2119 POSTER

Clinical activity of the novel epothilone B analog, ixabepilone, across the breast cancer disease continuum

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Background: Ixabepilone is a member of a new class of antineoplastic agents, the epothilones. Ixabepilone, a semi-synthetic analog of epothilone B, was developed to overcome drug resistance mechanisms. Despite advances in breast cancer treatment, many women experience progressive disease secondary to primary or acquired resistance, which may occur from the earliest stage of disease. We report activity of ixabepilone in several settings of breast cancer.
Methods: Ixabepilone has been administered as monotherapy, 40 mg/m^2 iv over 3h on day 1 q 3 wks, as well as at the same dose in combination with capecitabine, 2000 mg/m^2 po on days 1–14. Data are presented from 5 phase 2 studies and one phase 3 study. Objective response rate (ORR), median response duration and main adverse events (AEs) were reviewed.
Results: Across the disease spectrum, ORRs in the phase 2 studies of ixabepilone ranged from 42% in the first line to 12% in multi-resistant metastatic breast cancer (MBC). In the neoadjuvant setting the pathologic complete response in breast (pCR_B) was 18%. In the large phase 3 study of anthracycline- and taxane-resistant MBC, ORR with combination therapy was 35%. In all studies, peripheral neuropathy was the most common treatment-related AE. Neuropathy was generally grade (G) 1/2; incidence of G3 ranged from 3% in the neoadjuvant population to 21% in anthracycline/taxane-pretreated disease. Neuropathy was reversible and manageable.

Setting	Phase	N	Response	Median duration
Neoadjuvant	2	164	18% pCR	N/A†
Taxane-naive MBC	2	65	42% PR‡§	8.2 mo
Taxane-resistant MBC	2	49	12% PR§	10.4 mo
	2	37	22% overall§; 3% CR‖; 19% PR	3.9 mo
Multi-resistant MBC	2	126	18%§ (12%*) PR	5.7 mo
Anthracycline/taxane-resistant MBC Ixabepilone + capecitabine	3	375	35% overall	6.4 mo

† N/A=not applicable, 4 cycles administered. ‡ PR = partial response. § By investigator. ‖ CR=complete response. *By independent radiology review.

Conclusion: Ixabepilone has consistently demonstrated antitumor activity, both as monotherapy and in combination with capecitabine, in various breast cancer settings. The antitumor activity of ixabepilone increases with earlier use.

2120 POSTER

Retreatment with trastuzumab after relapse following adjuvant trastuzumab treatment (the RHEA trial): preliminary efficacy data

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Background: Trastuzumab (Herceptin®; H) is established as the standard of care in the treatment of HER2-positive breast cancer. While new HER2-targeted therapies are emerging, it is essential to know if H can be used effectively in metastatic disease following previous adjuvant H therapy. Earlier studies of multiple lines of H-based treatment have demonstrated overall response rates of 20−30%, indicating that HER2-positive disease is not refractory to multiple lines of H (Bartsch et al. BMC Cancer 2006;6:63). The Phase II **R**etreatment after **HE**rceptin **A**djuvant (RHEA) trial is assessing whether patients (pts) who relapse following adjuvant H therapy respond to retreatment with H.
Methods: RHEA is an ongoing, Phase II, non-randomised, 2-stage, open-label, multicentre trial recruiting pts who have relapsed ⩾12 months after completing ⩾10 months of adjuvant H therapy. All pts must have central confirmation of HER2-positive primary breast cancer (IHC 3+/FISH+) and baseline left ventricular ejection fraction values of ⩾50%. H is administered as monotherapy (4 mg/kg loading dose, 2 mg/kg qw) [Cohort A] or in combination with docetaxel (100 mg/m^2 q3w × 6) or paclitaxel (175 mg/m^2 q3w × 6 or 75 mg/m^2 qw × 18) [Cohort B]. Planned cohort size is 40 pts in each. Pts are assigned to a cohort at the investigator's discretion. The primary end point is overall response rate; secondary end points include clinical benefit rate, survival and safety. Both cohorts will be analysed independently of each other. Recruitment into stage 2 will continue if ⩾1 confirmed response in Cohort A or ⩾3 confirmed responses in Cohort B are observed among the first 19 pts in a cohort.
Results: To date, 10 pts have been enrolled in the H + taxane group; all 10 have received docetaxel and 9 have undergone ⩾1 post-baseline tumour assessment. Of these, partial responses have been reported in 4 pts (duration of response 4.2−12 months) and stable disease has been observed in a further 4 pts. Seven pts in this cohort continue to receive treatment.
Conclusions: The predefined early stopping rule for the H + taxane cohort has been surpassed, with 10 pts recruited. Recruitment into both cohorts is ongoing. These preliminary data reinforce the hypothesis tested and confirm the need to further explore re-exposure to H.

2121 POSTER

Axillary recurrence after negative sentinel node procedure in breast cancer patients

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Background: Nowadays the minimal invasive sentinel node biopsy (SNB) has been installed as the standard staging method for breast cancer patients in most clinics in the Netherlands. As axillary dissection can be omitted in patients with a negative SNB, it is therefore associated with less post-operative morbidity. The reported false negative rate for SNB is about 5%. The recurrence rate is, however, less than 1%.
The aim of this analysis was to evaluate the axillary recurrence rate in patients with a negative sentinel node biopsy and the factors that can influence the false negative rate.
Methods: Since the introduction of the minimal invasive SNB in our hospital, 718 patients with invasive breast cancer and clinically negative axillary nodes underwent a sentinel node biopsy. This procedure was performed using a peri-areolar intradermal deposition of 40 MBq Tc-99m labelled human nanocolloid particles in four deposits of 0.1 cc each, in the involved quadrant of the breast the day before surgery. Prior to surgery vital blue dye (1 cc) was administered intracutaneously and periareolarly in the same quadrant to visualize the lymphatic system. With the use of a gamma detection probe (Europrobe®) the location of the nodes was determined. The sentinel node was identified in 683 patients. A negative sentinel node was found in 503 (73%) patients and in these patients an axillary lymph node dissection was not performed.
Results: In our series we found an axillary recurrence in 8 patients (1.6%) after a follow-up of 14−46 months. According to the literature surgeon experience, tumor size and location and the number of sentinel nodes removed are factors that can influence the false negative rate. The most important factor in our study is the pathologic examination: in 6 out of 8 patients the revision of original pathologic examination or new made slices were not conform the original findings. This can be attributed to sampling error.
Conclusion: The SNB is a procedure with a low clinical recurrence rate. It is thought desirable to remove more than 1 sentinel node to reduce the false negative rate. Further analysis will be neccesary to evaluate the part of sampling error and the role of individual tumor cells and how this should be treated.