
<tr>
<td>Len-Cyclo-Dex</td>
<td>35</td>
<td>69</td>
<td>63</td>
<td>60 / 11</td>
<td>32</td>
<td>38 mo</td>
</tr>
<tr>
<td>Len-Cyclo- Dex</td>
<td>37</td>
<td>65</td>
<td>57</td>
<td>55 / 8</td>
<td>29</td>
<td>3-yr ~33%</td>
</tr>
<tr>
<td>Pom-Dex</td>
<td>33</td>
<td>0</td>
<td>82</td>
<td>48 / 3</td>
<td>28</td>
<td>28 mo</td>
</tr>
</tbody>
</table>

Bortezomib is highly effective in AL amyloidosis

<table>
<thead>
<tr>
<th>Regimen</th>
<th>N. of patients [newly diagnosed]</th>
<th>Overall hematologic Response (CR) [upfront]</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bort¹</td>
<td>70</td>
<td>67% (29%)</td>
<td>median 5.1 years</td>
</tr>
<tr>
<td>BDex²</td>
<td>94 [18]</td>
<td>71% (25%) [81% (47%)]</td>
<td>76% @ 1 y</td>
</tr>
<tr>
<td>CyBorD³</td>
<td>43 [20]</td>
<td>81% (42%) [90% (65%)]</td>
<td>98% @ 2 y</td>
</tr>
<tr>
<td>CyBorD⁴</td>
<td>17 [10]</td>
<td>94% (71%) [90% (60%)]</td>
<td>-</td>
</tr>
<tr>
<td>BMDex⁵</td>
<td>[16]</td>
<td>[94% (56%)]</td>
<td>-</td>
</tr>
<tr>
<td>BMDex⁶</td>
<td>[87]</td>
<td>[69% (42%)]</td>
<td>83% @ 2 y</td>
</tr>
<tr>
<td>CyBorD⁷</td>
<td>[69]</td>
<td>[71% (40.5%)]</td>
<td>65% @ 1 y</td>
</tr>
<tr>
<td>CyBorD⁸</td>
<td>[60]</td>
<td>[86% (17%)]</td>
<td>57% @ 1 y</td>
</tr>
<tr>
<td>CyBorD⁹</td>
<td>[230]</td>
<td>[60% (23%)]</td>
<td>55% @ 5 y</td>
</tr>
</tbody>
</table>

¹Reece et al. Blood 2014
²Kastritis et al. JCO 2010
³Venner et al. Blood 2012
⁴Mikhael et al. Blood 2012
⁵Gasparetto et al. JCO 2010 [abstract]
⁶Palladini et al. Leukemia 2014
⁷Venner et al. Leukemia 2014
⁸Jaccard et al. Haematologica 2014
⁹Palladini et al. Blood 2015
Changes in Therapy and Outcome 2000 - 2014

- Newly diagnosed AL patients with a visceral disease seen in 2000-2014

- Three equal-length periods were compared:
  - 2000-2004 (n=422, 27%)
  - 2005-2009 (n=604, 39%)
  - 2010-2014 (n=525, 34%)

- Objectives of assessment:
  - Disease extent
  - 1st line treatment
  - Response
  - Survival, early death

Muchtar et al, Blood. 2017 Jan 26. [Epub ahead of print]
Non-ASCT treatments

Muchtar et al, Blood. 2017 Jan 26. [Epub ahead of print]
Response to 1st line tx

• Rate of ≥VGPR increased over time: 51% to 58% to 66%

• Rate of those who did not achieved any response decreased: 30% to 20% to 12%

• ASCT patients – stable response over time (70-77%)

• Non-ASCT patients: improved response over time 24% to 49% to 58%

• Organ response was parallel to ≥VGPR rates

Muchtar et al, Blood. 2017 Jan 26. [Epub ahead of print]
≥VGPR by regimen type

Muchtar et al, Blood. 2017 Jan 26. [Epub ahead of print]
Changes in OS over time

A. Whole study population
B. ASCT patients
C. Non-ASCT patients
D. Landmark 6-month non-ASCT population

Muchtar et al, Blood. 2017 Jan 26. [Epub ahead of print]
Eligibility for ASCT

Transplant Eligibility Criteria

- “Physiologic” Age ≤ 70 years
- Performance Score ≤ 2
- Systolic BP ≥ 100 mmHg
- TnT < 0.06 ng/ml
- CrCl ≥ 30 ml/min * (unless on chronic dialysis)
- NYHA Class I/II*
- No more than 2 organs significantly involved

*Selected patients may become eligible for PBSCT with cardiac and renal transplantation
Newly Diagnosed AL Amyloidosis

- **Transplant Eligible**: 
  - BM PC ≥ 10% or CRAB
  - Not wanting transplant

- **Transplant Ineligible**: 
  - Mel-Dex or CyBorD

**Induction**: 2-4 cycles

**Observation**: ≥ PR

**≥ Hematologic VGPR**: 
- Low risk? 
  - Yes
  - No: More chemotherapy

**Mel 200 HSCT**:

1. Criteria for ASCT: Troponin T <0.06 & BP >90 mmHg
2. Induction also used if delay in proceeding to ASCT, or as clinically indicated
3. If < PR at 2 months consider changing therapy
4. For Age >70 or CrCl <30, use Mel 140 mg/m2
5. Mayo 2012 stage I or II
6. Day 100 ASCT or after 4-6 cycles of chemo
Overall survival improvement

Targeting Amyloid deposits

- Major cause of morbidity and Death in AL amyloidosis is Organ failure (eg heart and kidney)
- Existing therapies reduce LC production
  - But they DO NOT address resident amyloid
  - ~75% of patients do not achieve organ response and have persistent organ dysfunction\(^1\)\(^-\)\(^6\) – a major unmet need
- NEOD001 is an investigational antibody designed to specifically target AL amyloid
- Chimeric Fibril-Reactive Monoclonal Antibody 11-1F4

AL, amyloid light chain; LC, light chain.
NEOD001 Phase 1/2 Trial (N = 69) Design

- Previous PC-directed treatment and persistent organ dysfunction

**Primary objectives**
- Evaluate the safety and tolerability of NEOD001 (NCT01707264)
- Determine MTD or recommended dose for future clinical study of NEOD001

**Secondary objectives**
- Evaluate the serum PK of NEOD001
- Assess the immunogenicity of NEOD001
- Evaluate organ response (cardiac, renal, peripheral neuropathy)

**Dose-escalation phase (3+3)**
- 27 patients with AL amyloidosis
- 7 cohorts; IV q28 days; determine MTD/RP3D
- All patients escalated to 24 mg/kg

- Maximum of 2500 mg per dose permitted – 24 mg/kg selected based on patient body weight.

**Expansion Cohorts**
- 42 additional previously treated patients with cardiac, renal, and/or peripheral neuropathy involvement

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*IV, intravenous; MTD, maximum tolerated dose; PC, plasma cell; PK, pharmacokinetics; q28d, every 28 days; RP3D, recommended phase 3 dose.*

Morie A. Gertz et al, ASH 2016
## Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (N = 69)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>61 (38-82)</td>
</tr>
<tr>
<td>Sex, n (% male)</td>
<td>42 (61)</td>
</tr>
<tr>
<td>Median time since initial diagnosis, years (range)</td>
<td>2.9 (0.4-16.0)</td>
</tr>
<tr>
<td>Median previous regimens, n (range)</td>
<td>2 (1-8)</td>
</tr>
<tr>
<td>No. (%) previous PCD regimens per patient</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>22 (32)</td>
</tr>
<tr>
<td>2</td>
<td>16 (23)</td>
</tr>
<tr>
<td>≥3</td>
<td>31 (45)</td>
</tr>
<tr>
<td>No. organ systems involved, n (%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>22 (32)</td>
</tr>
<tr>
<td>2</td>
<td>29 (42)</td>
</tr>
<tr>
<td>≥3</td>
<td>18 (26)</td>
</tr>
<tr>
<td>Median months since last PCD treatment, months (range)</td>
<td>5.8 (0.5-85.8)</td>
</tr>
<tr>
<td>Median NT-proBNP (pg/mL) at baseline, median (range)</td>
<td></td>
</tr>
<tr>
<td>Total cardiac evaluable [n = 36 patients]</td>
<td>1507 (651-5620)</td>
</tr>
</tbody>
</table>

PCD, plasma cell-directed.

Morie A. Gertz et al, ASH 2016
NEOD001: Renal Biomarker Response
Best Response Analysis

Total renal evaluable (n = 36)
23 responders (64%)
13 stable (36%)

Median time to initial response: 4 months

Response: >30% decrease in proteinuria or a decrease to <0.5 g/24 hours in the absence of renal progression
Progression: >25% worsening in eGFR
Stable disease: Neither response nor progression

eGFR, estimated glomerular filtration rate.
Evaluable patients had baseline proteinuria >0.5 g/24 hours

Morie A. Gertz et al, ASH 2016
NEOD001 Renal Responses Continues to Deepen for 30 Months

61-Year-Old Man

Previous treatment: LDex then Bor-LDex then HDM/ASCT

Baseline proteinuria (24 hours): 5129 mg/d

Best proteinuria (24 hours): 294 mg/d (−94%)

Safety: No SAEs; no grade ≥3 AEs; no dose interruptions

Clinical outcome:
Progressive functional improvement; edema completely resolved; patient no longer has fatigue

NEOD001 Start: 40 months after hematologic CR with no change

ASCT, autologous stem cell transplantation; Bor-LDex, bortezomib, lenalidomide, dexamethasone; HDM, high-dose melphalan; LDex, lenalidomide, dexamethasone

Morie A. Gertz et al, ASH 2016
NEOD001: Cardiac Biomarker Response
Best Response Analysis

Total cardiac evaluable (n = 36)
19 responders (53%)
17 stable (47%)

Median time to initial response: 2 months

Evaluable patients had baseline NT-proBNP ≥650 pg/mL without progressive renal dysfunction.¹ ²

- **Response:** >30% and >300 pg/mL decrease in NT-proBNP
- **Progression:** >30% and >300 pg/mL increase in NT-proBNP
- **Stable disease:** Neither response nor progression

*30% decline, 453 pg/mL reduction from baseline. † 42% decline, 271 pg/mL reduction from baseline.

NEOD001 Cardiac Responses Continue to Deepen for 36 Months

47-Year-Old Man

Previous treatment: CyBorD
Baseline NT-proBNP: 3312 pg/mL

Best NT-proBNP: 513 pg/mL (~85%)

Safety: 1 grade 3 SAE (chest pain), not related; no dose interruptions

Clinical outcome: Progressive functional improvement; edema significantly improved with reduction in diuretic needs

NEOD001 Start: 10 months after hematologic CR with no change

NEOD001 Treatment #

-30% "response" threshold
-60% "progression" threshold
90%

38 doses of NEOD001
Chimeric Fibril-Reactive Monoclonal Antibody 11-1F4 in AL Amyloidosis

κ Bence Jones protein isolated and used to develop Ab

Native

Structure of soluble light chain in circulation – not reactive with mAb 11-1F4

“Loop-Flip”

Structure of light chain in fibril – reactive with mAb 11-1F4

• Fibrillogenesis
• Surface adsorption

Suzanne Lentzsch et al, ASH 2016
Courtesy of Alan Solomon and Jonathan Wall Lab
Specificity of Antibody Binding

Co-localization of $^{124}$I-m11-1F4 with Hepatosplenic and Bone AL Amyloid

Phase 1a/1b Dose Escalation

<table>
<thead>
<tr>
<th>Level</th>
<th>Dose (mg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-2</td>
<td>0.125</td>
</tr>
<tr>
<td>-1</td>
<td>0.25</td>
</tr>
<tr>
<td>1</td>
<td>0.5*</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>250</td>
</tr>
<tr>
<td>7</td>
<td>500</td>
</tr>
</tbody>
</table>

Ch mAb 11-1F4 infusion
Clinical Evaluation

Phase 1a
No dose limiting toxicity observed
MTD = 500 mg/m²

Phase 1b

Suzanne Lentzsch et al, ASH 2016
# Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (N=21 patients)</strong></td>
<td>67 yrs (Range: 34 – 77)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>N=15 (68%)</td>
</tr>
<tr>
<td>Female</td>
<td>N=6 (32%)</td>
</tr>
<tr>
<td><strong>Light Chain type</strong></td>
<td></td>
</tr>
<tr>
<td>λ</td>
<td>N=13 (52%)</td>
</tr>
<tr>
<td>κ</td>
<td>N=8 (48%)</td>
</tr>
<tr>
<td><strong>Revised Mayo Stage</strong></td>
<td>II (Range: I to IV)</td>
</tr>
<tr>
<td><strong>Organ Involvement (No.)</strong></td>
<td>2 (Range: 1 – 4)</td>
</tr>
<tr>
<td>Heart</td>
<td>N=11 (52%)</td>
</tr>
<tr>
<td>Kidney</td>
<td>N=11 (52%)</td>
</tr>
<tr>
<td>Skin/Soft tissue</td>
<td>N=10 (48%)</td>
</tr>
<tr>
<td>GI</td>
<td>N=8 (38%)</td>
</tr>
<tr>
<td>Nervous system</td>
<td>N=4 (19%)</td>
</tr>
<tr>
<td>Liver</td>
<td>N=3 (14%)</td>
</tr>
<tr>
<td>Lung</td>
<td>N=2 (10%)</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>N=1 (5%)</td>
</tr>
<tr>
<td><strong>Best Hematologic Response to Therapy</strong></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>N=3 (14%)</td>
</tr>
<tr>
<td>VGPR</td>
<td>N=15 (71%)</td>
</tr>
<tr>
<td>PR</td>
<td>N=2 (10%)</td>
</tr>
<tr>
<td>SD</td>
<td>N=1 (5%)</td>
</tr>
<tr>
<td><strong>Previous Regimen (No.)</strong></td>
<td>2 (Range: 1 – 6)</td>
</tr>
<tr>
<td><strong>Baseline NT-proBNP (ng/L)a</strong></td>
<td>2359 (Range: 894 – 13,131)</td>
</tr>
<tr>
<td><strong>Baseline 24 hr Urine Protein (mg/24hr)b</strong></td>
<td>4998 (Range: 1078 – 10,170)</td>
</tr>
<tr>
<td><strong>Time Since last Exposure to Chemotherapy (mos)</strong></td>
<td>6 (Range 1 – 51)</td>
</tr>
</tbody>
</table>

*a Baseline NT-proBNP in patients with cardiac involvement who were evaluable for response (Baseline NT-proBNP> 650pg/mL)

*b Baseline 24 hour urine protein in patients with renal involvement who were evaluable for response (Baseline 24 hour urine protein > 500mg/24 h)
Marked and Sustained Renal Response with 11-1F4 mAb

**PATIENT 7 PROFILE:**

λ AL Amyloidosis

Baseline 24-hr urine protein in mg/24hr approx. 10,000

Previous treatments 6

Organ response to chemotherapy
No organ response
Persistence of significant proteinuria

24 hour urine protein in a patient before and during Phase 1a/b clinical trial of 11-1F4 antibody

Suzanne Lentzsch et al, ASH 2016
Summary Results

- 21 patients were accrued and are evaluable for toxicity
- 18 patients evaluable for response (N=1 had no measurable disease, N=2 did not complete treatment)
- 12 out of 18 patients (67%) showed organ response
  - Phase 1a: 63% of patients (5 of 8) with measurable disease burden demonstrated organ response
    - 2 renal, 2 cardiac and 1 GI
  - Phase 1b: 70% of patients (7 of 10) with measurable disease burden showed organ response
    - 3 patients with cardiac response
    - 4 patients with renal response
    - 1 patient with GI response
    - 1 patient with soft tissue response with improvement of arthritis °3 → °1

Suzanne Lentzsch et al, ASH 2016
Advances in AL Amyloidosis

- There has been improvement in the outcome of AL amyloidosis
  - **Subtyping Amyloid:** Mass spectrometry is the gold standard
  - **sFLC assays:**
    - Is a more sensitive screening test (potentiate an earlier diagnosis)
    - Also provides a better response assessment and superior to m-spike in determining outcome
  - **Treatment options:**
    - ASCT provides a better depth of response in eligible patients
    - Effective non-transplant regimens since MDex (Palladini, 2004)
    - Amyloid tissue directed therapy may result in reduction of early mortality
Thanks