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612 Poster Session (Board #101)

Saturday, 8:00 AM-11:30 AM

ONT-380 IN THE TREATMENT OF HER2– BREAST CANCER CENTRAL NERVOUS SYSTEM METASTASES

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Background: Up to half of patients with HER2– metastatic breast cancer will develop central nervous system metastases. Surgery and/or radiation remain the mainstay of treatment for HER2– central nervous system disease as systemic treatment options have limited efficacy and are often associated with significant gastrointestinal and skin toxicity. ONT-380, a potent, selective, small molecule inhibitor of HER2 with minimal epidermal growth factor receptor-like side effects, has been associated with increased survival compared to lapatinib or neratinib in animal models of HER2– central nervous system disease. Here we describe nine patients with central nervous system metastases treated with ONT-380 in combination with other systemic therapies. **Methods:** Patients with untreated asymptomatic or post-treatment progressive central nervous system metastases were enrolled in central nervous system expansion cohorts of ongoing phase Ib studies of ONT-380 – ado-trastuzumab emtansine (T-DM1) or ONT-380 – trastuzumab/capecitabine. All patients received treatment in 21 day cycles including ONT-380 300 mg orally twice daily and approved doses of either T-DM1 or trastuzumab/capecitabine. Eligibility criteria included prior treatment with trastuzumab and a taxane, and for patients receiving trastuzumab/capecitabine, prior T-DM1. Prior lapatinib was allowed. Assessments included safety and central nervous system tumor response on magnetic resonance imaging per modified RECIST 1.1 every two cycles. **Results:** Nine patients (four with asymptomatic metastases and five with progressive disease after local therapy) have received ONT-380 plus T-DM1 (n = 5), trastuzumab (n = 4) or trastuzumab/capecitabine (n = 1) for 1-8 cycles. Eight patients are evaluable for response (at least one follow-up MRI): three partial responses (T-DM1 n = 2; trastuzumab/capecitabine n = 1) and four stable disease (T-DM1 n = 2; trastuzumab n = 2). One patient with 15% increase in target lesion underwent resection; pathology, however, revealed only necrotic tissue. Patients with PR (one with hx prior lapatinib) all had – 50% decrease in central nervous system target lesions. One non-evaluable patient (T-DM1) discontinued early due to treatment-related Grade 3 AST/ALT elevation. One other patient in the T-DM1 cohort with Grade 3 ALT/AST increase remains on study following dose reduction. No other Grade 3 ONT-380-related events have been reported. **Conclusions:** ONT-380 has previously shown activity in the central nervous system in pre-clinical models. This case series demonstrates early clinical signs of promising activity of ONT-380 against HER2– central nervous system metastases in combination with other systemic agents. Further study of the central nervous system activity of ONT-380 is ongoing. Updated results will be reported. Clinical trial information: NCT01983501, NCT02025192.

537 Poster Session (Board #25)

Saturday, 8:00 AM-11:30 AM

AN INDIRECT EVALUATION OF BONE SATURATION WITH ZOLEDRONIC ACID AFTER LONG-TERM Q4 WEEK DOSING USING PLASMA AND URINE PHARMACOKINETICS. FIRST

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Background: Zoledronic acid has a high binding affinity for human bone. This post-hoc analysis from the OPTIMIZE-2 trial evaluated whether there is evidence for bone saturation of zoledronic acid following long-term dosing at the standard every four weeks dosing. We hypothesized that if bone saturation of zoledronic acid would occur, then (i) plasma and urinary levels of zoledronic acid would increase with prolonged dosing, and (ii) switching to a reduced dosing frequency of every 12 weeks would reduce plasma and urinary zoledronic acid levels. **Methods:** OPTIMIZE-2 was a randomized, double-blind, multicenter trial in female patients with bone metastases from breast cancer who previously received long-term zoledronic acid treatment (1-7 years) with standard every four weeks (infusion time of 15 minutes). Patients were randomized (1:1) to receive zoledronic acid 4 mg IV every four weeks or every 12 weeks for one year. Zoledronic acid levels were analyzed in plasma and urine during 0-6 hours after the first dose (week 1) and after the week 36 dose in zoledronic acid-pretreated (1-7 years) patients with evaluable zoledronic acid levels (n = 38). **Results:** Baseline creatinine clearances were comparable between the zoledronic acid every four weeks (n = 21) and every 12 weeks (n = 17) groups. Pre-infusion urine and plasma concentrations (ng/ml) at either time point (week 1 and 36) were in most cases near or below the lower limit of quantification. The table shows mean of zoledronic acid excreted in urine (in % of dose) and AUC (in hours x mg/l) of zoledronic acid plasma concentrations, after the first and week 36 dose of zoledronic acid in OPTIMIZE-2. The plasma levels in the two dosing frequency groups (every four and every 12 weeks) and both time points were similar. Urine zoledronic acid levels were also similar between the two dosing frequencies at both time points. These plasma and urine levels were also similar to levels from newly dosed patients receiving every four weeks zoledronic acid dosing for the first time (Chen, et al. J Clin Pharmacol 2002; Skerjanec, et al. J Clin Pharmacol 2003). Switching zoledronic acid dosing frequency from every four to every 12 weeks did not reduce plasma and urinary zoledronic acid levels. **Conclusions:** Based on plasma and urinary zoledronic acid levels with standard and reduced dosing frequencies, our data does not suggest that prolonged treatment with zoledronic acid every four weeks results in bone saturation of zoledronic acid. Clinical trial information: NCT00320710.

First dose; every four weeks; Week 36; every four weeks; First dose; every 12 weeks; Week 36; every 12 weeks; Plasma AUC 0-6 hours 0.37 (0.03) 0.43 (0.06) 0.40 (0.02) 0.43 (0.05); Urine 0-6 hours 26.0 (4.4) 36.6 (6.6) 23.7 (5.6) 30.8 (4.7).

603 Poster Session (Board #92)

Saturday, 8:00 AM-11:30 AM

SAFETY OF TRASTUZUMAB EMTANSINE (T-DM1) IN 373 PATIENTS 65 YEARS OR OLDER WITH HER2-POSITIVE ADVANCED BREAST CANCER: A SUBGROUP ANALYSIS OF THE KAMILLA STUDY

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Background: T-DM1 is approved for HER2-positive metastatic breast cancer. A pooled analysis of T-DM1 trials (n = 884) suggested a higher rate of grade 3 adverse events in patients ≥ 65 years (n = 122) versus those < 65 (51.6 vs. 44.0%). We report the safety profile of T-DM1 in patients ≥ 65 years from the ongoing phase IIIb global safety study Kamilla. **Methods:** Kamilla enrolled patients with HER2-positive, locally advanced or metastatic breast cancer with progression after chemotherapy and a HER2-directed agent for metastatic breast cancer or within six months of completing adjuvant therapy. T-DM1 3.6 mg/kg was given every three weeks until unacceptable toxicity, withdrawal of consent, or disease progression. **Results:** As of 20 October 2014, Kamilla enrolled 2001 patients; 373 patients ≥ 65 yrs. Patients ± 65 years had a longer median time since initial breast cancer diagnosis than patients < 65 yrs (6.3 vs. 4.8 years) and a lower prevalence of brain metastases (10.2 vs. 21.6%). Median exposure was eight cycles in each group (IQR 4.0-13.0 older; 4.0-15.0 younger). Adverse events by age group, including known T-DM1-associated adverse events, are shown. The incidence of grade ≥ 3 adverse events and adverse event-related discontinuations were greater in older patients. This resulted from many small differences in adverse events rather than any single adverse event. **Conclusions:** In this largest population of T-DM1-treated pts ≥ 65 years studied to date, while overall incidence of grade ≥ 3 adverse events and discontinuation due to adverse events was greater, the most common grade ≥ 3 adverse events were infrequent and similar between age groups. Known T-DM1-associated adverse events also occurred with a similar frequency in both groups, suggesting a similar safety profile in older and younger patiets. Clinical trial information: NCT01702571.

568 Poster Session (Board #56),

Sat, 8:00 AM-11:30 AM

META-ANALYSIS OF CLINICAL OUTCOMES TO SECOND-LINE ENDOCRINE THERAPY FOR VISCERAL AND NON-VISCERAL METASTASES

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Background: A previous meta-analysis reported that patients with hormone receptor-positive visceral metastases who respond to first-line endocrine therapy benefit for as long as those with only non-visceral metastases. Here, we assess outcomes in the second-line setting. **Methods:** We meta-analyzed five phase III randomized controlled trials of second-line endocrine therapy for hormone receptor-positive breast cancer (anastrozole, exemestane and fulvestrant 500 and 250 mg; Table). All reported objective response rate, clinical benefit rate, time to progression and duration of clinical benefit. **Results:** Combined objective response rate was similar

for non-visceral metastases (10%) vs. visceral metastases (9.2%) (Peto method p = 0.485); only CONFIRM was an exception (objective response rate: 5.4% [non-visceral metastases] vs. 13.2% [visceral metastases]); Tarone's test for heterogeneity: p = 0.0014). Clinical benefit rate for non-visceral metastases (38.8%) vs. visceral metastases (31.9%) was significantly different (Peto method p = 0.001; Tarone's test: p = 0.068). Combined median duration of clinical benefit was 420 days (non-visceral metastases) vs. 338 days (visceral metastases) (odds ratio, 0.79; 95% CI: 0.68-0.91; Yusuf-Peto method p = 0.001; Tarone's test: p = 0.028). The odds ratio of time to progression (non-visceral vs. visceral metastases)

was 0.71 (0.65-0.77) (Yusuf-Peto method p = 0.001; Tarone's test: p = 0.022). **Conclusions:** Visceral and non-visceral metastases had similar overall response rates. Approximately a third of patients with visceral metastases (31.9%) achieve clinical benefit, 7% less than non-visceral metastases (38.8%). Visceral metastases which achieve clinical benefit have prolonged periods of disease control, the median being almost one year. Endocrine therapy remains the well tolerated treatment of choice for hormone-responsive disease in the second-line setting until newer agents, alone or in combination with endocrine therapy, exhibit better efficacy than endocrine monotherapy.

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563 Poster Session (Board #51)

Saturday, 8:00 AM-11:30 AM

HORMONAL TREATMENT AND LATE RECURRENCE IN EARLY-STAGE BREAST CANCER PATIENTS

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Background: Breast cancer patients who are disease free after five years of diagnosis still remain at risk of developing a late recurrence. We assessed the effect of hormonal treatment on the risk of late recurrence in early-stage breast cancer patients with hormone-receptor-positive, HER2-negative disease from a large institutional database. **Methods:** We retrospectively identified a cohort of female early-stage (I to III) breast cancer patients who had hormone-receptor-positive, HER2-negative (or not tested) disease, diagnosed between January 1997 and August 2008, who had received initial treatment at MD Anderson, and had remained disease free for ≥ 5 years. We excluded patients who had incomplete hormonal treatment data and those who received ± 10 years of HT. The primary endpoint was recurrence-free survival measured from the initial breast cancer diagnosis to the first local-regional or distant recurrence. Hormonal treatment agents were categorized as aromatase inhibitors, tamoxifen, sequential tamoxifen and aromatase inhibitors, and other. The length of hormonal treatment was categorized as "< 5 years", "5 years", "> 5- < 10 years" and "10 years". We used a multivariable Cox proportional hazard model to calculate hazard ratios and 95% confidence intervals for recurrence-free survival adjusted for patient demographics, tumor characteristics and treatments received. **Results:** We identified 2,839 patients; 155 (5.5%) developed late recurrence (median follow-up of 8.8 years, range 5-16 years). Compared to patients who received five years of hormonal treatment (72%), those who received 10 years (4.4%) had a 79% reduced risk of late recurrence (HR: 0.21; 95% CI: 0.05-0.88), while patients who received ± 5 years (14%) had an increased risk (HR: 1.88; 95% CI: 1.23-2.89), with no difference in the hormonal treatment length category "> 5- < 10 years". Compared to patients who received tamoxifen alone (32%), those who received sequential tamoxifen and aromatase inhibitors (26%) had a significantly lower risk of late recurrence (HR: 0.52; 95% CI: 0.32-0.85), with no difference for patients who received aromatase inhibitors alone or other. **Conclusions:** In this retrospective cohort, hormonal treatment duration of 10 years, and the sequential use of sequential tamoxifen and aromatase inhibitors were both factors independently associated with a significantly lower risk of late recurrence, after adjusting for several other known prognostic factors. 24s Breast Cancer-HER2/ER.

556 Poster Session (Board #44)

Saturday, 8:00 AM-11:30 AM

EFFECT OF TUMOR INFILTRATING LYMPHOCYTES AND STROMAL CD68 ON TRASTUZUMAB BENEFIT IN EARLY STAGE HER2-POSITIVE BREAST CANCER

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Background: The presence of high tumor infiltrating lymphocytes has been implicated as a predictor of pathologic complete response and decreased recurrence rates in breast cancer patients. However, there is conflicting data for the benefit of trastuzumab in the adjuvant setting for HER2 positive (HER2+) breast cancer patients with high tumor infiltrating lymphocytes. In addition, greater numbers of CD68 (+) cells (macrophage marker) in tumor stroma has been shown to be an independent prognosticator for reduced breast cancer-specific survival. **Methods:** Core biopsies from 52 Her2+ breast cancer patients treated with neoadjuvant chemotherapy with or without trastuzumab were identified. Two pathologists independently quantified stromal tumor infiltrating lymphocytes and CD68 ratio (inside the tumor infiltrating lymphocytes population) using hematoxylin/eosin and immunohistochemistry, respectively. The association of tumor-infiltrating lymphocytes and CD68 with pathologic complete response rates was determined by Mann-Whitney U, Chi-square, or Fisher's exact test. Prognostic significance of tumor-infiltrating lymphocytes and CD68 ratio on pathologic complete response rates, disease-free survival, and overall survival was assessed by Kaplan-Meier analysis and log-rank test. **Results:** The median age and follow-up for the cohort were 52.0 and 2.8 years, respectively. In the neoadjuvant setting, 40 patients received conventional chemotherapy and trastuzumab (77%) and 12 patients were treated with chemotherapy alone (23%). Overall, the pathologic complete response rate in the studied population was 40%. Eight patients (15%) had high levels of tumor infiltrating lymphocytes ($\geq$ 60%) and 20 patients (38%) had low CD68 ratio ($\pm$ 60%). A high percentage of tumor infiltrating lymphocytes was significantly correlated to low CD68 ratio ($p < 0.0001$). High levels of tumor infiltrating lymphocytes and low CD68 ratio were each associated with greater pathologic complete response rates for the cohort of patients who received neoadjuvant trastuzumab, respectively ($p = 0.05$, $p = 0.03$). Furthermore, pathologic complete response was predictive of better overall survival ($p = 0.02$) for the patients treated with neoadjuvant trastuzumab. However, these associations were no longer significant when we performed the analysis on the whole population ($p = 0.09$, $p = 0.32$). **Conclusions:** Our results show that high levels of tumor-infiltrating lymphocytes are associated with low CD68 ratio, and both are predictors of pathologic complete response in patients with HER2+ breast cancer receiving neoadjuvant trastuzumab. Importantly, pathologic complete response as determined by CD68 and tumor infiltrating lymphocytes translated into an overall survival benefit. Tumor infiltrating lymphocytes and CD68 ratio represent potential prognostic and predictive markers in patients with HER2+ breast cancer.