JSMO/JASTRO Joint Symposium

‘Breast cancer treatment strategy from biological perspective’

### JS4 – 1 HISTOLOGICAL SIGNIFICANCE OF INTRINSIC SUBTYPE CLASSIFICATION

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For a long time, biological properties of breast cancer have been classified histologically in view of histological type and grades. Although these histological classifications were effective for the description of pathology report and for the prediction of patients’ prognosis, they were not very specific for the prediction of response of the cancer cells to systemic drug therapies. In 2000, Perou et al. proposed the molecular classification of breast cancer based on molecular profiles identified by using DNA microarray technique. They classified invasive ductal/lobular carcinomas and ductal carcinoma in situ into five subtypes: luminal A, luminal B, HER2 (-erbB-2)-enriched, basal-like, and normal breast-like. These subtypes were not only correlated with patient prognosis but also useful for choosing effective drug therapies to patients. Because the assay system of molecular classification was expensive and was not established for diagnostic use, a surrogate ‘intrinsic subtype’ classification has come to be used widely. In the ‘intrinsic subtype’ classification, invasive breast cancers were categorized into four groups according not only to the expression status of hormone receptors (HR) and HER2 but also to Ki67 labeling index. If Ki67 labeling index is unreliable, substitution by histological/nuclear grade is allowed. Therefore, today’s pragmatic ‘intrinsic subtype’ classification is based on the markers for indication of hormonal therapy and anti-HER2 therapy and a marker for tumor cell proliferation. Luminal A is defined as HR(+)HER2(−)/Ki67-low, luminal B as either HR(+)HER2(−)/Ki67-high or HR(+)HER2(+), HER2-enriched as HR(−)/HER2(+), and triple-negative breast cancer (TNBC) as HR(−)/HER2(−). Problems remain in the classification in the cut-off value of the HR status; the method and cut-off value on Ki67 measurement; retesting with in situ hybridization of immunohistochemically HER2-equivocal cases; and subclassification of TNBC according to biological properties and sensitivity to therapies. Detailed histopathological and/or immunohistochemical examinations based on further research data might aid for much more useful classification toward individualized therapies.

### JS4 – 2 THE ROLE OF SENTINEL NODE BIOPSY AND LOCAL TREATMENT OF BREAST CANCER

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Sentinel node biopsy has been developed to assess accurately the axillary nodal status without removing most of the axillary contents. The sentinel node is defined as the first node in the lymphatic basin that receives the primary lymphatic flow. The sentinel node biopsy has become the standard of care for the patients with clinically negative breast cancer. The elimination of axillary clearance is regularly indicated for negative sentinel node patients through the multicenter studies. The recent challenge is the preservation of axilla for positive sentinel node patients. The ACOSOG Z0011 study showed the safety of avoiding the routine use of axillary dissection for sentinel node metastatic patients. However, we should consider the potentiality of non-sentinel axillary lymph node metastases and the expansion of radiation fields for the axilla. We developed a nomogram as a predictor of non-sentinel axillary lymph node metastases with positive sentinel nodes, based on Japanese large dataset. This research was analyzed by using a clinical database of 11,228 Japanese breast cancer patients who registered to cohort study as the sentinel node biopsies between March 2008 and October 2009 in Japan. We reviewed data retrospectively to extract patients with sentinel node metastases who underwent complementary axillary dissection. Tumor size (P < 0.001), lymphatic invasion (P < 0.001), and the size of SN metastases (P < 0.001) were associated with non-sentinel node metastases in multivariate analysis. Based on the multivariate analysis, we developed a nomogram to predict the likelihood of non-sentinel node metastases in breast cancer patients with sentinel node involvement. The discriminatory ability of our nomogram, as measured by the AUC, was 0.712. Validation study and prospective registered study are necessary for the elimination of axillary clearance for positive sentinel node patients in the future investigation.

### JS4 – 3 RECENT PROGRESS AND FUTURE PERSPECTIVE OF ENDOCRINE THERAPY FOR BREAST CANCER

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Endocrine therapy is the classical target therapy applying to major part of breast cancer patients. At present, there are sub-classes of drug called aromatase inhibitor (AI), selective estrogen receptor modulator (SERM), selective estrogen receptor down-regulator (SERD), progestin and estrogen derivatives. Although novel predictive factor for endocrine therapy has never been added to date other than the presence of ER and/or PgR, recent progress gave us some insight of such factors related to patient herself. CYP2D6 genotype for tamoxifen metabolism and body mass index for AI response are those arising from individual patient difference, but related to the response of drug in some degree. In addition, combination with other molecular pathway drugs such as anti-HER2 agents, mTOR inhibitor and anti-angiogenesis drug have been intensively investigated, showing double, triple or more simultaneous pathway blocking approach may have dramatic response to hormone receptor (HR) + breast cancer. From the point of view that these HR + tumors generally showed poor response to conventional chemotherapy, these approaches seem to be leading edge for improvement of this subtype of cancer patients.

### JS4 – 4 PROGRESS OF MOLECULAR TARGETED AGENTS AND ITS ROLE IN BREAST CANCER MANAGEMENT

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Human epidermal growth factor 2 (HER2) receptor and estrogen receptor have been regarded as the biologically relevant biomarker that plays an important role in the natural history of breast cancer. Increasing number of drugs targeting HER2 has been developed since introduction of trastuzumab and their role in the management of HER2-positive breast cancer are to be defined in on-going and future clinical trials. Combination of anti-HER2 molecular targeted treatments can produce pathological complete response in pre-operative setting, which envisons the cure of HER2-positive cancer without using cytotoxic. Moreover, some of molecular targeted drugs have shown promising results in overcoming endocrine resistance in hormone-receptor positive disease. On the other hand, effective strategy for so-called ‘basal-like’ breast cancer, which has worse prognosis compared with other subtypes, is behind in its development. Various efforts have been put to narrowing down ‘basal-like’ to further subtypes, to identify clinically relevant biomarkers and to develop effective molecular targeted treatments for this subtype. Introduction of expensive molecular targeted drugs have raised contemporary issues: valid endpoints for registration and other clinical trials need of more accurate predictive markers, quality control of biomarkers, etc. Because of limited resources, there is a need for innovative clinical trial design that enables simultaneous investigation of efficacy and rational biomarkers for newly developed molecular targeted agents. The development of appraisal system for molecular targeted drugs involving multiple stake-holders is warranted in drug-approval process and also in individual decision-making in a clinical setting.
PROGRESS AND FUTURE OF BONE-TARGETED THERAPY

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Breast cancer is known to be associated with a high incidence of bone metastases. Recent advances in treatment of breast cancer have improved the prognosis, including in patients with bone metastases, highlighting the importance of treating bone metastasis to reduce incidence of skeletal complications and improve patients’ quality of life (QOL). It has become evident that bone microenvironment such as interaction of cancer cells and osteoclasts or osteoblasts is important for establishment and progression of bone metastases. Bone-targeted therapy that modulates osteoclasts or osteoblasts has been developed recently.

Bisphosphonates (BPs), especially zoledronic acid, decrease skeletal-related events (SRE) and are commonly used for the treatment of bone metastasis. BPs have shown evidences of anti-tumor efficacy in several clinical trials, such as ABCSG-12 and AZURE. However, the outcomes of BP therapy leave room for the improvement with regards to their efficacy, safety and convenience, and other bone-targeted therapies are also being developed.

Many studies have indicated that receptor-activator of NFkappaB ligand (RANKL) plays an important role in bone resorption by osteoclasts. Denosumab is a fully human monoclonal anti-RANKL antibody, which suppresses differentiation, activation, and survival of osteoclasts by inhibiting the binding of RANKL to its receptor, RANK. In a phase III clinical trial, denosumab significantly decreased the time-to-first and time-to-first and subsequent SRE compared with zoledronic acid in advanced breast cancer patients with bone metastases, and denosumab was recently approved for bone lesions of solid cancer and myeloma. Other targeted agents such as SRC inhibitors and c-MET inhibitors are also being developed. Bone metastasis treatment for cancer patients is expected to evolve further with the development of new bone-targeted agents in the near future.