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Overall survival analysis of a randomized phase III trial comparing nab-paclitaxel with solvent-based paclitaxel in patients with metastatic breast cancer previously treated with anthracycline

N. Davidson[1], S. Tjulandin[2], J. O'Shaughnessy[3], P. Bhar[4], W. Gradishar[5]. *[1]Broomfield Hospital, Oncology, Chelmsford, United Kingdom; [2]Blokhin Cancer Research Center, Oncology, Moscow, Russian Federation; [3]US Oncology, Oncology, Houston, USA; [4]Abraxis Bioscience Inc., Biostatistician, Los Angeles, USA; [5]Northwestern University Feinberg School of Medicine, Medicine, Chicago, USA*

Background: Nanoparticle albumin-bound (nab)-paclitaxel demonstrated superior antitumor activity compared with solvent-based paclitaxel in a phase III trial of patients with metastatic breast cancer (MBC). The current retrospective analysis aimed to determine the efficacy of nab paclitaxel in patients with MBC previously treated with anthracycline.

Material and Methods: This was a retrospective analysis of a randomized, phase III efficacy trial of nab-paclitaxel (CA-012). Patients (⩾18 years of age) received either nab-paclitaxel 260 mg/m^2 or solvent-based paclitaxel 175 mg/m^2 intravenously every 3 weeks for treatment of MBC.

Results: Of 460 patients randomized, 351 (76%) had received prior anthracycline therapy in the metastatic or adjuvant setting (176 and 175 were randomized to nab-paclitaxel and solvent-based paclitaxel, respectively). A total of 245 patients received prior anthracycline therapy specifically in the metastatic setting (115 and 130 were randomized to nab-paclitaxel and solvent-based paclitaxel, respectively). The overall response rate, time to disease progression, and overall survival were significantly higher for patients randomized to nab-paclitaxel compared with solvent-based paclitaxel for patients with any prior anthracycline therapy, and for those with prior anthracycline therapy for metastatic disease.

Safety profiles of nab-paclitaxel and solvent-based paclitaxel were similar. The most frequent grade 3/4 adverse event was neutropenia. Treatment-related grade 3 sensory neuropathy was more frequent in the nab-paclitaxel arm but improved to grades 1/2 in 22 days (median) and was readily managed.

Conclusions: Patients treated with nab-paclitaxel had a ~30% reduction in the risk of disease progression compared with solvent-based paclitaxel, regardless of prior anthracycline exposure. Additionally, nab-paclitaxel prolonged survival in patients with MBC that was resistant to anthracycline after treatment in the adjuvant or metastatic setting. Nab-paclitaxel is an effective option for the treatment of MBC in patients previously treated with anthracycline.

	Metastatic anthracycline			Metastatic or adjuvant anthracycline		
	Nab-paclitaxel (n = 115)	Solvent-based paclitaxel (n = 130)	P-value	Nab-paclitaxel (n = 176)	Solvent-based paclitaxel (n = 175)	P-value
ORR, %	27.0	13.8	0.010	34.1	18.3	0.002
TTP, weeks	21.0	15.7	0.011	23.0	16.6	0.004
Median OS, weeks	56.4	46.7	0.022	65.0	52.4	0.049

ORR = Overall response rate; TTP = Time to progression; OS = Overall survival.

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POSTER SESSION

Targeted treatment

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Colloidal immunochemogene formulation SEVINA-VI composed of anti-MUC1 MAbs, clamp PNA against mRNA of eIF3c, and vinorelbine in stealth liposomes induce PCD in HRBC resistant to trastuzumab, cetuximab, and taxanes

J. Giannios[1], E. Seraj[1], E. Maragudakis[1], J. Peristeris[2], N. Alexandropoulos[3], A. Kanellopoulos[4]. *[1]Erasinio Oncology Hospital, Oncology, Athens, Greece; [2]IASO Hospital, Oncology, Athens, Greece; [3]Ip. Hospital, Biopathology, Athens, Greece; [4]American University of Athens, Drug Delivery, Athens, Greece*

Background: HRBC with overexpressed MUC-1 causes resistance to tyrosine kinase inhibitors (TKIs). Upregulated eIF3c and bcl-2 cause potent chemoresistance inhibiting induction of PCD in HRBC. Our aim is to circumvent all these resistant factors.

Materials and Methods: We developed xenograft animal models from TKI resistant HRBC cells, obtained from stage-V patients overexpressing eIF3c, MUC1, and bcl-2. We formulated stealth liposomal anti-MUC1 Mab in the biological recognition layer, vinorelbine in the lipid phase, and clamp PNA anti-eIF3c oligomers composed of 6 mer homopyrimidine triplex [(PNA)2/RNA) for hybridization to 5′ end (Leader), and 10 mer purine/pyrimidine dublex (PNA/RNA) for hybridization to the 3′-end (Trailer)of the AUG start codon region on the mRNA, in the polar phase. The human HRBC xenograft animal models were treated with SEVINA-VI.

Results: Post-treatment, downregulated glycosylated MUC1 blocked binding of TKIs, by inhibiting direct steric hindrance onto HER2, EGFR, and IGF-IR. Inhibition of MUC1 phosphorylation, blocked downstream signaling pathways Ras/Raf/Erk1/2/MAPK, PI3K/AKT, VEGF, and MMP-2. ADCC was induced. The clamp PNA hybridized to the leader, and trailer region of the AUG start codon region on mRNA eIF3c forming Watson-crick double helices, and steric hindrance of the translation machinery inhibiting expression of eIF3c, after assembly inhibition of the 80 ribosome initiation complex. The RNA helicase activity of eIF3c has been silenced, disabling cellular cap-dept scanning/initiation. It inhibited mTOR preventing downstream activation of mRNA translation and blocked ribosome biogenesis inhibiting S6K1, and 4E-BPI, which led to inhibition of ribosomal protein, elongation factors, and ODC/cyclinD1. Thus, chemoresistant 4E-BPI induced by taxanes was inhibited. Cycline/CDK2-p27 and p53 were upregulated, inhibiting CDK1/2 and cyclinD1 activity. Signal transduction initiated by VEGF was inhibited, and translation of antiapoptotic FLIPS, and c-myc was blocked. Type I PCD or apoptosis was induced. Vinorelbine phoshorylated bcl-2 leading to its inactivation, and subsequent circumvention of oncogene addiction. Furthermore, it released beclin-1 inducing typeII PCD or autophagy. Also, vinorelbine by depolymerizing MT blocked cell cycle at G2/M. TEM exhibited type III PCD or necrosis. DNA and metabolic activity of tumor cells were blocked.

Conclusion: SEVINA-VI has circumvented oncogene transcriptional intervention in HRBC resistant to TKIs, and taxanes via protein translational inhibition of eIF3c downstream of mTOR pathways, and downregulation of MUC1, which led to induction of ADCC, and PCD in synergy with cytostatic agent vinorelbine.

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Growth and molecular interactions of the anti-EGFR antibody cetuximab and the DNA cross-linking agent cisplatin: new prospects in the treatment of triple-negative/basal-like breast cancer

J. Menendez[1], C. Oliveras-Ferraros[1], A. Vazquez-Martin[1], J. Brunet[1]. *[1]Fundació d' Investigació Biomèdica de Girona, Institut Catalá d'Oncologia de Girona, Spain*

Background: Two prominent hallmarks of triple-negative/basal-like breast carcinomas – a subtype of breast cancer-gene expression signature associated with poor relapse-free and overall survival – are overexpression of the Epidermal Growth Factor Receptor (EGFR) and high sensitivity to DNA-damaging agents. The interaction between EGFR inhibitors (*i.e.,* monoclonal antibodies and small molecule tyrosine kinase inhibitors) and DNA cross-linking agents (*e.g.,* platinum derivatives) may represent a promising combination for the treatment of triple-negative/basal-like breast tumors that are dependent upon EGFR-signaling.

Methods: We evaluated the growth and molecular interactions of Cetuximab (Erbitux®) and cisplatin in the gefitinib-resistant MDA-MB-468 breast cancer cell line, an in vitro model system showing many of the recurrent basal-like molecular abnormalities including ER-PR-HER2-negative status, *TP53* deficiency, EGFR overexpression, *PTEN* loss, and constitutive activation of the MEK/ERK pathway.

Results: Low-scale phospho-proteomic approaches (*i.e.,* Phospho-Receptor Tyrosine Kinase [RTK] and Phospho-Mitogen-Activated Protein Kinases [MAPKs] Array Proteome Profiler™ capable to simultaneously identify the relative levels of phosphorylation of 42 different RTKs and 23 different MAPKs and other serine/threonine kinases, respectively) revealed the ability of Cetuximab, as single agent, to paradoxically induce hyperphosphorylation of EGFR while concomitantly deactivating p42/44 (ERK1/ERK2) MAPK. Concurrent treatment with sub-optimal doses of Cetuximab significantly enhanced cisplatin-induced apoptosis. However, a mathematical assessment of the nature of the interaction revealed a loss of synergism when employing high-dose Cetuximab. ELISA-based quantitative analyses demonstrated that simultaneous exposure to high-dose Cetuximab and cisplatin triggered a complete depletion of the EGFR protein accompanied by a drastic up-regulation of the DNA repair protein BRCA1.

Conclusions: Although these results preclinically support, at least in part, ongoing clinical trials for "triple-negative/basal-like" metastatic breast cancer patients who are receiving either Cetuximab alone *versus* Cetuximab plus carboplatin (http://www.clinicaltrials.gov/ct/show/NCT00232505), they further suggest that treatment schedules, Cetuximab doses, and