# Application and Clinical Qualification for a Surrogate End Point in Pivotal Clinical Trials in Patients With AL Amyloidosis

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## BACKGROUND

- Amyloid light chain (AL) amyloidosis is a complex disease in which abnormal immunoglobulin light chain (LC) proteins, secreted by plasma cells, misfold and form amyloid fibrils that deposit in organs[1]
  - AL amyloidosis is rare; an estimated 8-14 cases per million are diagnosed annually in the United States and Europe[2,3]
  - AL amyloidosis can affect a single organ or multiple organs, including the heart and kidneys, and can cause their dysfunction; cardiac amyloidosis is particularly lethal
- There are no approved therapies for AL amyloidosis; however, patients are often treated with plasma cell–directed agents that reduce LC production by eliminating the offending clone (hematologic response [HR])
  - Although HR improves survival, plasma cell–directed therapies do not directly address existing amyloid deposits or accelerate organ recovery
  - Factoring HR into efficacy measures is important but is of limited long-term value in the absence of organ improvement
  - Overall survival as an end point requires a large study population and a long assessment period, which is a challenge for a rare disease with a median overall survival time of 40 months
- Outcome measures clinically qualified to inform on organ function and validated as surrogates for time-to-event end points such as overall survival must be integrated into the clinical study designs and regulatory pathways
- Approval of organ biomarkers as surrogate end points for pivotal AL amyloidosis clinical trials will accelerate the evaluation of potentially lifesaving novel agents
- Elevations in the myocyte-secreted cardiac hormone N-terminal probrain natriuretic peptide (NT-proBNP) indicate poor survival for patients with cardiovascular disease
  - BNP levels may increase in patients with AL amyloidosis in response to structural impairments in cardiovascular function caused by extracellular amyloid accumulation
  - BNP expression appears to be directly modulated by amyloidogenic LC-elicited signal transduction pathways in cardiomyocytes
- Multiple retrospective studies and a recently completed prospective study[4] support that NT-proBNP is an indicator of survival

## OBJECTIVE

- To assess evidence for the use of NT-proBNP as a surrogate survival end point in the development of therapies to treat patients with AL amyloidosis

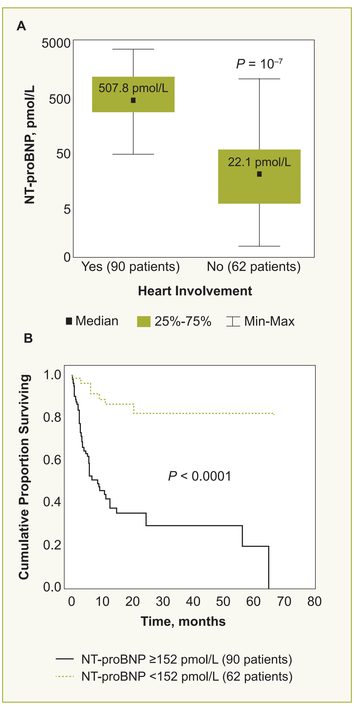
## METHODS

- All clinical trials that assessed overall survival and NT-proBNP in patients with AL amyloidosis were reviewed

## RESULTS

### Baseline NT-proBNP Indicates Prognosis

**Figure 1.** NT-proBNP levels indicate cardiac involvement (**A**) and predict overall survival (**B**) in Palladini et al.[5] Adapted with permission from Palladini et al.[5] Max, maximum; Min, minimum; NT-proBNP, N-terminal probrain natriuretic peptide.




- Palladini et al[5] reported an association between baseline NT-proBNP levels with cardiac involvement and survival in 152 patients with AL amyloidosis (**Figure 1**)

### NT-proBNP Response After Intervention Predicts Clinical Outcome

**Table 1.** Summary of Clinical Data Demonstrating That NT-proBNP Response After Intervention Predicts Clinical Outcome

| Study | Patient Population (median age) | Cardiac Involvement, %[a] | Subjects, n (% male) | Treatment Regimen | Median Survival[b] | |
|---|---|---|---|---|---|---|
| | | | | | NT-proBNP Responders | NT-proBNP Nonresponders |
| Palladini et al, 2006[6] | No previous treatments (63 years) | 100 | 51 (53) | MDex, TDex, Dex, MP, T | >80% at 40 months | ~13 months |
| Kastritis et al, 2010[7] | Newly diagnosed and previously treated (62 years) | 62 | 94 (52) | Bor, BDex | >80% at 36 months | ~12 months |
| Palladini et al, 2010[8] | Newly diagnosed (64 years) | 37 | 171 (58) | MDex, CyTDex, Dex, ASCT, "other" | >80% at 60 months | 8 months |
| Madan, et al 2012[9] | Newly diagnosed (57 years) | 100 | 187 (122) | HDM + ASCT | Not reached | 58 months |
| Kastritis et al, 2015[10] | Newly diagnosed (57 years) | 44 | 85 (57) | BDex, L-based, risk-adapted BDex | ~45 months | ~10 months |

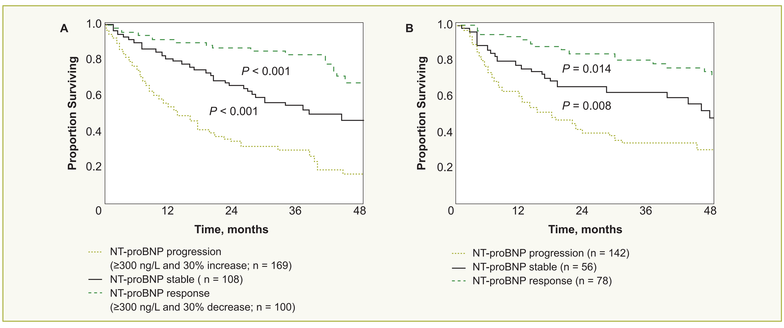
ASCT, autologous stem cell transplantation; BDex, bortezomib plus dexamethasone; Bor, bortezomib; CyTDex, cyclophosphamide plus thalidomide and dexamethasone; Dex, high-dose dexamethasone; HDM, high-dose melphalan; L, lenalidomide; MDex, melphalan plus high-dose dexamethasone; MP, melphalan plus prednisone; NT-proBNP, N-terminal probrain natriuretic peptide; T, thalidomide; TDex, thalidomide plus intermediate-dose dexamethasone.

[a]Percentage of patients with New York Heart Association class ≥2.

[b]Median survival not reached.

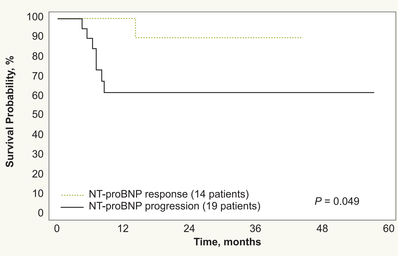
- In the context of interventional therapy, 5 large independent studies[4,6-10] have established that the NT-proBNP response, defined as a decrease in NT-proBNP of >30% and >300 ng/L in evaluable patients (those whose baseline NT-proBNP levels were ≥650 ng/L), predicts clinical outcome and survival
- NT-proBNP is a survival marker independent of therapy type, treatment class, and regimen; these studies were conducted in patients treated with 9 combinations of therapies and 3 individual therapies, including chemotherapies and ASCT as well as steroids, immunomodulatory drugs, proteasome inhibitors, and alkylating agents (**Table 1, Figures 2-4**)

**Figure 2.** Survival versus NT-proBNP response and progression in testing (A) and validation (B) groups in Palladini et al.[4] Adapted with permission from Palladini et al.[4] NT-proBNP, N-terminal probrain natriuretic peptide.



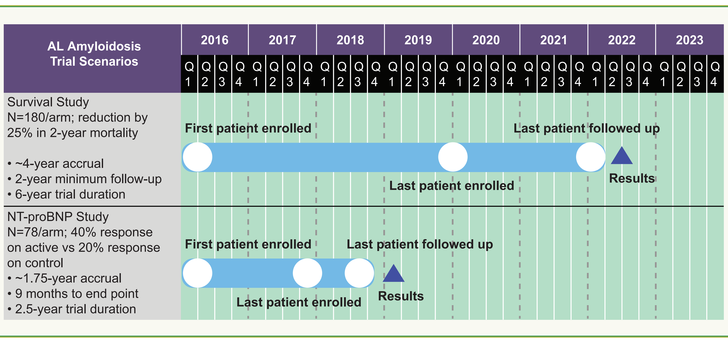

- The International Society of Amyloidosis established and validated NT-proBNP response as an indicator of organ response and as a surrogate marker of survival in AL amyloidosis. NT-proBNP response predicted a significant survival benefit both in testing (n = 816) and in validation (n = 374) populations treated primarily with MDex,T-based, lenalidomide (L)-based, Bor-based, Dex, MP, or ASCT treatments (**Figure 2**)

**Figure 3.** Survival according to NT-proBNP response in an ongoing phase 3 trial comparing MDex with MBDex (NCT01277016). MDex, melphalan-dexamethasone; MBDex, melphalan-bortezomib-dexamethasone; NT-proBNP, N-terminal probrain natriuretic peptide.




- In an ongoing, prospective, phase 3 study comparing MDex with MBDex (NCT01277016), the preliminary outcome analysis indicates that NT-proBNP response translates to a significant survival benefit (**Figure 3**)

**Figure 4.** Estimated time to complete a trial in patients with AL cardiomyopathy using overall survival rather than NT-proBNP response as the end point. AL amyloidosis, amyloid light chain amyloidosis; NT-proBNP, N-terminal probrain natriuretic peptide.




- Overall survival as an end point requires a larger study population and a longer assessment period; a trial using NT-proBNP could be half as long (**Figure 4**)

## CONCLUSIONS

- NT-proBNP indicates cardiac response in all interventional studies in which it has been assessed, despite differences in patient population and treatment regimen
- Without acceptance of surrogate end points, clinical trials in AL amyloidosis will remain handicapped by lengthy timelines and large study sizes, necessary because of the end points used to demonstrate efficacy (eg, overall survival and organ failure) with appropriate statistical power
- The use of NT-proBNP will both facilitate the evolution of plasma cell–directed therapies and make the development of anti-amyloid therapies for AL amyloidosis possible

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