Leveraging Recent Advances in Plasma Biomarkers to Optimize Early Phase Drug Development in Alzheimer's Disease

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HOW TO LEVERAGE 80% OF THE SIGNAL FOR 20% OF THE COST

INTRODUCTION

Biomarkers are now used in both Alzheimer's Disease (AD) diagnosis and prediction of disease progression. Several clinical trials have utilized biomarker outcomes (amyloid-PET scans and cerebrospinal fluid (CSF) measures of Aβ and tau). Blood-based biomarkers offer advantages of lower costs and easier sample collection. Given their potential to predict both disease trajectory and clinical benefit, we investigated the relationship between biomarkers and clinical outcomes in recent trials of anti-amyloid antibodies for AD.

METHODS

1. **Patient-level correlations** between biomarkers and clinical endpoints are based on pairs of data from each *patient*. Intent is to understand how well biomarkers predict individual patient clinical outcomes and use biomarkers as a diagnostic or as an indicator of when to start or stop treatment.

2. **Group-level correlations** are based on pairs of data for each *group*. Intent is to understand how well the mean biomarker result (treatment effect from baseline to change) predicts the mean treatment effect on the clinical outcome and use biomarkers as clinical trial endpoints.

3. **Cohen's d effect size** is used for **standardization.**

4. **Weighted Pearson correlation** is used to assess the group-level associations.

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RESULTS

Figure 1. Group-level associations between standardized effect sizes (Cohen's d) of plasma pTau with Amyloid PET Centiloid at 6, 12, and 18 months.

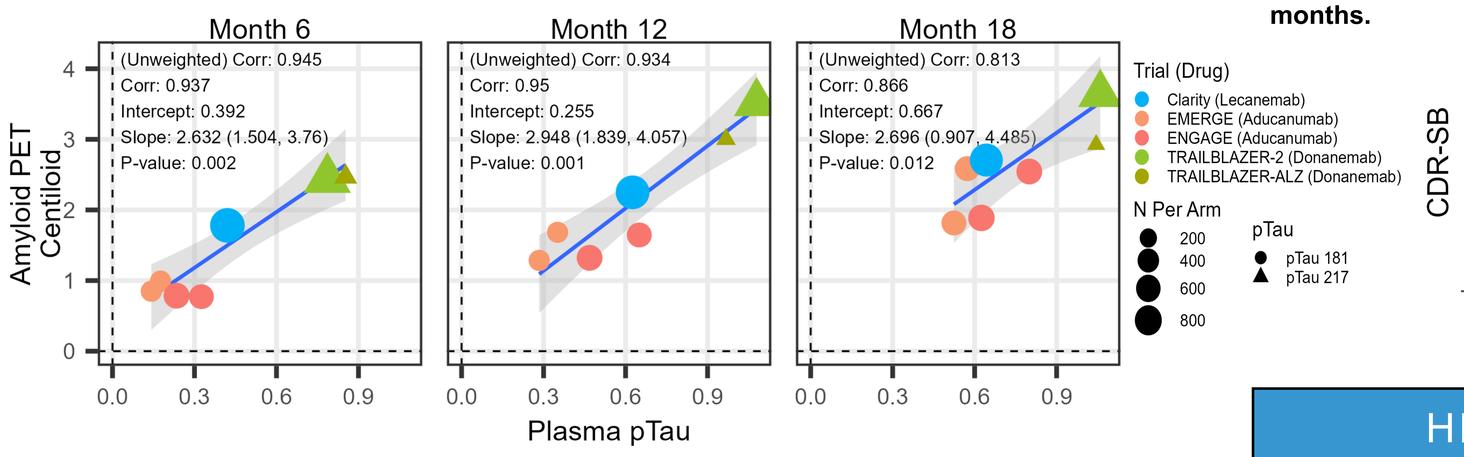
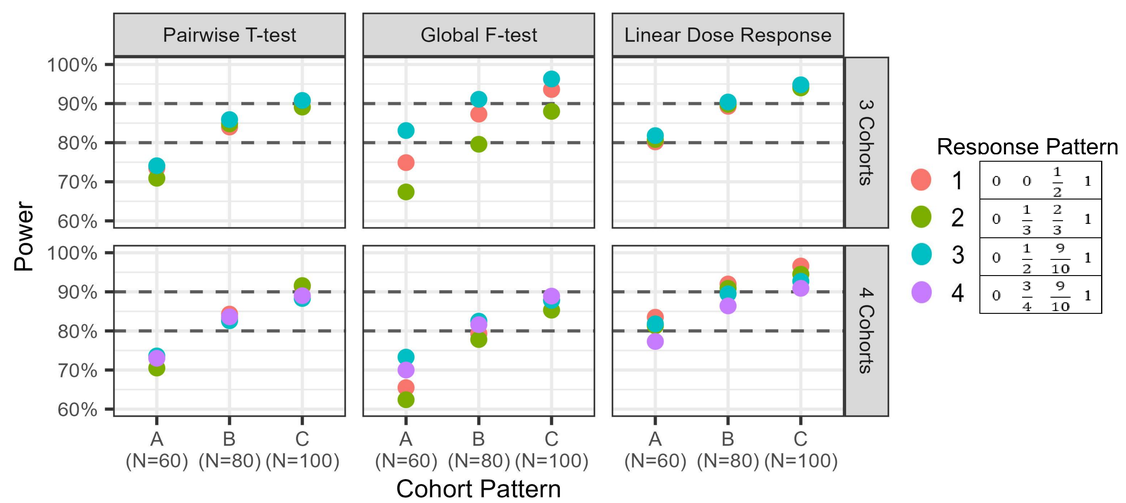


Table 1. Standardized treatment effects for plasma pTau and Amyloid-PET at 6 months and CDR-SB at 12 months.

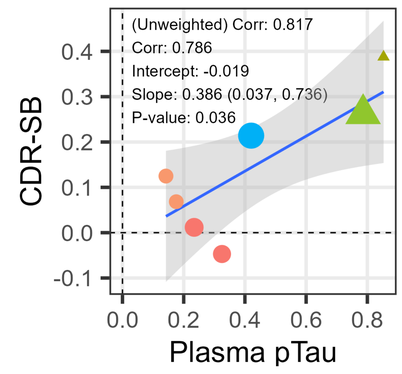
Drug	Trial	Dose	Cohen's d at 6 months: Plasma pT181 or pT217 sample size	Cohen's d at 6 months: Plasma pT181 or pT217	Cohen's d at 6 months: Amyloid PET sample size	Cohen's d at 6 months: Amyloid PET	Cohen's d at 12 months: CDR-SB
Aducanumab	EMERGE	3-6 mg/kg	174	0.142	129	0.849	0.125
Aducanumab	EMERGE	6-10 mg/kg	172	0.176	134	0.993	0.068
Aducanumab	ENGAGE	3-6 mg/kg	300	0.234	168	0.786	0.012
Aducanumab	ENGAGE	6-10 mg/kg	272	0.325	162	0.772	-0.047
Donanemab	TRAILBLAZER-2	1400 mg	710	0.786	782	2.44	0.262
Donanemab	TRAILBLAZER-ALZ	700/1400 mg	110	0.853	113	3.32	0.388
Lecanemab	Clarity	10 mg/kg	688	0.42	280	1.78	0.214

Figure 3. Power results for a cohort dose escalation proof-of-concept study.



RESULTS

Figure 2. Group-level associations between plasma pTau at 6 months with CDR-SB at 12 months.



HIGHLIGHTS

- The group-level correlation between a biomarker treatment effect and clinical endpoint treatment effect is a measurement of the biomarker's ability to predict clinical outcome in a clinical trial.

- Cohen's d effect size of plasma pT217 or pT181 as a biomarker outcome was three times greater than the Cohen's d values of clinical outcome CDR-SB, leading to higher power or lower sample sizes (about one ninth since it is a squared relationship).

- The correlation of group-level plasma pT217 or pT181 with clinical outcome CDR-SB was approximately 0.786 with p values of 0.036, which are comparable to the published amyloid PET, CDR-SB correlation of 0.78.

DISCUSSION

The approach presented here has the promise of obtaining sufficient information for proof-of-concept and dose-finding by using a plasma pTau biomarker in a study of approximately 100 patients with at least 6 months follow up.

When comparing to amyloid β biomarkers, downstream biomarkers like plasma pTau have the potential to provide a more broadly applicable read-out for treatment efficacy, especially for treatments whose mechanism of action is not directly aimed at plaque removal.