New drug development

RESULTS OF A RANDOMIZED PHASE 2 STUDY OF PD 0332991, A CYCLIN-DEPENDENT KINASE (CDK) 4/6 INHIBITOR, IN COMBINATION WITH LETROZOLE VS LETROZOLE ALONE FOR FIRST-LINE TREATMENT OF ER +/HER2- ADVANCED BREAST CANCER (BC)

R.S. Finn1, J.P. Crown2, K. Boer3,1, I. Lang4, R.J. Parkh5, A. Brezaxa6, S.N. Ho7, S.T. Ramv1, S. Randolph7, D.J. Slamon8

1Department of Hematology and Oncology, University of California, Los Angeles, CA, UNITED STATES OF AMERICA, 2Irish Cooperative Oncology Research Group, St. Vincent’s Hospital, Dublin, IRELAND, 3Onkologie, Szszent Margit Korhaz, Budapest, HUNGARY, 4Department of Medical-oncology and Clinical Pharmacology “b”, National Institute of Oncology, Budapest, HUNGARY, 5Sienna Location, Comprehensive Cancer Centers of Nevada, 6Department of Oncology, Clinical Development, Pfizer Oncology, New York, NY, UNITED STATES OF AMERICA, 7Translational Oncology, Pfizer Oncology, La Jolla, CA, UNITED STATES OF AMERICA, 8Clinical Development, Oncology Business Unit, Pfizer Oncology, La Jolla, CA, UNITED STATES OF AMERICA

Background: PD 0332991, a selective inhibitor of CDK 4/6, prevents cellular DNA synthesis by blocking cell cycle progression. Preclinical studies in a BC cell line panel identified the luminal ER subtype, elevated expression of cyclin D1 and Rb protein, and reduced p16 expression as being associated with sensitivity to PD 0332991 (Finn et al. 2009). Synergistic activity was also observed in vitro when combined with tamoxifen. Based on these observations, a phase 1/2 study in combination with letrozole was initiated. We present results from the randomized phase 2 portion.

Methods: The phase 2 portion is a two-part study: Part 1, ER +/HER2- selected; Part 2, further biomarkers. We present results from Part 1. The primary endpoint is progression-free survival (PFS); secondary endpoints include response rate, overall survival, safety, and correlative biomarker studies. Post-menopausal women with ER +/HER2- advanced BC were randomized 1:1 to receive either letrozole 2.5 mg QD plus PD 0332991 125 mg QD on Schedule 3/1 (L + P arm) or letrozole 2.5 mg QD alone (L). Pts continue on assigned study treatment until disease progression, unacceptable toxicity, or consent withdrawal, and are followed for tumor assessments every 2 months.

Results: 66 pts were randomized. Baseline characteristics were balanced between the two arms. As of data cut-off, median duration of treatment was 47 wks for the L + P arm and 24 wks for the L arm. The most commonly reported treatment-related AEs in the combination arm were neutropenia, leukopenia, and fatigue. The response rate was 27% vs. 23% of (26 and 22 pts with measurable disease, L + P vs. L respectively), clinical benefit rate (PR + SD ≥ 24 weeks) was 59% vs. 44%, respectively. Two vs. 7 pts had best response of progressive disease for L + P, respectively.

Conclusion: The combination of PD 0332991 and letrozole is well tolerated with encouraging clinical benefit, confirming the preferential sensitivity of ER+ BC observed in preclinical models.

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PHASE 3 STUDY OF NKTR-102 Versus TREATMENT OF PHYSICIAN’S CHOICE (TPC) IN PATIENTS (PTS) WITH LOCALLY RECURRENT OR METASTATIC BREAST CANCER (MBC) PREVIOUSLY TREATED WITH AN ANTHRACYCLINE, A TAXANE, AND CAPECITABINE (ATC)

J. Cortes1, E. Perez2, The BEACON Study Group3

1Breast Cancer Program, Vall d’Hebron University Hospital, Barcelona, SPAIN, 2Division of Hematology / Oncology, Mayo Clinic, Jacksonville, FL, UNITED STATES OF AMERICA, 3Clinical Development, Nektar Therapeutics, San Francisco, CA, UNITED STATES OF AMERICA

Background: NKTR-102 is a next-generation topoisomerase I inhibitor-polymer conjugate that provides continuous exposure to SN-38. A phase 2 trial of single-agent NKTR-102 was conducted in pts with 3rd line MBC; 2 schedules (q14d; q21d) investigated a dose of 145 mg/m². ORR was 29% (including 3% CR) with the prior ATC subset demonstrating an ORR of 31%. Dosing q21d was better tolerated; in this arm, median PFS and OS equalled 5.3 and 13.1m, respectively. Trial Design: Pts will be randomized 1:1 to receive either single-agent NKTR-102 or TPC in an open-label, randomized, multicenter Phase 3 study in pts with advanced breast cancer. Key Entry Criteria: Adult females, with ECOG 0 or 1 with adequate liver, kidney and marrow function. All pts must have received prior therapy with ATC (these drugs may have been administered in the neo/adjuvant or locally advanced/metastatic setting). Prior A is not mandated if contraindicated for a pt. Prior toxicities must have resolved to ≤ Grade 1 (except sensory neuropathy ≤ Grade 2; complete resolution of prior diarrhea). Pts with brain metastases may be eligible, if lesions are stable for prior 3 weeks without steroids.
Methods: Primary efficacy endpoint is OS. Secondary endpoints include: ORR by REGIST v.1.1, clinical benefit rate (ORR + SD > 6 months), PFS and QoL. NCTR-102 is given IV at 145 mg/m2 over 90-min every 21 days without premedications. Pts randomized to TPC receive 1 of the following: eribulin, ixabepilone, vinorelbine, gemcitabine, paclitaxel, docetaxel or nab-paclitaxel (the agent must be available at the treating institution). Pts are stratified by region, prior eribulin and receptor status (TNBC, Her2+ or Other). Target Accrual: ~480 pts will be required for sufficient events to occur in the planned follow-up time. OS will be compared using a two-sided log-rank test; 1 interim analysis will occur when 50% of the deaths are reported. PK sampling is performed in a subset of pts. CTCs (isolated by ApoCell ApoStream™ technology) are separately assessed for potential predictive markers of response and toxicity. Enrollment is expected to remain open until late 2013.

Disclosure: J. Cortes and E. Perez: Co-Chair of Protocol Steering Committee. All other authors have declared no conflicts of interest.

Disclosure: All authors have declared no conflicts of interest.

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PHASE II RANDOMIZED STUDY OF PRE-OPERATIVE PF-04691502 PLUS LETROZOLE COMPARED WITH LETROZOLE (L) IN PATIENTS WITH ESTROGEN RECEPTOR-POSITIVE, HER2-NEGATIVE EARLY BREAST CANCER (BC)

M. Dowsett1, M. Koehler2, R. Milham3, G. Borzillo4, R. Ahern4, K. Pierce4, J. Barton5, C. Giorgetti2

1Royal Marsden Hospital, Breakthrough Research Centre, London, UNITED KINGDOM, 2Oncology, Pfizer, New York, NY, UNITED STATES OF AMERICA, 3Oncology, Pfizer, Groton, CT, UNITED STATES OF AMERICA, 4Translational Oncology, Pfizer, Groton, CT, UNITED STATES OF AMERICA, 5Statistics, CTSU, Institute of Cancer Research, London, UNITED KINGDOM, 6Biotechnology Unit & Oncology, Clinical Research, Pfizer, San Diego, CA, UNITED STATES OF AMERICA

Background: Acquired hormone independent BC cell growth is associated with upregulation of the PI3K/mTOR pathway in vitro and in neo-adjuvant studies of aromatase inhibition (Ghazouei AACR Breast Cancer Symposium, 2011). Preclinical and clinical studies suggest that the combination of hormone therapy and a PI3K/mTOR inhibitor can restore sensitivity to hormone resistant tumours. Luminal B BCs are more frequently associated with endocrine resistance, hyperactivation of the PI3K signaling pathway, and increased expression of the Ki-67 proliferation marker than Luminal A BCs. This particular population may be a suitable target for PI3K directed therapy. A reduction in Ki-67 in the neo-adjuvant setting by endocrine therapy has been shown to correlate with efficacy of that same therapeutic in the adjuvant setting. Thus, a pre-operative study in high Ki-67-expressing BCs with short term reduction in Ki-67 as a primary endpoint could be used to drive a formally designed adjuvant study with a conventional disease free endpoint.

Study design: This pre-operative trial is designed to test the hypothesis that the addition of a PI3K/mTOR antagonist, PF-04691502, to L can reduce Ki-67 levels after six weeks of administration to a greater degree than L alone, thus supporting the concept that the compound might mitigate the intrinsic or acquired resistance to hormonal therapy in a high risk patient population in the adjuvant setting. The trial is being conducted in postmenopausal women with ER positive, HER-2 negative BC. After the lead-in phase in women with advanced BC to assess PF-04691502/L tolerability, a randomized Phase 2 will start in women with early BC selected based on a high level of Ki-67 (>10%). 204 patients will be randomized to receive PF-04691502/L or L alone for 6 weeks. Patients will undergo three sequential core-biopsies (baseline, weeks 2 and 6) to compare the changes in Ki-67 value from baseline to the end of the treatment. To test pharmacodynamic effects associated with PI3K/mTOR pathway modulation. This trial is open to enrollment in several European countries.

Disclosure: M. Koehler, R. Millham, G. Borzillo, K. Pierce, J. Barton and C. Giorgetti: Pfizer employee. All other authors have declared no conflicts of interest.

Background: There is limited success with current therapies for triple negative (TN) breast cancer. Overexpression of EGFR has been linked to an aggressive breast tumor phenotype with a poor prognosis. Previous work showed that 64% of 66 TN tumors were EGFR positive. We selected patients for EGFR expression; there may be TN MBC patients who benefit from an EGFR TKI.

Methods: Nine patients had TN-EGFR-positive MBC. EGFR positivity was defined as staining >10% of tumor cells by IHC. Patients required measurable disease, prior treatment with anthracycline and taxane (adjuvant or metastatic setting). Patients received erlotinib 150mg daily. Primary endpoint was progression-free survival (PFS). Initially, 9 patients were to be accrued.

Results: In total, 9 patients enrolled. Mean age 46.7y, all patients were from kurdish ethnicity in west of Iran. Six patients had prior chemotheraphy for MBC. Three patients progressed rapidly, median PFS was 3 months for others. However, 1 patient had stable disease for five months. Treatment was well-tolerated. Toxicities in the 6 patients included grade 2 rash, grade 1 diarrhea.

Conclusions: Although most patients progressed rapidly, 6/9 patients had prolonged stable disease. This suggests there may be a subset of TN, EGFR positive MBC for whom EGFR-directed therapy may be suitable or that the natural history of their disease was indolent. Future studies to determine molecular and clinical profiles of patients likely to benefit from EGFR-TKI therapy.

Disclosure: All authors have declared no conflicts of interest.
**107P** CISPLATIN AND GEMCITABINE COMBINATION IN TRIPLE NEGATIVE BREAST CANCER: COMMUNITY HOSPITAL EXPERIENCE

I. Hilderson¹, F.J. Geurs¹, M. Criel¹, P. Debrucker²

¹Medical Oncology, REG ZH Sint Maria, Halle, BELGIUM, ²Breast Cancer Clinic, REG ZH Sint Maria, Halle, BELGIUM

**Background:** The management of metastatic breast cancer has moved to tailored treatment following the discovery of different tumor types by genotyping. Triple negative breast cancer was proven to be a chemosensitive disease where platinum salts were also effective besides anthracyclines and taxanes. The experience with cisplatin combination chemotherapy in a more general population is however, lacking.

**Patients and methods:** We reviewed the files of 12 patients who presented with liver metastases (9 patients, two of which had synchronous brain metastases) and locally advanced breast cancer (3 patients). All biopsies showed triple negative breast cancer on immunohistochemistry. Median age was 70y (40-76y). They were treated with an ambulatory cisplatin and gemcitabine regimen, consisting of gemcitabine 1000 mg/m² on day 1 + 8 and cisplatin 35 mg/m² on day 2 + 9, q3w. Two patients died two weeks after starting chemotherapy. Response rates were 66% (2 CR, 6 PR). Time to progression was 5 months (1-14 months) median survival was 7 months (1-24 months). Three patients had subsequent mastectomy, in one case there was down staging to pT0, in the two other cases there was down staging to pT3N1 disease. Breast surgery was performed after a median of two weeks after chemotherapy.

**Conclusion:**
1. Cisplatin-gemcitabine combination is feasible on an outpatient basis and has similar efficacy as reported in more selected patients.
2. In patients presenting with liver metastasis this regimen was effective, even in patients presenting with severe jaundice. Two patients with synchronous brain metastases also had a partial response on cerebral imaging.
3. In line with prior observations our patient population was older than the initial study population nevertheless these data confirm similar efficacy.

**Disclosure:** All authors have declared no conflicts of interest.

**108P** TREATMENT OF METASTATIC BREAST CANCER WITH ALTERNATIVE VINORELBINE AND GEMCITABINE

A. Bensámèm¹, M. Merrouche¹, A. Ammari², A. Benmerzouk¹, K. Bouzid³

¹University Freres Mentouri, Medical Oncology Constantine, Constantine, ALGERIA, ²Batna, Medical Oncology, Batna, ALGERIA, ³Medical Oncology, EHS P & M Curie Center, Algiers, ALGERIA

**Background:** Most breast cancer cases are locally advanced or metastatic. Single agent therapy with gemcitabine or vinorelbine showed good tolerability and efficacy in metastatic breast cancer.

**Methods:** To evaluate safety profile and efficacy of alternatively gemcitabine and vinorelbine regimen in pretreated metastatic breast cancer, 32 patients were included between January 2009 and June 2010. All patients had prior chemotherapy with anthracycline or taxane. They had progression or recurrence within 6 month of prior treatment. They had measurable or evaluable disease. Median age was 47 years. Performance status was ECOG 0-2. Metastatic sites: liver - 9 patients, lung - 8 patients, bone - 17 patients, soft tissue - 6 patients. Treatment schedule: Gemcitabine 1250 mg/m² given on day 1, 8 and vinorelbine 25 mg/m² given on day 1, 8. The median duration of administration was six month.

**Results:** The treatment was well tolerated. Grade 1-2 myelosuppression was commonly observed; grade 3-4 neutropenia - 4 patients (12.5%), never complicated with septicemia, grade 3 anemia - 2 patients (6.2 %), grade 3 thrombocytopenia - 1 patient (3.1 %). Grade 2 neurotoxicity was observed in 3 patients (9.3 %). Grade 1-2 gastrointestinal toxicity (nausea/emesis) occurred in 13 patients (40.6 %). Malaise or flu-like syndrome were mild and occurred in 9 patients (28.1 %). No treatment-related death was observed with gemcitabine - vinorelbine alternative regimen. No patients required dose reduction. One patient was not evaluable for tumor response. Overall response rate was 31.2 % (3 patients (9.3%) complete response, 7 patients (21.8 %) partial response; 14 patients had stable disease (43.7 %) and 8 patients progressive disease (25%). The median time to progression was 9 months.

**Conclusion:** Our results suggest that gemcitabine and vinorelbine alternative administration has an acceptable efficacy and a favorable safety profile.

**Disclosure:** All authors have declared no conflicts of interest.