436 Proffered paper oral

Trastuzumab- (H) and everolimus- (RAD001) containing regimens are safe and active when reintroduced in patients (pts) with HER2-overexpressing metastatic breast cancer (MBC) pre-treated with lapatinib

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Introduction: Appropriate treatment of patients with HER2+ MBC who have progressed after treatment with lapatinib-containing regimens is an open question. The objective of this analysis was to explore the safety and activity of RAD001, H, and paclitaxel (P) or vinorelbine (V) in patients pre-treated with lapatinib (L) to those who were not pre-treated (N-L).

Methods: This analysis was performed on pooled data from 2 multicentre Novartis-sponsored studies (NCT00426556 Ph I/II;NCT00426530 Ph I), with comparable study designs and patient populations, and conducted according to previous treatment with L. Regimens were: oral RAD001 daily (5 or 10 mg) or weekly (20 or 30 mg); weekly H 2 mg/kg IV; P 80 mg/m^2 IV D1−8-15 q4w (74 pts) or V 25 mg/m^2 IV D1−8 q3w (50 pts).

Results: In 41% of pts (51/124) prior L-based treatment was recorded. Baseline characteristics of L and N-L pts were: median age 55 and 57 years; visceral disease 88% and 71%; median number of previous chemolines for metastatic disease: 3 and 1; H-resistance, prior taxanes, and anthracyclines in 96%/97%, 98%/97%, and 76%/75% of L and N-L pts. All but 2 L-pts were considered resistant to L. A similar safety profile was observed in the two groups (Table 1). No relevant differences were recorded for mean left ventricular ejection fraction in L and N-L groups: baseline 63%(±7%) and 64%(±7%); end of therapy 62%(±7%) and 61%(±10%). Efficacy was evaluated in 41 L and 57 N-L pts. An overall response rate of 22% (9 partial responses [PR]) and 30% (3 complete responses + 14 PR) was observed in L and N-L pts, respectively. The stabilization rate was 61% in L pts and 53% in N-L pts. Survival data will be presented.

Conclusions: This exploratory pooled analysis seems to imply that L-pretreated pts benefit from H- and RAD001-containing regimens without a higher risk of toxicity.

Table 1. Most frequently reported toxicities

	Number (%) of pts experiencing treatment related adverse events	
	Lapatinib-pretreated (n = 51)	Not lapatinib-pretreated (n = 73)
Grade 3/4 neutropenia	25 (49)	44 (60)
Febrile neutropenia	4 (8)	3 (4)
Grade 3 stomatitis	8 (16)	10(14)
Grade 3 asthenia/fatigue	3 (6)	3 (4)
Grade 3 diarrhea	1 (2)	2 (3)
Grade 1/2 rash	10 (20)	20 (27)

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CLINICAL SCIENCE SYMPOSIUM

Precursors and pre-invasive lesions

437 Invited

Radiological diagnosis of precursor and pre-invasive breast lesions

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The precursor lesions of invasive breast cancer according to the WHO classification consist of lobular neoplasia (LCIS, ALH), ductal intraepithelial neoplasia (DIN) and intraductal papillary neoplasms. The DIN group includes flat epithelial atypia (FEA), atypical ductal hyperplasia (ADH) and ductal carcinoma in situ grade 1−2-3 (DCIS). In the group of the intraductal papillary neoplasms, benign intraductal papilloma, noninvasive papillary carcinoma and encysted papillary carcinoma can be found. A complex sclerosing lesion/radial scar is classified as a benign epithelial neoplasm, but as there is an increase in ADH and DCIS in these lesions, they are discussed as well.

Precursor lesions are frequently diagnosed by screening programs, performed to detect early stages of breast cancer.

Microcalcifications are the most frequent presentation of lobular neoplasia and DIN lesions. Whereas ADH was previously incidentally diagnosed in biopsies for palpable masses, the incidence of ADH increases as more biopsies are performed for BIRADS-3 and 4 microcalcifications and as larger needles are used. Approximately 80% of the comedo type DCIS shows a typical branching pattern, but 20−25% and the non-comedo DCIS fail to exhibit these characteristics. Other presentations of DCIS include a spiculated lesion, a mass (usually without calcifications) or single duct nipple discharge.

Sonography is less important in the evaluation of microcalcifications, but is excellent to guide percutaneaous biopsies for the evaluation of a radial scar, papillary and palpable lesions. Vacuum assisted biopsy has a higher accuracy compared to large core biopsy for the evaluation of precursor lesions and is therefore the preferred technique for their preoperative evaluation.

Although mammography can detect up to 83% of DCIS, it underestimates the extent of the disease. Magnetic resonance imaging (MRI) is better in predicting the extent and the multifocality of the disease.

MRI screening in the follow up of patients with ADH and LCIS is associated with a high false-positive rate resulting in unnecessary breast biopsies: differentiation between the grades of proliferation is not yet possible.

438 Invited

Pathology of early lesions: biopathology of ductal carcinoma in situ of the breast

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In situ carcinomas are neoplastic epithelial cell proliferations in the terminal ductulo-lobular units that spare myoepithelial cells and the basement membrane, considered to be a precursor of invasive carcinoma. Classifications based on nuclear grade and presence of necrosis distinguish three nuclear grades: low, intermediate and high. Molecular analyses have demonstrated the existence of two different multi-step molecular pathways based on grade (low and high) for the transition from normal epithelium to DCIS. Low-grade carcinogenesis encompasses a spectrum of lesions ranging from flat epithelial atypia, atypical ductal hyperplasia, and low-grade DCIS to low-grade invasive carcinoma, being part of the luminal A spectrum. The precursors of high-grade DCIS lesions remain unknown. Phenotypic analyses of DCIS showed that estrogens receptor expression is higher in low-grade DCIS (83−91% of cases) than in high-grade (ER positive in 37 to 74% of cases).

ERBB2 is overexpressed in 28 to 50% of all cases of DCIS and in up to 91% of high-grade cases with necrosis. DCIS can also be triple negative, i.e. ER-ve, PR-ve, ERBB2-ve and express basal-like markers such as keratin 5/6, 14 or EGFR in a lower range than that observed in invasive carcinoma, as only 5 to 7% of cases are basal-like in DCIS compared to 10 to 15% of cases in invasive carcinoma. DCIS represent only 4% of the tumors diagnosed in BRCA1 patients and are high-grade lesions, while the prevalence of DCIS in BRCA2 patients is similar to that of the general population.

Activation of oncogenes and inactivation of tumor suppressor gene through copy number alterations and mutations are numerous and complex in DCIS, are different between low- and high-grade carcinogenesis pathways, between luminal versus ERBB2 and basal-like carcinogenesis pathways. The transcriptomic analyses showed that differences are more marked between normal epithelium and DCIS than between DCIS and IDC. DCIS and IDC of the same grade share a high level of transcriptomic similarities. Molecular classes described in IDC (ERBB2, luminal A and B, basal-like) already exist in DCIS.

Reports have shown the co-existence of various grades within DCIS lesions or different ERBB2 status between invasive and *in situ* components in a single case. These observations suggest the existence of intratumoral heterogeneity of genomic alterations possibly related to intratumoral clonal diversity.