Targeted Endocrine Agents should be the Dominant Systemic Therapies Prescribed in Luminal A Breast Cancer

Breast Cancer: Basic and Clinical Research
Volume 17: 1–2

DOI: 10.1177/11782234221145409

Matthew G Davey and Michael J Kerin

Discipline of Surgery, The Lambe Institute for Translational Research, National University of Ireland, Galway, Ireland.

KEYWORDS: Endocrine therapies, targeted therapies, personalized medicine

RECEIVED: April 11, 2022. **ACCEPTED:** October 21, 2022.

TYPE: Commentary

FUNDING: The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: MGD received funding from the National Breast Cancer Research Institute, Ireland.

COMPETING INTERESTS: The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

CORRESPONDING AUTHOR: Matthew G Davey, Discipline of Surgery, The Lambe Institute for Translational Research, National University of Ireland, Galway H91YR71, Ireland. Email: m.davey7@nuigalway.ie

Adjuvant endocrine therapy (ET) prescription represents the cornerstone of systemic therapies in estrogen receptor positive (ER+) breast cancer. It is refreshing to read the recent phase III, randomized trial by Del Mastro et al. which further emphasized the importance of ET prescription in achieving long-term oncological control in ER+ disease.[1] The Gruppo Italiano Mammella (GIM) investigators accentuate the value of sequential ET (2-3 years of Tamoxifen followed by 5 years of letrozole) for postmenopausal patients being treated for ER+ disease. In a similar fashion to the ATLAS and DATA trials,[2,3] this study pragmatically reinforces the ideology that luminal A breast cancer (LABC) is an endocrine responsive disease, where optimal oncological control is best achieved through surgical resection subsequently combined with robust adjuvant ET prescription for several years following surgery. These trials encapsulate how the modern oncological paradigm has evolved to recognize LABC as a disease cured surgically with best long-term oncological control achieved using targeted ET prescription.

The trials refute previously accepted hypotheses: Since Bernard Fisher's conclusion of the National Surgical Adjuvant Breast and Bowel Project B-20 trial in 1997,[4] the candidacy and perceived benefit for all breast cancer patients to receive systemic chemotherapy has been emphasized and overestimated, irrespective of the intrinsic biological properties of each tumor. In fact, until the recent landmark TAILORx and RxPONDER trials successfully challenged Fisher's hypothesis,[5,6] there had been limited consideration paid to the inherent chemoinsensitivity of LABC, as evident from the obvious lag between the surgical and systemic de-escalation in the management of the disease.[7] Although TAILORx and RxPONDER promote the appropriate therapeutic de-escalation of chemotherapy for patients with early-stage ER+ breast cancer, there remains a slight paradoxical aftertaste in support of systemic chemotherapy prescription for small subgroups within the trial,[6] which disregards the importance of ET as the primary and secondary systemic therapy which should prescribed in LABC. Therefore, trials such as that of the GIM investigators are invaluable in the current promotion of ET use in ER+ disease, particularly as the identity of LABC is fixated on the endocrine responsive nature of the disease. Nevertheless, identifying the most appropriate ET regimens remains a challenge to the oncologist.

It appears lessons may be learned from a readjustment in focus away from the blunderbuss approach of systemic chemotherapy. At present, the most relevant trials being conducted in LABC are those evaluating the role of single or dual targeted therapies in controlling ER+ disease, as has been in vogue in the metastatic setting for some time now.[8] The current generation of phase III trials seeking to investigate targeted adjuncts to current standard of care ET in early-stage ER+ disease provide encouraging results: In the monarchE trial, patients in receipt of ET and Abemaciclib, a cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor, illustrated a 2-year absolute enhanced disease-free survival of 3.5%, which translates into a relative improvement of 25%.[9] Moreover, data from the recent MONALEESA-7 and PALOMA-3 trials further emphasize the survival advantage of adding CDK4/6 inhibitors to conventional ET have enhanced overall survival outcomes for premenopausal women who develop metastatic LABC (MONALEESA-7—hazard ratio [HR]: 0.71, PALOMA-3—HR: 0.81]).[10,11]

Although trials such as that from the GIM group extenuate the importance of adjusting ET prescription patterns to maximize oncological control,[1] these studies illustrate how the combination of conventional ET and novel targeted therapies (such as CDK4/6 inhibitors) synergistically modulate steroid hormone receptor signaling, which may translate into more rigorous control of metastatic dissemination in ER+ disease. Surely, the next generation of phase III randomized clinical trials for early-stage ER+ disease should be designed to identify ET combinations which maximize disease control as a priority, while reducing unnecessary toxicities, as so commonly observed in years gone by through robust systemic chemotherapy prescription.

Declarations

Ethical Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Author Contributions

Matthew G Davey: Conceptualization; Data curation; Funding acquisition; Methodology; Validation; Visualization; Writing—original draft; Writing—review & editing.
Michael J Kerin: Conceptualization; Data curation; Methodology; Project administration; Resources; Supervision; Validation; Visualization; Writing—review & editing.

Acknowledgements

None.

Availability of Data and Material

Not applicable.

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