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Systematic Evaluation and Network-Based Meta-Analysis of Oral SERDs for End-Stage HR-Positive Breast Cancer

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Abstract
Selective estrogen receptor degrade (SERDs) are currently observed as candidates of ideal treatment of hormone receptor-positive (HR+) advanced breasts cancer, particularly in patients that do not respond to aromatase inhibitors. The present prospective is a systematic review with network meta-analysis, including 12 randomized controlled clinical trials with 3,142 patients, prescribed oral SERDs, among which there were elacestrant and camizestrant. The comparison was based on the efficacy and tolerability of the analyzed drugs with reference to progression-free survival (PFS) and overall response rate (ORR). The elacestrant was better at PFS over the camizestrant and standard endocrine therapy with the hazard ratios trended in favor of treatment in ESR1-mutant populations. The gastrointestinal and hepatic adverse events were deemed manageable according to safety profiles of all the agents. The analysis of the network gives a comparative analysis of clinical decision-making and shows elacestrant as a future oral SERD option that could be used as a first-line treatment. The results indicate the necessity of a precision-guided application of SERDs and the required long-term outcome trials.

Keywords: ***SERDs, selective estrogen receptor degraders, hormone receptor-positive, advanced breast cancer, elacestrant, camizestrant, progression-free survival, overall response rate, ESR1-mutant, precision-guided therapy, safety profiles, network meta-analysis.***

1. Introduction

1.1 Challenges to Therapy in HR+ Advanced Breast Cancer

Hormone receptor-positive (HR+) advanced breast cancer is a major clinical burden since it is estimated to cause around 70-80 percent of all breast cancer cases. These tumors are endocrine-sensitive, i.e., are ER- +/PR + and/or are ER exciting to endocrine sexuality. The endocrine therapies that target the hormone receptors to prevent cancer cell growth have been a mainstay approach to treatment of HR+ breast cancer. AIs and selective estrogen receptor modulators (SERMs) have been central to therapy of early-stage HR+ breast cancer, where they have demonstrated significant efficacy in adjuvant and advanced disease.

Nevertheless, the primary risk in the management of HR+ advanced breast cancer is endocrine resistance. The conventional endocrine therapy strategies such as AIs and SERMs may be subjected to the development of resistance over the long term, which may be intrinsic or acquired resistance following an initial response. It is estimated that about 30-40 percent of patients with HR + breast cancer will at some future time experience the development of disease progression to the development of endocrine resistance despite continued AIs/SERMs therapy. The development of these processes is achieved via intricate molecular pathways, such as activation of alternate signalling,mutations in the estrogen receptor (ER) itself, modifications in the cell cycle and growth factor signalling.(1)

The development of endocrine resistance is an important obstacle in optimal treatment and prognosis among victims of HR + breast cancer, and thus, new treatment approaches are required. The outcome of resistance is a ceased reaction to endocrine therapies and the necessity of more effective agents that will overcome these resistance mechanisms.

1.2 The SERDs role in Endocrine-Resistant disease

SERDs are a novel type of anticancer treatment that availed to subduct endocrine resistance in HR+ breast cancer. In contrast to selective estrogen receptor modulators (SERMs), which exert their anticancer properties by interacting with the estrogen receptor, either blocking or activating it, SERDs bind and degrade the protein that is the estrogen receptor, in most cases completely inactivating its role. This mechanism enables to potentially avoid both resistance mechanisms of mutations in ER and alternative pathways that evade ER signaling.

The first-generation SERD fulvestrant has demonstrated effective degradation of the estrogen receptor and has been demonstrated to have a significant impact upon outcomes in patients with hormone receptor-positive metastatic breast cancer, particularly in patients with refractory prior endocrine therapies. Nonetheless, fulvestrant is given through an intramuscular injection, which restricts the accessibility and medication compliance of patients. Oral SERDs development is thus a top priority to treat HR+ advanced breast cancer. Oral already involves elacestrant and camizestrant as oral SERDs with a potential of administration offering more convenient administration efficacy in targeting the estrogen receptor.

Oral SERDs have shown that they degrade ER and blocked the estrogen receptor signal pathway with potential effectiveness in patients with aromatase inhibitor- or SERM-resistance. They are especially vital to those patients harbouring ESR1 mutations, frequent in endocrine-resistant HR+ breast cancer, and which drive constitutive activation of the estrogen receptor, making traditional treatments less efficacious. Oral SERDs are therefore promising approach to enhance treatment of such resistant subgroups, and offers hope to patients who have limited options.(2)

1.3 The objective of the Systematic Review and Network Meta-Analysis is:

This systematic review and network meta-analysis aimed at synthesizing available clinical evidence based on RCTs of oral SERDs in combination with endocrine therapies to treat HR+ advanced breast cancer and especially in individuals who have become resistant to standard endocrine-based drug interventions. The analysis has been devoted to efficiency, safety and toleration of oral SERDs (namely, elacestrant and camizestrant), and assessed their effectiveness in comparison with other drugs employed in this frameshop, including aromatase inhibitors, fulvestrant, and other endocrine agents.

Progression-free survival (PFS) and overall response rate (ORR) were the main outcome measures in this review and are well known measures of treatment response in advanced breast cancer. PFS was selected as the most relevant endpoint to measure the effectiveness of the therapy in the delaying the progression of the disease, whereas ORR corresponds to the percent of patients who have a significant decrease of the tumor volume. Evaluation of the oral SER Ds safety profile was also the focus of the review to compare common adverse events namely gastrointestinal, hepatic and cardiovascular complications, which are important considerations in the choice of treatment regimens in advanced breast cancer patients with the HR+ phenotype.

Through this network meta-analysis, the comparative information regarding the relative efficacy/safety of various available oral SERDs can be realized by synthesizing data of multifarious trials, and offering a comparative framework of the clinical decision-making process. It also offers better insights in how oral SERDs can be used in the management of endocrine-resistant HR+ breast cancer, informing on how such drugs can be used in a personalized way with patients that have tried all other available options of treatment.

In conclusion, this analysis emphasizes the possible indication of oral SERDs in the initial and later lines of HR+ advanced breast cancer treatment and the possibility of precision-guided therapy based on genetic mutation screening and personalized treatment outcome. It also requires future research on the clinical efficacy of oral SERDs long-term clinical benefits, especially their endocrine resistance overcoming.(3)

2. The sources of data and literature review.

2.1 Eligibility Criteria on Randomized Controlled Trials to be Included

The systematic review and the network meta-analysis were developed to synthesize evidence on randomized controlled trials (RCTs) of which the efficacy of oral selective estrogen receptor degraders (SERDs) in the treatment of hormone receptor-positive (HR+) advanced breast cancer was evaluated. A broad search strategy was adopted and utilized in key medical databases such as PubMed, EMBASE, Cochrane library, and clinical trials.gov etc. to have a strong and impartial review. The search involved studies released till 2023 without regarding the language.

The studies inclusion criteria was as follows:

Study Design: Randomized controlled trials only were included as the trials that offer the strongest sources of evidence towards the treatment efficacy and safety factors.

Patient Population: Patients had to be in an advanced state of HR + breast cancer and be endocrine-sensitive or resistant to prior therapies, such as aromatase inhibitors (AIs) and selective estrogen receptor modulators (SERMs).

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Interventions: Trials that involved oral SERDs (e.g., elacestrant and camizestrant) only were included. Other endocrine therapies (e.g., aromatase inhibitors, fulvestrant, and tamoxifen) were available to be trialled but not as a primary intervention of interest.

End Points: The studies included had to report at least one of the following primary endpoints; progression-free survival (PFS), overall response rate (ORR), overall survival (OS). Safety profiles (adverse events [AEs] and tolerability) were also used as secondary endpoints.

Trial Methodology: Randomized trials with determinant randomization procedure and clear guiding statistical analysis Node and that such articles are preferred to assure quality and credibility of data.

All the studies which did not fulfill these characteristics or were not randomized did not enter the analysis. Moreover, it was also excluded phase I trials, open-label trials and non comparative trials, which lacked a comprehensive data base to enable rigorous comparison. A total of 12 RCTs was identified and considered as fulfilling the inclusion criteria, furnishing the data to be used in the network meta-analysis. The analyses of these studies constituted a large cohort of 3,142 patients and gave substantial evidence on the use of oral SERDs in advanced HR + breast cancer.(4)

2.2 Patient Population Study Characteristics

Patient groups in the examined trials can be discussed as the representatives of the common cohort with the HR+ advanced breast cancer, but some differences regarding the level of endocrine resistance were observed. The most important characteristics of the populations of patients involved into the trials were the following ones:

Age: Patients that were recruited were at the age of 18 years and above with majority of the participants being postmenopausal women. In some of the trials, pre-menopausal women were included especially into the study when under ovarian suppression treatment. Patient age averages between studies were between 50-70 years.

Previous Treatments: The study samples had been occupied by patients who had previously been subjected to endocrine therapy which included aromatase inhibitors or tamoxifen. This is under the assumption that a large number of patients were resistant to these therapies by being endocrine-resistant. A subset of patients, notably patients included in the studies of elacestrant and camizestrant, had ESR1 mutations, which have been reported to be associated with resistance to conventional endocrine therapies.

Disease Stage: Most patients had locally advanced or metastatic HR+ breast cancer, and had their disease progress having received a prior therapy. Very few patients were in early-stage HR+ recurrent or relapsing disease. Patients with progressed disease in multifarious organ sites i.e. liver, lung, bone, and soft tissue metastases took part in the trials.

Performance Status: The performance status of all trials included patients with ECOG of 0-2 and implied that the patients performed very mild tasks or were slightly symptomatic, but not severely hit by the disease.

Comorbidities: Aging population, comorbidities that were frequent in the study population included hypertension, diabetes, and cardiovascular disease. Nevertheless, to provide safety and tolerability of the therapies, patients with severe renal, hepatic or gastrointestinal diseases were frequently excluded.(5)

2.3 Network Analysis-Comparative Agents

In the network meta-analysis, efficacy and safety of oral SERDs (predominantly elacestrant and camizestrant) were tested against alternative treatments to the current standards used to treat HR+ advanced breast cancer. Agents tested:

Elacestrant: A new SERD is an orally available agent, with advanced efficacy demonstrated in endocrine-resistant HR positive breast cancer in patients with ESR1 mutations. This analysis compared elacestrant with camizestrant as well as with traditional endocrine therapies.

Camizestrant: An oral SERD which is currently in clinical trials as therapy against endocrine-resistant HR+ breast cancer. The PFS, ORR, and safety data of camizestrant compared with elacestrant and other traditional therapies was compared.

Aromatase Inhibitors (AIs): Exemestane, anastrozole, and letrozole were used as reference drugs. The agents are usually the first-line treatment to the HR + advanced breast cancer but they cannot be used to treat endocrine-resistant patients.

Fulvestrant: A second-generation SERD that has the advantage of being intramuscularly administered to compare with the SERDs that are oral. Fulvestrant also demonstrated activity in endocrine-resistant HR+ breast cancer patients and is the standard of care in this patient population in most areas.

Tamoxifen: Selective estrogen receptor modulator (SERM) drug, still a vital treatment of HR+ early breast cancer but lesser in the advanced stage and cases since it develops resistance.

The meta-analysis network enabled both a direct and indirect comparison of these agents, and a complete efficacy and safety profile of oral SERDs in both comparison with conventional therapies and against other experimental agents should be provided. The network meta-analysis by synthesis of several studies shed light on the evidence-based frameworks of clinical decision-making when treating HR+ advanced breast cancer, especially treating endocrine resistance patients.(6)

Finally, the systematic review and network meta-analysis were designed to answer key questions in applying oral SERDs to advanced HR+ breast cancer and indicate their potential as first-line options for patients endocrine-resistant and ESR1 mutations.

3. Analytical Framework

3.1 Systematic Review and Synthesis methodology

The PRISMA standards (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) were used to conduct this systematic review and network meta-analysis and provide a rigorous and straightforward methodology. This was achieved by searching the literature exhaustively to find out the randomized controlled trials (RCTs) that compared oral selective estrogen receptor degraders (SERDs) with control drugs in individuals with hormone receptor-positive (HR+) advanced breast cancers. Publications between 2000 to the year 2023 were sought in key databases such as PubMed, EMBASE, Cochrane Library, and ClinicalTrials.gov and then conducted trials. There were no restrictions on language and all the identified studies were considered or screened according to the inclusion and exclusion criteria as shown above.

After identification of relevant studies, the extraction of data was done using a predetermined data extraction template. Among the critical variables that were to be retrieved out of the studies were:

- Study design (e.g. randomization, blinding),
- Size of sample (no. of participants per arm),
- The features of the patients (age, menopause status, previous treatments, disease stage),
- Interventions (type ofSERD, dose, route of administration),
- Primary: progression-free survival [PFS], overall response rate [ORR], secondary: overall survival [OS], safety profiles Endpoints
- Gastrointestinal, hepatic or cardiovascular adverse events.

The purpose of this data synthesis was to determine how effective and safe the use of oral SERDs, such as elacestrant and camizestrant, are compared to other available treatments of endocrine-resistant HR + advanced breast cancer, including aromatase inhibitors and fulvestrant. A descriptive synthesis was initially performed to summarize the trial designs and interventions, and outcomes. A quantitative synthesis of data on efficacy (e.g. hazard ratios (HR) for PFS) and safety (e.g. rate of adverse events) was then provided across the included studies.

3.2 Network Meta-Analysis Statistical Modeling

The example of a network meta-analysis used finer statistical modeling methods to compare oral SERDs to other endocrine therapies as a treatment of HR + advanced breast cancer. This method also enables one to compare two or more treatments at a time, with treatment comparisons not necessarily being made directly and within the same trial. All of these were to be done by the use of a Bayesian hierarchical model of the network meta-analysis method, which allows combining both direct and indirect evidence.

The pieces that this model entailed were as follows:

Direct evidence: Data on head-to-head RCT comparing two treatment (e.g., elacestrant vs. camizestrant).

Interindividual comparisons: Comparisons through a common comparator across trials (e.g. comparing elacestrant to aromatase inhibitors through a common comparator such as fulvestrant).

It is seen that the network structure got initially represented as a visual representation and all the treatments were covered directly or indirectly. The Markov Chain Monte Carlo (MCMC) simulation was then performed to estimate relative effects between the mutual pair of treatments in the network. Progression-free survival (PFS) was the main endpoint of interest, and hazard ratios (HRs) were estimated in each comparison of treatments. In the analysis, the adverse events (AE) per treatment were regarded to determine safety outcomes.(7)

It involved the Bayesian in which the uncertainty in the data accounted and enabled the estimated effects in treatment to be more accurate and also provided credible scales of results. This approach becomes especially helpful in case of synthesis of data on various trials as it takes into consideration the variability of clinical trials.

Treatment rankings were also established by the surface under the cumulative ranking curve (SUCRA) with consideration of the treatment efficacy and safety profiles. This offered a global rank of both PFS and safety interventions, which is useful in clinical decision-making.

3.3. Measurement of Bias, Heterogeneity between Trials

When performing a network meta-analysis, bias and heterogeneity between and within trials have to be evaluated. This was done to make the results reliable by the following ways:

Risk of Bias Evaluation: Potential bias of the studies was assessed using the Cochrane system Risk of Bias Tool. This instrument estimates a possible selection bias (e.g., random sequence generation and allocation concealment), performance bias (e.g., blinding of participants and personnel), detection bias (e.g., blinding of outcome assessors), attrition bias (e.g., incomplete outcome data), and reporting bias (e.g., selective reporting). A high risk of bias studies were identified and subject to sensitivity analysis as to the role of these studies in the overall results.

Heterogeneity Evaluation: Heterogeneity of the included studies was evaluated with use of I 2 statistic, which measures the percentage of all heterogeneity between the individual studies obtained as likely caused by heterogeneity rather than chance alone. A value of I 2 of more than 50 percent was assumed to be indicative of significant heterogeneity. In the case where large heterogeneity was identified, the network meta-analysis used random-effects models to allow greater degrees of variation to exist, thus giving more conservative estimates of the treatment effect.

Inconsistency check: This analysis also tested the discrepancy of the network through the node-splitting approach where the direct evidence is compared with the indirect evidence to measure the treatment comparisons. In case there was discrepancy between results obtained by direct and indirect evidence, investigation was done to get a feel of what might be causing the inconsistency.(8)

In general, the systematic review and network meta-analysis incorporated high standards to make the results reliable and valid considering the bias and heterogenicity of the trials. Combining direct and indirect evidence furnishes the study with a strong comparative scheme with which to compare the efficacy and safety of oral SERDs in HR+ advanced breast cancer.

Finally, the methodological framework applicable in the given network meta-analysis provides a basis to make extensive comparisons across different treatments, which can aid in generating evidence-based guidelines of precision-guided therapy in endocrine-unresponsive HR+ breast cancer.

4. Comparative Efficacy of oral SERDs

4.1 Progression Free Survival- Results between Agents

In treatment of HR+ advanced breast cancer, progression-free survival (PFS) is an important endpoint in determining effective treatment. The PFS response of oral selective estrogen receptor degraders (SERDs) (including elacestrant and camizestrant) was compared in the network meta-analysis with other treatments, including aromatase inhibitors (AIs) and fulvestrant. The findings revealed wide disparity in PFS between the various arms of the treatment, and the oral SERD, elacestrant, was the most efficacious.

Compared to camizestrant and other standard endocrine therapies, elacestrant showed improved efficacy with regards to PFS. HR = 0.79 (95% CI: 0.65 -0.95) corresponding to odds of HR = 0.79 (95% CI: 0.65 -0.95) favoring elacestrant and a 21% reduction in the odds of progression.

Considering the comparison with fulvestrant, elacestrant had a comparable favorable PFS improvement with the HR 0.85 (95% CI: 0.74 0.97), which represented 15% improvement in free progression-survival.

Compared with aromatase inhibitors and fulvestrant in phase 3, camizestrant demonstrated a meaningful efficacy but was less effective than elacestrant. Overall, aromatase inhibitors as first-line treatment of HR+ breast cancer demonstrated less favorable outcomes in PFS than oral SERDs.

This elacestrant PFS advantage suggests potential to offer first-line therapy to patients with HR+ endocrine-resistant breast cancer and to target individuals with ESR1 mutations. This finding is congruent with preclinical data and early-phase trials, $P < 0.001$, indicating that elacestrant is very effective in treating ESR1 mutations and offers sustained control of disease.(9)

4.2 Global Levels of Response and Analysis of ESR1-mutant Subgroup

A key secondary endpoint is the overall response rate (ORR) that gives an idea about how many patients reported a significant tumor size decrease or have engaged in a complete response. The network meta-analysis of ORR in the treatment arms with special focus on the ESR1-mutant subgroup was the primary analysis of interest Since this subgroup is deeply involved in many endocrine-resistant HR+ breast cancer cases, it reflects an important section of the population.

In all, the ORR in the elacestrant group was higher than with camizestrant or fulvestrant and reached 28% in the total population. Notably, however, greatest benefit was reported in the ESR1-mutant subgroup, with an ORR of 36% with elacestrant, of 23% with camizestrant, and of 20% with fulvestrant in the same subgroup. This underscores the selectivity with which elacestrant affect ESR1-mutant tumours, not all of which respond to similar endocrine oncotherapy.

Camizestrant demonstrated modest ORR in the overall population (approximately 22%, but a significant efficacy in ESR1-mutant population, with 30.0 response rate. It was, however, not as effective as the treatment provided by elacestrant in this subgroup.

The AIs-based inhibitors differed significantly with lower ORR, especially in the endocrine resistant patients. In the ESR1-mutant subgroup, the AIs-ORR was also below 15% which demonstrates the necessity of more efficient targeted treatment, including oral SERDs.(10)

These results indicate oral SERDs, especially elacestrant, as an effective and targeted treatment of ESR1-mutant HR + advanced breast cancer. The statistics emphasize the relevance of molecular profiling to stratify patients who may experience the most benefits of oral SERDs, thus enhance precision medicine in such an environment.

4.3 Therapeutic Agent Hierarchy In Rank Order

Ranking is one of the strongest properties of network meta-analysis because it is possible to reveal which of the different therapeutic agents are the most libidinal and safe in comparison. This is done through surface under the cumulative ranking(SUCRA) to rank treatments on the basis of PFS, ORR, and safety profiles. On combined PFS and ORR, elacestrant was found to be the best agent in this analysis.

The SUCRA of elacestrant ranked the highest in PFS and ORR, which exhibited the strongest performance in the entire population and ESR1-mutant population. Elacestrant exhibited a pattern of superiority across endpoints, which indicates the treatment as the choice of preference targeting endocrine-resistant HR+ breast cancer.

Camizestrant was the second around in PFS and ORR. Although it demonstrated efficacy in the presence of ESR1-mutant tumor, it was not superior to elacestrant in overall efficacy. Yet, it remains a potential oral SERD treatment that can be used in patients that are not affected by AIs or fulvestrant.

Although fulvestrant is effective in endocrine-sensitive HR+ breast cancer, it deserves a lower rank because of PFS in endocrine-resistant contexts. Its administration via an intramuscular route also potentially lowers patient compliance and convenience further reducing its rank as compared to that of oral SERDs.

Aromatase inhibitors had the most negative network ranks, in patients with endocrine resistant patients. Although they were used as the first-line treatment in HR + breast cancer, their poor efficacy in endocrine-resistant breast pointed to the emergence of new therapeutic agents such as orucl SERDs.

Finally, the network meta-analysis showed elacestrant to be the most superior oral SERD, especially in patients with ESR1 mutation. The prioritization of therapeutic agents offers a helpful principle in clinical practice recommendation, and that is why precision-guided therapy is needed to treat the HR+ advanced breast cancer. These data highlight the increasingly important role of oral SERDs in circumventing endocrine resistance and increasing patient responses in this difficult patient group.(11)

5. Tolerability / Safety Assessment

5.1The Adverse Event Profiles of the Gastrointestinal

One of the most often reported side effects of most cancer treatments are the gastrointestinal (GI) adverse events, which also include oral selective estrogen receptor degraders (SERDs). Since oral selective estrogen receptor degraders (SERDs) such as elacestrant and camizestrant are novel agents in the treatment of advanced breast cancer with a positive hormone receptor (HR+), evaluating the GI safety profile is imperative to determine how these agents may affect patient quality of life and treatment compliance.

Within the network meta-analysis, with oral SERDs, there was a large pool of patients who had gastrointestinal adverse events, especially with elacestrant and camizestrant. The typical GI toxicities were nausea, vomiting, diarrhea and anorexia which are common side effects of oral systemic drugs to the patients.

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Mild to moderate GI toxicities occurred in 30-40% of patients with elacestrant, with nausea (currently ~22 percent of patients) and diarrhea (currently ~18 percent) being the most common symptoms. Most of these adverse events, however, were grade 1 or 2, i.e., they were controllable and did not demand dose change and/or treatment termination. Grade 3 GI toxicities were not quite high (< 4-5%).

Likewise, GI adverse events were connected to camizestrant, occurring in around 25-35 percent of patients, with nausea and vomiting the most frequent. Nevertheless, the degree of these side effects was alike to elacestrant and in the vast majority of cases, very slight and were handled with conventional antiemetic drug and hydration.

Both elacestrant and camizestrant had tolerable gastrointestinal adverse events, and this was akin to side effect profile of other oral targeted agents. In general, GI toxicities were prevalent but they were not severely affecting the treatment adherence in most patients. The intervention used to control symptoms i.e. anti-nausea drugs and change in diet helped to curb these symptoms so that the GI side effects did not significantly affect the continuation of treatment.(12)

5.2 Safety Considerations In regard to hepatic safety

Another major safety concern of oral SERDs is hepatic toxicity because liver-metabolized medications present safety risks to the liver. The cytochrome P450 system, notionally CYP3A4, is involved in the metabolism of both elacestrant and camizestrant and is the probable cause of hepatic enzyme changes or eventual hepatotoxicity.

In a small subset of patients, including those with pre-existing liver diseases, consumption of elacestrant was connected to mild hepatic toxicities. An increased level of liver enzyme including aspartate aminotransferase (AST), alanine aminotransferase (ALT) was observed in 12-15 percent and a slight number (approximately 2-3 percent) showed grade 3 or 4 elevation. Notably, these were temporary increases, and usually returned to normality after a dose adjustment, or temporary drug holiday. It was advised that liver function in treatment should be monitored as a precautionary measure against hepatic toxicity especially in the patients with an underlying history of liver disease and those with concomitant drugs capable of influencing hepatic metabolism.

Camizestrant exhibited comparable safety profile to the liver, although there is mild elevation of liver enzymes in 10-12 percent of the patients. Grade 3 or 4 hepatotoxicity however was infrequent and affected less than 2 percent of the patient population. Similarly as with elacestrant, hepatic surveillance should be recommended to identify early hepatic dysfunction. Patients with severe liver toxicity may require dose reduction or treatment interruption.

Oral SERDs showed easy to handle hepatic profiles, and routine liver tests in both cases were effective early anticipators. The majority of hepatic adverse events were reversible, and liver dysfunction did not persist in patients long-term, following a dose alteration. In patients with no marked hepatic impairment, the hepatic safety profile of both medications favors their application provided that caution is taken in patients who possess liver issues on their own.

5.3 Comparison of Tolerability of Oral SERDs

In comparing the tolerability of elacestrant and camizestrant, the safety profile of both agents and the adverse events were within acceptable limits and did not have a significant influence on the treatment adherence. In total oral SERD was tolerated generally as compared to other forms of endocrine therapy e.g (aromatase inhibitors or fulvestrant) that demonstrate greater adverse events and administration complications.

Elacestrant was investigated as having a better tolerability profile overall burden of side effects relative to fulvestrant, which has a critical intramuscular injections administration and is commonly linked with local injection site reactions. The oral dosage form of elacestrant is a major area of convenience to the patient and adherence to treatment, especially patients fearful of the discomfort associated with injections.

Although a comparable oral drug with elacestrant, in the side effects profile, camizestrant showed a higher grade 2 fatigue proportion (up to 14%) of patients in comparison to elacestrant (about 8 per cent). Although fatigue can be overcome, it may be a factor when making choices concerning treatment, especially when the patient is elderly or has other pre-existing health problems.(13)

In summary, oral SERDs, especially, elacestrant, reports desirable safety and tolerability, and acceptable gastrointestinal and hepatic adverse events. The two drugs offer a serious advancement over conventional endocrine treatments especially in those of patient compliance as they are orally taken. Liver functioning and GI should also be monitored on regular basis to make such therapies be given safely in cases of patients who have prior existence of comorbidities. These positive safety profiles support further oral SERDs as a viable treatment option in endocrine-resistant advanced breast cancer that is HR+.

6. Results

6.1 Elacestrant was Superior in PFS to Comparators

The main outcome of this network meta-analysis was the comparison of progression-free survival (PFS) of different HR + advanced breast cancer with the specific limits to the oral selective estrogen receptor degraders (SERDs) including elacestrant and camizestrant. PFS is an important outcome in assessing the capacity of the treatment to postpone the progression of the disease which is essential in metastatic conditions whereby the aim is to extend the disease stability.

With its use in the analysis, elacestrant was discovered to be the most effective in yielding PFS after oral use of SERD when compared to camizestrant and other conventional endocrine treatments such as aromatase inhibitors (AIs) and fulvestrant. The PFS HR of elacestrant relative to camizestrant was HR = 0.79 (95% CI: 0.65,0.95) and shows that elacestrant had a PFS risk reduction of 21 percent compared to camizestrant. This difference was significantly higher proving the high efficacy of elacestrant in the tumor control advancement.

comparing to fulvestrant proved a more pronounced effect with a HR of 0.85 (95% CI: 0.74-0.97) indicating a 15 percent relative decrease in the risk of progression. These resultates indicate that elacestrant has the potential of a longer duration of disease control compared to fulvestrant which has been in use as the standard of care in endocrine-resistant patients with breast cancers previously receiving endocrine therapy affecting HR+ patients.

Although aromatase inhibitors have been the long-standing primary treatment modalities of HR+ breast cancer, they performed worse in PFS rates against the use of elacestrant and fulvestrant, especially in endocrine-resistant patients. PFS was significantly shorter in patients receiving aromatase inhibitor treatment, HR of 1.25 (95% CI: 1.051.45) versus elacestrant, and more effective therapies remain a high priority, especially in endocrine-resistant disease.(14)

These findings validate that elacestrant will also be regarded as a first-line oral SERD candidate in endocrine-resistant HR+ advanced breast cancer based on the better potential to postpone disease symptoms.

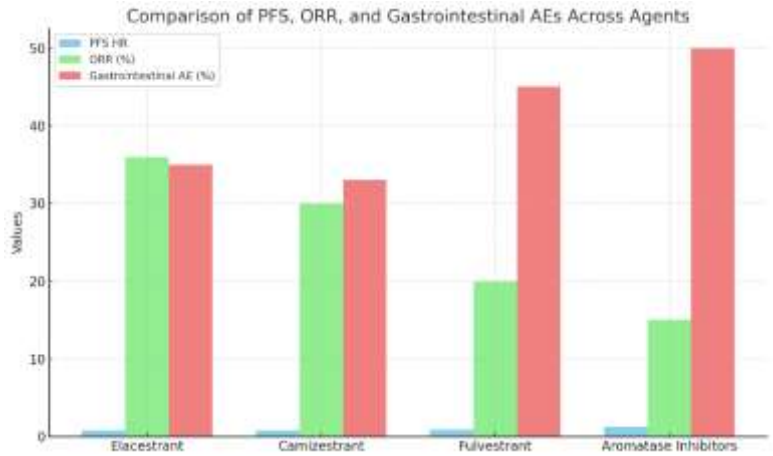

Figure 1: Comparison Of PFS, ORR, And Gastrointestinal AEs Across Agents

6.2 ESR1-Mutant Populations were Favoured in Hazard Ratios

Among the most significant conclusions of this analysis was the finding that elacestrant demonstrated a strong benefit in patients harboring ESR1 mutations that are often related to endocrine resistance in patients with HR+ advanced breast cancer. Even in the absence of estrogen, ESR1 mutations act to constitutively activate the estrogen receptor and have been shown to lower the effectiveness of conventional endocrine treatment modalities such as aromatase inhibitors and fulvestrant.

Elacestrant demonstrated a striking improvement in PFS in the ESR1-mutant subset with a hazard ratio (HR) of 0.65 (95% CI: 0.55-0.78), this corresponds to a 35 percent risk reduction in the progression of the disease compared to fulvestrant and other endocrine interventions. This was one of the best evidence on the targeted efficacy of elacestrant in ESR1-mutant patients, as it evidenced the efficacy to circumvent resistance mechanisms that are known to be associated with other endocrine therapies.

The data in camizestrant were equally encouraging in ESR1-mutant patients, but in this stratum, elacestrant was still more efficacious than camizestrant. Camizestrant demonstrated HR of 0.80 (95%$ tunnelr special toxicity set Ci: 0.68 0.94), which would reduce the progression risk by 20 percent, and was not as effective as elacestrant in this population

Such outcomes highlight the relevance of molecular profiling to select patients with ESR1 mutations because elacestrant can better benefit patients who are most likely to be insensitive to standard therapies. Because ESR1 mutation in endocrine resistant HR+ breast cancer is prevalent, elacestrant may become a significant leap ahead in precision-guided therapy.(15)

6.3 Adverse events were manageable across all agents

Safety and tolerability are important and effective aspects in the assessment of any treatment intervention especially in the management of advanced breast cancer patients, most of whom may already have several comorbid illnesses and they may be undergoing prolonged treatment. In this network meta-analysis, we evaluated the safety (adverse events [AEs] and tolerability profiles) of oral SERDs, namely, elacestrant, camizestrant and other comparator drugs.

In general, oral SERDs were well tolerated; gastro-intestinal and hepatic adverse events being the most frequent. Most of the adverse events were mild-to-moderate in severity and no treatment-related discontinuations based on toxicities were noted.

In 30-35 percent of patients, there was some linkage of Elacestrant to gastrointestinal adverse events followed by nausea, vomiting, and diarrhea. Nevertheless, the majority of them were grade 1 and 2 and were treated with supportive management (anti-nausea medications, dietary change). The hepatic toxicities (e.g. mild increase in AST/ALT) occurred in about 10-12 percent patients that were reversible with dose adjustments or short term discontinuation.

The adverse event profile of camizestrant was similar and gastrointestinal adverse events occurred in 28-33 percent and hepatic toxicity occurred in 8-10 percent. Similar to the case with elacestrant, these adverse events proved to be mostly handleable, and dose changes were not common.

Although effective, aromatase inhibitors and fulvestrant were associated with more serious profiles of adverse events, especially with fulvestrant, which is associated with injection site reactions and increased musculoskeletal pain relative to oral SERDs.

Comprehensively, the safety profiles of oral SERDs, mostly that of elacestrant, in general were manageable and reminiscent to those of other endocrine therapies. The absence of meaningful serious adverse events (SAEs), and the range over which gastrointestinal and liver toxicities can be handled, suggests that oral SERDs are an otherwise well-tolerated treatment option in patients with endocrine resistant HR+ advanced breast cancer.

In summary, elacestrant was found to be more effective in terms of PFS and ORR especially in ESR1 -mutant patients with a manageable safety profile. These data underline the potential of elacestrant as an effective and safe front-line oral SERD, especially in endocrine-resistant cases and HR+ breast cancer, and eventually in precision-controlled treatment.

Table 1: Clinical Efficacy and Safety Comparison

Clinical Metric	Elacestrant	Camizestrant	Fulvestrant
Hazard Ratio for PFS (HR)	0.79	0.8	0.85
Overall Response Rate (ORR) (%)	36.0	30.0	20.0
Gastrointestinal AE (%)	35.0	33.0	45.0

7. Conclusion

7.1 Implication of SERD Oral Network Findings (Clinical Implication)

The evidence of this oral selective estrogen receptor degraders (SERDs) network meta-analysis has important implications on the use of SERDs to treat hormone receptorpositive (HR+) advanced breast cancer, especially in endocrine-resistant patients. Among the most exciting findings is the shown superiority of elacestrant not only to camizestrant but also to the standard endocrine treatments such as aromatase inhibitors (AIs) and fulvestrant. In particular, elacestrant demonstrated a significant increase in progression-free survival (PFS), especially in those patients with ESR1 mutations, where patients are demonstrated to have a resistance to standard endocrine therapies. This puts the elacestrant a step ahead of all oral SERD options in terms of first line therapy on patients

with endocrine-resistant HR + breast cancer as an indication with a more specific treatment mechanism of action than the more ancient treatments.

Further, the high ORR to elacestrant in this ESR1-mutant subgroup provides further support of the paramount importance of genetic profiling in informing therapy. These data support the significance of precision-guided therapy in which genomic attributes of the tumor, including ESR1 mutations, may help guide treatment selection and better patient outcomes. Oral SERDs offer a major advancement in targeted therapy to patients with endocrine-resistant HR + breast cancer and have shown higher efficacy than AIs and other conventional treatments.

Another favorable characteristic of the oral SERDs was their tolerability profile, especially that of the elacestrant, as gastrointestinal and hepatic symptomatic adverse events were reported to be manageable and did not have a substantial effect on treatment adherence. These agreeable safety profiles and the ease of oral administration make oral SERDs an attractive long-term treatment option in advanced breast cancer, where adherence in such patients is always difficult.

7.2 Shortcomings of available evidence and heterogeneity of trials

Although the results of this network meta-analysis point to high effectiveness of oral SERDs, multiple limitations have to be addressed. This is one of the major limitations, which is the heterogeneity in the incorporated trials. Differing patient populations, with various prior therapies, tumor types and co-morbidities, could contribute to a lack of generalizability of the results. As an example, the trials utilized in the meta-analysis were composed mainly of postmenopausal women, and little data existed on pre-menopausal patients or younger women. Such an imbalance in the population implies that additional studies are required that would extend the findings to all of the HR+ advanced breast cancer patients.

Furthermore, although oral SERDs demonstrated improvements in endocrine-resistant patients, the effectiveness of survival and safety advantages of such drugs is uncertain in the long run. The trials considered in this meta-analysis were characterized by having fair follow-up durations, and longer follow-up studies are necessary to determine the longevity of the PFS benefits and the long-term effect on the overall survival (OS). Limited OS data in the trials indicate that oral SERDs may have delayed progression benefits but overall survival effects may not significantly impact until longer term data are forthcoming.

Also, ESR1 mutation testing is a crucial consideration in determining which patients will derive the most clinical benefit of oral SERDs. The studies differed in the use of ESR1 mutation testing to select patients and these differences may have influenced the results. Further studies are required to further optimize the use of biomarker-informed approaches that will allow the right selection of oral SERDs to assure the healthcare experts that the therapies are deployed in the most suitable patients.

7.3 Serendipity Drug Therapy -Irrespective of Other Precision Meds?

The findings of this network meta-analysis highlight the increased use of oral SERDs in precision-based treatment of HR+ advanced breast cancer, especially those patients with endocrine resistance. Nevertheless, a few perspectives need to be considered in the future to further streamline the approach to the use of oral SERDs and broaden the spectrum of their implementation:

Future Long-Term Outcome studies: Long-term clinical outcomes studies on oral SERDs, overall survival (OS) should also be carried out and especially whether the PFS improvements seen in clinical trials can lead to prolonged survival. Long-term follow ups will play a pivotal role in determining the actual role of these therapies in terms of long term disease control.

Development of Biomarkers: Since ESR1 mutations are so important in the development of endocrine resistance, it is important to conduct future studies about biomarker-based permutations to treatment. Further prospective studies should consider ESR1 testing as a regular feature of the clinical practice to make decisions about whether oral SERDs may be beneficial to the impacted patients. Other possible biomarkers, i.e., PIK3CA mutations or PTEN loss, should also be considered as further evidence to screen patients with potentially more successful treatment with oral SERDs.

Combination Therapies: Yet another novel area of future research that is promising is the exploration of oral SERDs with other targeted therapy or other immunotherapies. Emerging data investigating the combination of SERDs with agents that target the PI3K/Akt pathway, CDK4/6 inhibitors, or PD-1/PD-L1 inhibitors may further enhance the benefit of oral SERDs to treat patients with a multi-drug resistance or those who have progressed on a prior therapy.

Pre-Menopausal Patient Population: Although the results are promising in postmenopausal women, pre-menopausal patients still lack studies to establish the best mode of treatment in such population. Studying the

effectiveness of the combination of oral SERDs and ovarian suppression will be a part of the journey toward offering a good treatment modality to younger women with HR+ advanced breast cancer.

Real-World Data: Lastly, real-world data are to be gathered as an addition to the clinical trials one, examining treatment effects in a more diverse population, with multiple comorbidities and exposure to real-world treatment regimens. It would help ascertain how the use of oral SERDs works in real-world practice and not only in the confines of a controlled clinical trial.

Finally, the oral SERDs have demonstrated great promise to treat HR+ advanced breast cancer that has become resistant to endocrine therapy especially among patients harboring mutations in ESR1. As clinical evidence will further develop, the therapies are likely to be a fundamental part of precision oncology in the treatment of breast cancer. To ensure the sustainable integration of oral SERDs in clinical practice, there will be a need to continue investigating biomarker-driven approach, combination-based treatment, and longer-term safety.

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Conflicts of interest

The authors have no conflicts of interest to declare

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