Everolimus (EVE) is an inhibitor of mammalian target of rapamycin (mTOR), a protein kinase central to a number of signalling pathways regulating cell growth and proliferation. Data from preclinical and phase I/II clinical studies indicated that adding EVE to trastuzumab (TRAS) plus chemotherapy may restore sensitivity to and enhance efficacy of human epidermal growth factor receptor 2 (HER2)-targeted therapy. The international BOLERO-3 phase III study evaluated the addition of EVE to TRAS plus vinorelbine.

Adult women with HER2-positive advanced breast cancer who received prior taxane therapy and experienced recurrence or progression on TRAS were randomized 1:1 to receive either EVE or placebo (5 mg/day) in combination with weekly TRAS and vinorelbine (25 mg/m2). The primary endpoint was progression-free survival (PFS). Secondary endpoints included overall survival (OS), response rate, clinical benefit rate, safety, quality of life and pharmacokinetics.

The trial accrued 569 patients having undergone previous therapy including TRAS (100%), a taxane (100%) and lapatinib (28%) between October 2009 and May 2012. Patients’ median age was 54 years; 76% had visceral metastases, 5% had stable brain metastases, 56% had hormone receptor-positive disease, 33% had an Eastern Cooperative Oncology Group performance status of 1 or 2, and 41% had 3 or more metastatic sites. Median number of prior chemotherapy lines in the metastatic setting was 1. As of February 4, 2013, 396 PFS events were reported.

Data from the interim analysis, presented at the conference, reported median PFS of 7.00 months in the EVE group compared with 5.78 months in the placebo group (hazard ratio [HR] 0.78; 95% confidence interval [CI] 0.65–0.95; p=0.0067). EVE appeared to improve PFS in hormone receptor-negative cases (HR 0.65; 95% CI 0.48–0.87) but not in hormone receptor-positive cases (HR 0.93; 95% CI 0.72–1.20). Patients who had received prior adjuvant or neoadjuvant TRAS derived more benefit from EVE than those who had not.

The overall response rate (complete or partial) was 40.8% in the EVE group and 37.2% in the placebo group (p=0.2108). Clinical benefit rate (objective response or stable disease at 24 weeks or more) was 59.2% with EVE vs 53.3% with placebo (p=0.0945). Quality-of-life measures also showed no differences between treatment arms. Differences in OS (220 deaths: 36.8% in patients on EVE patients and 41.1% in patients on placebo) did not reach statistical significance at the time of the interim analysis. Completion of the analysis is planned once 384 deaths have occurred.

Commentary: The phosphatidylinositol 3-kinase (PI3K)/AKT pathway, of which the mammalian target of rapamycin (mTOR) protein is an important component, is often dysregulated in breast cancer, and mTOR signalling plays a key role in cell growth and proliferation and regulation of apoptosis. In breast cancer, the PI3K/AKT pathway can be activated by the human epidermal growth factor receptor (HER) family, the insulin-like growth factor receptor (IGFR) and the estrogen receptor (ER). Resistance to trastuzumab may be caused by hyperactivation of this PI3K/mTOR pathway and treatment with mTOR inhibitors may potentially overcome trastuzumab resistance.

Everolimus is an inhibitor of mTOR currently approved in Canada for the treatment of postmenopausal women with hormone receptor (HR)-positive, HER2-negative advanced breast cancer in combination with the steroidal aromatase inhibitor exemestane, after recurrence or progression following a nonsteroidal aromatase inhibitor. Trastuzumab is a key component of treatment in HER2-positive metastatic breast cancer (MBC), but tumours eventually become resistant to this agent. However, results from phase I and II clinical studies suggest that adding everolimus to trastuzumab plus chemotherapy may overcome trastuzumab resistance in HER2-positive MBC.

In the BOLERO-3 study, patients with metastatic or locally advanced HER2-positive breast cancers were eligible for enrolment if they had received prior taxanes and if there was disease progression (PD) on trastuzumab during adjuvant or metastatic therapy. They could also participate if there was PD within 4 weeks of the last dose of trastuzumab for metastasis. The trial met its primary endpoint of improved PFS with the addition of everolimus to trastuzumab and vinorelbine, and it is the first phase III study showing a benefit of mTOR pathway inhibition in HER2-positive MBC.

There were, however, no significant differences in ORR, CBR or overall survival or global health status scores. There were no unexpected adverse events, with increased incidence of stomatitis, pyrexia, decreased appetite, hyperlipidemia, hyperglycaemia, anaemia and febrile neutropenia, and a low incidence of noninfectious pneumonitis with everolimus.
The BOLERO-3 study demonstrates clinical activity of the combination of an mTOR inhibitor with chemotherapy and trastuzumab in a “trastuzumab-resistant” population. However, the effect is modest, with a 1.2-month improvement in PFS and with no differences noted in other efficacy outcomes, and everolimus is associated with increased toxicities. There are other active agents in the setting of trastuzumab resistance. The EMILIA trial studied women with HER2-positive MBC who had PD while on trastuzumab for metastasis or disease recurrence during or within 6 months of completing adjuvant trastuzumab. Patients received capecitabine and lapatinib or trastuzumab emtansine (T-DMI), a novel antibody-drug conjugate. There was a 3.2-month absolute improvement in PFS and a 5.8-month absolute improvement in OS, favouring T-DMI. Other strategies include continuing trastuzumab in combination with a different chemotherapy backbone such as capecitabine, or using the dual EGFR/HER2 tyrosine kinase inhibitor, lapatinib in combination with chemotherapy. These strategies all improved PFS compared to standard therapy and with similar hazard ratios, but the EMILIA study was the only trial to show an OS benefit with T-DMI. It is unknown how these different strategies compare to mTOR inhibition used in the BOLERO-3 trial in treating women with advanced trastuzumab-resistant HER2-positive breast cancers. The overall survival data is not yet mature in the BOLERO-3 trial, with 384 deaths needed for a final OS analysis expected in 2014. Certainly, if an OS benefit emerges, the addition of everolimus to standard systemic therapy will have to be considered in these patients.

An interesting observation in the BOLERO-3 study was the significant benefit of everolimus in the HR-negative population, but not in the HR-positive cases. There is known crosstalk between the mTOR pathway and ER signalling, and therefore, blocking both pathways may be essential in this population. The other subgroup that had additional benefit from everolimus were those with prior adjuvant or neoadjuvant trastuzumab. The optimal dose of everolimus is also unknown. In BOLERO-3, everolimus was dosed at 5 mg once a day (od) in combination with chemotherapy, compared to 10 mg od in other trials. Whether a higher dose of everolimus in this trial confers additional benefit is unknown and would undoubtedly be associated with increased toxicities.

In summary, the BOLERO-3 trial showed activity of the combination of the mTOR inhibitor, everolimus with vinorelbine and trastuzumab in patients with tumours deemed to be trastuzumab-resistant. However, the improvement in PFS of 1.2 months is modest, with no improvement yet in OS, ORR or CBR, and there are additional toxicities with everolimus.

Trials that compare the different strategies to overcome trastuzumab resistance are required as well as a critical need to identify biomarkers that predict sensitivity/resistance to mTOR inhibition, and such studies are ongoing. It may be that mTOR inhibition is essential earlier in the treatment trajectory for HER2-positive MBC, and whether the combination of trastuzumab and mTOR inhibitors upfront enhances tumour sensitivity to trastuzumab is unknown. The BOLERO-1 study is exploring the combination of everolimus and paclitaxel and trastuzumab as first-line therapy for HER2-positive MBC. The trial is completed but there are no results at this time.

Mature survival data from BOLERO-3 are eagerly awaited, and until further information is available, everolimus cannot be endorsed as a standard of care in this HER2-positive MBC population.

**References:**