5022 POSTER DISCUSSION

Association Between Circulating Tumour Cells and Bone Turnover Markers in Patients With Breast Cancer and Bone Metastases on Treatment With Bisphosphonates (ZOMAR Study)

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Background: Quantification of Circulating Tumour Cells (CTC) has demonstrated an important role in assessing disease progression and outcomes, and pathological CTC levels are an independent prognostic factor of disease progression. The presence of bone metastases alters the balance of bone remodeling and consequently, levels of bone turnover markers (BTM). Increased levels of these biomarkers have been associated with the risk of skeletal-related events (SREs), disease progression and death. The aim of this study is to determine the relation between BTM, CTC and SREs in patients with bone metastatic breast cancer (mBC) treated with zoledronic Acid.
Patients and Methods: Observational, prospective and multicenter study. Patients with mBC; no previous bone treatment in the last 6 months prior to study entry. CTC (fluorescently labelled with nucleic acid dye 4,6-diamidino-2-phenylindole DAPI, monoclonal antibodies specific for leukocytes CD45-allophycocyanin and epithelial cells cytokeratin 8,18,19 − phycoerythrin. Cell Search System Veridex); urinary aminoterminal telopeptide of collagen I (NTX, Osteomark NTx Urine, Wampole Laboratories, USA); urinary alpha-alpha-isomer of carboxyterminal telopeptide of collagen I ($\alpha\alpha$-CTX, ALPHA Crosslaps EIA, ids, UK) and serum bone alkaline phosphatase (BALP, OSTASE BAP, ids, UK) were determined at baseline (V0) and after 3 mo of treatment (V1). Pts were treated with zoledronic acid (ZOL) at inclusion and every 3−4 weeks.
Results: Data of CTCs and BTM at basal visit (V0) and after 3 mo of treatment (V1) are presented. Population basal characteristics: mean age: 61 years; ER+: 80%; PR+: 67%; HER 2+: 18%. 52% of patients (n = 102) had detectable CTC (CTC$\geqslant$1) at V0, and 70% of them presented pathological (CTC$\geqslant$5) at V0. A significant decrease was observed at V1, 27% of patients with pathological CTC levels ($p < 0.05$). 55%, 29% and 81% patients (n = 83) presented elevated levels of NTX, $\alpha\alpha$-CTX and BALP at V0. A significant decrease was observed between V1 vs V0, of 16%, 6% and 54% of NTX, $\alpha\alpha$ -CTX and BALP levels respectively ($p < 0.05$). A positive correlation was observed between CTC and each time point with BTM ($p < 0.05$). At V1 the positive significant correlation remained for CTC and NTX and BALP ($p < 0.05$). 17 patients presented SRE between V0 and V1.
Conclusion: Over 50% mBC patients presented basal detectable CTC levels (CTC$\geqslant$1), and the majority − 70% had pathological levels (CTC$\geqslant$5). A significant decrease was observed at V1 in 27% patients with pathological CTC levels ($p < 0.05$). ZOL significantly reduced CTC and BTM levels after 3 mo of treatment. Due to the low number of SRE, no correlation was observed either with CTC or with BTM after 3 mo of treatment. Longer follow up is needed.

5023 POSTER DISCUSSION

Cyfra 21-1 Correlation With Circulating Tumour Cells (CTC) Detection and Patient Outcome in Metastatic Breast Cancer: Results of a Substudy of the Prospective IC 2004−06 Trial

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Background: The Cyfra 21-1 epitope is a polypeptide originating from cytokeratin-19 fragments possibly released by cell death and was an interesting serum marker in small and/or retrospective studies in breast cancer. On the back of circulating tumour cell (CTC) detection, the prospective IC 2006−04 study planned serum markers (CEA, Ca15.3, Cyfra 21-1) measurements.
Methods: Metastatic breast cancer patients were included in a multicentric non-interventional study before the start of the 1st line chemotherapy. Blood biomarkers, including CTC detection (CellSearch, 5CTC/7.5 ml), were analyzed at 4 different times: before the start of the chemotherapy, before cycle 2 (*ie* mostly at day 21), at first tumour evaluation (*ie* before cycle 3/4) and at tumour progression.
Results: 191 of the 267 patients included had Cyfra 21-1 assessed at inclusion. CTC level was 5CTC/7.5 ml in 44% of the cases. Cyfra 21-1>ULNV (in 65% of pts) was not correlated with tumour ER/PR/HER2 status but strongly correlated with PS ($p = 8 \times 10^{-4}$), number of metastatic sites ($p = 0.0001$), Ca15.3 ($p = 0.009$), CEA ($p = 0.005$), LDH ($p = 7 \times 10^{-8}$) and CTC detection ($p = 2 \times 10^{-6}$).
Logistic regression showed that LDH ($p = 0.0005$) and CTC ($p = 0.0004$) were the two independent predictors of Cyfra 21-1 elevation. Baseline Cyfra 21-1>ULNV was associated with early tumour progression (RECIST, $p = 0.03$). In multivariate analysis including standard biomarkers (without CTC), baseline Cyfra 21-1 was independently associated with PFS ($p = 0.008$, RR), together with PS ($p < 0.001$), triple-negativity ($p < 0.001$) and CEA ($p = 0.02$). Multivariate analysis with CTC, subsequent Cyfra 21-1 analyses (cycles 2, 3−4 and progression) and correlation with tumour response and PFS will be will be shown at the meeting.
Conclusion: Cyfra 21-1 is a commonly elevated serum marker in metastatic breast cancer and has an independent prognostic value. Although highly correlated, Cyfra 21-1 appears to be more frequently positive in metastatic breast cancer patients than CTC count. Multivariate analyses comparing CTC and Cyfra 21-1 at different time points will be shown at the meeting.

5024 POSTER DISCUSSION

Clinically Used Breast Cancer Markers are Heterogeneous Throughout Tumour Progression

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Background: As of today, clinical management of metastatic breast cancer patients is frequently based on primary tumour marker status.
Methods: The cohort includes breast cancer patients in the Stockholm health care region who relapsed during January 1, 1997 to December 31, 2007. Biochemical or immunohistochemical (IHC)/ immunocytochemical (ICC) methods were used for determination of oestrogen receptor (ER), progesterone receptor (PR) and Her2-neu amplification (HER2) (confirmed also by Fluorescence In Situ Hybridization for IHC/ICC 2+ and 3+).
Results: Information on ER and PR in multiple relapse sites was assessed in 119 and 116 patients, respectively. Interestingly, the markers were unstable throughout tumour progression also in the advanced setting. For ER, 33.6% of patients had discordant ER status between different sites of relapse, whereas 36.1% and 30.3% of patients were stable positive and negative, respectively. Further, 16.0% of patients changed ER status from positive to negative, 12.6% changed from negative to positive, and 5.0% altered ER status forth and back throughout tumour progression (labelled heterogeneity in table). For PR, 30.2% of patients altered their hormone receptor status with a majority of the change from PR positive to negative (19.8%).

Table: Information on multiple sites of relapse in the same patient: Hormonal receptor discordance in the relapse setting

ER*	Hormonal receptor status			
		PR*		
	Number of patients	Percent	Number of patients	Percent
Between relapse sites				
Stable positive	43	36.1	15	12.9
Stable negative	36	30.3	66	56.9
Positive to negative	19	16.0	23	19.8
Negative to positive	15	12.6	8	6.9
Heterogeneity	6	5.0	4	3.5
Total	119	100.0	116	100.0

*Cut-off value of 0.05 fmol/μg DNA and 10%, for monoclonal antibody based biochemical and IHC/ICC methods, respectively.

Conclusions: Breast cancer patients alter hormone receptor status throughout tumour progression. Hence, this dynamics will make clinical

decisions harder bringing forward the potential need of taking biopsies in a continuous manner also in the advanced setting to enable optimized treatment decisions for the patient.

5025 POSTER DISCUSSION

Phase 3 Study of Iniparib (I) Plus Gemcitabine (G) and Carboplatin (C) in Metastatic Triple-negative Breast Cancer (mTNBC) − Results of an Exploratory Analysis by Prior Therapy

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Background: Iniparib (I) (BSI-201), an anticancer agent whose mechanism of action is under active investigation, demonstrated improved efficacy outcomes in a randomized phase 2 study when combined with GC in patients (pts) with mTNBC. A confirmatory randomized, open-label phase 3 study (Clinicaltrials.gov number NCT00938652) was conducted (O'Shaughnessy *et al.* ASCO 2011), but did not meet the pre-specified criteria for its co-primary endpoints of overall survival (OS) and progression-free survival (PFS). Here we report results of an exploratory subset analysis from the phase 3 study according to number of prior therapies received.
Methods: Pts were stratified based on receipt of either 0 (n = 297) or 1−2 (n = 222) prior chemotherapies (CT) for metastatic disease. Randomized pts (1:1) received either GC or GCI and, upon central confirmation of disease progression on GC, crossover to GCI was permitted.
Results: From July 2009 to March 2010, 519 pts were randomized. In the overall pt population and within each stratum (1st vs. 2nd/3rd line), demographics, disease characteristics, and prior CT received, were balanced between treatment arms. An exception was receipt of prior bevacizumab (bev) which, although balanced between treatment arms, differed according to strata; 5% of pts in the 1st line received prior bev compared to 63.2% in the 2nd/3rd line. Analysis of PFS and OS by number of lines of therapy − ITT population is detailed in the table.

Prior lines of therapy	GC N	GC Median, mos (95% CI)	GCI N	GCI Median, mos (95% CI)	HR (95% CI)	P-value*
OS†						
All	258	11.1 (9.2–12.1)	261	11.8 (10.6–12.9)	0.88 (0.69–1.12)	0.28
0	149	12.6 (11.9-NC)	148	12.4 (10.6-NC)	1.1 (0.78–1.56)	
⩾1	**109**	**8.1 (6.6–10.0)**	**113**	**10.8 (9.7–13.1)**	**0.65 (0.46–0.91)**	
PFS†						
All	258	4.1 (3.1−4.6)	261	5.1 (4.2−5.8)	0.79 (0.65–0.98)	0.027
0	1 9	4.6 (3.9−5.7)	148	5.6 (4.2−6.9)	0.88 (0.67–1.17)	
⩾1	**109**	**2.9 (1.9−4.1)**	**113**	**4.2 (3.8−5.7)**	**0.68 (0.50–0.92)**	

*2-sided unstratified log-rank test; † pre-specified alpha 0.04 for OS and 0.01 for PFS.

GCI was tolerable with a clinically manageable side effect profile, and adverse events were consistent with the safety profile of GC alone.
Conclusions: In this exploratory analysis by prior therapy, an efficacy benefit was observed in pts receiving GCI vs. GC as 2nd/3rd-line therapy for mTNBC; benefit was not seen for the 1st-line subgroup of pts. The significance of these findings remains uncertain and will need to be validated in future studies.

5026 POSTER DISCUSSION

Sorafenib (SOR) Plus Chemotherapy (CRx) for Treatment (tx) of Patients (pts) With HER2-negative Locally Advanced (adv) or Metastatic (met) Breast Cancer (BC) and Prior Bevacizumab (BEV): Subgroup Analysis of AC01B07

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Background: SOR is a multikinase inhibitor that targets angiogenesis and proliferation. AC01B07 is a double-blind, randomised, placebo (PL)-controlled phase 2b screening trial that assessed SOR when added to CRx in pts with HER2-negative adv BC whose disease progressed during/after a BEV regimen. Primary analysis showed adding SOR significantly prolonged the primary endpoint of progression-free survival (PFS). Tx was tolerable with events consistent with the individual agents. Survival data are pending. Here we report PFS results for predefined and exploratory subgroups.
Methods: Pts were randomised to CRx+SOR (400 mg po twice daily [BID]) or matching PL. The initial CRx used was gemcitabine (GEM 1000 mg/m^2 IV, days 1, 8 of 21) but capecitabine (CAP 1000 mg/m^2 po BID, days 1−14 of 21) became an alternative option later in the study. (NCT00493636; Sponsor, ACORN)
Results: A total of 160 pts were assigned to SOR (n = 81) or PL (n = 79). Prior BEV was for met BC in 156 pts and non-met BC in 4. As expected, more pts received GEM (n = 132) than CAP (n = 28). Overall, PFS was significantly longer for SOR+CRx vs PL+CRx (median 3.4 vs 2.7 mo; hazard ratio [HR] 0.65; 95% confidence interval [CI] 0.45–0.95; 1-sided $P = 0.01$). PFS data across subgroups consistently favored SOR over PL (Table), with the exception of the small (n = 28) CAP subgroup.
Conclusions: Planned subgroup analyses, including the hormone receptor negative subgroup, were consistent with the overall PFS results from AC01B07, demonstrating activity for SOR when added to CRx in the phase 2 setting. This supports further clinical development in all subsets of CRx-treated pts. More studies are needed to understand the disease course and tx options after BEV tx in HER2-negative BC and the various subgroups.

	n	Median PFS (mo)		HR (95% CI)
	n	SOR+CRx	PL+CRx	
Predefined				
Hormone receptor				
Positive	106	3.6	2.7	0.75 (0.48–1.18)
Negative	50	3.1	2.6	0.57 (0.30–1.09)
Visceral disease				
Yes	135	3.2	2.6	0.64 (0.43–0.95)
No	25	4.0	2.9	0.79 (0.29–2.14)
Combination CRx				
GEM	132	3.2	2.5	0.54 (0.36–0.81)
CAP	28	3.6	5.7	2.39 (0.79–7.23)
Exploratory				
Duration of BEV				
⩾6 mo	85	3.1	2.5	0.63 (0.38–1.03)
>6 mo	74	3.9	3.1	0.73 (0.42–1.26)
Time from progression on BEV (met)				
⩽1 mo	129	3.4	2.7	0.65 (0.43–0.97)
>1 mo	27	4.1	2.5	0.75 (0.32–1.76)
Age				
<65 y	135	3.4	2.7	0.64 (0.43–0.95)
⩾65 y	25	3.6	2.7	0.79 (0.28–2.25)
Measurable disease				
Yes	144	3.1	2.6	0.72 (0.49–1.05)
No	15	9.5	2.8	0.26 (0.06–1.06)
Overall	160	3.4	2.7	0.65 (0.45–0.95)