PP-7-10 A Phase II Trial on High Dose (240 MG) Toremifene in the Treatment of Advanced Breast Cancer

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Toremifene (TOR) is a new triphenylethylene derivate that like other non-steroidal antiestrogen exhibits tumoristatic action, but at higher concentrations *in vitro* possesses also cytocidal ability. The aim of this open phase II multicentric study was to evaluate the efficacy, safety and tolerability of 240 mg TOR as a first line treatment for advanced breast cancer. From Oct 1986 to Jan 1991 altogether 73 menopausal pts were enrolled in this trial. 69 pts were evaluable for tolerability and 56 met the criteria for response evaluation. Complete response (CR) was evaluated in 12/56 pts (21.4%); partial response (PR) – 21/56 (37.5%); disease stabilisation (ST) – 16/56 (28.6%) and disease progression (PD) – 7/56 (12.5%). Objective response (CR + PR) was 58.9% with the median duration of response 653 days (range 28–2586). Median overall survival was 69 mo (23–92) for CRs: 37 mo (5–94) for PRs; 16 mo (2–73) for STs and 14 mo for PDs. Altogether 33/69 pts (47.8%) reported on transient mild to moderate drug related side effects. Majority of all the registered adverse reactions could have been attributed to antiestrogenic property of the drug (19/33). Less often were the gastrointestinal (10/33), CNS (4/33) and allergic (4/33) reactions. *Conclusions:* 240 mg TOR as a well tolerated medication could be safely used as a first-line treatment for metastatic breast cancer and could be recommended as an induction treatment also for menopausal pts with primary inoperable breast cancer.

PP-7-11 Phase I Study of Combination Docetaxel with Cyclophosphamide in the Treatment of Metastatic Breast Cancer

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Purpose: To determine the dose limiting toxicity and maximum tolerated dose of Docetaxel (D) plus Cyclophosphamide (C) combination in Metastatic Breast Cancer (MBC) patients and examine pharmacokinetics.

Background: D is a highly active drug in MBC. In Japanese late phase II study, 67 of 133 pts (50.4%) had responses (8 CR, 59 PR) at dose of 60 mg/m^2. *In vitro* and *in vivo* study, D plus C showed synergistic action. Based on these results we planed combination study of D with C.

Method: D was administered 1–2 hour infusion followed by C was given by IV bolus. DLT was defined 1) Grade 4 leukopenia or neutropenia for longer than 3 days, 2) Fever with Grade 4 leukopenia or neutropenia caused infection, 3) Other grade 3 or worse toxicity except alopecia, nausea/vomiting or anorexia. At least 3 pts were entered in each level.

Results: Dose levels-Level 1 D 40 mg/m^2, C 200 mg/m^2(3 pts); Level 2 D 40 mg/m^2, C 400 mg/m^2(3 pts); Level 3 D 50 mg/m^2, C 400 mg/m^2(6 pts); Level 4 D 60 mg/m^2, C 400 mg/m^2(3 pts). Fifteen pts with MBC were entered onto the study. DLT of Grade 4 neutropenia for longer than 3 days and grade 4 thrombocytopenia occurred in 3 of 3 pts treated with D 60 mg/m^2 and C 400 mg^2(Level 4).

PP-7-12 Dose-Finding Study of Weekly Oral Vinorelbine (VRL) in Patients (PTS) with Advanced Breast Cancer (ABC): Preliminary Results

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The aims of this Phase I study were to determine the maximum tolerated dose (MTD) of oral VRL administered weekly (= more than 50% incidence of grade 4 hematological or grade 3/4 non hematological toxicity), to define a recommended dose (RD) for further trials and to evaluate pharmacokinetic and activity profiles. The initial dose level was 60 mg/m^2/week and the dose was increased by a 20 mg/m^2 stepwise increment in subsequent cohorts of 6 patients each. The study was performed in PTS with ABC. Interim results are available on 24 PTS (mean age: 58.6 yo; range: 37–78): 7 at 60 mg/m^2, 11 at 80 mg/m^2 and 6 at 100 mg/m^2. PTS were pretreated by previous adjuvant chemotherapy for 5 of them and for advanced/metastatic disease for 15 of them. 50% of PTS had predominantly visceral disease (7 liver, 7 lung). 6 PTS had bone metastasis and 13 locally advanced/metastatic disease. 100 mg/m^2/week was shown to be the MTD (3 grade 4 neutropenia, 2 grade 3/4 constipation and 2 grade 3 vomiting). 80 mg/m^2/week was defined as the RD: Grade 3/4 neutropenia over 24% of cycles; no grade 3/4 nausea or grade 4 vomiting (grade 3: 1% of cycles; no grade 3 constipation, grade 4 over 1% of cycles. Alopecia never exceeded grade 2. Over 13 evaluable PTS treated at 80 and 100 mg/m^2/week, 6 partial responses were observed, 3 of them on visceral disease (2 lung, 1 liver).

It is concluded that oral VRL administered at the weekly dose of 80 mg/m^2 is well tolerated and has interesting activity in ABC.

PP-7-13 Phase I–II Trial of Mitoxantrone (M) and Taxol (T) in Advanced Breast Cancer (ABC)

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We reported an ongoing phase I–II study of T and escalating dose of M in patients with ABC. T was administered at 175 mg/m2 iv over 3 hrs, d-1 and M was escalated by 2 mg increments, starting from 10 mg/m2 (level I) to 12–14 mg/m2 (level II–III) iv d-1; cycles were repeated every 3 wks. From 11/94, 39 females were treated with TM. Pt characteristics: median age of 58 yrs (range: 34–70), KPS was 100–80% in 35 (90%) and < 80 in 4 (10%); primary tumors were ER+ in 12 and PgR+ in 6 pts; prior adjuvant CT was administered in 24 pts, CT for ABC in 17 pts and hormonal in 16 pts. Twelve pts received 3 or more chemotherapy treatments before TM. Disease sites included: lung 10 pts, bone 25 pts, lymph-nodes and skin 16 pts, liver 9 pts and others 16 pts (23 pts have 2 or more sites of disease). Ten pts received M at dose of level I, 14 pts at level II and 15 pts at level III. Of 31 evaluable pts, 4 (13%) obtained *CR* and 17 *(55%) PR (OR: 21/31 68%),* 8 had NC disease, 2 P disease. Nine pts were too-early. Myelosuppression was the most frequent toxicity: 2 pts (6%) experiencing leukopenia Gr. 1, 19 pts (61%) Gr. 2–3, 2 pts (6%) thrombocytopenia Gr. 2 and 6 pts (19%) anemia Gr. 2–3. Non-hematological toxicities superior to Gr. 2 included: Vomiting (22%), alopecia (80%), neurotoxicity (42%) and cardiotoxicity (6%). No dose limiting toxicities occurred at level III.

PP-7-14 Third-Line Chemotherapy with Bendamustin for Metastatic Breast Cancer — A Prospective Pilot Study

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From 9/1994–2/1996 18 patients with metastatic breast cancer were treated with Bendamustin monochemotherapy. 15 pts. were evaluable.

The median age was 53.4 years. All pts had been pretreated with chemotherapy, 13 pts with hormontherapy. 4 pts were pre- and 11 pts postmenopausal.

The following regimen was used: Bendamustin at 150 mg/m2 D1–2 every 3 weeks. A total of 38 courses had been given (2.5/patient – ranging from 1 to 6).

Tumour response (according to WHO criteria): PR 3/15 (20%) pts., NC 9/15 (60%) pts., PD 3/15 (20%) pts. Progression-free survival (Kaplan-Meier) was 5.87 months (PR 7.13; NC 4.68 months). Survival after therapy (K-M) was 7.87 months (PR 10.16; NC 9.37; PD 7.38 months).

Side effects of this treatment modality were moderate (WHO criteria): Only 2 pts showed anemia grade III–IV, grade III–IV leucopenia occured in 4 patients, grade III thrombopenia in 6 pts. No pts with grade III–IV vomiting/nausea or alopecia grade II–IV were observed.

PP-7-15 Org-OD14 Significantly Inhibits DMBA Induced Mammary Tumor Growth in Rats: Effects of Combination Therapy with Tamoxifen or the Antiprogestin Org-31710

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The steroid Org-OD14: (7α, 17α)-17-hydroxy-7-methyl-19-norpregn-5(10)-en-20-yn-3-one which has weak estrogenic, progestational and androgenic