Reply to R.L. Bowen et al, M. Froehner et al, J.L. Leow et al, and C. Brady et al

Regarding our article¹ on the association of androgen deprivation therapy (ADT) with increased Alzheimer's disease risk, Bowen et al,² Froehner and Wirth,³ Leow et al,⁴ and Brady et al⁵ highlight a number of significant considerations that will prove important in the design of future studies that investigate the association of ADT and Alzheimer's disease.

We agree with Bowen et al² and Leow et al⁴ that stratification by the form of ADT is a critical future step to understand the association of ADT and Alzheimer's disease risk. They reasonably point out that our article lacked discussion of a relevant study by D'Amico et al⁶ that showed an association between gonadotropin-releasing hormone agonists and decreased risk of death from Alzheimer's disease. As these authors illustrate, there are many distinct categories of ADT, with differing and complex effects on the hypothalamic–pituitary–gonadal axis. In our article, we did not undertake this subgroup analysis secondary to limited power, given 125 new diagnoses of Alzheimer's disease during the study period. In addition, many individuals were exposed to multiple forms of ADT, which further increased the required sample size to accurately examine the effect of individual forms of ADT. This limitation in power, even in our multi-institutional study with data on > 5 million patients, underscores the need for improved data sharing between medical centers⁷ to answer critical questions in health care.

A number of authors raised important points regarding the potential mechanisms for bias in our analysis. Froehner and Wirth,³ Leow et al,⁴ and Brady et al⁵ point out that patients who receive ADT likely have a greater baseline risk of developing Alzheimer's disease that is difficult to fully account for in a non-randomized analysis. As we discussed in the limitations section of our article, we agree with this assessment, and it is possible that confounding factors that were both unmeasured and incompletely accounted for could have contributed to our result. In our analysis, we therefore adjusted for a wide range of confounding factors and used both traditional and propensity score matched analyses. Leow et al⁴ also make the excellent point that patients administered ADT may have more frequent exposures to the health care system and, therefore, may be more likely to have an outcome of interest recorded. We accounted for duration of follow-up in addition to conducting falsification analyses to protect against and examine the impact of this source of bias. Although these results were reassuring, we cannot completely exclude this source of bias. Clearly, more work is needed to completely unlock the potential of electronic health record data mining for translation into clinical tools to generate personalized evidence.^{8,9} In addition, alternative methods, such as Mendelian randomization analyses,¹⁰ should be considered to account for confounding in the absence of a randomized trial.

We also agree with Brady et al⁵ that the age of patients in our study is not only a source of confounding, but also a reminder of

the importance of fully considering the implications of cancer therapies on our patients' long-term health. This applies not only to the geriatric population as Brady et al⁵ illustrate, but also to younger oncology patients, given the rapidly growing population of long-term survivors of cancer.¹¹ This is particularly important when considering the impact of medical treatments on cognitive outcomes, given that risk of dementia is a primary health concern among older individuals.¹²

Finally, we fully agree that the results of this study should be communicated to patients with caution. ADT has been shown in multiple randomized trials to offer a survival benefit in men with prostate cancer,^{13,14} whereas our study provides data to support further research of the impact of ADT on risk of Alzheimer's disease.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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DOI: 10.1200/JCO.2016.67.9449; published online ahead of print at www.jco.org on June 13, 2016.

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No relationship to disclose

Greg Gaskin

No relationship to disclose

Cariad Chester

No relationship to disclose

Samuel Swisher-McClure

No relationship to disclose

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Stock or Other Ownership: LAM Therapeutics, NuMedii

Honoraria: Janssen Pharmaceuticals

Consulting or Advisory Role: LAM Therapeutics, NuMedii

Research Funding: AstraZeneca, GlaxoSmithKline, Janssen Pharmaceuticals, LEO Pharma

Patents, Royalties, Other Intellectual Property: US Patent No. 8700337

Travel, Accommodations, Expenses: LEO Pharma

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No relationship to disclose

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Patents, Royalties, Other Intellectual Property: Inventor on patents owned by Stanford University that enable the use of clinical text for data-mining; Methods for Ontology-based Analytics and numbers: US13/273,038, US13/420,402, US13/424,375, and US13/424,376.