# Evaluation of NT-proBNP as surrogate endpoint in AL amyloidosis: development of a platform for federated, multi-institution meta-analysis of randomized trials

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## BACKGROUND

- Amyloid light chain (AL) amyloidosis is a rare, complex, fatal disease caused by the accumulation in various tissues of misfolded free light-chain derived amyloid fibrils produced by clonal plasma cells, ultimately leading to multi-system organ impairment.
- The potential to use well-validated surrogate endpoints is of high interest for drug development in AL amyloidosis, as surrogates would enable faster trials and reduce the need for accrual of organ damage and mortality events during follow-up.
- N-terminal pro B-type natriuretic peptide (NT-proBNP) has been identified as a strong candidate for use as a surrogate endpoint for drug evaluation in AL amyloidosis, based on strong and consistent predictive associations with survival and other clinical outcomes.[1]
- While necessary, such predictive associations are insufficient for establishing surrogacy; further evidence, from multiple randomized trials, is needed to evaluate whether treatment effects on NT-proBNP are predictive of treatment effects on survival. [2,3]
- Data from multiple trials in AL amyloidosis are available, but the data reside across different institutions and countries and thus cannot be readily pooled for research.

## OBJECTIVES

- To collaboratively implement a system for federated analysis of multiple randomized trials in AL amyloidosis, i.e., a system in which
  - (1) patient-level trial data are analyzed locally, without need for cross-institution data transfers, and
  - (2) results of local analyses are pooled centrally to produce final evidence
- To replicate predictive associations between NT-proBNP and overall survival using the federated analysis system for platform validation

## METHODS

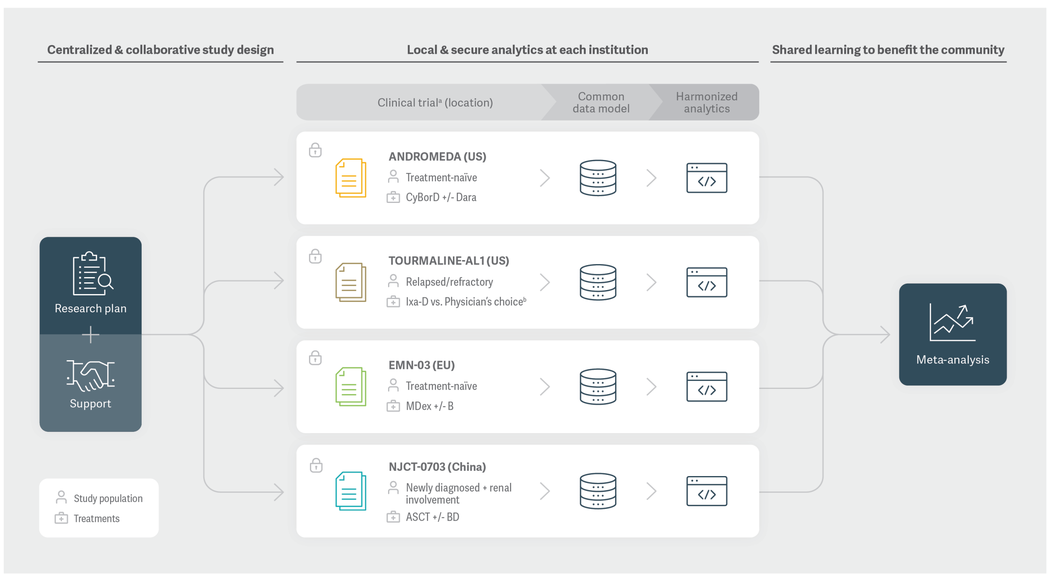
*Data Sources*

- A literature review identified eleven completed randomized trials in AL amyloidosis. Among these, five trials included assessments of NT-proBNP; four trials were made available for this research, with data originating from three different geographic locations (**Figure 1**).

*Federated Analytics Platform Design*

- A hub-and-spoke platform for federated analytics was established, with the 'hub' including a central research team, common data model (CDM), statistical analysis plan, and standardized analytical programs, all centrally developed with collaborator input (**Figure 1**).
- Researchers at each institution ('spokes') transformed their local data to the CDM, ran analytical programs, reviewed output, and shared aggregate analytical results with the hub.

**Figure 1. Platform architecture for federated analytics and clinical trials included**




**Notes:**
[a] Clinicaltrials.gov identifiers for the included trials: NCT03201965 (ANDROMEDA); NCT01277016 (EMN-03); NCT01998503 (NJCT-0703); NCT01659658 (TOURMALINE-AL1)
[b] Participants received one of the following treatment options as selected by the physician: 1. dexamethasone; 2. dexamethasone + melphalan; 3. dexamethasone + cyclophosphamide; 4. Dexamethasone + thalidomide; 5. dexamethasone + lenalidomide
**Abbreviations:** ASCT: autologous stem cell transplantation; B/Bor: bortezomib; D/Dex: dexamethasone; Cy: cyclophosphamide; Dara: daratumumab; EU: European Union; M: melphalan; US: United States

- Real-world challenges encountered and solutions implemented for the federated system are summarized in **Table 1**.

**Table 1. Key Challenges and solutions for federated analytics**

| Challenge | Solution |
|---|---|
| **Trials have different study designs, data structures, study measure definitions, etc.** | A CDM was developed to translate different datasets into a standardized structure. Error checks were implemented for the most common errors to allow for rapid troubleshooting of each local analysis. Discussions with each team were conducted, based on summary statistics, to validate the transformed data. |
| **Each institution has a different local software environment** | A self-contained file package including a portable installation of R statistical software and necessary analytical packages was distributed to each institution in addition to the analytical code. |
| **Runtime errors can arise due to data issues and local environment settings** | Video calls with researchers in each spoke helped troubleshoot issues. Collaborators reported 9-16 person hours were needed at each institution to set-up the data. |
| **Changes in or additions to analytical methods are often needed to address collaborator input, unforeseen data patterns and emergent research needs** | When changes or additions to the analyses are needed, updated analytical code is developed centrally and provided to each center. This reduces the resource burden on centers once the CDM is validated and in place. |

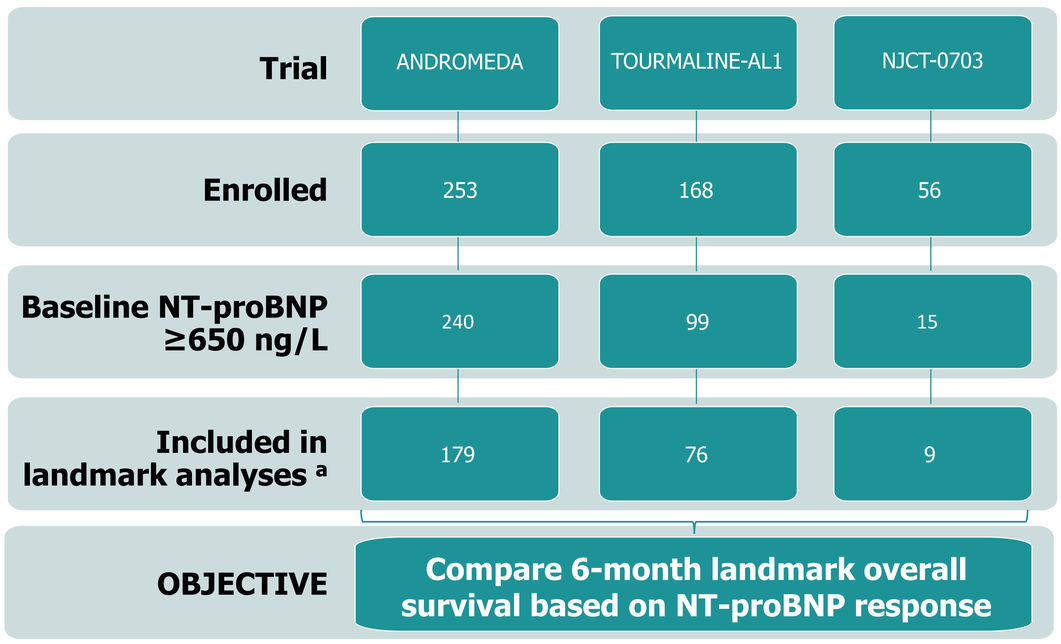
*Predictive Associations Analysis*

- The primary candidate for surrogacy was NT-proBNP response at month 6, defined as a decrease in NT-proBNP of >30% and >300 ng/L relative to baseline among evaluable patients with baseline NT-proBNP ⩾650 ng/L (**Figure 2**).
- Associations between month 6 NT-proBNP response and survival were assessed in landmark analyses using Kaplan-Meier estimators.
- A random-effects meta-analysis was conducted using a mixed effects generalized linear model with a Poisson distribution and log link to assess pooled associations between NT-proBNP response and subsequent survival across all trials.
- Future sensitivity analyses will consider responses at months 3, 9, and 12, and NT-proBNP progression-free survival.

## RESULTS

- Interim results are presented here for ANDROMEDA, TOURMALINE-AL1, and NJCT-0703.
- Among the n=477 patients included in these trials, n=354 had elevated NT-proBNP at baseline. Among these, n=264 were evaluable for response at month 6, with n=66 classified as responders and n=198 classified as non-responders (**Figure 3**).

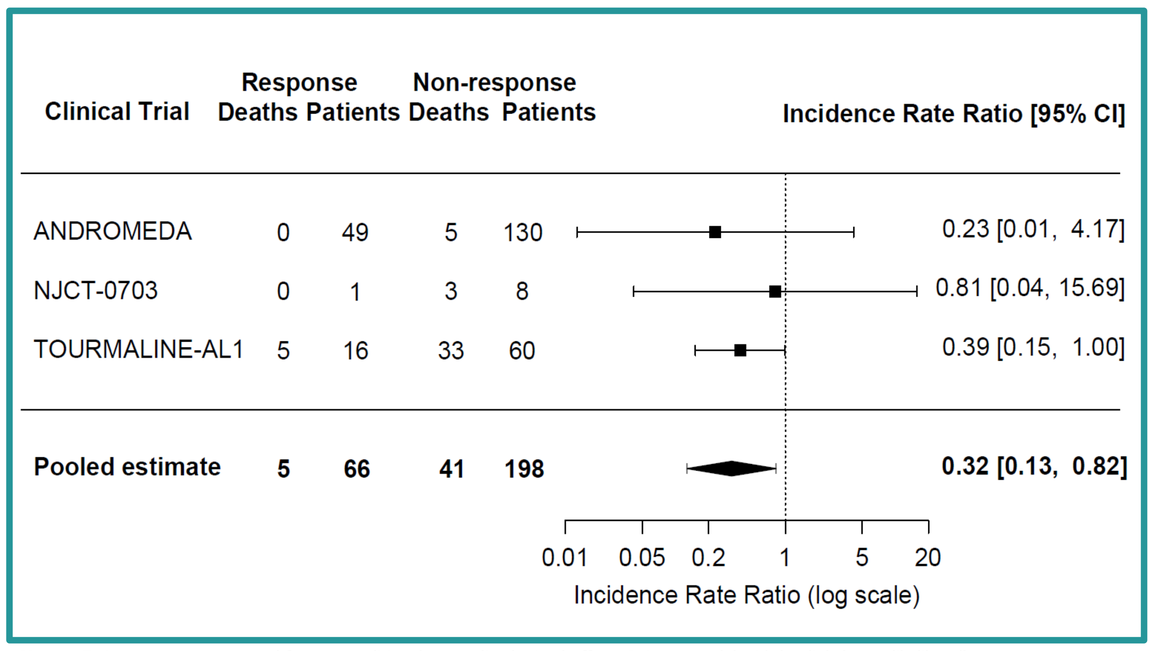
**Figure 2. Sample selection flowchart and sample size by clinical trial**




[a] Excluded if dead or censored before month 5. Reasons for censorship include missing value or missing follow-up

- In the random-effects meta-analysis, NT-proBNP response vs. non-response at month 6 was associated with a statistically significant decrease in subsequent risk of death: 68% relative risk reduction, 95% confidence interval (CI) = [17%, 82%], p-value = 0.018 (**Figure 3**).

**Figure 3. Random-effects meta-analysis estimates of landmark associations between NT-proBNP response at 6 months and risk of subsequent death**




**Notes:** Estimates were generated from a conditional generalized mixed-effects Poisson model with log link (exact likelihood). The log number of patient-years of follow-up in each trial was included in the model as an offset.
**Abbreviations:** CI: confidence interval

## CONCLUSIONS

- A platform for federated analytics of randomized trials in AL amyloidosis was successfully implemented across institutions in the US, EU and China, enabling collaborative analyses of multiple data sources that could not be shared or pooled.
- The modular structure of the platform allows for the inclusion of additional trials as data become available in the future.
- In interim analyses, conducted to test the platform, NT-proBNP response was associated with lower subsequent risk of death, consistent with previously demonstrated associations.
- This platform will ultimately be used for timeline surrogate validation, as additional trial data become available, by measuring the association between effects on NT-proBNP and effects on survival across trials.

## REFERENCES

**1.** Merlini et al. Leukemia. 2016;30(10):1979-1986. **2.** Fleming & DeMets. Ann Intern Med. 1996;125(7):605-613. **3.** Fleming & Powers. Statist Med. 2012;31(25):2973-2984.

## DISCLOSURES

**AD** is on the Advisory Board and Independent Review Committee for Janssen; Data Safety Monitoring Committee for Oncopeptides and Sorrento; and receives research funding from Alnylam, Pfizer, Takeda, and BMS. **PD** is an employee of Janssen. **DVF** is an employee of Oryzon Genomics, Inc. and former employee of Takeda. **RL** is an employee and shareholder of Takeda. **MSM** has grant support from NIH R01HL139671; consulting income from Eidos, Prothena, Ionis, Alnylam, Novo-Nordisk and Intellia; and institutional support in the form of clinical trial funding from Pfizer, Attralus, Ionis, Eidos and Alnylam. **VS** has research support and is PI on studies for Celgene, Millennium-Takeda, Janssen, Prothena, Sorrento, Karyopharm, Oncopeptide, Caleum; consultant for Pfizer, Janssen, Attralus; and is on the Scientific Advisory Board for Proclara, Caelum, Abbvie, Janssen, Regeneron, Protego, Pharmatrace, Telix, and Prothena. **LX** is an employee of Janssen.

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