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Conference Summary

Clinical Advances in the Treatment of Early and Advanced High-risk Breast Cancer

Highlights from the ESMO 2023 meeting

Abstract

The European Society for Medical Oncology (ESMO) Congress, 2023, which was held in Madrid, Spain, witnessed participation from researchers globally. Experts from various fields of oncology discussed advances in the diagnosis and screening of various cancers, existing and emerging cancer therapies, data from clinical trials, and cancer nursing avenues.

This summary article highlights the key aspects of managing early and advanced hormone receptor positive (HR+), and human epidermal receptor 2 negative (HER2-) breast cancer based on information from abstracts presented at the conference. The abstracts describe the efficacy of abemaciclib — a cyclin-dependent kinase (CDK) inhibitor, the impact of treatment adherence on efficacy, and emerging clinical data on imlunestrant — a selective oestrogen receptor degrader.

Efficacy of abemaciclib in high-risk early breast cancer – findings from the monarchE study

Abemaciclib is an oral selective inhibitor of CDK4 and CDK6, which has been approved in combination with endocrine therapy for the treatment of HR+/HER2- advanced breast cancer.

The monarchE study evaluated the safety and efficacy of abemaciclib in patients with high-risk node-positive, early-stage, HR+/HER2- breast cancer. Abemaciclib treatment as an adjuvant to endocrine therapy, resulted in significant improvement in Invasive Disease-Free Survival (IDFS) and Distant Relapse-Free Survival (DRFS). Furthermore, treatment benefits are sustained beyond 2 years of discontinuing treatment.

The carryover benefit of abemaciclib was found to sustain for up to 5 years after stopping treatment at 2 years, (while continuing endocrine therapy) with absolute improvement rates of 7.6% and 6.7% in IDFS and DRFS, respectively. Extended follow-up data will reflect potential benefits in overall survival. Overall, clinically meaningful and robust reductions were noted in the risk of invasive and incurable metastatic disease in high-risk patients. Findings from the monarchE trial thus, support the use of abemaciclib in the management of high-risk patients with HR+/HER2- breast cancer.

Goetz and coworkers discussed the prognostic and predictive impact of biomarkers on treatment outcomes and benefits of abemaciclib by analysing data from the monarchE study, focusing on oestrogen receptor (ER)/progesterone receptor (PR) and Ki67 (a marker of cell proliferation) expression. Their findings revealed that abemaciclib treatment benefited all patients regardless of their ER/PR and Ki67 expression levels. Similar benefits in terms of IDFS were noted for patients with ER+/PR+ and ER+/PR- tumours. Notably, although Ki-67 ≥20% and PR negativity were associated with poorer clinical outcomes, they were not predictive of abemaciclib treatment benefit.

Given that biomarkers did not stratify patients in terms of treatment benefits, the authors suggest that abemaciclib may be selected as the adjuvant treatment of choice for high-risk patients. Further, robust and sustained IDFS and DRFS benefits support its use in patients who have not responded well to chemotherapy and endocrine therapy. However, since benefits are sustained beyond two years, it may be important to ascertain the ideal duration of treatment while weighing the risk versus benefit of the treatment.

O'Shaughnessy and colleagues discussed the impact of dose reduction on treatment efficacy by analysing data from the monarchE study. Findings revealed that 44% of patients from the study required dose reduction to manage treatment-related adverse effects (AEs). Also, dose reduction did not significantly alter IDFS; relative dose intensity groups of ≤66%, 66%-93%, and ≥93% had IDFS rates of 87.1%, 86.4%, and 83.7%, respectively. Given that dose reduction of abemaciclib does not significantly impact its efficacy, it may be considered an effective alternative to treatment discontinuation in case of AEs. However, dose reduction *a priori* in the absence of toxicity may not be ideal and may compromise treatment efficacy. Moreover, the authors emphasized on why it is more practical to titrate the drug to lower doses while starting with the standard dose if AEs emerge, rather than starting with a lower dose with lesser efficacy.

Regular initial follow-ups can help clinicians decide upon the most optimal dose that ensures efficacy with minimal toxicity, as well as help patients draw treatment benefits.

Abemaciclib not only induces cell-cycle arrest, but also promotes apoptosis, and therefore, bears curative potential in the treatment of patients with a high risk of recurrence. Overall, these results highlight the potency of abemaciclib in the treatment of high-risk breast cancer.

Emerging data on CDK inhibitors like abemaciclib are revolutionizing the treatment of patients who do not respond well to traditional chemotherapy or endocrine therapies using aromatase inhibitors.

Treatment adherence

Treatment adherence and persistence can significantly impact treatment efficacy, particularly in patients who are taking long-term oral medications. In this regard, supportive care programs have been shown to positively influence patients by preventing incorrect medication intake and dosing, decreasing treatment-related symptoms, and reducing hospitalization due to AEs.

Welslau and coworkers from Germany presented data from IMPACT — a prospective, randomized study investigating the impact of the MASCC oral agent teaching tool (MOATT) on persistence and therapy management, compared to local routine patient coaching.

Patients with HR+/HER2- advanced breast cancer receiving abemaciclib plus endocrine therapy were randomized to receive MOATT coaching or local coaching (LC). At 24 weeks, the authors assessed patients' persistence and compliance rate, number of dose reductions, and dose interruptions.

Notably, the study revealed a persistence probability of 0.71 with LC and 0.82 with MOATT at 24 weeks. Further, in the LC vs. MOATT group, the rates of permanent discontinuation (14.1% vs. 7.8%), dose reductions (24.5% vs. 17.2%), and therapy interruptions (14.9% vs. 10.1%) were significantly higher. Additionally, coaching with the MOATT tool reduced the probability of permanent therapy discontinuation by 40% within the first 6 months. Overall, these findings deem the MOATT educational tool as a valuable strategy to improve patient adherence and therapy management with oral treatments such as abemaciclib.

Further, the authors suggest that educating nurses and other support providers in addition to patients can help improve adherence and treatment efficacy.

Additionally, the conference highlighted other autonomous digital education and monitoring platforms that incorporate patient-reported outcomes and feedback. Such systems can help patients address AEs in a timely manner and improve their quality of life.

Imlunestrant – emerging clinical data

Imlunestrant is an investigational oral selective ER degrader (SERD) that has demonstrated a favourable pharmacokinetic and safety profile along with preliminary efficacy in heavily pre-treated patients with ER+ early as well as advanced breast cancer. Researchers presented analyses from the EMBER study which investigated the safety and efficacy of imlunestrant as a monotherapy or in combination with abemaciclib in early breast cancer and metastatic settings.

Neven and colleagues investigated the pre-operative effect of three different doses of imlunestrant — 200/400/800 mg in post-menopausal women with operable ER+/HER2- untreated early breast cancer. They evaluated changes in pharmacokinetic biomarkers including ER, PR, and Ki67 expression, and the safety and tolerability of imlunestrant treatment.

Remarkably, treatment led to a significant decrease in the level of the evaluated biomarkers at all three doses, suggesting effective targeting by the drug. Moreover, treatment with imlunestrant did not result in any treatment-emergent AEs or discontinuation and was tolerated well among all patients. These findings support the development of imlunestrant as an adjuvant therapy in early and advanced breast cancer.

Jhaveri and coworkers presented clinical data of imlunestrant in combination with everolimus (mTORC1 inhibitor) or alpelisib (PI3K inhibitor). Patients with advanced disease who had been heavily pre-treated were included: prior oestrogen therapy (100%), CDK4/6i (100%), fulvestrant (35%) and chemotherapy (17%).

Analysis revealed that a combination of imlunestrant with either everolimus or alpelisib demonstrated a better efficacy profile in terms of progression-free survival compared with imlunestrant treatment alone. Safety profile was consistent with those previously reported for everolimus or alpelisib.

Compared to monotherapy, a combination of endocrine therapy with CDK4/6i inhibitors or other newer agents like imlunestrant holds significant promise for advanced and metastatic disease which responds poorly to traditional therapies.

Conclusions

- **IDFS and DRFS should be considered as surrogate factors rather than overall survival for selecting abemaciclib treatment in high-risk patients**
- **Selection of a monotherapy or treatment modality should be based on clinical and molecular features of the disease and patients' specific features**
- **Dose reduction of abemaciclib does not impact its efficacy and should be encouraged to manage AEs instead of treatment discontinuation**
- **Abemaciclib holds promise in the treatment of patients who respond poorly to endocrine therapy and chemotherapy, or those with a high clinical risk of recurrence, irrespective of their ER/PR and Ki67 status**
- **Digital education tools and support programs can help improve treatment adherence and treatment effectiveness**
- **Imlunestrant in combination with abemaciclib or other therapies has demonstrated promising benefits and may be considered in adjuvant settings**