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RESEARCH ARTICLE

The relationship of soluble tau species with Alzheimer's disease amyloid plaque removal and tau pathology

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Abstract

BACKGROUND: Tau-derived cerebrospinal fluid (CSF) biomarkers correlate with amyloid-beta (Aβ) plaques or tau tangles in Alzheimer's disease (AD). This study assessed the effects of long-term anti-Aβ antibodies on amyloid plaques, tau tangles, and CSF tau species to determine the relationships between them.

METHODS: A post-hoc analysis of the DIAN-TU-001 trial (NCT01760005) examined 142 participants at risk for dominantly inherited AD randomized to solanezumab ($n = 50$), gantenerumab ($n = 52$), or placebo ($n = 40$). High-resolution mass spectrometry quantified CSF tau species over four years.

RESULTS: Phosphorylated tau (p-tau) species (153, 181, 217, 231) increased early in preclinical AD but were reduced with gantenerumab-mediated Aβ plaque reduction. Nearly a decade later, MTBR-tau243 and p-tau205 increased, showing no association with Aβ reduction, aligning with tau tangle pathology progression.

DISCUSSION: Initially changing soluble p-tau species track Aβ plaque reduction, while ptau205 and MTBR-243 reflect tau tangle pathology, informing different pathways of therapeutic strategies.

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KEYWORDS
amyloid beta plaque reduction, dominantly inherited Alzheimer's disease, microtubule-binding region, phosphorylated tau

Highlights

- p-tau217 and p-tau231 correlate with Aβ-PET and respond to Aβ-plaque lowering therapies.
- Aβ immunotherapy trials support a direct link between p-tau changes and Aβ plaques
- Gantenerumab reduces Aβ plaques but does not affect tau NFT-related biomarkers.
- Blood-based p-tau217 assays may provide a non-invasive tool to monitor Aβ therapies.
- MTBR-tau243 strongly correlates with tau PET and tracks NFT pathology progression.
- Further studies are needed to validate tau biomarkers for tracking NFT-targeting therapies.

1 | BACKGROUND

Recent studies in dominantly inherited Alzheimer's disease (DIAD) and sporadic AD (sAD) suggest a sequence of changes in CSF and blood tau-related measures that correlate with and bridge Aβ-plaque and neurofibrillary tangle pathologies.[1–5] Relatively early increased phosphorylation of three specific sites (217, 231, and 181) correlates with Aβ-PET positivity, followed after by increased phosphorylation of site 205 before symptom onset; later, levels of the microtubule binding region tau 243 fragment (MTBR-tau243) and non-phosphorylated tau increase near the time of clinical symptom onset, in parallel with tau-PET signal increases.[1,6–8]

The initial rise of soluble phospho-tau, decades before the expected onset of clinical symptoms and years before substantial neurofibrillary tangles (NFT) are present, has generated uncertainty about the clinical and pathological meaning of the initial phospho-tau species.[9,10] Soluble p-tau217, p-tau231 and p-tau181 species seem to correlate more closely with Aβ-plaque pathology than with hyperphosphorylated NFT pathology. Related to this, Aβ-plaque-lowering therapies appear to reduce levels of some blood and CSF phospho-tau species.[11–16] Clearly, natural history and interventional studies suggest causal links between the increase in certain soluble phospho-tau measures and Aβ-plaque pathology. However, a comprehensive assessment of soluble phospho-tau levels before and after removing aggregated Aβ is needed to validate which phospho-tau isoforms are markers of Aβ-plaque pathology vs. tau tangle pathology.

The identification of soluble tau related biomarkers that rise in parallel with NFT pathology supports the original notion that levels of some forms of cerebrospinal fluid (CSF) tau reflect the release of aggregated tau pathology, rather than a response to established Aβ-plaque pathology. These forms of tau include p-tau205, and fragments that include the non-phosphorylated N-terminal domain and the central proline-rich domain (known as total tau, t-tau), or the microtubule binding repeat (MTBR) domain.[6,8,17,18] Compared to most phospho-tau species, p-tau205, t-tau, and MTBR-tau243 appear to have stronger correlations with clinical symptoms, cerebral atrophy, and tau-PET and, thus, may serve as a surrogate measure of clinical symptomatology. Yet, the recent studies demonstrating a decrease in Aβ-plaque pathology have not shown clear evidence of an influence on NFT burden by tau PET, nor evaluated these recently identified soluble tau biomarkers including relative abundance of p-tau measured as ptau/tau ratios (%p-tau). Interventional studies are needed to assess the relationships between soluble tau-related biomarkers, Aβ-plaques, and NFTs.

Previously, we have shown that gantenerumab (an Aβ-plaque targeting therapy), but not solanezumab (a Aβ-monomer targeted therapy) substantially reduced Aβ-plaques in DIAD.[15] In this study, we explored the effect of both drugs on the longitudinal rate of change of multiple CSF soluble tau-related biomarkers and tau PET in individuals with DIAD in the Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU) 001 study. Based on our and other trial results,[19] we hypothesized that Aβ-plaque reduction would associate with a selective normalization of *initial-changing* soluble tau biomarkers; whereas, consistent with the absence of a change in tau PET signal, *later changing* soluble tau biomarkers would be unaffected by Aβ-plaque reduction.

2 | METHODS

2.1 | Study participants

Eligibility criteria for the DIAN-TU-001 included participants at-risk for or known to have a DIAD mutation, who were between 15 years before to 10 years after the expected age of symptom onset,[20] and had a global Clinical Dementia Rating® (CDR®) of 0 (cognitively normal), 0.5

RESEARCH IN CONTEXT

1. **Systematic review:** The measurement of multiple tau-related biomarkers in observational cohorts of at-risk or symptomatic Alzheimer disease has suggested that soluble tau changes in the cerebrospinal fluid may reflect both Aβ-plaque and NFT tangle pathology. However, no studies have comprehensively assessed the effect of Aβ plaque reduction on 'early' (e.g. p-tau217) and 'late' (e.g. MTBR-tau243 and tau PET) tau biomarkers.
2. **Interpretation:** Aβ-plaque, but not soluble Aβ, reduction was associated with a distinct reduction of multiple 'early' tau biomarkers without a change in 'late' tau biomarkers. These findings support recent diagnostic criteria for Alzheimer's disease classifying early and later changes in tau-related biomarkers and suggests the use of specific phospho-tau biomarkers to monitor the response to Aβ-plaque lowering therapies.
3. **Future directions:** A comparative analyses of recently approved Aβ immunotherapies on tau-related biomarkers is needed to better understand if these soluble measures can be used to monitor long-term treatment effects.

(very mild dementia), or 1 (mild dementia).[21] DIAD mutation carriers were randomized 3:1 to active drug (gantenerumab or solanezumab) or placebo with a minimization procedure.[22] Study personnel, sponsors, and participants were blinded to treatment assignment. The DIAN Observational study (DIAN-OBS) participants included individuals of age 18 or older who were at-risk for or known to have a DIAD mutation and who had provided CSF. The DIAN-OBS and DIAN-TU studies have similar protocols, including cognitive, clinical, imaging and biomarker measures and both studies excluded participants with the APP E693Q (Dutch) mutation. Full details for the DIAN-TU-001 and DIAN-OBS are available in previous publications.[15,23,24] The studies were conducted in accordance with the Declaration of Helsinki (version 7) and the International Conference on Harmonization and Good Clinical Practice guidelines and had ethics committee approval at each participating site. Participants provided written informed consent.

2.2 | Study design

DIAN-TU-001 was conducted at 25 sites in 7 countries from December 2012 through November 2019. The trial registration number is NCT01760005. Investigators are listed on the DIAN-TU webpage https://dian.wustl.edu/for-investigators/diantu-investigator-resources/dian-tu-study-team/. Biomarkers were assessed at baseline and in years 1, 2, and 4. Target drug doses were increased approximately halfway through the study as previously detailed.[15] Gantenerumab was increased from 225 mg (subcutaneously, every 4 weeks) to 1200 mg in 2016. Solanezumab was increased from 400 mg (intravenously, every 4 weeks) to 1600 mg in 2017. The current CSF study includes only those participants who had CSF and brain imaging measured at all time points; the biomarker assessment between years 2 and 4 represents the time during which the drug doses were increased. This is an exploratory, post-hoc analysis that was not part of the original clinical trial statistical analysis plan. Therefore, some analyses are underpowered, and the results should be interpreted as descriptive in nature.

For the DIAN-OBS participants ($n = 247$), the study was conducted at 22 sites and data underwent yearly quality-control assessments for irregular results and missing data from January 26, 2009 to June 30, 2017.

2.2.1 | Cerebrospinal Fluid Analyses

For both DIAN-TU-001 and DIAN-OBS, CSF was collected via standard lumbar puncture procedures using an atraumatic Sprotte spinal needle (22 Ga), typically in the morning and in fasting state. DIAN-OBS CSF samples were centrifuged immediately upon collection and flash frozen, whereas DIAN-TU-001 samples were flash frozen immediately upon collection and shipped to the DIAN Biomarker Core. For the CSF tau-related analyses, each sample underwent two freeze-thaw cycles. Full details of the CSF preparation and LC-MS/MS processing have been previously outlined in detail[5,6] and were consistent for both DIAN-OBS and DIAN-TU-001. Importantly, except for non-phosphorylated (total tau) and the microtubule binding region 243 (MTBR-tau243) concentrations, all phospho-tau measures represent the phosphorylated to unphosphorylated (pT## / T##) ratios for each modified residue or expressed as percentage (%phospho-tau).

2.2.2 | Tau and Amyloid PET Imaging

Full details on the imaging protocols for 11C-Pittsburgh Compound B (PiB) PET and 18F-AV-1451 (flortaucipir) PET have been provided previously.[25,26] Region of interest PET data were converted to regional standard uptake value ratios (SUVRs) — 47-60 minute window for PiB PET and 80-100 for flortaucipir — using the cerebellar grey as a reference and were partial volume corrected using a regional spread function for each region, which when combined form a geometric transfer matrix.[27,28] Of note, the tau PET results are derived from DIAN-TU study data only, due to limited longitudinal tau PET in the DIAN observational cohort.

2.3 | Study outcomes

The primary outcome of the DIAN-TU-001 study was the DIAN multivariate cognitive endpoint[1]. For this exploratory study, the primary outcomes were the differences in the soluble CSF tau-related biomarkers in the treatment groups relative to the shared placebo group at

the end of year 4. The two active treatment arms were compared to placebo but were not directly compared to each other.

2.3.1 | Statistical Analyses

DIAN Observational Data

For each marker, the standardized mean value for mutation carriers (MCs) were estimated at each estimated years to symptom onset (EYO) point using linear mixed effects (LME) models using only baseline data, then plotted over EYO. These values were transformed into a value scaled from 0-100 (see below) to better project the magnitude of change across the disease spectrum. The LME models included the fix effects of mutation status (MC vs. non-carrier [NC]) and baseline EYO. All possible two-way interaction terms along with second and third order of EYO terms were examined to reach a final model that fit the data well for each marker. A random effect was also included to account for the family affiliation.

To evaluate the biomarker abnormality rate across EYO, percentage of abnormality for each biomarker was calculated by every five-year EYO bin (i.e. -15 to -11, etc.). The 95th percentile of the NC group was set as abnormality cutoff for all measurements except for CSF Aβ42/40 where 5th percentile (lower ratio is more advanced disease) was used as the cutoff for abnormality.

DIAN-TU Data

For the trial data, which had protocol specific biomarker collection intervals, a mixed model for repeated measures (MMRM) was employed to estimate the change from baseline within each group and to compare differences between these changes. The MMRM analysis incorporated the treatment group (including either treatment group and the shared placebo group), baseline values, post-baseline visit times as categorical values, and the interaction between visit times and treatment as fixed effects; and employed an unstructured covariance matrix. We have recently developed a method to standardize different biomarkers to a scale of 0-100, called CentiMarker[29] (similar to the Centiloid scale,[30] using the 95th percentile of the greatest abnormal values for all MCs and the mean from the NCs. This method provides a way of quantifying the change for each biomarker in a similar scale to better interpret the magnitude of drug effects on each biomarker. To evaluate the correlation between amyloid PiB-PET or tau PET and each soluble biomarker, Spearman correlations were computed based on the individual annual rate of change estimated using the least squares method. This method was chosen due to the relatively small sample size of the trial as opposed to a bivariate mixed model which could be more subject to model convergence issues.

To visualize the drug effect of gantenerumab on the normal disease progression pattern of the soluble tau biomarkers and amyloid and neurodegeneration, LOESS curves were generated over cognition-adjusted EYO for gantenerumab-treated MCs, a combined MC group of placebo and solanezumab and NCs. To more intuitively compare disease progression patterns across different biomarkers, each was standardized to a scale of 0-100, called CentiMarker[29] using the 95th percentile of the greatest abnormal values for all MCs and the mean from the NCs. EYO was adjusted using the baseline values of International Shopping List Test-Delayed Recall and Digit Symbol Substitution Test, employing a simplified disease progression model based on cross-sectional data.[31] This adjusted EYO[31] can more accurately delineate the disease progression pattern compared to an unadjusted EYO (calculated using only mutation and familial information,[32] and is referred to as the cognition adjusted EYO. Because the adjustment utilized only baseline values, inclusion of two endpoints in the model was necessary for identifiability. Although any two endpoints can meet the model requirement, these ones were selected due to their greater sensitivity to disease severity and amyloid levels.[33]

3 | RESULTS

Participant demographics and values of the key biomarker measurements are listed in Table 1.

3.1 | Temporal ordering of soluble CSF tau biomarkers

Our previous study from the natural history population[5] suggested an ordering of changes in phospho-tau and total tau levels in the progression of disease including pT217/T217, pT181/T181, and pT205/T205. Here we expand on the order and magnitude of changes by including the pT153/T153, pT231/T231, and MTBR-tau243 in the DIAN-OBS cohort, Figure 1A. The figure highlights a near decade difference between the time that amyloid PET, pT153/T153, pT231/T231, pT217/T217 and pT181/T181 rise substantially in MCs, and the time when CSF pT205/T205, total tau, and MTBR-tau243 increase. Further, using 5-year time bins to track stage of disease, we assessed the proportion of MCs who had abnormal levels for each CSF tau-related biomarker, amyloid PET, Figure 1B. In alignment with the temporal pattern identified in Figure 1A, we found that there were consistencies between the proportion of MCs who had abnormal levels of specific phospho-tau ratios and amyloid PET, which were sequentially followed by increases in the proportion of MCs with abnormal levels of pT205/T205, MTBR-tau243 and CSF tau as the age of symptom onset approached; specifically, 50% of MCs had abnormal pT217/T217 levels between 20 to 15 years before symptom onset (EYO -20 to -15), whereas 50% of MCs had abnormal pT205/T205 and MTBR-tau243 between 10 to 5 years before symptom onset (EYO -10 to -5), a 10 year difference. Subsequently, we classify these groups of soluble tau biomarkers into amyloid-related CSF tau biomarkers versus tau tangle-related CSF tau biomarkers.

Based on these findings that indicate a temporal ordering of soluble tau biomarkers and distinct associations with Aβ-PET, we then explored the effect of amyloid targeting therapies on these soluble tau measures to better determine relationships of soluble CSF tau biomarkers with amyloid plaque and NFT pathologies.

TABLE 1 Clinical Dementia Rating and biomarker values at trial baseline by randomization.

	Active gantenerumab $n = 52$	Active solanezumab $n = 50$	Shared placebo $n = 40$
CDR 0 (n (%))	31 (60)	30 (60)	22 (55)
CDR > 0 (n (%))	21 (40)	20 (40)	18 (45)
pT153/T153	0.16 ± 0.08	0.18 ± 0.08	0.17 ± 0.08
pT181/T181	35.92 ± 8.83	38.23 ± 10.41	36.43 ± 9.25
pT205/T205	1.16 ± 0.52	1.24 ± 0.53	1.23 ± 0.60
pT217/T217	12.56 ± 7.03	14.25 ± 8.04	12.90 ± 6.93
pT231/T231	19.15 ± 12.22	21.89 ± 11.67	19.63 ± 8.81
MTBR-tau243 ng/ml	0.73 ± 0.79	0.66 ± 0.58	0.57 ± 0.46
PiB-PET Composite (Centiloid)	64.8 ± 51.9	65.2 ± 53.6	64.3 ± 50.1
Tau PET SUVR Summary Region	1.63 ± 0.60	2.64 ± 1.36	2.04 ± 1.12
Hippocampal Volume (mm3)	7933 ± 1154	8238 ± 1342	8026 ± 1390

Abbreviations: CDR, Clinical Dementia Rating; MTBR, Microtubule binding region; PiB, Pittsburgh compound B; SUVR, Standard Uptake Volume Ratio.

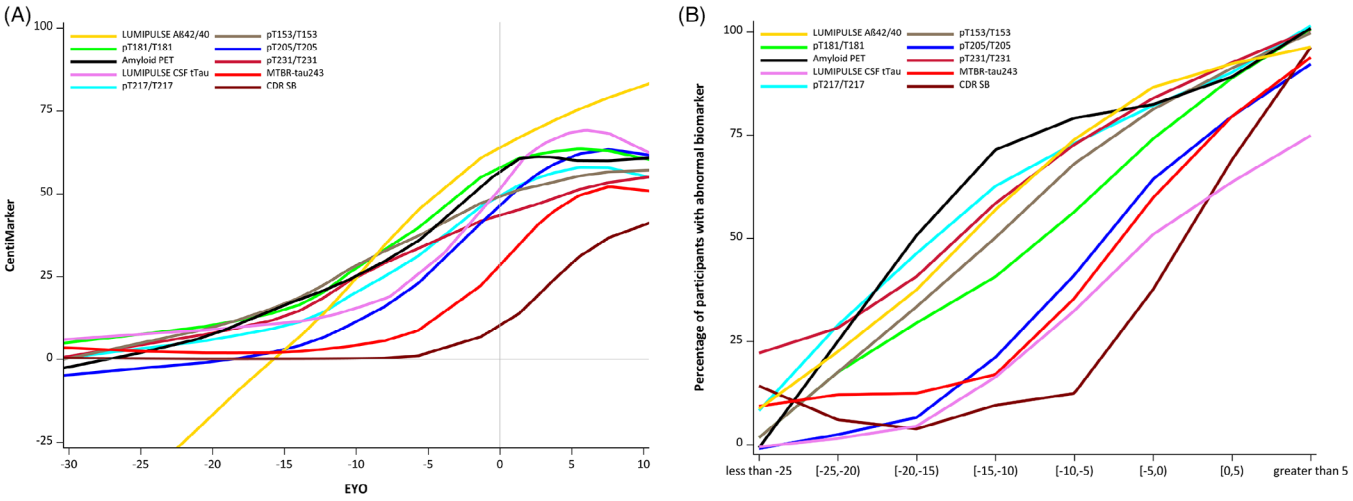

FIGURE 1 Soluble tau biomarkers track disease progression in Dominantly inherited Alzheimer disease natural history cohort. (A) mean cross-sectional standardized values (y-axis) for soluble tau-related biomarkers (in CentiMarkers), clinical dementia rating sum of boxes (CDR-SB) and amyloid PET for MCs across the estimated year of onset (EYO) (x-axis). (B) percentage (y-axis) of MCs with abnormal levels (greater than 2 SD above mean of NC) of soluble tau-related biomarkers, CDR-SB and amyloid PET across the EYO (x-axis) in 5-year intervals.

3.2 | Effects of Aβ-PET change on soluble CSF tau related biomarkers

Because we previously demonstrated a substantial Aβ-plaque lowering effect by PET of gantenerumab,[15] we first assessed the changes in each of the CSF tau biomarkers in the gantenerumab treated group, compared to placebo-treated MCs, using a MMRM analysis at each timepoint of CSF collection, Figure 2. Following gantenerumab treatment, phospho-tau measures from the amyloid-related CSF tau biomarkers had the most consistent reduction with Aβ-PET. Tau tangle-related CSF tau biomarkers were unchanged despite the significant reduction of Aβ-PET. Solanezumab treatment was not associated with differences in PiB PET levels or any of the CSF tau related biomarkers relative to the placebo group, apart from a higher level of MTBR-tau243 in the solanezumab group compared to placebo.

We next assessed the association between the change in Aβ-PET and the change in each of the CSF tau biomarkers by assessing the correlations between the annual rates of change using the combined data from all three groups (Figure 3). Consistent with the temporal association of Aβ-PET increase and the amyloid related CSF tau biomarkers, we found that the rate of change of the amyloid-related CSF tau biomarkers correlated with changes in Aβ-PET (correlation range –pT217/T217 $\rho = 0.50$, [95% CI 0.30 – 0.66], $p < 0.0001$ to pT231/T231 $\rho = 0.35$, [95% CI 0.13 – 0.54], $p < 0.0027$); whereas the tau tangle-related CSF tau biomarkers rates of change had no association with change in Aβ-PET (correlation range pT205/T205 $\rho = 0.14$, [95% CI -0.10 – 0.36], $p < 0.2531$ to MTBR-tau243 $\rho = 0.15$, [95% CI -0/09 – 0.38], $p < 0.2018$).

Together, these findings show that the pathological accumulation and treatment-associated reduction of Aβ-plaques with the levels of

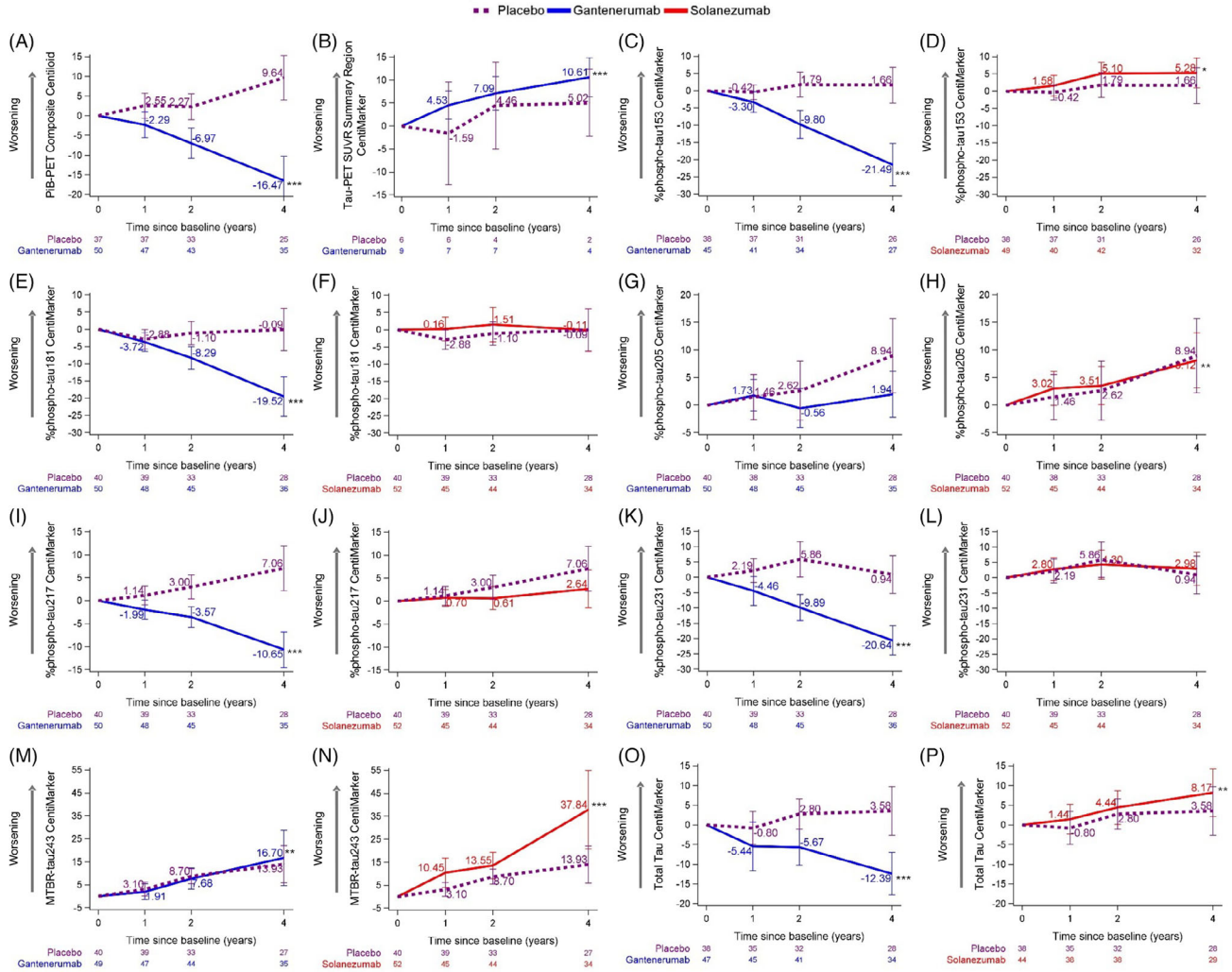

FIGURE 2 Gantenerumab and solanezumab treatment has distinct effects on amyloid PET and tau biomarkers. Estimated mean change in CentiMarkers from baseline with 95% confidence intervals for the treatment (gantenerumab (blue), solanezumab (red)) and shared placebo groups using MMRM analyses. (A, B) Estimated mean change from baseline in amyloid (PiB) PET and Tau-PET for gantenerumab. (C, D) Estimated mean change from baseline in %phospho-tau153. (E, F) Estimated mean change from baseline in %phospho-tau181. (G, H) Estimated mean change from baseline in %phospho-tau205. (I, J) Estimated mean change from baseline in %phospho-tau217. (K, L) Estimated mean change from baseline in %phospho-tau231. (M, N) Estimated mean change from baseline in MTBR-tau243. (O, P) Estimated mean change from baseline in total tau (Lumipulse immunoassay). Sample sizes at yearly assessments are listed below the x axes. Each drug group was compared to the shared placebo group independently using the MMRM model. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

phosphorylation at specific sites in soluble CSF tau are linked and suggest that pT153/T153, pT231/T231, pT217/T217 and pT181/T181 ratios may serve as surrogate markers of Aβ-plaque pathology in the context of AD amyloid plaque removal.

3.3 | Change in tau PET and soluble CSF tau biomarkers

Recent biomarker studies of tau PET and soluble tau species in sAD suggest that pT205/T205 and MTBR-tau243 are more closely correlated with NFT burden than pT217/T217 and other *amyloid-related CSF tau biomarkers*.[1,6,8,17,18] Therefore, we assessed the relationship between longitudinal rates of change for each of the soluble tau-biomarkers and tau PET (Figure 3). We found the strongest positive correlations with tau PET change were with the change in the tau tangle-related CSF tau biomarkers: CSF MTBR-tau243 (ρ = 0.48, CI [0.28, 0.64] $p < 0.0001$), followed by pT205/T205 (ρ = 0.22, CI [-0.02, 0.43] p = 0.067). For the amyloid-related CSF tau biomarkers, we found no associations or a negative correlation which was greatest for pT181/T181 (ρ = -0.40, CI [-0.58, -0.19] p = 0.0004) and pT231/T231 (ρ = -0.25, CI [-0.46, -0.02] p = 0.0314), indicating reduction of amyloid-related CSF tau biomarkers by gantenerumab despite tau PET increases at later stages. These results further support the independence of *tau* tangle-related CSF tau biomarkers, particularly MTBR-tau243, with amyloid plaque amounts and removal, while hav-

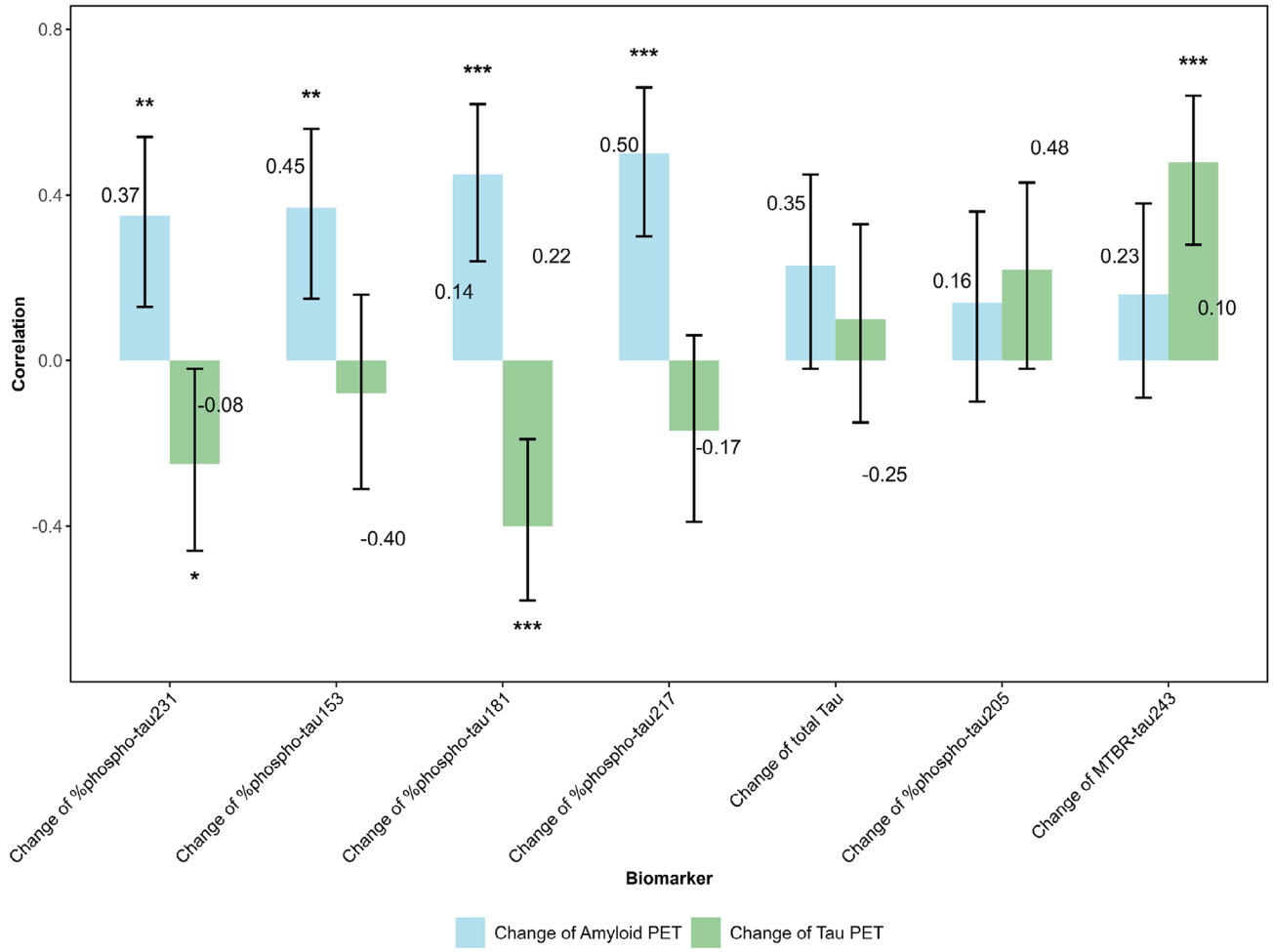

FIGURE 3 Change in CSF tau biomarkers and PET measures of tau and amyloid-beta show distinct relationships. Correlation (ρ) between the estimate annual rate of change in amyloid PiB-PET (blue) or tau PET (green) and in each tau biomarker. %phospho-tau153 and amyloid PiB-PET ($\rho = 0.37$, CI [0.15, 0.56] $p = 0.001$) and tau PET ($\rho = -0.08$, CI [- 0.31, 0.16] $p = 0.52$); %phospho-tau181 and amyloid PiB-PET ($\rho = 0.45$, CI [0.24, 0.62] $p < 0.0001$) and tau PET ($\rho = -0.40$, CI [-0.58, -0.19] $p < 0.001$); %phospho-tau205 and amyloid PiB-PET ($\rho = 0.14$, CI [-0.10, 0.36] $p = 0.25$) and tau PET ($\rho = 0.22$, CI [-0.02, 0.43] $p = 0.07$); %phospho-tau217 and amyloid PiB-PET ($\rho = 0.50$, CI [0.30, 0.66] $p < 0.0001$) and tau PET ($\rho = -0.17$, CI [-0.39, 0.06] $p < 0.15$); %phospho-tau231 and amyloid PiB-PET ($\rho = 0.35$, CI [0.13, 0.54] $p = 0.0027$) and tau PET ($\rho = -0.25$, CI [-0.46, -0.02] $p = 0.03$); MTBR-tau243 and amyloid PiB-PET ($\rho = 0.15$, CI [-0.09, 0.38] $p = 0.2018$) and tau PET ($\rho = 0.47$, CI [0.28, 0.64] $p < 0.001$); total tau and amyloid PiB-PET ($\rho = 0.23$, CI [-0.02, 0.45] $p = 0.06$) and tau PET ($\rho = 0.1$, CI [0.-15, 0.33] $p = 0.44$).

ing strong relationships with NFT tau pathology. The disassociation between amyloid-related CSF tau biomarkers and tau PET indicates these Aβ-PET associated soluble tau biomarkers, including p-tau217 phosphorylation, are not fully causally related with tau PET NFT pathology.

3.4 | Gantenerumab effect on tau-related disease progression

Lastly, as EYO was utilized to explore how fluid tau biomarkers change over the disease course (Figure 1), we next assessed how the treatment effect of gantenerumab changed this disease progression trajectory relative to the placebo and solanezumab groups and NCs (Figure 4). For these analyses, each measurement was scaled to a CentiMarker range.[29] Notably, the CentiMarker range is typically between 0 (completely normal) to 100 (highest level for symptomatic MCs). Therefore, the greater the CentiMarker change, the closer it is likely getting towards a normal value. The figure shows that for most amyloid-related CSF tau biomarkers, gantenerumab resulted in a normalization of trajectories of approximately 50% during the asymptomatic phase (EYO < 0); this effect diminished after symptom onset (EYO > 0). There was not a biologically significant effect of gantenerumab on the trajectories of the tau tangle-related CSF tau biomarkers, with gantenerumab treated and placebo treated participants following the same trajectories). Using this approach, we better demonstrate the magnitude of changes in these biomarkers in response to treatment, relative to normal disease progression.

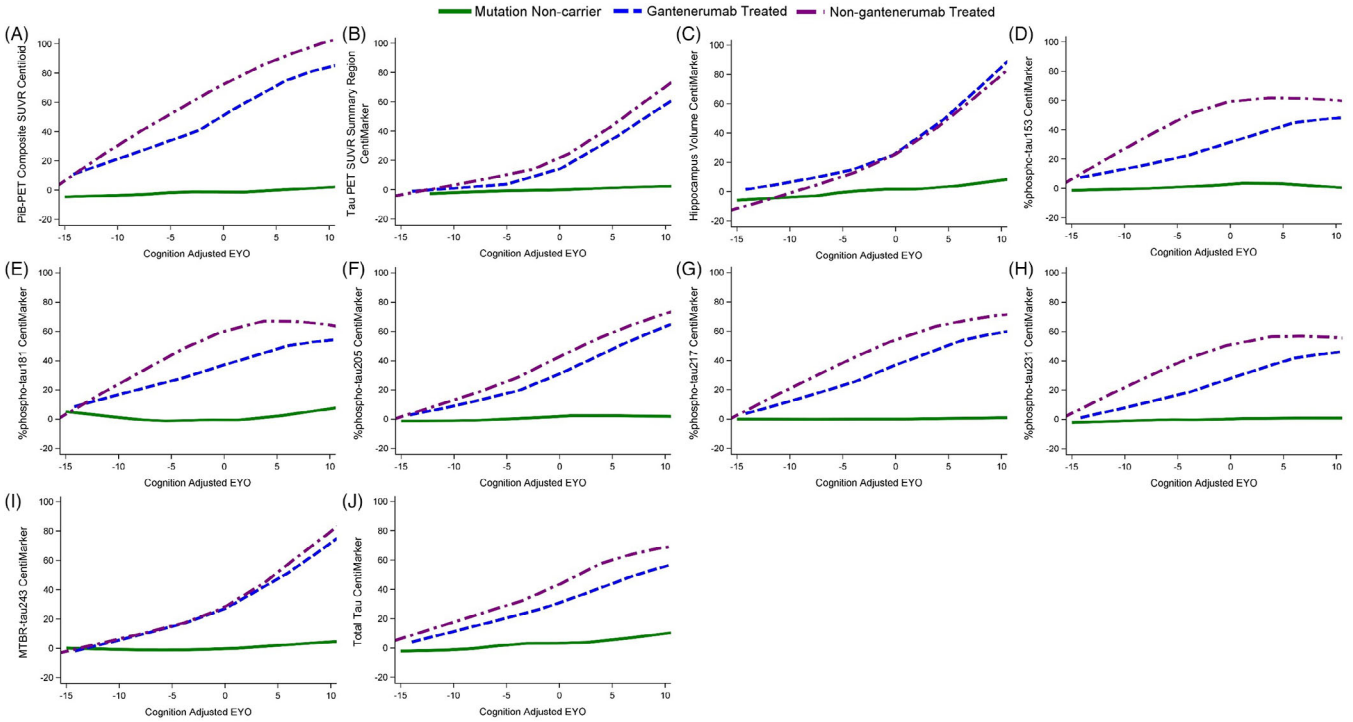

FIGURE 4 Gantenerumab effects on the biomarker trajectories of DIAD. Purple hashed-dot represents mutation carrier placebo-control; blue hashed represents mutation carrier gantenerumab treated group; green solid line represents non-carrier placebo-control. EYO- estimated years to onset of symptoms; (A) PiB-PET (standard uptake value ratio (SUVR)); (B) Tau-PET (SUVR), (C) hippocampal volume (based on MRI) mm^3; (D) %phospho-tau153; (E) %phospho-tau181; (F) %phospho-tau205; (G) %phospho-tau217; (H); (G) %phospho-tau23; (I) Microtuble binding region (MTBR)- tau243; (J) total tau level.

4 | DISCUSSION

The co-development of effective Aβ-plaque lowering therapies and methods for comprehensively measuring soluble tau proteins has provided the opportunity to validate recent natural history studies linking the two canonical pathologies of AD (Aβ-plaques and tau tangles). Specifically, interventional studies like this provide key information to move from association to causal relationships. In this study, we assessed the effects of both Aβ-plaque targeting and soluble Aβ-monomer targeting therapies on multiple CSF tau biomarkers. Our findings clearly indicate that increased phosphorylation of specific regions of the tau protein correlate with Aβ-PET in the setting of DIAD; they are temporally linked to the initial rise in Aβ-PET and decrease as Aβ-PET is pharmacologically reduced. In contrast, we confirmed the relationship between selected tau tangle-related CSF tau biomarkers, particularly MTBR-tau243 and p-tau205, and tau PET, but not amyloid PET. These findings demonstrate that amyloid-related CSF tau biomarkers phosphorylated at tau residues 181, 217, and 231 indicate the amount and change in amyloid plaques, while p-tau205 and MTBR-tau243 are biomarkers of tau NFT pathology measured by tau PET. The combination of biofluid and PET biomarkers of Aβ and tau, along with the selective Aβ-plaque reduction from gantenerumab, provides strong experimental support for recent natural history studies that suggest state dependent tau changes in AD.

Multiple natural history studies of DIAD and sAD[1,2,4,5,7,34–37] have identified correlations between the development of Aβ-pathology and the increase in multiple CSF phospho-tau levels, particularly p-tau217 and p-tau231. Likewise, Aβ-lowering immunotherapy trials in sAD have demonstrated decreases in plasma measurements of p-tau181 and 217[38–40] in parallel with reductions in Aβ-PET.[15,16,41] Our current results, along Aβ-plaque lowering trials in sAD[14,16,41] validate increases in p-tau217 as a marker of Aβ-plaque pathology as measured by PET. Although this does not mechanistically prove Aβ-plaques cause the elevation of amyloid-related CSF tau biomarkers, the unique association of these changes of p-tau in AD and not other proteinopathies, the temporal links with Aβ-plaque changes, and now the clear associations with an intervention that lowers Aβ-plaques, but not tau NFTs, provides strong validation for a direct link of these initial stage CSF p-tau measures and amyloid plaques. Our findings of a consistent negative association between the rate of change of amyloid-related tau biomarkers and tau PET, Figure 3, reinforces the distinction between the tau biomarkers that first emerge with Aβ-plaques and respond to therapies that lowers Aβ-plaques but have minimal effect on tau PET. The difference in the magnitude of the negative associations of the amyloid related tau biomarkers may reflect differences in the concentrations, and thus variability, and/or could also reflect differences how these biomarkers change with NFTs. There is increasing evidence that pT217 has a more dynamic relationship based on the stage of disease

-i.e. early elevation with Aβ-plaques, but a greater association with tau PET at later stages of disease.[42]

The high concordance between a normal Aβ-PET level and a normal pT217/T217 ratio also suggests that p-tau217 could be used to monitor for an initial and substantial response to Aβ-plaque lowering therapies in the context of AD. This could be particularly advantageous given the availability of blood-based p-tau217 assays, and the minimally invasive nature of phlebotomy. However, recent trials in sAD that have resulted in Aβ-PET levels decreasing to levels near normal, have resulted in phosphorylated tau measures decreasing to approximately fifty percent of normal levels.[19] Whether this discrepancy in magnitude reduction of Aβ-PET and soluble p-tau with amyloid immunotherapy represents a continued contribution of NFTs to all p-tau measures, or whether there are other amyloid aggregates not detectable by PET still driving p-tau phosphorylation, or longer treatment with Aβ-plaque lowering therapies is needed, remains to be determined. Despite the engagement of Aβ-monomers by solanezumab, there was no effect on any of the Aβ-plaque associated phospho-tau biomarkers. This, again, reinforces the unique association with initial phospho-tau biomarkers as a reaction to substantial Aβ-plaque pathology.

In contrast to the progress in therapies lowering Aβ-plaque pathology, significantly less progress has been made in identifying agents that can lower NFT pathology. An exception is recent phase 1 trial data on antisense oligonucleotide therapies.[43] Future studies should evaluate the potentially causal link between putative tau tangle-related CSF tau biomarkers, pT205/T205 and MTBR-tau243, and NFT (tau PET). Although neither gantenerumab nor solanezumab influenced these soluble late-stage CSF NFT pathology measures or tau PET, with the exception of a potential increase in MTBR-tau243 in solanezumab treated group, we were able to demonstrate important longitudinal associations between these tau tangle-related CSF tau biomarkers and tau PET. For all groups in this study, the correlations for the rate of change were highest between MTBR-tau243 and tau PET. Interestingly, although pT205/T205 levels increased closer to disease onset, when tau PET increases, the rate of change was not highly correlated with tau PET change. Yet, the reduction of PiB PET and pT217/T217 in the gantenerumab treated group was not replicated with pT205/T205. This suggests that the phosphorylation of T205 marks a distinct phase in the course of tauopathy in AD.[44,45] Despite the relatively small number of individuals included in this study, the association of late-stage fluid biomarkers with tau-PET support recent cross-sectional studies from larger numbers of at-risk and symptomatic sAD.[6]

Together, these results further the concept that tau-related fluid biomarkers inform the state and stage of AD. This has resulted in different soluble tau biomarkers being included in the updated Alzheimer Association's Diagnosis and Staging of AD criteria.[46] Specifically, p-tau217 is now proposed as a core biological marker of amyloid pathology, sufficient to identify this key pathobiological process of AD. Likewise, p-tau205 and MTBR-tau243 and other soluble tau measures are included as potential markers of a later biological pathobiological stage of AD more closely associated with clinical symptoms. Additional clinical trial data from larger Aβ-immunotherapy trials will further validate this staging. Further work is needed with therapies that lower NFT pathology to validate measures like MTBR-tau243 as biomarkers of tau aggregates.

An important limitation for this work is the inclusion of DIAD participants only, which may limit generalizability to sAD. However, recent analyses of these same CSF tau-related measures have identified very similar temporal associations with disease progression in sAD (amyloid- and tau-related biomarkers), and similarly strong correlations between Aβ-plaque or tau PET and initial- and later-stage tau biomarkers. Moreover, recent clinical trials of multiple Aβ-plaque lowering therapies that have evaluated soluble (plasma or CSF) phospho-tau measures have demonstrated similar associations between Aβ-plaque reduction and substantial reductions of initial tau biomarkers.[11,13,16,41,47] This suggest the results from our study in DIAD are likely applicable to sAD, but analyses on the late-stage tau biomarkers are needed in sAD interventional trials that remove plaques or lower tangles, to further assess this. Another limitation of this work is the lack of plasma tau biomarkers available to assess for similarities to CSF measures. Lastly, the *post-hoc* nature of these studies and the relatively limited numbers do not support sub-group analyses, although the strong and consistent biological effects provide sufficient power for conclusions.

This study suggests that, in AD, the presence and reduction of Aβ-plaque pathology can be measured not only by Aβ specific biomarkers but certain phospho-tau biomarkers as well. The development of blood-based phospho-tau measures, like p-tau217 concentrations and ratios, offers an important opportunity to monitor the initial response to anti-Aβ-plaque therapies through repeated measures using non-invasive, more accessible techniques. Ongoing and future studies targeting tau pathology may clarify the associations between specific soluble biomarkers and NFTs and determine whether tau therapies could also be monitored with blood or CSF measures.

AUTHOR CONTRIBUTIONS

All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. E.M., N.B, R.J.B. contributed to the conception and design of the study; E.M., N.B, R.J.B, B.G., T.B., A.G., A.R., A.F., J.H., R.J.P., C.X., C.C., S.S., C.M., G.S., S.B., J.L., E.R., C.VD., S.G., R.H., M.M., J.C., P.C., B.B., K.S., H.S., J.L., M.J., J.R., D.W., Y.M., T.I., JH. L., JH. R., P.S., R.M., N.F., J.V., C.L., J.N., M.F., E.H., G.D., R.A., R.S., J.C.M., contributed to the acquisition and analysis of data; GW, YL, YC performed the statistical analyses; E.M., N.B, G.W., Y.L., Y.C., R.J.B. contributed to the drafting the text or preparing the figures; B.G., T.B., A.G., A.R., A.F., J.H., R.J.P., C.X., C.C., S.S., C.M., G.S., S.B., J.L., E.R., C.VD., S.G., R.H., M.M., J.C., P.C., B.B., K.S., H.S., J.L., M.J., J.R., D.W., Y.M., T.I., JH. L., JH. R., P.S., R.M., N.F., J.V., C.L., J.N., M.F., E.H., G.S.D., R.A., R.S., J.C.M., T.B., R.Y., J.R., C.K., L.I., A.D., C.SB., A.L., P.RN reviewed and edited the draft.

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CONFLICT OF INTEREST STATEMENT

There are several inventions that have been filed by Washington University for patents, including "Methods of diagnosing AD with phosphorylation changes" and "Methods to detect MTBR-tau isoforms and use". These intellectual properties owned by Washington University can be or are licensed and some licensing income may be distributed to Drs. Barthelemy, Bateman, McDade and other inventors. These intellectual properties being licensed by Washington University from C2N

and currently being utilized in our research have been reviewed by the Washington University COI and ICOI committees.

All co-inventors, including some lab members, the University, and Drs. Barthélemy, Bateman, McDade could receive part of the profits from any sales of these tests by C2N, which is in the process of licensing or has licensed some IP from the University. These activities have been reviewed by Washington University's (WU) Conflicts of Interest Review Committee in accordance with WU's Research Conflicts of Interest Policy and WU's Institutional Conflict of Interest Review Committee in accordance with WU's Institutional Conflict of Interest Policy.

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YL is the co-inventor of the technology "Novel Tau isoforms to predict onset of symptoms and dementia in Alzheimer disease" which is in the process of licensing by C2N. She may receive royalties related to the licensing agreement.

NCF reports consulting fees from Biogen, Eisai, Ionis, Lilly, Roche, and Siemens – all paid to UCL; he has served on a Data Safety Monitoring Board for Biogen; he acknowledges grant support from the Alzheimer Society, Alzheimer Research UK, Rosetrees Trust, the Sigrid Rausing Trust, the UK Dementia Research Institute and the UK NIHR UCLH Biomedical Research Centre.

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RJ P reports no competing interests directly relevant to this work.

JV served as a consultant for Lilly and Eisai, and received coverage for conference and travel expenses from Biogen, Eisai, the Alzheimer's Association, the Austrian Alzheimer's Society and the German Society of Nuclear Medicine.

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TLSB has received grants or contracts from Siemens paid to her institution; consulting fees from Biogen** ($5,000-10,000), Eli Lilly, Eisai** ($5,000-10,000), Bristol Myers Squibb, J&J, and Merck; payment for CME activity from Medscape, PeerView, and Neurology Today; and travel reimbursement from Cedars Sinai Medical Center, Hong Kong Neurological Association and the Alzheimer's Association. She reports the following patents planned, issued or pending: US patent 16/097, 457 (DIFFUSION BASIS SPECTRUM IMAGING (DBSI), A NOVEL DIFFUSION MRI METHOD USED TO QUANTIFY NEUROINFLAMMATION AND PREDICT ALZHEIMER'S DISEASE (AD) PROGRESSION), and US Patent 12,016,701 (Quantitative Differentiation of Tumor Heterogeneity Using Diffusion MR Imaging Data). She has participated in a Data Safety Monitoring Board or Advisory Board of Siemens and served as an external advisor for NIH-funded studies (no payments). She has served as the co-chair of ASNR Alzheimer's, ARIA and Dementia Study Group, and RSNA Quantitative Imaging Committee (QuIC) (all unpaid). She has served as a committee member of the American College of Radiology/ALZ NET imaging, NIH CNN Study Section Chair, and had a leadership or fiduciary role in the ACR Commission on Neurology (all unpaid). She has received technology transfer and precursors for radiopharmaceuticals from Avid Radiopharmaceuticals/Eli Lilly, LMI, and Lantheus, as well as a scanner loan from Hyperfine to her institution.

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Neuroscience, EISAI and Biogen, author fees from Thieme medical publishers and W. Kohlhammer GmbH medical publishers and is inventor in a patent "Oral Phenylbutyrate for Treatment of Human 4-Repeat Tauopathies" (PCT/EP2024/053388) filed by LMU Munich. In addition, he reports compensation for serving as chief medical officer for MODAG GmbH, is beneficiary of the phantom share program of MODAG GmbH and is inventor in a patent "Pharmaceutical Composition and Methods of Use" (EP 22 159 408.8) filed by MODAG GmbH, all activities outside the submitted work.

AG reports serving on Scientific Advisory Boards for: Genentech and Muna Therapeutics and as a consultant for: Merck, Biogen and Voyager Therapeutics. She reports royalties for: Taconic Biosciences, Athena Diagnostics

GW reports serving on a Data Safety Committee for Eli Lilly and Company and statistical consultant for Eisai inc. and Alector Inc.

MM reports no competing interests.

LI reports no competing interests.

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RSV has served in Advisory boards Meetings for Wave Life Sciences, Ionis, UCB, Prevail, Pfizer and Novo Nordisk and received personal fees for participating in educational activities from Roche Diagnostics and Neuroxpharma.

EDR Is an advisor for AGTC, DMC for Lilly, royalties on licensing to Genentech, owner of additional IP related to tau.

PCM reports no competing interests.

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SG reports activity as a scientific advisor to Alzheon, AmyriAD, Eisai Canada, Lilly Canada, NovoNordisk Canada, Enigma USA.

JCM reports no competing interests.

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AD reports no competing interests.

CS reports no competing interests.

RJB is Director of DIAN–TU and Principal Investigator of DIAN–TU-001. He receives research support from the NIA of the NIH, DIAN–TU trial pharmaceutical partner (Hoffman-La Roche Ltd), Alzheimer's Association, GHR Foundation, Anonymous Organization, DIAN–TU Pharma Consortium (Active: AbbVie, Biogen, BMS, Eisai, Eli Lilly & Co., Ionis, Janssen, Prothena, Roche/Genentech. Previous: Amgen, AstraZeneca, Forum, Mithridion, Novartis, Pfizer, Sanofi, United Neuroscience). He has been a scientific advisor for NAPA Advisory Council Biogen, F. Hoffman-La Roche/Genentech Ltd, UK Dementia Research Institute at University College London and Stanford University. He has been an invited speaker for Alzheimer's Association, Duke Margolis Alzheimer's Roundtable, BrightFocus Foundation, Tau Consortium, NAPA Advisory Council on Alzheimer's Research, CTAD, FBRI, Beeson, Adler Symposium and Fondazione Prada. R.J.B. is a co-founders of C2N Diagnostics and receive income from C2N Diagnostics for serving on the scientific advisory board. Washington University has equity ownership interest in C2N Diagnostics. R.J.B. is a co-inventors of the stable isotope labeling kinetics and blood plasma assay technology licensed by Washington University to C2N Diagnostics. Through these relationships, Washington University, R.J.B. is entitled to receive royalties and/or equity from the license agreement with C2N. Author disclosures are available in the supporting information.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study can be requested from DIAN at https://dian.wustl.edu/for-investigators/dian-observational-study-investigator-resources/ and Data access to DIAN-TU trial data will follow the policies of the DIAN-TU data access policy, which complies with the guidelines established by the Collaboration for Alzheimer Prevention. Patient-related data not included in the paper were generated as part of a clinical trial and may be subject to patient confidentiality. Any data and materials that can be shared will be released via a Dat/Material Sharing Agreement. A link to the DIAN-TU-001 trial data website request can be accessed via: https://dian.wustl.edu/for-investigators/diantu-investigator-resources/

CONSENT STATEMENT

The studies were conducted in accordance with the Declaration of Helsinki (version 7) and the International Conference on Harmonization and Good Clinical Practice guidelines and had ethics committee approval at each participating site. Participants provided written informed consent.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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