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PTEN, EGFR, MAPK and Akt status by immunohistochemistry (IHC) in HER2-positive (HER2+) metastatic breast cancer (MBC) patients (pts) treated with trastuzumab (T) ± chemotherapy (CT): correlation with clinical outcome

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T alone or in combination with CT has been shown to be an active therapy in HER2+ MBC pts. However, not all pts will benefit and mechanisms of resistance to T are still poorly understood. The aims of this study were to evaluate the IHC expression of EGFR, MAPK and Akt (two downstream effectors of the EGFR family signaling) and PTEN and their correlation with clinical outcome in HER2+MBC pts treated with T ± CT.

Methods: 133 consecutive HER2+ MBC pts were treated between 04/99 and 03/06 but tumor tissue was available for this analysis only from 45 pts. HER2 evaluated by CB11 was scored according to Herceptest.Tumors were considered EGFR positive if ⩾1% positive tumor cells and MAPK positive and Akt positive if the percentage of positive tumor cells was ⩾10%. PTEN expression was assessed by IHC on a scale from 0 to 400 (percentage of positive cells × staining intensity) as described by Hirsch F et al (JCO 21:3798;2003).

Results: At median follow up of 57 months (range 5–229) from the start of T, 45 pts were evaluable for TTP and OS and 42 for response to T. Median age of pts was 53 years (23−77). We observed 27 responses (CR+PR) to T ± CT (64.28%); median TTP was 24 months (3.3–179.8). In 11 of the 27 responsive pts (40.7%), progression was observed in CNS ± other sites. Median OS from the start of T was 74 months. EGFR+ tumors were 10 (22.2%), MAPK+ tumors were 16 (35.5%) and Akt+ tumors were 23 (51.1%). Only 2 pts had PTEN expression score of 0−99 (PTEN−). We analyzed the correlation of HER2, EGFR, MAPK, Akt and PTEN status with response to T, TTP and OS. HER2 was significantly correlated with response to T ($p = 0.013$): in HER2 3+ tumors we observed 22 (9 CR and 13 PR) out of 27 objective responses but no significant correlation was found between HER2 status and TTP and OS. EGFR, MAPK, Akt and PTEN status of tumors were not significantly associated with response to T, TTP and OS in our series.

Conclusions: We did not find any significant correlation between EGFR, MAPK, Akt, PTEN status evaluated by IHC and clinical outcome in HER2+ MBC pts treated with T ± CT. Only HER2 status evaluated by IHC significantly correlated with response to T ± CT.

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An open-label study of capecitabine (C) and docetaxel (D) as neoadjuvant treatment for patients with recently diagnosed HER2-neu negative (HER2−) breast cancer (BC) plus trastuzumab (T) for HER2-neu positive (HER2+) BC

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Background: Since C+D is highly active for metastatic BC, the study of C+D±T in the neoadjuvant setting is warranted. The addition of T to C+D for HER2+ BC reflects the standard of care in this patient population.

Methods: The primary objective was to define the rate of pathological complete response (pCR) and near pCR (npCR) [T1a] in the affected breast after 4 cycles of neoadjuvant treatment with C+D±T. Eligible females were newly diagnosed with infiltrating (invasive) HER2−/+ BC, T2N0−1M0 and T3N0−1M0, M0. Four 3-week cycles were administered of C 825 mg/m^2 BID on days 1−14 and D 75 mg/m^2 on day 1. HER2+ pts also received T 4 mg/kg on day 1 followed by 2 mg/kg weekly. Simon's optimal 2-stage design was used to independently assess effectiveness of T.

Results: 109 HER2− and 31 HER2+ pts were enrolled. Clinical or pathological data are available for 60 HER2− and 22 HER2+ pts. Average age: HER2− 50 y (29−74), HER2+ 50.5 y (32−66). ER +: HER2− 63%, HER2+ 45%.

Only 14 pts discontinued treatment due to adverse events (AEs): 10 HER2− and 4 HER2+. The most frequent AEs have been hematological and hand–foot syndrome. No grade IV AEs were reported.

Conclusions: Early clinical and pathological data suggest that 4 neoadjuvant treatment cycles of C+D±T is active as shown by the clinical ORR of 82.5% for HER2− and 79.9% for HER2+ pts; only 6.5% and 6.6%, respectively, of pts experienced disease progression during treatment. Combined pCR and npCR results were 16.0% for HER2− and 52.3% for HER2+. C+D±T is a viable alternative to non-anthracycline systemic therapy in the neoadjuvant setting and appears to be well tolerated. Results will be updated at the meeting.

	Response (%)	
	HER2−	HER2+
Clinical response after 4 cycles of treatment		
Total no. of patients	N = 46	N = 15
No response	0 (0)	6.6 (1)
Stable disease	19.5 (9)	13.3 (2)
Partial response	56.5 (26)	26.6 (4)
Complete response	26.0 (12)	53.3 (8)
P + C response	**82.5 (38)**	**79.9 (12)**
Progressive disease	6.5 (3)	6.6 (1)
Pathological response after 4 cycles of treatment		
Total no. of patients	N = 50)	N = 21
pCR	4.0 (2)	28.5 (6)
npCR	12.0 (6)	23.8 (5)
Combined (up to T1a)	**16.0 (8)**	**52.3 (11)**
⩾5 mm	84.0 (42)	47.6 (10)
Mean tumor sizes (cm)		
Initial	6.0	5.7
After 4 cycles	2.5	2.1
At surgery	2.1	1.1

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Updated analysis of an international phase II study evaluating an all-oral combination of oral vinorelbine and capecitabine as first-line chemotherapy in HER2-negative metastatic breast cancer (MBC)

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Background: Oral chemotherapy (CT) is attractive for patients (pts) with MBC. The all-oral regimen of oral vinorelbine (NVBo) and capecitabine (X) is active with good tolerability in MBC. We report updated efficacy and safety data from an international phase II study of NVBo plus X.

Materials and Methods: Main eligibility criteria included: measurable HER2-negative, CT-naive MBC, relapse ⩾6 months after completing (neo)adjuvant CT, Karnofsky PS ⩾70%, age ⩾18 years. Study treatment: 3-weekly cycles of NVBo 80 mg/m^2 (after a first cycle at 60 mg/m^2 in the absence of G3/4 neutropenia) d1 and d8, plus X 1000 (750 if ⩾65 years) mg/m^2 twice daily d1−14. Treatment was continued until progression or unacceptable toxicity.

Results: 55 pts were enrolled (54 were treated): median age: 58.5 years (41% ⩾65); prior (neo)adjuvant CT in 63%; type of CT: anthracycline 67%, anthracycline + taxane 18%, CMF 15%; visceral involvement in 78%; >2 metastatic sites in 46%. Median 7 cycles; median relative dose intensity: NVBo 87%, X 87%; NVBo dose escalated to 80 mg/m^2 in 94% of pts. G3/4 NCI CTC v2 adverse events (n = 54): neutropenia 49% of pts, vomiting 9%, stomatitis 7%, asthenia 7%, febrile neutropenia 6%, infection with G3/4 neutropenia 6%, nausea 4%, diarrhoea 4%, hand–foot syndrome 4%, thrombosis/embolism 4%. Efficacy (n = 47 evaluable pts): objective response (OR) rate (RECIST) 51% (95% CI [36−66]), CR 2%, PR 49%, SD 30%, PD 19%. OR for liver metastases: 54%. Disease control (CR+PR+SD ⩾6 months) 64%. Median progression-free survival was 8.4 months. With a median follow-up of 21 months, median overall survival has not yet been reached.

Conclusions: The all-oral combination of NVBo and X is an effective and well-tolerated first-line therapy for MBC. Based on these results and the high convenience of oral CT, evaluation of this regimen as front-line chemotherapy vs i.v. combinations in a randomised trial is ongoing.