Biomarker and clinical correlations for amyloid targeting monoclonal antibody (mAb) treatment responses

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Background: Pathological features of Alzheimer disease include Amyloid plaques and neurofibrillary tangles. Clinical trials have demonstrated positive clinical outcomes for lecanemab, donanemab and aducanumab, specifically linking Amyloid PET lowering to clinical benefit. While not achieving clinical benefit bapineuzumab, gantenerumab and solanezumab added to and are in line with this correlation. A growing body of treatment response data is accumulating including clinical assessment, Amyloid PET, and fluid biomarker outcome data for aforementioned mAbs. The objectives of the present work were to: (i) extract and quantify treatment response effect sizes for amyloid targeting mAbs; (ii) explore quantitative relationships between different treatment responses across these mAbs.

Reference	Study/Arm Display Label	Duration & Subject Numbers (placebo/treatmen	AD stage (MMSE score for inclusion)	mAb, dose	Primary Efficacy Outcome(s)	Other Cognitive, Functional Measures	Biomarker/ Neuroimaging Outcomes	Extracted Data Sources
Salloway et al. N Engl J Med. 2014 January 23; 370(4): 322–333.	301-Low	78-weeks (493/315)	Mild/moderate (16-26)	Bapineuzumab, 0.5mg/kg	ADAS- Cog 11, DAD	NTB, CDR-SB, MMSE, DS	SUVR (PIB-PET), CSF ptau181, whole brain vMRI	Supplementary: Fig. S1, Table S2, Table S3
	301-High	78-weeks (493/307)	Mild/moderate (16-26)	Bapineuzumab, 1.0mg/kg	ADAS- Cog 11, DAD	NTB, CDR-SB, MMSE, DS	SUVR (PIB-PET), CSF ptau181, whole brain vMRI	
Salloway et al. N Engl J Med. 2014 January 23; 370(4): 322–333.	302	78-weeks (432/658)	Mild/moderate (16-26)	Bapineuzumab, 0.5mg/kg	ADAS- Cog 11, DAD	NTB, CDR-SB, MMSE, DS	SUVR (PIB-PET), CSF ptau181, whole brain vMRI	Supplementary: Fig. S1, Table S2, Table S3
Vandenberghe et al. Alzheimer's Research & Therapy 2016; 8:18	3000 pooled	78-weeks (328/508)	Mild/moderate (16-26)	Bapineuzumab, 0.5mg/kg	ADAS-Cog 11, DAD	CDR-SB, NTB, DS	SUVR (PIB-PET), plasma Abeta1-40, CSF ptau181, whole brain vMRI	Fig.1, Fig.2, Fig.3
				Bapineuzumab, 1.0mg/kg				
Vandenberghe et al. Alzheimer's Research & Therapy 2016;8:18	3001	78-weeks (431/650)	Mild/moderate (16-26)	Bapineuzumab, 0.5mg/kg	ADAS-Cog 11, DAD	CDR-SB, NTB, DS	SUVR (PIB-PET), plasma Abeta1-40, CSF ptau181, whole brain vMRI	Fig.1, Fig.2, Fig.3
Honig et al. N Engl J Med 2018;378:321-30	EXPEDITION3	80-weeks (1072/1057)	Mild (20-26)	Solanezumab, 400mg	ADAS-Cog 14	MMSE, ADCS-ADL, ADCS-iADL, CDR-SB, FAQ, iADRS, NPI	Plasma Abeta1-40 & Abeta1-42, CSF Abeta1-40 & Abeta1-42, CSF total tau, CSF ptau, hippocampal and whole brain vMRI, SUVR (18F-florbetapir-PET and flortaucipir-PET)	Fig.1, Fig.2, Table2, Supplementary: Fig. S1, Fig. S2
Ostrowitzki et al. Alzheimer's Research & Therapy 2017;9:95	SCARLET-Low	104-weeks (266/271)	Prodromal, MMSE (> 23)	Gantenerumab, 105mg	CDR-SB	ADAS-Cog-13, MMSE, CANTAB, FCSRT, NPI-Q, FAQ	SUVR (18F-florbetapir-PET), hippocampal and whole brain vMRI, CSF Abeta1-42, CSF total tau, CSF ptau181, CSF Neurogranin, plasma ptau181	Fig.1, Table 2, Fig. 2, Fig. 3, Fig. 4, Poster AAIC 2022
	SCARLET-High	104-weeks (266/260)		Gantenerumab, 225mg				
Van Dyck et al. N Engl J Med 2023; 388:9-21	CLARITY	78-weeks (857/859)	Mild (22-30)	Lecanemab, 10mg/bi-weekly	CDR-SB	ADAS-Cog14, ADCOMS, ADCS-MCI-ADL, MMSE	Centiloids (Florbetapir, Florbetaben, or Flutemetamol), CSF Abeta1-40 & Abeta1-42, CSF Abeta1-42 to 1-40 ratio, CFS total tau, CSF ptau181, CSF Neurogranin, CSF NfL, plasma Abeta1-42 to 1-40 ratio, plasma ptau181, plasma GFAP, plasma NfL, vMRI, tau-PET	Table 2, Fig. 2, Poster CTAD-2022
Swanson et al. Alzheimer's Research & Therapy 2021;13:80	201-10mg bi-weekly	78-weeks (238/152)	Early AD, MCI or Mild (>22)	Lecanemab, 10mg/kg bi-weekly	ADCOMS	ADAS-Cog 14, CDR-SB, MMSE	SUVR (18F-florbetapir-PET), vMRI, CSF Abeta1-42, CSF ptau181, CSF total tau, CSF Neurogranin, CSF NfL	Fig. 2, Fig. 3, Fig. 5.
Haberlein et al. J Prev Alz Dis 2022;2(9):197-210	EMERGE-Low	78-weeks (548/543)	Early AD, MCI or Mild (24-30)	Aducanumab 6mg/kg	CDR-SB	MMSE, ADAS-Cog13, ADCS-MCI-ADL, NPI	SUVR (18F-florbetapir-PET), SUVR (tau-PET 18F-NK-6240), CSF total tau, CSF ptau181, CSF Abeta1-42, plasma ptau181	Table 1, Fig. 2, Table 2
	EMERGE-High	78-weeks (548/547)		Aducanumab 10mg/kg				
Haberlein et al. J Prev Alz Dis 2022;2(9):197-210	ENGAGE-Low	78-weeks (545/547)	Early AD, MCI or Mild (24-30)	Aducanumab 6mg/kg	CDR-SB	MMSE, ADAS-Cog13, ADCS-MCI-ADL, NPI	SUVR (18F-florbetapir-PET), SUVR (tau-PET 18F-NK-6240), CSF total tau, CSF ptau181, CSF Abeta1-42, plasma ptau181	Table 1, Fig. 2, Table 2
	ENGAGE-High	78-weeks (545/555)		Aducanumab 10mg/kg				
Mintun et al. N Engl J Med 2021; 384:1691-1704, Pontecorvo et al. JAMA Neurol. 2022;79(12):1250-1259	TRAILBLAZER	76-weeks (126/131)	Mild/moderate (20-28)	Donanemab 1400mg	iADRS	CDR-SB, ADAS-Cog13, ADCS-iADL, MMSE	SUVR (18F-florbetapir-PET), SUVR (tau-PET flortaucipir), vMRI, plasma ptau217, plasma Abeta1-42 to 1-40 ratio, plasma GFAP, plasma NfL	Mintun et al. Fig.1, Fig.3 Pontecorvo, Fig. 2, Supplementary: eFig. 3
Sims et al. JAMA. 2023 Aug 8;330(6):512-527	TRAILBLAZER-ALZ 2	76-weeks (876/860)	Early AD, MCI or Mild (20-28)	Donanemab 1400mg	iADRS	CDR-SB, ADAS-Cog13, ADCS-iADL, MMSE	SUVR (18F-florbetapir-PET), SUVR (tau-PET flortaucipir), vMRI, plasma ptau217,	Fig.2, Fig.3

Table 1: Overview of clinical studies for which assessment data was extracted from the scientific literature and public domain presentations and the sources of extracted data.

Methods: A prior meta-analysis of amyloid targeting mAbs was updated [Avgerinos K.I. et al. Ageing Research Reviews 2021;68:101339] to include donanemab and lecanemab clinical trials. Table 1 provides an overview of the clinical trials and corresponding mAbs included in the present analysis. Public domain documents reporting clinical trial treatment responses from these studies were sourced and response data for placebo and active treatment arms extracted including corresponding variability measures for the following assessment measures: (i) ADAS-Cog & CDR-SB clinical endpoints; (ii) Amyloid PET; (iii) the plasma fluid biomarkers Abeta1-40, Abeta1-42, Abeta1-42/Abeta1-40 ratio, pTau181, pTau217, Total Tau, GFAP, NfL & Neurogranin and (iv) the CSF fluid biomarkers Abeta1-40, Abeta1-42, Abeta1-42/Abeta1-40 ratio, pTau181, pTau217, Total Tau, NfL & Neurogranin. Treatment response effect sizes were calculated as the difference between active and placebo arm changes from baseline (CBL) standardized by the estimated pooled standard deviation for these CBLs, i.e., Hedge's g, across all times for which data was available. To explore quantitative relationships between treatment responses across these mAbs, pairwise linear correlations between End-of-Study (EoS) response effect sizes for assessment measures reported for at least 3 mAbs, i.e., ADAS-Cog, CDR-SB, Amyloid PET, plasma pTau181, CSF pTau181, CSF Total Tau & CSF Abeta1-42, were calculated and graphed. For all such pairings, Pearson's correlation coefficients and corresponding p-values were calculated. A predefined p-value of <0.05 was deemed statistically significant. To explore how treatment responses developed with time, longitudinal data and estimated effect sizes were explored graphically for the two mAbs with the largest reported clinical treatment effect sizes, i.e., lecanemab & donanemab. Specifically, for these mAbs, longitudinal treatment effect sizes were plotted for the ADAS-Cog, CDR-SB, Amyloid PET, plasma pTau181 (only reported for lecanemab) and pTau217 (only reported for donanemab), responses. Longitudinal profiles were subsequently normalized to compare temporal profiles across the different responses.

Results: **Relationship between Amyloid PET and fluid biomarker effect sizes:** Linear correlations of Amyloid PET effect sizes versus corresponding fluid biomarker effect sizes were strong for CSF pTau181 (r=0.79, p=0.002), very moderate for CSF Abeta1-42 (r=-0.58, p= 0.129), moderate for plasma pTau181 (r=0.37, p=0.42) & very weak for CSF Total Tau (r=-0.08, p=0.863) (Figure 1).

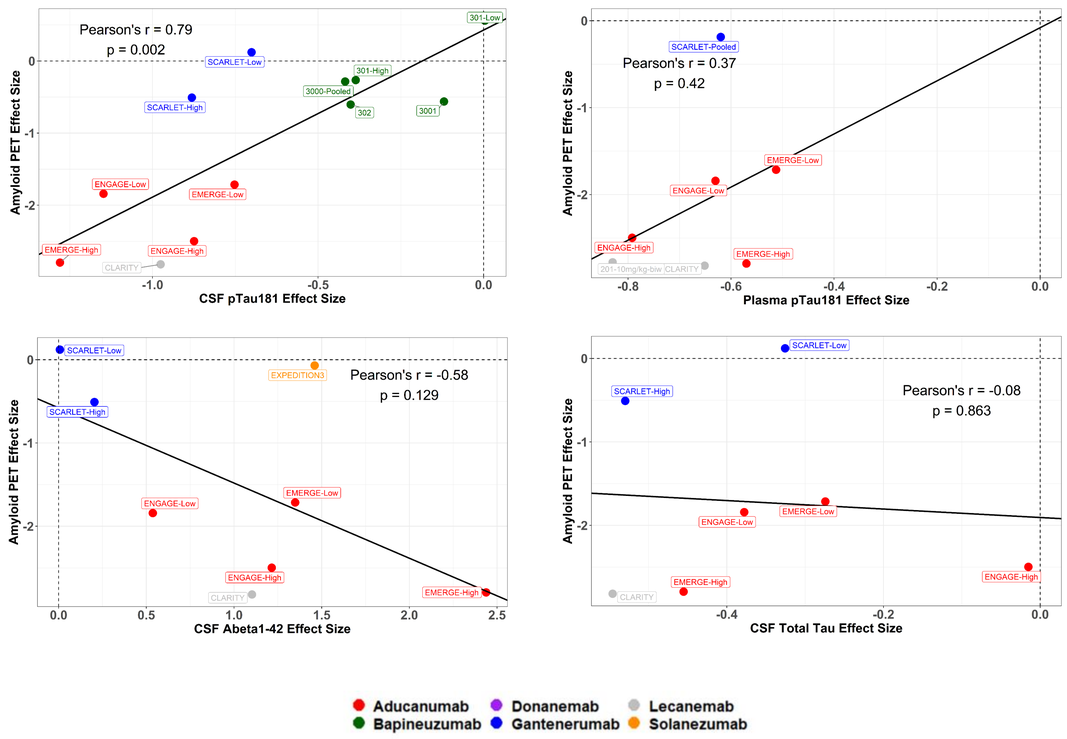

Figure 1: Correlation plots between EoS fluid biomarkers effect sizes (top left: CSF pTau181; top right: plasma pTau181; bottom left: CSF Abeta1-42; bottom right: CSF Total Tau) and corresponding EoS Amyloid PET effect sizes. Black solid line represents best linear fit. Two-sided p-value against null hypothesis of no linear correlation reported.

Relationship between clinical assessment and biomarker effect sizes: Linear correlations between ADAS-Cog effect sizes versus corresponding biomarker effect sizes were strong for Amyloid PET (r=0.71, p<0.001), CSF Abeta1-42 (r=-0.69, p= 0.059), CSF pTau181 (r=0.7, p=0.011), moderate for plasma pTau181 (r=0.41, p=0.358) & weak for CSF Total Tau (r=0.26, p=0.574). Linear correlations of CDR-SB effect sizes versus corresponding biomarker effect sizes were very strong for Amyloid PET (r=0.81, p<0.001), strong for CSF Abeta1-42 (r=-0.74, p= 0.037), very moderate for CSF pTau181 (r=0.47, p=0.125) and only weak for CSF Total Tau (r=0.32, p=0.479) and very weak for plasma pTau181 (r=-0.08, p=0.863) (Figure 2). Note that all CSF Total Tau correlation plots are excluded from Figure 2.

Relationship between fluid biomarker effect sizes: No linear correlations between fluid biomarker effect sizes (plasma pTau181, CSF pTau181, CSF Total Tau, CSF Abeta1-42) were statistically significant. All correlations of CSF Total Tau with the other three biomarkers were weak or very weak, except for plasma pTau181 (r=-0.55, p=0.258). The correlation between CSF pTau181 and CSF Abeta1-42 was moderate (r=-0.58, p=0.169). A weak correlation was apparent between plasma pTau181 and CSF Abeta1-42 (r=0.22, p=0.681) and a very weak correlation between CSF pTau181 and plasma pTau181 (r=-0.07, p=0.901).

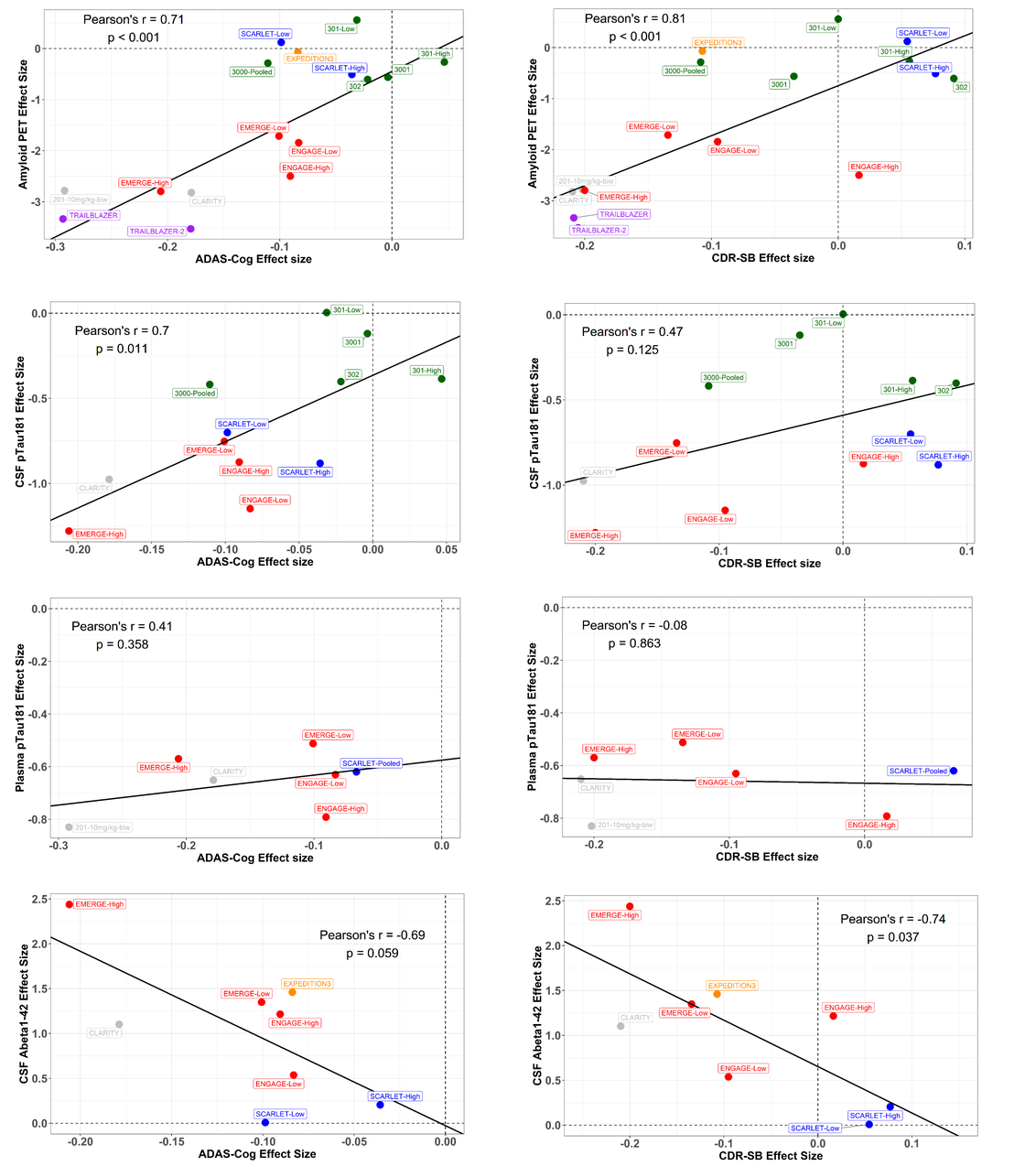

Figure 2: Correlation plots between EoS clinical scale effect sizes (left column: ADAS-Cog; right column: CDR-SB) and corresponding EoS Amyloid PET and fluid biomarkers effect sizes (top to bottom: Amyloid PET, CSF pTau181, plasma pTau181, CSF Abeta1-42). Plots for CSF Total Tau omitted as all correlations were weak or very weak. Black solid line represents best linear fit. Two-sided p-value against null hypothesis of no linear correlation is reported.

Dynamics of Amyloid PET and pTau lowering: Lecanemab and donanemab demonstrate large effect sizes for Amyloid PET and pTau lowering relative to those for the ADAS-cog and CDR-SB endpoints. For both mAbs, the time courses of Amyloid PET and plasma pTau lowering were well described by mono-exponential declines. Estimated donanemab treatment effect sizes for plasma pTau217 were approximately twice those of lecanemab treatment effect sizes for plasma pTau181 at all time points for which both were assessed. TRAILBLAZER-ALZ2 individual longitudinal effects sizes over time are shown for ADAS-Cog, CDR-SB, Amyloid PET and plasma pTau217 treatment responses. Note the dramatic difference in effect sizes for these assessments across all assessment times (Figure 3, left panel). Interestingly, when estimated TRAILBLAZER-ALZ2 individual longitudinal effect sizes are normalized to compare treatment effect size temporal profiles across all measures (Figure 3, right panel), they show similar non-linear time profiles with no major time lag between biomarker effects (Amyloid PET/pTau) and clinical effects (ADAS-Cog/CDR-SB). Specifically, at 6-months, 68%, 76%, 72% and 74% of corresponding maximal treatment effects were already apparent for the ADAS-Cog, CDR-SB, Amyloid PET and plasma pTau181 responses, respectively. By 12-months, these respective normalized effect sizes were 100%, 100%, 91% and 96%, respectively, and at 18-months, 88%, 91%, 100% and 100% (Figure 3, right panel).

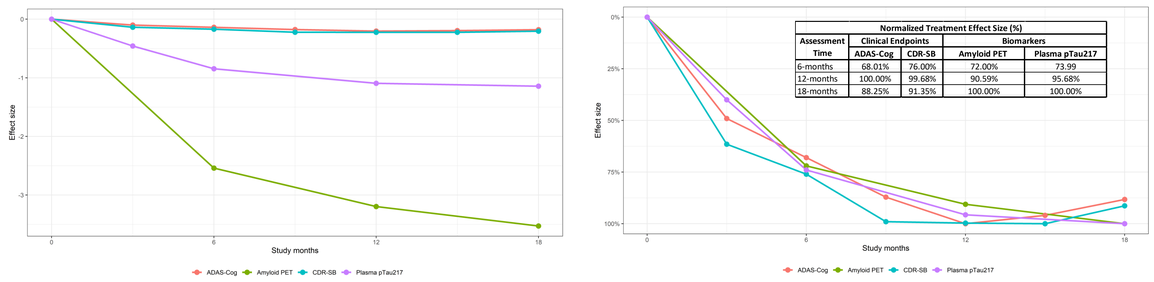

Figure 3: TRAILBLAZER-ALZ2 (donanemab) longitudinal effect sizes for ADAS-Cog, CDR-SB, Amyloid PET and plasma pTau217 treatment responses (left). Corresponding individually normalized longitudinal effect sizes (right).

Conclusion: There is a strong statistically significant correlation between clinical benefit and corresponding Amyloid PET, CSF Abeta1-42 and CSF pTau181 effect sizes. Amyloid PET effect sizes were strongly correlated with corresponding CSF pTau181 effect sizes. This confirms the strong utility of biomarkers in AD drug development and in this case specifically the conversation from a target related pharmacodynamic marker (Amyloid PET) to a downstream marker (specifically, pTau181) demonstrating impact on disease modification in addition to clinical response.