A Preliminary Assessment of Knowledge, Attitudes, and Awareness Surrounding Precision Medicine, ESR1 Mutations, and Biomarker Testing Amongst Medical Oncologists

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INTRODUCTION

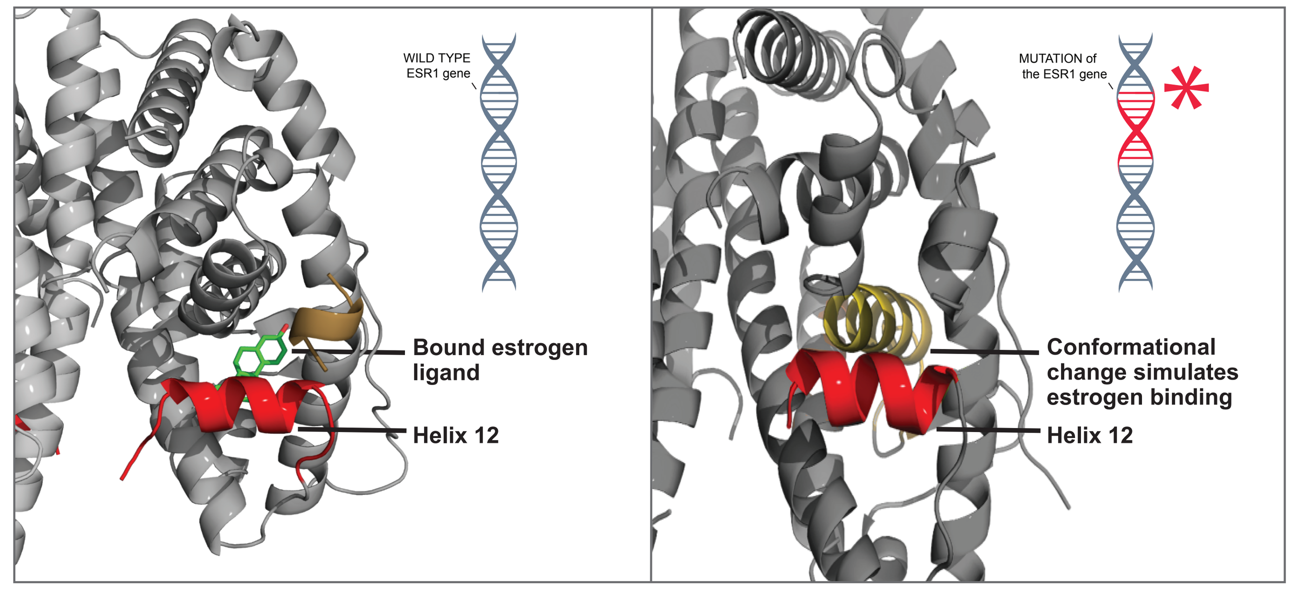
The estrogen receptor has long been known to be a target for hormone receptor positive cancers and continues to guide therapy decisions[1]. Since the identification of HER2 as a target, there has been significant progress in the use of biomarkers in breast cancer, and recent advances in treating BRCA germ-line mutations are being translated into clinical development and treatment practice paradigms. However, to date, there have not been significant developments in the ER+HER2- biomarker arena of somatic mutations.

Mutations of the ESR1 gene are recognized as a fundamental mechanism of endocrine therapy resistance, with acquired endocrine resistance having been shown to evolve under selective pressure from endocrine treatments[2]. Recent findings suggest that ESR1 mutations are present in up to 40% of metastatic breast cancer patients treated with previous aromatase inhibitors (AIs), confer constitutive activity to the receptor even in the absence of estrogen, are insensitive to AIs, and have decreased binding affinity to currently available endocrine therapies such as fulvestrant[3,4]. A biomarker to identify ESR1 mutations, especially from a liquid biopsy, in women with ER+HER2- metastatic breast cancer (mBC) would provide the ability to target the mutations with a precision medicine approach.

The objective of this study was to evaluate the perceptions of precision medicine and biomarker testing specific to ESR1 mutations among medical oncologists. In addition, clinicians' perceptions of the future extent and implications of ESR1 mutation testing through the use of a companion diagnostic and treatment implications were explored.

FIGURE 1.

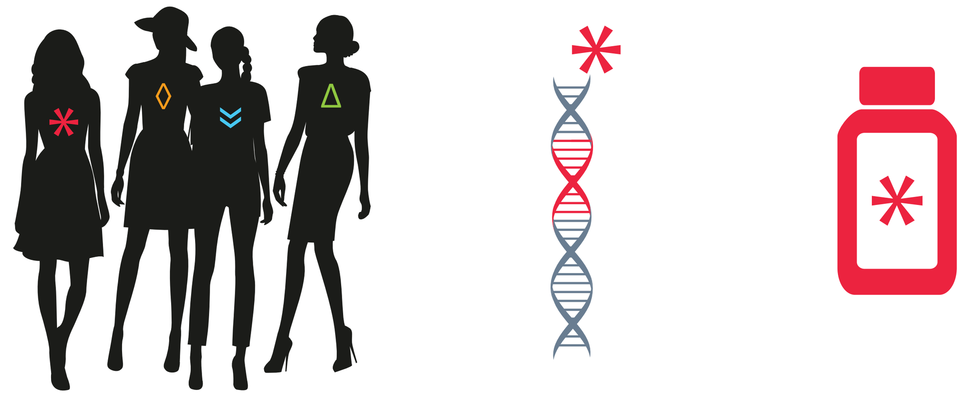
ESR mutations stabilize active conformation of ESR1 ligand binding domain in the absence of estrogen agonists. *Xray crystallographic images courtesy of Dr. Geoffrey Greene, U of Chicago; Also at this conference, see abstract #177/program #PD7-09 for further xray structures relating to ESR mutations.*



E2 Bound to Wild Type Estrogen Receptor | ESR1 D583G Mutation, No Ligand

FIGURE 2.

Precision medicine: Developing custom therapies to treat breast cancer based on the presence of the ESR1 mutation in ER+HER- breast cancer patient population.



METHODOLOGY

Web-assisted, sixty-minute telephone interviews were conducted with ten non-academic medical oncologists.

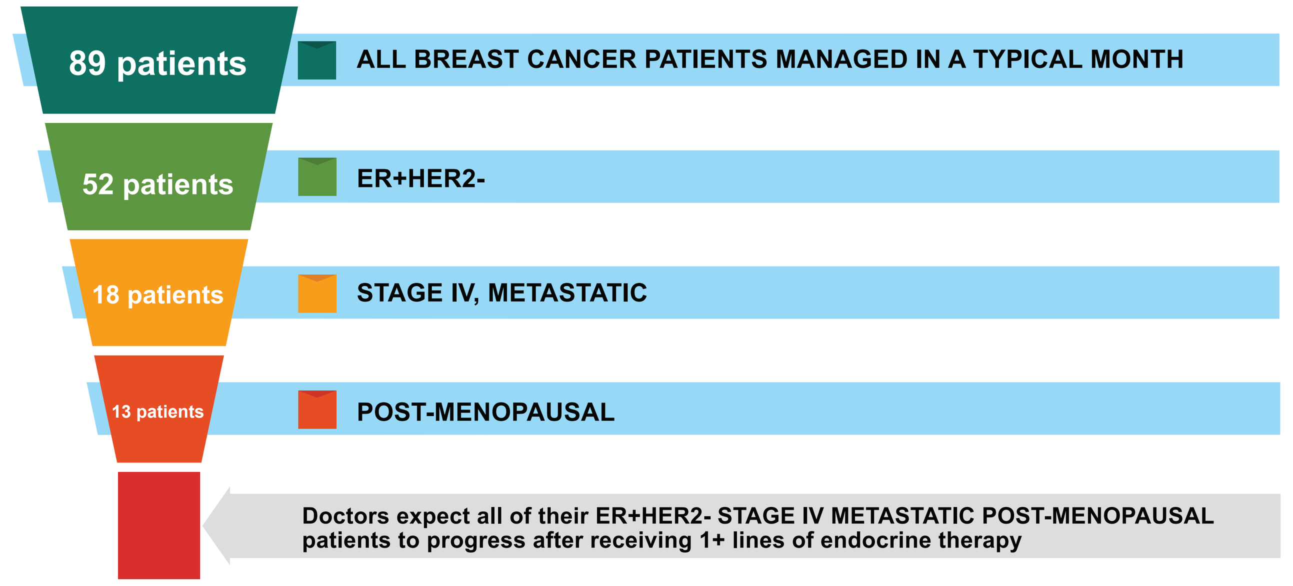
Physicians were prescreened to ensure board certification and practice experience between 2 and 35 years.

Each participant spent >30% of their time on direct patient care and managed the treatment of more than 30 different cancer patients per month, with a minimum of 15 breast cancer patients, including at least 5 with mBC and at least 1 patient with an ESR1 mutation.

Physicians quantitatively assigned treatment allocation for 1st, 2nd and 3rd line therapies and quantitative research findings were also captured by an expert interviewer during the web-based portion of the survey.

FIGURE 3.

Interviewed physicians' breast cancer patient cascade.



PRACTICING CLINICAL ONCOLOGIST INTERVIEW RESULTS

PHYSICIANS BELIEVE PERSONALIZED MEDICINE WILL:

- allow for better efficacy
- help increase overall survival rates by targeting ESR1 mutation

PHYSICIANS HAVE:

- a high desire for personalized treatment in breast cancer
- limited awareness of new somatic genetic mutation markers
- expectation that more genetic markers will emerge in 2-3 years
- some knowledge of ESR1 mutations
- satisfaction with 1st line treatments in ER+HER2- mBC
- less satisfaction with 2nd and 3rd line treatments in ER+HER2- mBC and with existing treatment options for ESR1 mutation patients

QUESTIONED ABOUT ESR1 MUTATIONS, PHYSICIANS SAID:

"It may have a role in the inability of currently used hormonal therapies to bind to the estrogen receptor"

"It is more common among treatment-experienced patients"

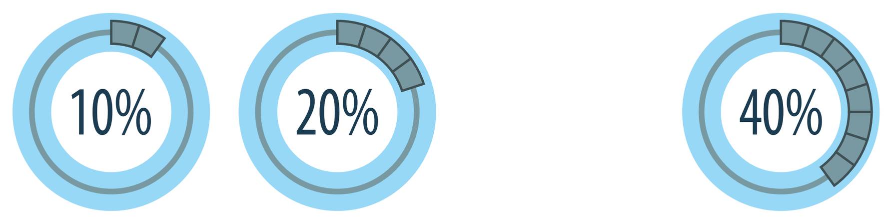
"It may be acquired with selective pressure from AIs or other endocrine therapies"

"It is associated with poorer outcomes"

"Some endocrine therapies should be avoided in patients with ESR1 mutations"

PHYSICIANS SAID REGARDING ESR1 DIAGNOSTIC TESTS:

- highly comfortable ordering them, as long as viable treatment options are available if a mutation is detected
- want to wait until progression of disease before ordering them, with a few physicians suggesting they would test early with metastatic patients to not lose time when the treatment is inevitably needed
- likely to wait for test results rather than treat patients empirically, especially if a liquid biopsy was readily available



Oncologists think there is a 10–20% ESR1 mutation prevalence

Oncologists accept the possibility that ESR1 mutation prevalence could be as high as 40%

PHYSICIANS WELCOME:

- more efficacious hormonal options for later line therapy
- better durability of remission, with improved progression-free survival and overall survival
- therapies with better tolerability profiles in initial and later line therapy
- lower treatment cost options

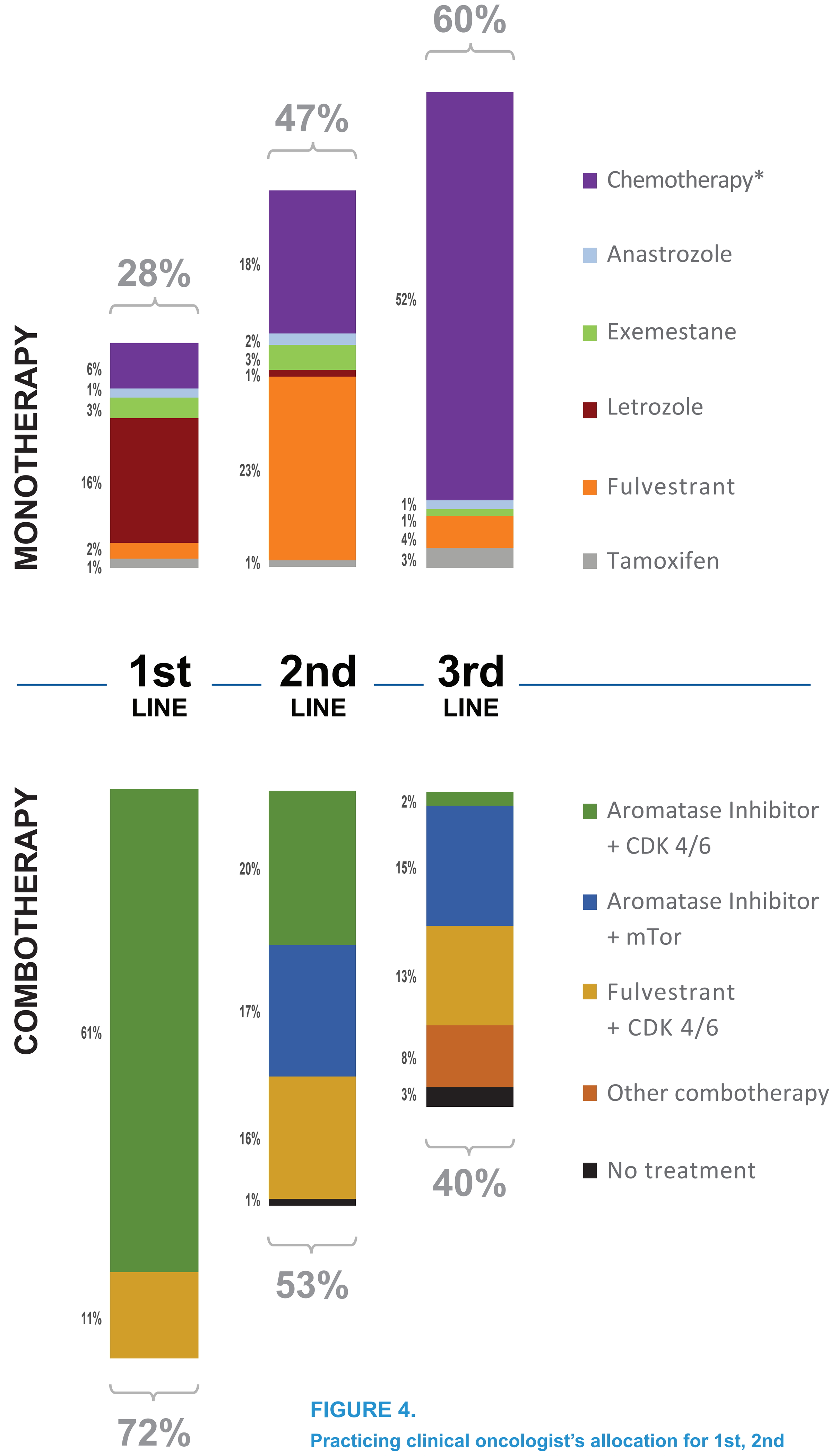


FIGURE 4.

Practicing clinical oncologist's allocation for 1st, 2nd and 3rd line treatment of ER+HER2- metastatic breast cancer (N=10 medical oncologists)

** chemotherapy could be either monotherapy or combotherapy*

CONCLUSIONS

PRACTICING CLINICAL ONCOLOGISTS:

- welcome targeted precision medicine in the ER+HER2- mBC setting
- see no drawbacks to precision medicine from patients, hospital formularies, or payers, especially if a liquid biopsy-based companion diagnostic is available
- believe that detection of mutations and targeting specific tumor genetic signatures will result in improved outcomes
- predict that genetic markers, ESR1 mutations, and diagnostic tests will increase in the future
- welcome the development of new endocrine therapies with documented efficacy, improved tolerability, dosing, and quality of life profiles

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