2107 POSTER

Preliminary results of a phase I study of sunitinib plus paclitaxel for first-line treatment of advanced breast cancer

M. Kozloff[1], E. Chuang[2], J. Roy[3], A. Starr[1], P.A. Gowland[1], M.J. Tarpey[2], M. Collier[4], L. Verkh[4], K. Kern[4], K. Miller[3]. [1]*Ingalls Memorial Hospital, Cancer Research Center, Harvey, USA;* [2]*Cornell University, Weill Medical College, New York, USA;* [3]*Indiana University, Cancer Center, Indianapolis, USA;* [4]*Pfizer Inc, Global Research and Development, La Jolla, USA*

Background: Sunitinib malate is an oral, multitargeted tyrosine kinase inhibitor of VEGFRs, PDGFRs, KIT, RET, and FLT3, with single-agent activity in patients (pts) with previously-treated metastatic breast cancer (BC). This phase I study investigated the safety and pharmacokinetics (PK) of sunitinib combined with paclitaxel for first-line treatment of advanced BC.
Materials and Methods: Eligible pts had metastatic or locally recurrent BC, ECOG PS $\leqslant 1$, and adequate organ function. Exclusion criteria included prior cytotoxic therapy for advanced disease and failure of taxane-based adjuvant therapy within 12 months. Pts received sunitinib starting dose 25 mg/day continuous dosing (escalation to 37.5 mg/day or reduction to 12.5 mg/day depending on tolerability) plus paclitaxel 1-hr infusion 90 mg/m^2/wk in 4-wk cycles (3 wks on treatment, followed by 1 wk off; reduction to 65 mg/m^2/wk as needed).
Results: 20 pts were treated on study, median age 57 yrs (range 37–74). 17 pts had measurable disease, and 7 pts were chemotherapy-naive. Disease sites included bone (55%), liver (40%), lung (30%), lymph node (55%), and local (40%). Median number of cycles delivered was 6 (range 2–13+); 9 pts continue on treatment. Discontinuations were due to disease progression (8 pts), non-treatment related illness (2 pts), and resection of remaining lesion (1 pt). Grade (Gr) 3 AEs included fatigue (29%), diarrhea (14%), hand–foot syndrome (10%), and neuropathy (10%). Neutropenia was the primary hematological toxicity. G-CSF was used when neutrophil count was <1500/μL to support delivery of full dose paclitaxel; neutrophil nadirs were sharp with rapid rebound despite continuous sunitinib dosing. Worst neutropenia was Gr 3 in 42% and Gr 4 in 21% of pts. Preliminary results indicate no PK interaction between paclitaxel and sunitinib. As of Mar 2007, 5 pts have confirmed objective responses (3 partial and 2 complete) according to RECIST; 3 pts have had stable disease $\geqslant$6 months.
Conclusions: Sunitinib administered with paclitaxel was generally well tolerated and showed promising activity as first-line treatment for advanced BC. A phase III trial comparing this combination to paclitaxel + bevacizumab is underway.

2108 POSTER

Cardiac safety of trastuzumab in combination with epirubicin/cyclophosphamide as first-line therapy in patients with HER2-positive metastatic breast cancer

M. Untch[1], S. Tjulandin[2], W. Jonat[3], H. Meerpohl[4], M. Lichinitser[2], G.M. Manikhas[5], F. Jänicke[6], M. Muscholl[7], M. Pauschinger[8], M. Lehle[9]. [1]*HELIOS Klinikum Berlin-Buch, Frauenheilkunde mit Geburtshilfe, Berlin, Germany;* [2]*Russian Cancer Research Center, Oncology, Moscow, Russian Federation;* [3]*Klinik für Gynäkologie und Geburtshilfe, Christian-Albrechts-Universität, Kiel, Germany;* [4]*Frauenklinik der St. Vincentius-Krankenhäuser, Oncology, Karlsruhe, Germany;* [5]*St Petersburg City Oncology Hospital, Department of Oncogynaecology, St Petersburg, Russian Federation;* [6]*Universitätsklinikum Hamburg-Eppendorf, Brustzentrum, Hamburg, Germany;* [7]*Ludwig-Maximilians-Universität, Medizinische Klinik und Poliklinik I Klinikum Grosshadern, Munich, Germany;* [8]*Charité – Universitätsmedizin Benjamin Franklin, Medizinische Klinik II Kardiologie und Pulmologie, Berlin, Germany;* [9]*F. Hoffmann-La Roche, Oncology, Basel, Switzerland*

Background: Trastuzumab (Herceptin®; H) is the standard of care for patients (pts) with HER2-positive metastatic breast cancer (MBC). A randomised Phase III trial (HO468g) showed that H in combination with the anthracycline doxorubicin is highly effective but also causes a significant level of cardiac dysfunction. The combination of H with the less cardiotoxic anthracycline epirubicin (E) may provide an effective treatment for MBC with fewer cardiac side effects. HERCULES is a prospective, multicentre, open-label, randomised Phase II trial evaluating the safety and efficacy of H in combination with two doses of E + cyclophosphamide (C). In parallel, HER2-positive pts were treated with chemotherapy alone.
Methods: Pts with HER2-positive (IHC3+ and/or FISH+) MBC received H (4 mg/kg iv loading dose, then 2 mg/kg qw) + E (60 or 90 mg/m^2)/C (600 mg/m^2) q3w (EC60 + H; EC90 + H) for 4−6 cycles. Sixty pts were randomised to each E dose level; 62 pts with HER2-negative MBC received EC90 only. The primary end point was cardiac safety of the EC + H regimens compared with EC alone (New York Heart Association class III/IV congestive heart failure [CHF] with absolute decrease in left ventricular ejection fraction [LVEF] of >10 percentage points [pp] to <50%); secondary end points included overall response rate (ORR) and time to progression (TTP). All enrolled pts had a baseline LVEF >55% and received a thorough cardiac evaluation.
Results: An absolute decrease in LVEF of >10 pp to <50% occurred in 4 pts (7%) receiving EC60 + H and 9 pts (15%) receiving EC90 + H. Of those, 1 pt (2%) in the EC60 + H group and 3 pts (5%) in the EC90 + H group experienced CHF, while in the EC90-alone HER2-negative group no LVEF declines of >10 pp to <50% or CHF were reported. There were no cardiac-related deaths. Grade 3/4 adverse events (AEs) occurred in 38 pts (63%) in each arm receiving H and in 45 pts (75%) receiving EC only. The most common grade 3/4 AEs were haematological. ORRs were 57% and 60% in the EC60 + H and EC90 + H arms, respectively, and 25% in the EC-alone group. Median TTP was 12.5 months (95% CI: 8.8, 15.2) in the EC60 + H arm, 10.1 months (95% CI: 9.2, 15.4) in the EC90 + H arm and 7.6 months (95% CI: 6.9, 10.8) with EC alone.
Conclusions: Combining H with EC is feasible for the treatment of pts with HER2-positive MBC. ORRs and TTP were not statistically significant at either dose level in pts receiving EC + H, but fewer cardiac events occurred in the EC60 + H group.

2109 POSTER

Lapatinib in combination with Taxanes (T) – tolerability data in 484 patients with breast cancer (BC)

H. Burris[1], J.P. Crown[2], S. Jones[1], C. Oliva[3], R.O.M.A. Parikh[3], S. Stein[3]. [1]*Sarah Cannon Research Institute, Nashville TN, USA;* [2]*St. Vincent's University Hospital, Dublin, Ireland;* [3]*GlaxoSmithKline, Clinical, Collegeville PA, USA*

Background: Lapatinib (Tykerb®/Tyverb®) (L) is an oral, dual ErbB1/B2 tyrosine kinase inhibitor. T are mainstay of BC treatment. The side-effects seen with T in combination with gefitinib and erlotinib include neutropenia, diarrhea and rash. Based on preclinical synergy, early clinical studies with L and paclitaxel (P) or docetaxel (D) were studied.
Methods: We summarize pharmacokinetics (PK) and preliminary safety data from 484 patients.
Results: PK analysis for EGF10009 (q3w), show systemic exposure was increased for both L (21%) and P (23%) at doses of 1500 mg daily and 175 mg/m^2/q3w, respectively. PK analysis in EGF10021 (L 1250 mg & D 75 mg/m^2 with prophylactic pegfilgrastim) indicated no significant effect on systemic exposure of either agent.
Toxicities across all studies include i.e., for all patients $\geqslant$ grade 3, neutropenia (13.8%), diarrhea (18.2%), rash (3.9%). The rate of adverse events for neutropenia and rash were similar to each agent alone, however diarrhea was more common. The frequency and severity of diarrhea was increased in studies EGF10009 and EGF102580 where no proactive treatment of diarrhea was introduced, whereas in EGF105764, with proactive treatment, currently no $\geqslant$ grade 3 diarrhea has been reported. For study EGF30001 and overall diarrhea in this pooled analysis, the $\geqslant$grade 3 diarrhea observed is similar to what is seen with lapatinib monotherapy clinical studies. The data show that the combination of L and P has clinical activity (>70% RR reported in EGF102580).
Conclusions: T plus L combinations have a predictable and manageable safety profile and clinical activity of P plus L combination was observed. Proactive diarrhea management is recommended for these combinations. Based on the PK data, no dose adjustments are mandated; however, toxicities should be carefully evaluated for possible needed dose modifications. Ongoing clinical studies investigating the combinations of L with T, and combinations of L with T plus trastuzumab will be reported in the future.

Study	Phase/ L+T	Dose L mg/d T mg/m^2	Tumor	N	Diarrhea $\geqslant$ G3 (%)
EGF10009	I/L+P	1250–1500/135–225 q3w	Refractory	44	7
EGF10009	I/L+P	1500/80 qw	Refractory	12	50
EGF105764	II/L+P	1500/80 qw	1L MBC	34	0
EGF102580	II/L+P	1500/80 qw	IBC	49	61
EGF10021	I/L+D	1000–1500/50−75 q3w	Refractory	52	10
EGF30001	III/L+P	1500/175 q3w	1L MBC	293	15