

VIEWPOINT

I-SPY 2 Breast Cancer Trial as a Model for Innovation in Alzheimer Disease Therapies

Mindi F. Messmer, BS
Program for Regulatory Science & Medicine, Georgetown University, Washington, DC; and VistaNova Consulting, Rye, New Hampshire.

Erin E. Wilhelm, MPH
Program for Regulatory Science & Medicine, Georgetown University, Washington, DC; and Department of Neurology, Georgetown University, Washington, DC.

Ira Shoulson, MD
Program for Regulatory Science & Medicine, Georgetown University, Washington, DC; and Department of Neurology, Georgetown University, Washington, DC.

Alzheimer disease (AD) causes significant economic and social burdens for patients, families, and the health care system. To date, the US Food and Drug Administration (FDA) has approved few treatments for AD, and these temporarily ameliorate symptoms but do not slow, stop, or reverse disease progression.¹ Meanwhile, 99.6% of AD trials conducted between 2002 and 2012 have encountered safety problems or failed to demonstrate benefit.¹ In the face of these challenges, there is global interest to innovate clinical trials that enable more effective outcomes. Adaptive clinical trials for AD treatment could advance understanding of biological mechanisms and clinical progression and access regulatory review avenues such as accelerated approval. Trial innovation could also reinvigorate investment in drug development.

Clinical trial failures result from many factors: inadequate understanding of actionable targets and pathways (molecular or biological), inappropriate dosage or treatment duration, and variance owing to heterogeneity of the research population. A major cause of many AD trial failures has been the inability to meet FDA-recommended functional and cognitive clinical end points.¹ At a recent FDA patient-centered drug-development meeting, patients and families stressed the need to alleviate cognitive impairment and its disabling consequences.² The FDA has indicated that delaying cognitive impairment before the onset of overt dementia may provide sufficient evidence of efficacy for clinical trials in AD.³

Innovative clinical trial designs have proved successful for other diseases, such as breast cancer, and have enhanced research by identifying relevant outcomes and encouraging financial investment. Since 2008, financing of breast cancer trials has increased while investment in AD trials has declined (Figure)⁴; total investment for breast cancer trials far exceeds that for AD. In addition, 34% of breast cancer trials are in later stages of development compared with 13% of AD trials. The decline in investment in AD trials has resulted in a narrow portfolio of drugs currently in development.

Alzheimer disease research might emulate the I-SPY (Investigation of Serial Studies to Predict Your Therapeutic Response With Imaging and Molecular Analysis) clinical trial, an adaptive clinical trial platform structured to expedite drug development. I-SPY 2 recruits women with triple-negative breast cancer who are at increased risk for tumor recurrence and death despite standard adjuvant treatment. The trial uses a hybrid umbrella/basket design⁵ with the "umbrella" consisting of concurrent testing of up to 12 experimental therapies in patient subgroup "baskets" defined by genetic markers and tumor type. Numerous parties col-

laborate for I-SPY 2, including the Foundation for the National Institutes of Health, the National Cancer Institute, the FDA, patient advocates, drug development companies, and 20 cancer research centers across the United States and Canada.

The primary end point in I-SPY is complete pathologic response as assessed in the breast and lymph nodes and tumor size at end-of-trial surgery. Unlike standard treatment for breast cancer, in triple-negative breast cancer tumors are not removed for pathologic examination until after experimental drug treatment. Tumor response to therapy is monitored during the trial using magnetic resonance imaging, blood biomarkers, and core-needle biopsies. Using data collected during the trial, Bayesian modeling predicts whether a therapy has an 85% or better chance to achieve the primary end point.² Four drugs have graduated to phase 3 since 2010 (HKI-272 [Puma Biotechnology], ABT-888 [AbbVie Inc], MK-2206 [Merck], and T-DM1 [Genentech/Roche]), and another 4 or 5 drugs will complete testing by 2019.

Unfettered data sharing has been key to the success of multisponsored adaptive trials such as I-SPY 2 as well as several large longitudinal observational AD trials. The Alzheimer's Disease Neuroimaging Initiative and Dominantly Inherited Alzheimer Network have modeled this approach by establishing a platform for sharing results with researchers, companies, and the public.

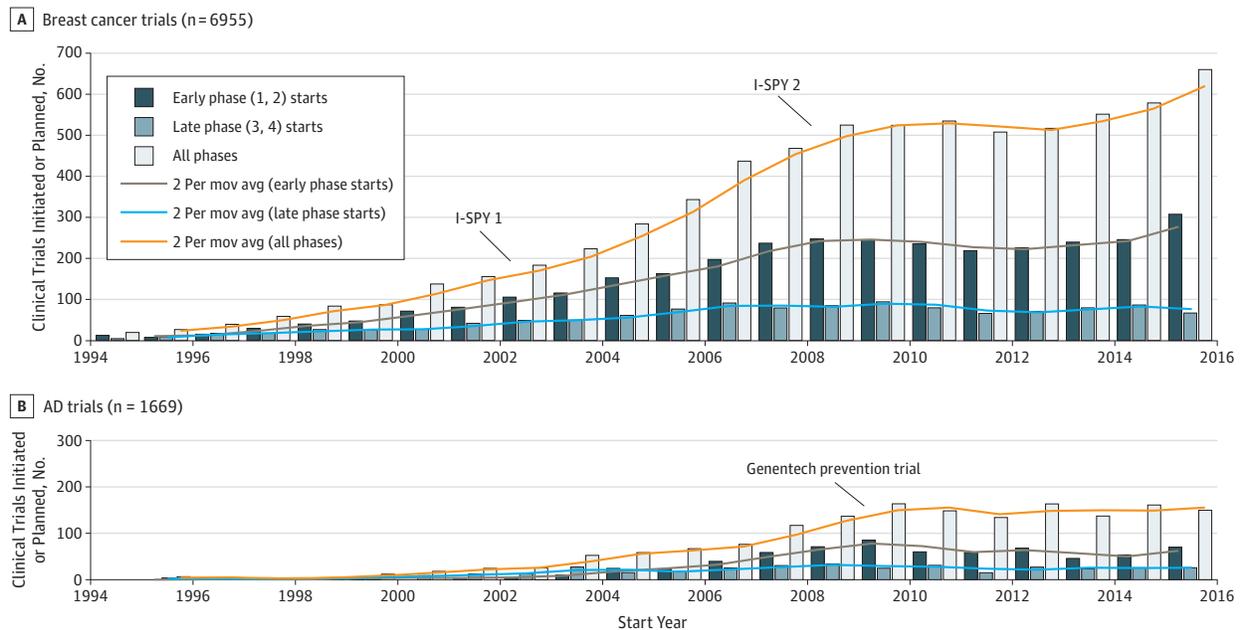
Although collaborations for AD have emerged, an adaptive trial structure has not been advanced. Collaborators for an AD adaptive trial could engage private (industry and foundation) and public (National Institutes of Health and Foundation for the National Institutes of Health) sponsors, patient advocacy groups, and academia. To facilitate uninterrupted trial adaptation, the trial could be operated with a centralized institutional review board and master application for investigational new drugs, as I-SPY has done.⁶

Benefits of an adaptive trial include centralized placebo arms, more homogeneous patient populations, and reduced clinical trial costs. As in I-SPY 2, Bayesian modeling could be used to inform adaptation for AD and predict success in phase 3. An adaptive trial could create a "snowball effect," with early results used to develop, refine, and validate Bayesian predictions. Information for model refinement could be derived from testing and/or reassigning therapies between baskets.

The trial could also test multiple composites of cognitive components and validate appropriate patient-reported outcomes that are increasingly incorporated into clinical trials. Patient-reported outcomes have been applied to mild or moderate cognitive impairment and could be used to inform trial adaptation and assess biomarker and cognitive composites.⁷

Corresponding Author: Mindi F. Messmer, BS, Program for Regulatory Science & Medicine, Georgetown University, 291 Washington Rd, Rye, NH 03870 (mm3875@georgetown.edu).

Figure. Clinical Trials Planned or Initiated for Breast Cancer and Alzheimer Disease (AD), 1994-2015



Only 13% of AD trials are currently in late stage, compared with 18% of breast cancer trials. I-SPY 1, implemented in 2002, and I-SPY 2, implemented in 2009, may have resulted in increases in clinical trial planning and initiation.

An increase in AD trial starts in 2012 is a possible result of the National Institutes of Health announcement in May 2012 to provide \$16 million of support for Genentech's preventive AD trial.⁴ Mov avg indicates moving average.

Adopting the I-SPY adaptive approach for AD has merit but is not without challenge. Less is known about AD biology and pathogenesis than about breast cancer; unlike breast tissue, brain tissue cannot readily be biopsied to assess treatment effects. And sufficiently sensitive cognitive and functional trial end points are lacking. Although AD is a heterogeneous disease, basket genotype or other subgroupings may not correlate with similarities in response to treatment, as is the case with breast cancer receptor types. Some genotypes seem to be correlated with severity of AD; however, we do not know if, for example, apolipoprotein E ϵ 4 predicts therapeutic response. There is no consensus in AD about intermediate or sur-

rogate end points that are recognized predictors of efficacy to support accelerated approval. An adaptive trial for AD would have to develop reliable intermediate end points that predict therapeutic success.

Investment in developing treatment that slows progression of AD is cost-effective: an effective disease-modifying drug approved by 2025 is projected to save \$83 billion in US health care costs by 2030 and reduce the number of patients with severe dementia by nearly half by 2050.⁸ An adaptive trial for AD is an opportunity for continued learning and progress toward effective therapies for those in need.

ARTICLE INFORMATION

Published Online: July 24, 2017.
doi:10.1001/jamaneurol.2017.1528

Conflict of Interest Disclosures: Ms Messmer is sole proprietor of Vista Nova Consulting. Dr Shoulson receives research and educational grants from the Food and Drug Administration (PI, Center of Excellence in Regulatory Science & Innovation, FDOO4319), The Pharmaceutical Research and Manufacturers of America (Regulatory Science Postdoctoral Fellowship), The Griffin Foundation, and The Michael J. Fox Foundation for Parkinson's Research. He is also a nonexecutive director and consultant for Prana Biotechnology Ltd, and a principal of Grey Matter Technologies LLC. He has received honoraria or consulting fees from Auspex Pharmaceuticals, AZTherapies, Banner Health, Columbia University, Dart Neurosciences, Decibel Therapeutics, Huntington Study Group, *JAMA Neurology*, Jazz Pharmaceuticals, Lysosomal Therapeutics, Michael J. Fox Foundation, Northwestern University, Partners Health Care,

Sarepta Therapeutics, Teva Pharmaceuticals, University of California Irvine, University of Michigan, and University of Rochester. No other disclosures were reported.

REFERENCES

- Cummings JL, Morstorf T, Zhong K. Alzheimer's disease drug-development pipeline. *Alzheimers Res Ther*. 2014;6(4):37.
- US Food and Drug Administration. The voice of the patient: Huntington's disease. <https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM491603.pdf>. Updated May 2016. Accessed May 2016.
- US Food and Drug Administration. Guidance for industry, Alzheimer's disease: developing drugs for the treatment of early stage disease. Draft guidance. <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm338287.pdf>. Accessed February 2013.

- Strobel G. NIH Director announces \$100M prevention trial of Genentech antibody. Alzheimer's Research Forum. <http://alzforum.org/new/detail.asp?id=3155>. Updated May 21, 2012. Accessed June 19, 2017.
- Simon R. Genomic alteration-driven clinical trial designs in oncology. *Ann Intern Med*. 2016;165(4):270-278.
- Barker AD, Sigman CC, Kelloff GJ, Hylton NM, Berry DA, Esserman LJ. I-SPY 2. *Clin Pharmacol Ther*. 2009;86(1):97-100.
- Aguirre E, Kang S, Hoare Z, Edwards RT, Orrell M. How does the EQ-5D perform when measuring quality of life in dementia against two other dementia-specific outcome measures? *Qual Life Res*. 2016;25(1):45-49.
- Alzheimer's Association. Changing the trajectory of Alzheimer's disease: how a treatment by 2025 saves lives and dollars. https://www.alz.org/documents_custom/trajectory.pdf. Published 2015. Accessed 2015.