Surrogate endpoint in Alzheimer's disease – Regulatory flexibility to accelerate drug development

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Disclaimer

Tianle Chen is an employee of Kura Oncology and holds stock and/or stock options. This presentation was based on the work when Tianle Chen was an employee of Biogen before joining Kura Oncology.

Outline

- Background of surrogate endpoint
  - Definition, rationale and examples
  - Regulatory positions
- Reduction in Aβ as a surrogate endpoint in Alzheimer's disease
  - Amyloid cascade hypothesis
  - Milestones of establishing reduction in Aβ plaques as a surrogate endpoint in AD
  - Statistical validation of surrogacy
- Reflections

What is a surrogate endpoint?

- A marker, such as a laboratory measurement, radiographic image, physical sign, or other measure, that is not itself a direct measurement of clinical benefit but is known to predict clinical benefit or is reasonably likely to predict clinical benefit

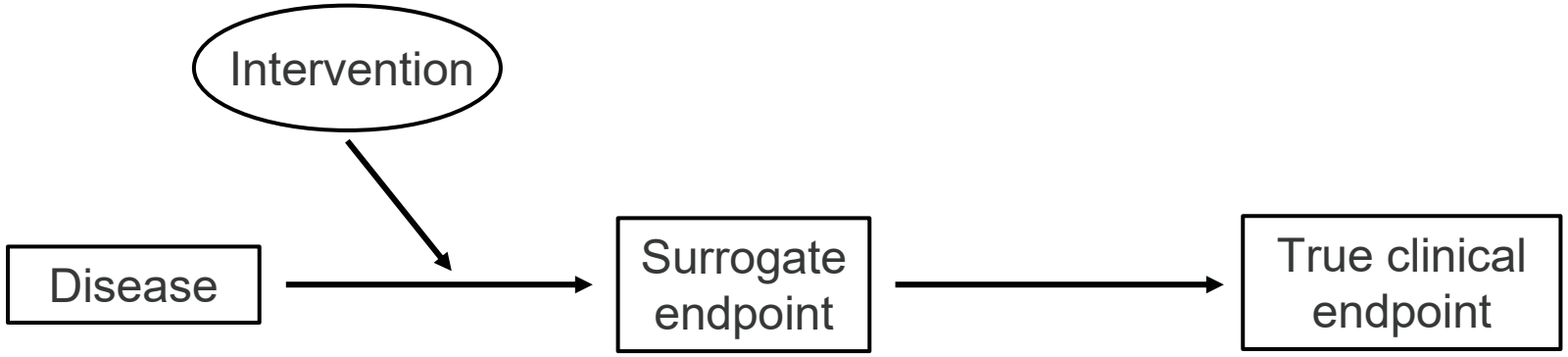
Examples of surrogate endpoints

- Tumor shrinkage and progression free survival for cancers
- Hemoglobin A1c (HbA1c) reduction for diabetes mellitus
- HIV-RNA reduction for HIV
- Blood pressure reduction for stroke prevention

Why do we need surrogate endpoints?

- Shorten study duration
- Reduce sample size
- Lower cost
- Accelerate treatment decision making
- Accelerate drug development

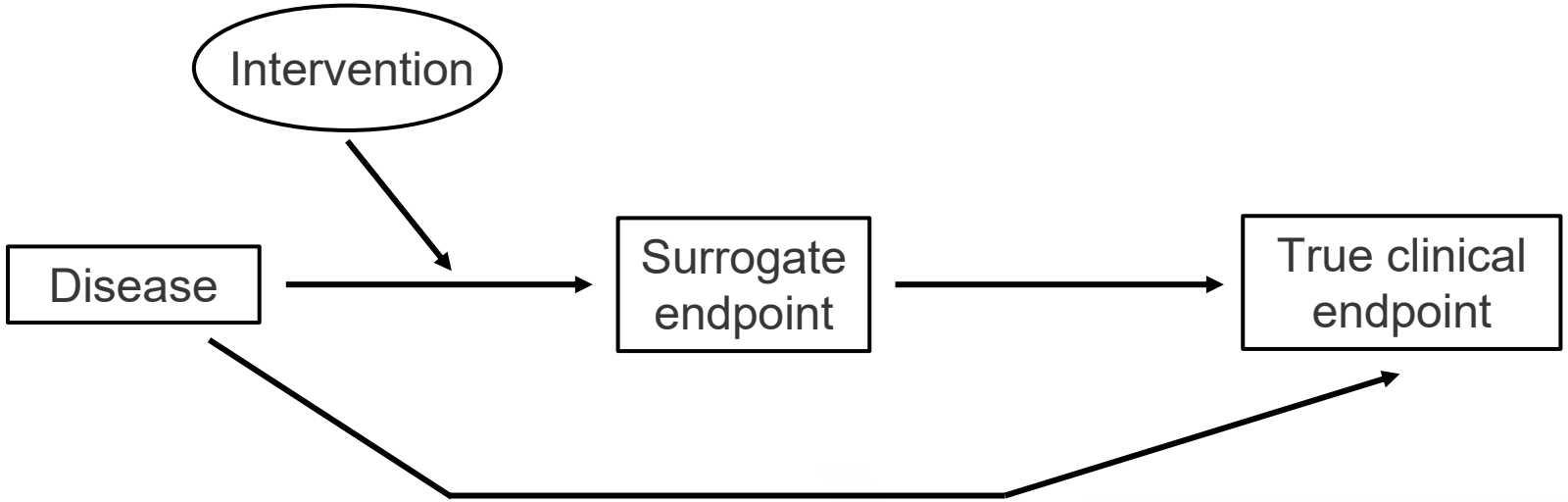
Potential pathways for surrogate endpoint[1]



- Hypothetical perfect case for surrogacy:
  - The surrogate endpoint is on the sole casual pathway of the disease progression
  - Drug effect is fully mediated through the surrogate endpoint

[1]Fleming TR and DeMets DL, Annals of Internal Medicine 1996, 125: 605-613

Potential pathways for surrogate endpoint[1]



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- Other disease pathways could exist, and the surrogate endpoint only partially mediates the drug effect.

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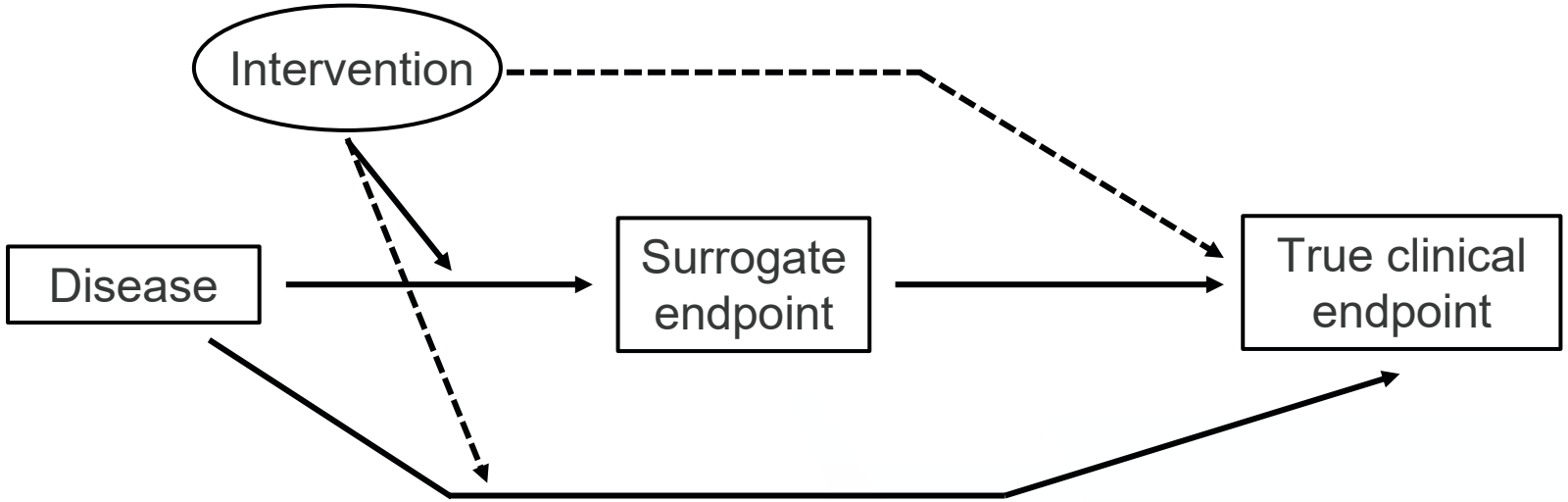
Potential pathways for surrogate endpoint[1]



- Hypothetical perfect case for surrogacy:
  - The surrogate endpoint is on the sole casual pathway of the disease progression
  - Drug effect is fully mediated through the surrogate endpoint
- Other disease pathways could exist, and the surrogate endpoint only partially mediates the drug effect.
- Intervention may also affect the true clinical endpoint by unintended mechanism of action independent of the disease process.

[1]Fleming TR and DeMets DL, Annals of Internal Medicine 1996, 125: 605-613

3 levels of surrogate endpoints defined by FDA

Level of Clinical Validation	Feature	Type of Approval	Additional Evidence
Validated	Known to predict clinical benefit with a clear mechanistic rationale	Traditional	No additional efficacy information is required pre- or post- approval
Reasonably likely	Reasonably likely to predict a drug's intended clinical benefit	Accelerated	Additional trial data assessing the effect of the intervention on the clinical benefit of endpoint of interest needs to be collected in the post-marketing setting to verify effect
Candidate	Still under evaluation as there is insufficient evidence	N/A	

(FD&C Act, section 507(e)(9)); BEST (Biomarkers, Endpoints, and other Tools) Resource, FDA-NIH Biomarker Working Group, 2021

Expedited approval pathways related to surrogate endpoints[1]

	US FDA
Pathway	Accelerated approval program
Start	1992
Criteria	Drugs treating serious conditions and filling an unmet medical need
Related to surrogate endpoint	Allow for earlier approval based on a reasonably likely surrogate endpoint

[1]Chen T, Tian Y and Millen B, WIREs Computational Statistics 2024, 17:e70014. PMDA = Pharmaceuticals and Medical Devices Agency; NMPA = National Medical Products Administration; EMA = European Medicines Agency

Expedited approval pathways related to surrogate endpoints[1]

	US FDA	Japan PMDA	China NMPA
Pathway	Accelerated approval program	Conditional accelerated approval system	Conditional approval procedure
Start	1992	2017	2020
Criteria	Drugs treating serious conditions and filling an unmet medical need	Drugs corresponding to any of the following: (1) Serious diseases, (2) High medical usefulness, (3) A confirmatory clinical study considered to be difficult to conduct, (4) A certain level of efficacy and safety is demonstrated by the clinical studies	Drugs used for treating serious life-threatening diseases for which no effective treatment is available and for some other public health emergencies
Related to surrogate endpoint	Allow for earlier approval based on a reasonably likely surrogate endpoint	Results of clinical trials other than the confirmatory clinical trials – for example, the results of a pharmacodynamic endpoint (not necessarily an established surrogate endpoint) or the results of an interim analysis using surrogate endpoints in a confirmatory clinical study – may be used to support the approval in this system.	Conditional approval may be granted based on a surrogate endpoint that is very likely to predict clinical benefit, an intermediate clinical endpoint, early-phase clinical data, or interim analysis results from phase 3 clinical studies.

[1]Chen T, Tian Y and Millen B, WIREs Computational Statistics 2024, 17:e70014. PMDA = Pharmaceuticals and Medical Devices Agency; NMPA = National Medical Products Administration; EMA = European Medicines Agency

Expedited approval pathways related to surrogate endpoints[1]

	US FDA	Japan PMDA	China NMPA	EMA*
Pathway	Accelerated approval program	Conditional accelerated approval system	Conditional approval procedure	Conditional marketing authorisation pathway
Start	1992	2017	2020	2006
Criteria	Drugs treating serious conditions and filling an unmet medical need	Drugs corresponding to any of the following: (1) Serious diseases, (2) High medical usefulness, (3) A confirmatory clinical study considered to be difficult to conduct, (4) A certain level of efficacy and safety is demonstrated by the clinical studies	Drugs used for treating serious life-threatening diseases for which no effective treatment is available and for some other public health emergencies	Drugs intended for treating, preventing or diagnosing seriously debilitating or life-threatening diseases
Related to surrogate endpoint	Allow for earlier approval based on a reasonably likely surrogate endpoint	Results of clinical trials other than the confirmatory clinical trials – for example, the results of a pharmacodynamic endpoint (not necessarily an established surrogate endpoint) or the results of an interim analysis using surrogate endpoints in a confirmatory clinical study – may be used to support the approval in this system.	Conditional approval may be granted based on a surrogate endpoint that is very likely to predict clinical benefit, an intermediate clinical endpoint, early-phase clinical data, or interim analysis results from phase 3 clinical studies.	May be granted on less comprehensive clinical data than normally required. The concept of surrogate endpoints that are reasonably likely to predict clinical benefit **does not exist** in the EU regulatory context.

*Listed just to show its difference versus other regulatory agencies.

[1]Chen T, Tian Y and Millen B, WIREs Computational Statistics 2024, 17:e70014. PMDA = Pharmaceuticals and Medical Devices Agency; NMPA = National Medical Products Administration; EMA = European Medicines Agency

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Related to surrogate endpoint	Allow for earlier approval based on a reasonably likely surrogate endpoint	Results of clinical trials other than the confirmatory clinical trials – for example, the results of a pharmacodynamic endpoint (not necessarily an established surrogate endpoint) or the results of an interim analysis using surrogate endpoints in a confirmatory clinical study – may be used to support the approval in this system.	Conditional approval may be granted based on a surrogate endpoint that is very likely to predict clinical benefit, an intermediate clinical endpoint, early-phase clinical data, or interim analysis results from phase 3 clinical studies.	May be on less compr clinical data than equired. Th of surrogate er at are r likely to predict cl nefit **does not exist** in the EU regulatory context.

Not available

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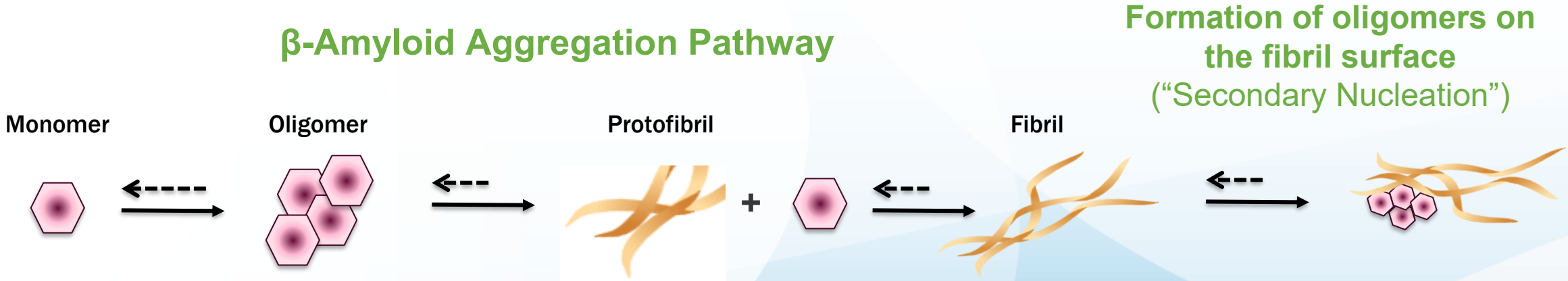
Alzheimer's disease and amyloid cascade hypothesis

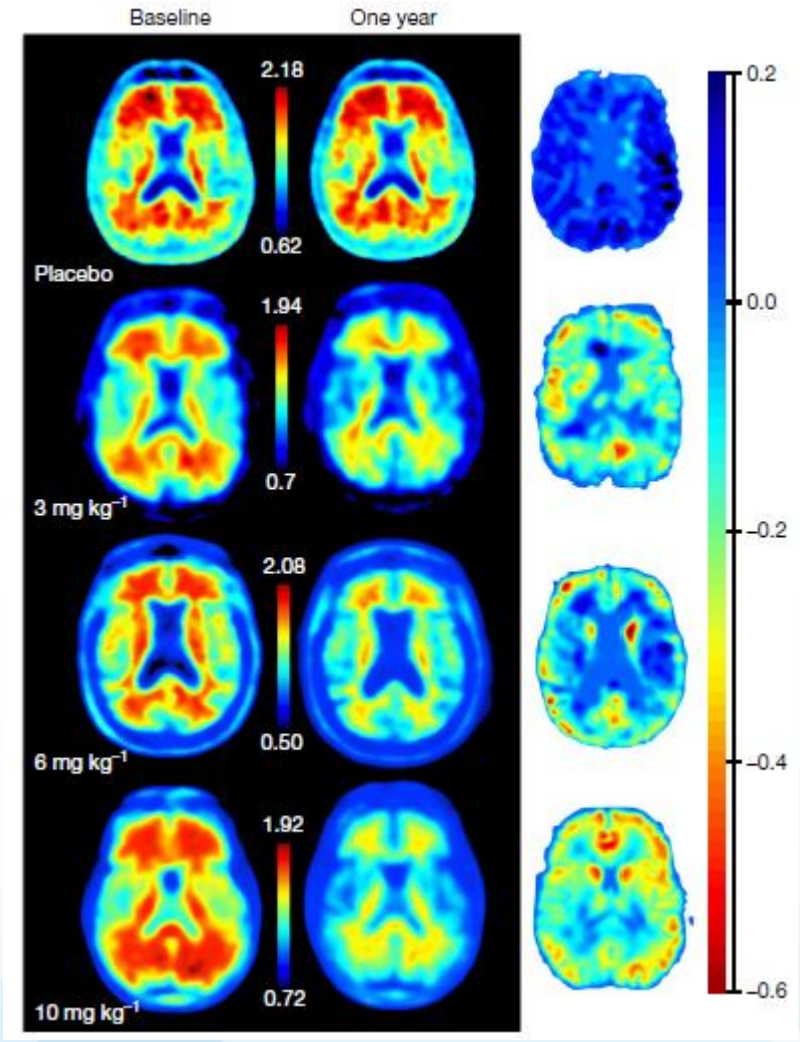
- Alzheimer's disease is a progressive neurodegenerative disorder characterized by insidious and unrelenting cognitive and functional decline.

- Amyloid cascade hypothesis – the driving force behind the disease process is the accumulation of Aβ resulting from an imbalance between Aβ production and Aβ clearance in the brain



Amyloid PET to measure Aβ

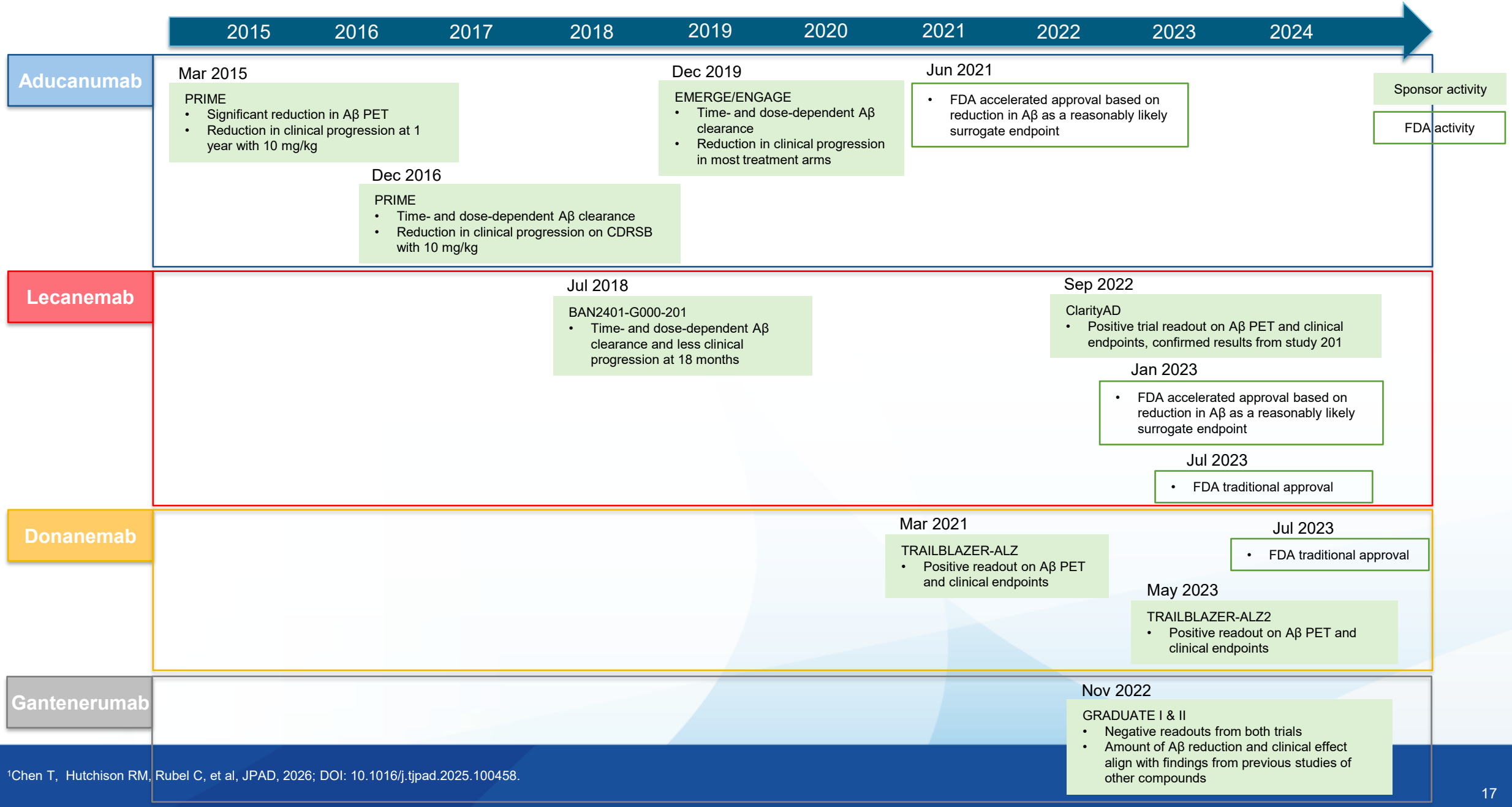
- Amyloid PET imaging was used to provide:
  - Qualitative assessment (visual interpretation) of brain Aβ plaque at screening
  - Quantitative assessment of the effect of aducanumab on brain Aβ plaque longitudinally
- Centiloid, a standardized scale on amyloid PET
  - Standardize amyloid results across ligands and pipelines
  - The default scale to use now



Sevigny J, *et al*. Nature 2016, 537: 50-56

PET = positron emission tomography

Milestones of establishing reduction in Aβ plaques as a surrogate endpoint in AD[1]



[1]Chen T, Hutchison RM, Rubel C, et al, JPAD, 2026; DOI: 10.1016/j.tjpad.2025.100458.

Establishing reduction in Aβ plaques as a surrogate endpoint in AD[1]

- Several second-generation compounds with similar mechanism were in their phase 2/3 stages in the past decade, including
  - Aducanumab
  - Lecanemab
  - Donanemab
  - Gantenerumab

- Reduction in Aβ plaques became a surrogate endpoint for accelerated approval upon the approval of Aducanumab in 2021

- Emerging data after the 1st approval further support the surrogacy

- The data from all 4 compounds contributed to the statistical validation of this surrogate endpoint.

[1]Chen T, Hutchison RM, Rubel C, et al, JPAD, 2026; DOI: 10.1016/j.tjpad.2025.100458.

Statistical validation of surrogate endpoints[1]

- Prentice criterion and proportion of treatment effect explained
- Causal inference approaches
- Correlation-based approaches
  - Individual-level correlation
  - Treatment group-level correlation
- Meta-analytical approach & surrogate threshold effect

[1]Chen T, Tian Y and Millen B, WIREs Computational Statistics 2024, 17:e70014

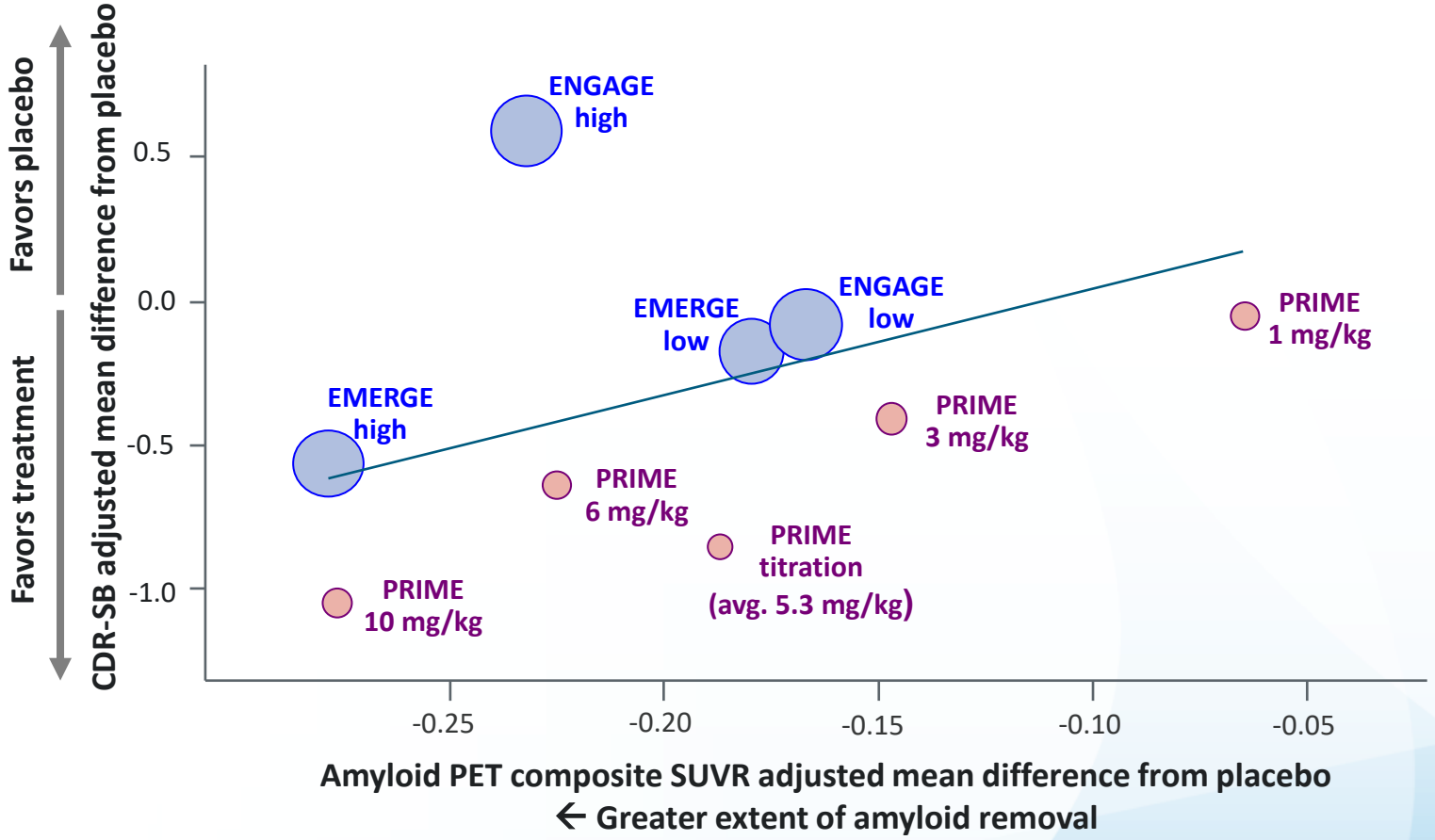
Statistical approaches most relevant to the surrogacy of Aβ[1,2]

- Treatment group-level correlation
  - Leverages the fundamental aspects of randomized placebo-controlled trials:
    - Directly associate the treatment benefit of biomarker with the treatment benefit of clinical
    - Individual heterogeneity addressed by randomization and the use of model-adjusted group means.
  - Instrumental in Alzheimer's disease given the emerging data from multiple clinical trials and the use of centiloid scale, which allowed cross-program comparison.
  - Require a lot of data from randomized clinical trials with a wide range of clinical effects

- Other statistical approaches used as supportive evidence

[1]Chen T, Hutchison RM, Rubel C, et al, JPAD, 2024; 5(11):1228-1240. [2]Chen T, Hutchison RM, Rubel C, et al, JPAD, 2026; DOI: 10.1016/j.tjpad.2025.100458.

Treatment Group-Level Correlation – Aducanumab Studies[1]

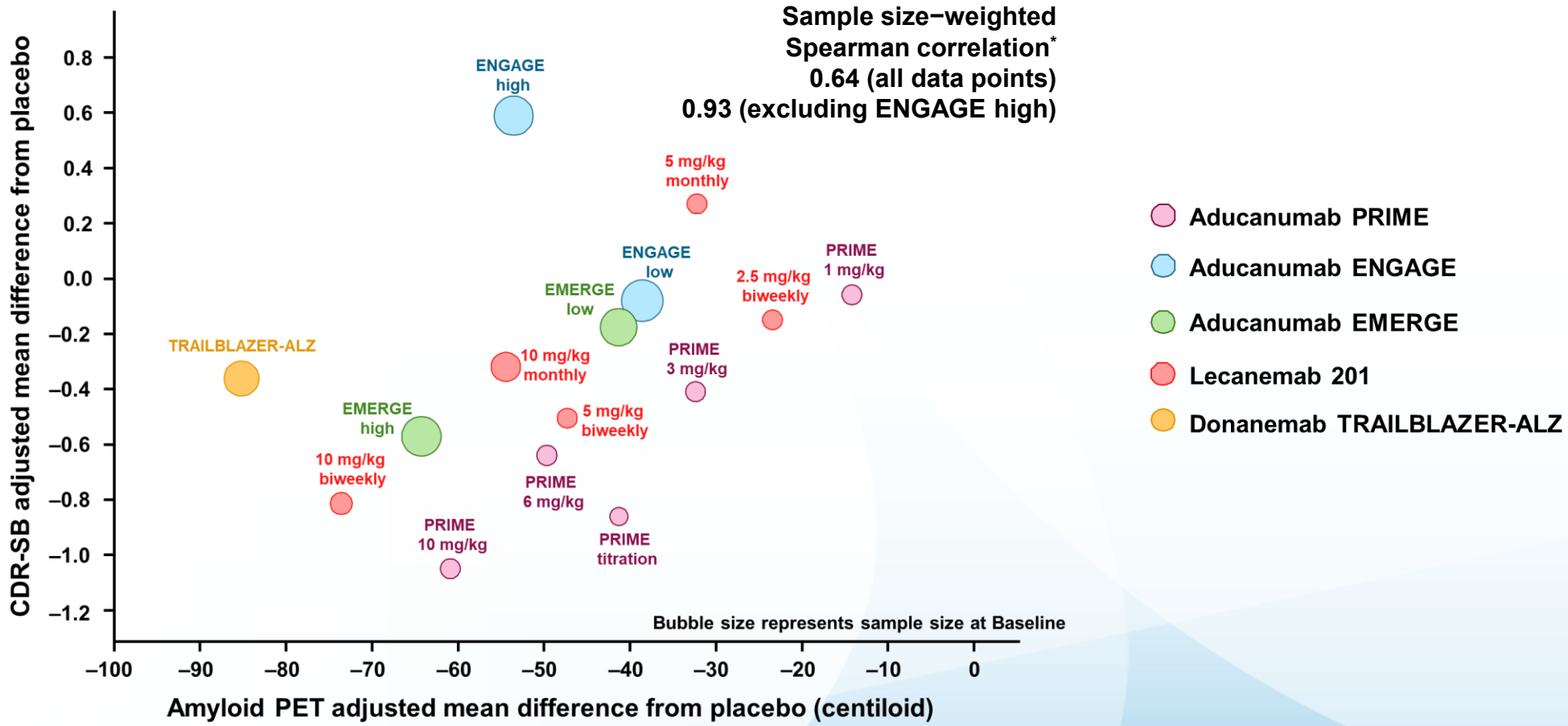


Sample-size weighted Spearman correlation	0.47 (all data points) 0.94 (excluding ENGAGE high)

- Bubble size represents sample size at baseline.
- Sample size weighted regression line using Study PRIME, ENGAGE [low dose] and EMERGE data

[1]Chen T, et al, data presented at BASS XXX 2023. Aβ=amyloid beta; CDR-SB=Clinical Dementia Rating Scale-Sum of Boxes; PET=positron emission tomography; SUVR=standardized value uptake ratio

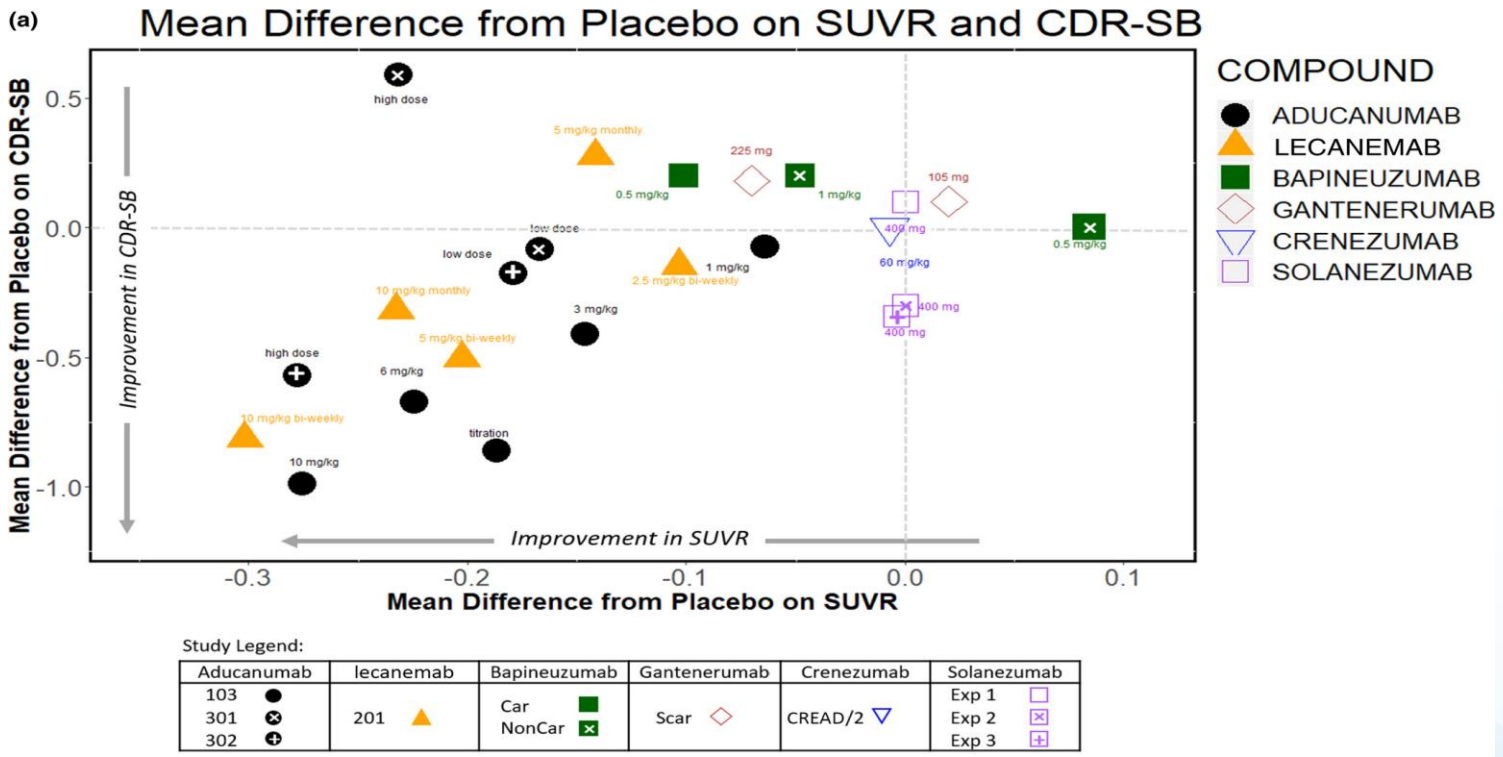
Treatment Group-Level Correlation – Second generation Anti-Aβ Drugs (at the time of accelerated approval for Aducanumab)[1]



*Sample-size weighted partial Spearman correlation adjusting for study indicator of Aducanumab PRIME, Aducanumab phase 3, Donanemab, and Lecanemab. Sample size and clinical results are based on the (sub)population with amyloid PET assessments.

[1]Chen T, Hutchison RM, Rubel C, et al, JPAD, 2024; 5(11):1228-1240. Aβ = amyloid beta; PET = positron emission tomography; CDR-SB = Clinical Dementia Rating–Sum of Boxes

Treatment Group-Level Correlation – FDA analysis[1]



Study Legend:

Aducanumab	lecanemab	Bapineuzumab	Gantenerumab	Crenezumab	Solanezumab
103 ●	201 ▲	Car ■	Scar ◇	CREAD/2 ▽	Exp 1 □
301 ⊗		NonCar ⊠			Exp 2 ⊠
302 ⊕					Exp 3 ⊞

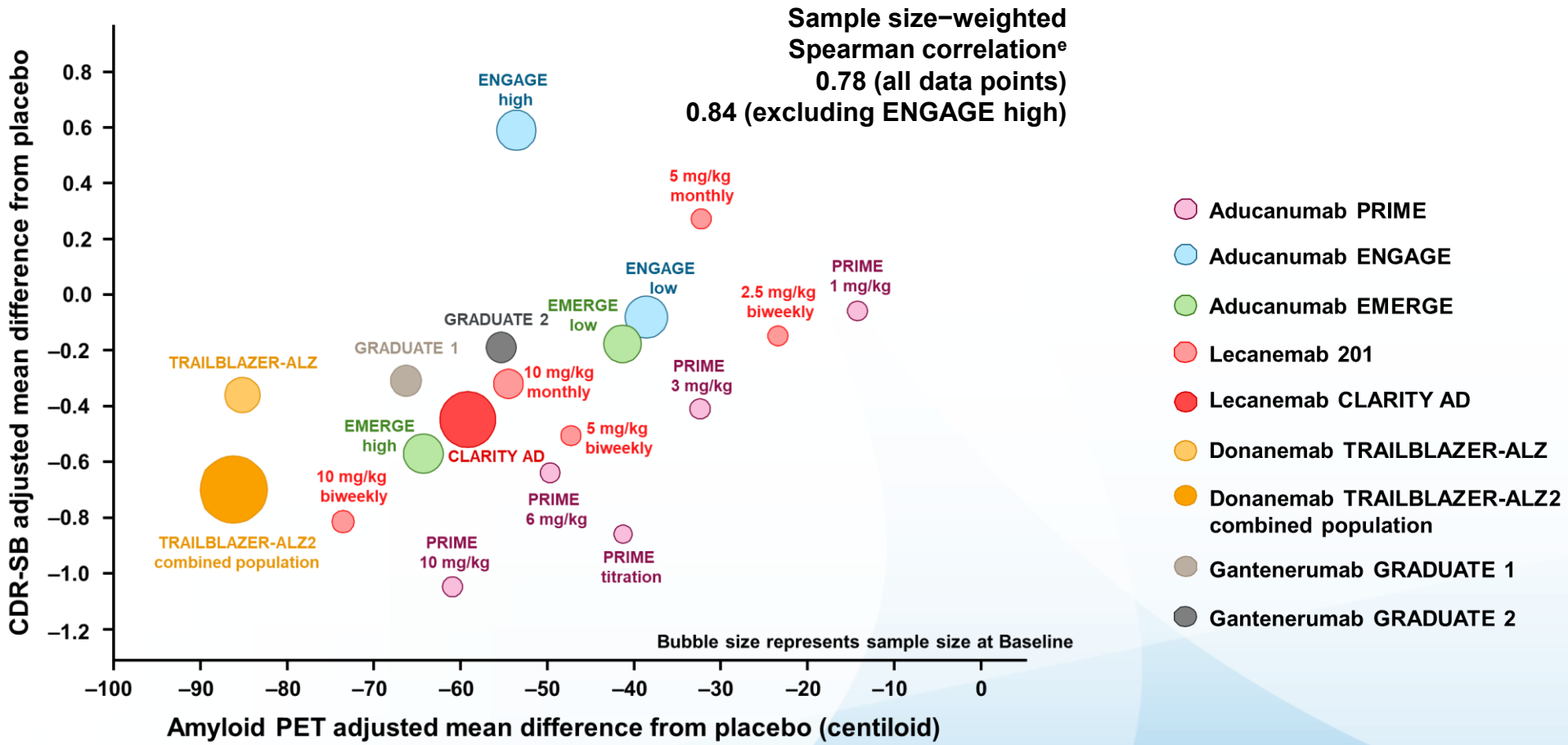
Notes:

[1] Mean baseline-corrected, placebo-adjusted values used to allow for cross-program comparison

[2] Donanemab also shows similar results in centiloids (CL)

[1]Zhu H, Mehta M, Huang SM and Wang Y. Clinical Pharmacology & Therapeutics 2022. 111(4): 728-731. Aβ=amyloid beta; CDR-SB=Clinical Dementia Rating scale Sum of Boxes; PET=positron emission tomography; SUVR=standardized value uptake ratio

Treatment Group-Level Correlation – Second generation Anti-Aβ Drugs (with read-outs from more trials)[1]



*Sample-size weighted partial Spearman correlation adjusting for study indicator of Aducanumab PRIME, Aducanumab phase 3, Donanemab, Lecanemab and Gantenerumab. Sample size and clinical results are based on the (sub)population with amyloid PET assessments, except for Lecanemab CLARITY AD and Gantenerumab GRADUATE 1 and 2 where ITT clinical results were used.

[1]Chen T, Hutchison RM, Rubel C, et al, JPAD, 2024; 5(11):1228-1240. Aβ = amyloid beta; PET = positron emission tomography; CDR-SB = Clinical Dementia Rating–Sum of Boxes

Reflections from Alzheimer's disease example

- Disease modifying therapy for AD was made available to patients 2 years ahead of the traditional approval based on a surrogate endpoint via the FDA accelerated approval pathway.
- Treatment group-level correlation analysis is an appropriate way for validating surrogate endpoint. It is instrumental in Alzheimer's disease given the emerging data from multiple clinical trials and the use of a standardized scale for the surrogate endpoint, which allowed cross-program comparison.
- Different disease areas and biomarkers have distinct features. Careful considerations are required to identify both the best regulatory pathway and the appropriate statistical approaches for establishing and validating the surrogate endpoint in each case.
- Surrogate endpoints have constantly been a challenging and controversial area. Early engagement with FDA and other regulatory agencies is highly recommended.