commencement of T respectively), 5 without disease relapse. Only 1 pt relapsed (with local in-breast recurrence) after T discontinuation. Eight pts are still alive and in CR (4 still on maintenance T). These pts are: ER negative 75%, liver only visceral disease 63%.
Conclusions: This is the largest series so far analysing long-term outcome of HER2+ MBC pts with DCR following T-containing CT. A small group of pts who show no further relapse at long-term FU can be identified. They are more frequently ER negative and have metastatic disease confined to liver. Our data suggests that in selected cases of CR lasting ⩾36 months maintenance T can be safely discontinued with very low risk of subsequent relapse. The molecular profile of this subset of pts should be specifically investigated to allow early identification of pts who are more likely to achieve DCR on T+CT.

5001 ORAL

Trastuzumab Emtansine (T-DM1) Vs Trastuzumab Plus Docetaxel (H+T) in Previously-untreated HER2-positive Metastatic Breast Cancer (MBC): Primary Results of a Randomized, Multicenter, Open-label Phase II Study (TDM4450 g/BO21976)

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Background: T-DM1 is a HER2-targeted antibody-drug conjugate in development for the treatment of HER2-positive cancer. It provides intracellular delivery of the cytotoxic agent DM1 while maintaining the antitumour activities of trastuzumab. We previously presented preliminary data from the first randomized phase II study of T-DM1 vs. H+T as first-line treatment in patients with HER2-positive MBC (Perez, et al. ESMO 2010, LBA3; TDM4450 g/BO21976; NCT00679341). Here we present the primary efficacy and updated safety results.
Methods: Patients (N = 137) were randomized 1:1 to T-DM1 3.6 mg/kg IV q3w, or H 6 mg/kg IV (8 mg/kg in cycle 1) + T 75 or 100 mg/m^2 IV q3w, until disease progression or unacceptable toxicity. Primary objectives were investigator-assessed progression-free survival (PFS) and safety. Results are based on a clinical data cutoff date of 15 November, 2010.
Results: Baseline characteristics were similar between groups. In the H+T arm, most patients (74.2%) initiated T at 75 mg/m^2. Median durations of follow-up were 13.5 mos (H+T) and 13.8 mos (T-DM1). Among safety evaluable patients, the most common adverse events (AEs) were alopecia (66.7%), neutropenia (63.6%), diarrhea (45.5%), and fatigue (45.5%) in the H+T arm; and fatigue (49.3%), nausea (47.8%), increased AST (39.1%), and pyrexia (39.1%) in the T-DM1 arm. Consistent with previously reported results, grade ⩾3 AEs were reported less frequently in the T-DM1 arm (46.4% vs 89.4%) as were treatment discontinuations due to AEs (7.2% vs 28.8%). Serious AEs occurred less frequently in the T-DM1 arm (18.8% vs 25.8%). One patient in each arm had an AE that resulted in death. At the data cut-off, 43.3% of patients were continuing T-DM1 vs 21.4% who were continuing H+T. Efficacy data, summarized in the table below, are notable for a significant improvement in PFS in the T-DM1 arm (14.2 vs 9.2 months, HR = 0.59, p = 0.035).
Conclusion: First-line treatment of HER2-positive MBC with T-DM1, compared to H+T, provided a significant improvement in PFS with a favorable safety profile. These results demonstrate the feasibility of T-DM1 in HER2-positive MBC.

	H+T	T-DM1
PFS	n = 70	n = 67
Median PFS (mos)	9.2	14.2
HR (95% CI), *P*-value	0.59 (0.36, 0.97), 0.035	
Objective Response	n = 69	n = 67
ORR, n (%), (95% CI)	40 (58.0), (45.5, 69.2)	43 (64.2), (51.8, 74.8)
Complete response, n (%)	3 (4.3)	7 (10.4)
Partial response, n (%)	37 (53.6)	36 (53.7)

5002 ORAL

Complications Associated With Chemotherapy in Patients With Metastatic Breast Cancer

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Background: Treatment with chemotherapy has been associated with significant rates of adverse events which may lead to expensive care or changes and delays in provided treatment. This study estimates the prevalence of chemotherapy-related complications in patients receiving chemotherapy for the treatment of metastatic breast cancer (mBC) in a real world setting.
Materials and Methods: The PharMetrics® Integrated Database (2004–2009) was used to select patients with mBC treated with chemotherapy and/or anti-HER2 targeted therapies. Episodes of mBC chemotherapy treatment with single-agent or combination of agents for a course of at least 30 days were identified. Complications were identified using medical claims with a diagnosis for one of the following events of interest: anemia, alopecia, arthralgia, bilirubin elevation, dehydration, dyspnea, infection, leukopenia, and neutropenia.
Results: A total of 1551 patients with 3157 eligible episodes of treatment met the inclusion criteria. The mean age of women was 57 years. The complication rates for the commonly used agents including anti-HER2 (i.e., trastuzumab and lapatinib), docetaxel, paclitaxel, gemcitabine, vinorelbine, and doxorubicin, are reported in the table.
Conclusions: Anemia, bilirubin elevation, and leukopenia were the most common complications during an episode of treatment, with substantial variations across types of regimen to treat mBC. Further research assessing the total impact (clinical, humanistic, and financial) of chemotherapy-related complications is required. There is a need for agents providing clinical efficacy without incurring significant toxicities.

	All episodes of treatment	Anti-HER2[1]	Trastuzumab + Vinorelbine[2]	Trastuzumab + Docetaxel[2]	Docetaxel[3,4]	Paclitaxel[3,4]	Gemcitabine[3,4]	Vinorelbine[3,4]	Doxorubicin[3,4]
Number of patients	1551	510	160	84	228	175	234	197	123
Number of episodes of treatment	3157	1157	172	90	264	188	240	207	133
Average by patient	2.0	2.3	1.1	1.1	1.2	1.1	1.0	1.1	1.1
Average duration (days)	131	158	169	141	118	115	94	107	95
Number of episodes with complications									
Anemia	51%	51%	70%	60%	55%	52%	70%	65%	50%
Arthralgia	12%	15%	18%	16%	9%	11%	9%	12%	10%
Bilirubin elevation	26%	29%	35%	31%	22%	31%	20%	21%	19%
Dehydration	10%	11%	14%	17%	11%	7%	10%	10%	13%
Dyspnea	19%	17%	24%	19%	21%	22%	24%	19%	20%
Infection	19%	20%	22%	22%	23%	14%	21%	16%	12%
Leukopenia	25%	18%	38%	20%	36%	23%	33%	46%	28%
Neutropenia	18%	13%	30%	14%	27%	15%	21%	30%	15%

[1]Based Regimen; Monotherapy or combination.
[2]Based Regimen; Including combination with anti-hormone therapy.
[3]Excluding anti-HER2-agents.
[4]Based regimen; Monotherapy or combination with anti-hormone therapy.

5003 ORAL

Inhibition of HER2 Positive Breast Cancer Cells by Drug Screening

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Background: About 20% of all breast cancers have an amplicon in 17q12−21 resulting in over-expression of the human epidermal growth factor receptor 2, *ERBB2*/*HER*-2. HER-2 is a receptor tyrosine kinase, belonging to the epidermal growth factor receptor (EGFR) family of proteins. Phosphorylation of the HER2 tyrosine domain activates downstream pathways like PI3K/Akt and MAPK that are involved in regulation of cell growth, survival, migration and proliferation. In the clinic, HER-2+ patients are treated with Trastuzumab (Herceptin), a monoclonal antibody targeted

against the extracellular domain of HER-2, which inhibits proliferation and survival of the tumour. Not all HER-2+ patients respond to Trastuzumab, although the patients have the HER-2 amplicon; over half of them become resistant to this treatment or show no response at all. Activation of the PI3K/Akt pathway has been suggested to play a role in HER-2+ patients without Trastuzumab-response. Searching for other drugs inhibiting cancer proliferation are therefore of vital importance to identify novel and combinatorial treatment strategies for HER-2+ patients.
Materials and Methods: Thirteen HER-2+ breast cancer cell lines (5 responsive and 8 non-responsive to Trastuzumab) were screened using 22 compounds targeting HER-2, the EGFR family, or HER-2 downstream signaling pathways for 5 days. The compounds were printed in 7 different concentrations with two replicates in 384 well plates, and the screenings for each cell line were done with two biological replicates. Cell viability using the CellTiter-Glo® Luminescent Viability Assay (Promega), detecting the ATP-levels, was used as an endpoint. The luminescence was measured with a MicroBeta LumiJET (Perkin Elmer). miRNA and mRNA profiling data together with copy number changes and PIK3CA mutation status are available for the same cell lines and will be used for integrative data-analysis.
Results: Drug inhibition data from four replicates for each compound were used to obtain EC_{50} (half maximal effective concentration)-values and growth inhibition curves for each cell line. Preliminary screening data show that several compounds inhibited growth of the cell lines that did not respond to Trastuzumab. Interestingly, several drugs were more efficient than Trastuzumab also for the Trastuzumab responding cell lines. Integration of the drug data together with PIK3CA mutation status and genomic profiling data from the same cell lines are ongoing.
Conclusions: Compound screening of HER-2+ breast cancer cell lines revealed that several compounds targeting the HER-2, the EGFR family, or HER-2 downstream signaling pathways are efficient for inhibiting the growth of these cancer cells. Therefore, we suggest alternative compounds for the treatment of the cells that do not respond to Trastuzumab. Finally, we believe that the integration of the genomic profiling data together with the compound screening data will lead to increased knowledge about the mechanisms of action of these drugs.

5004 ORAL

HER2-HER3 Signaling Pathway Regulates NK Cell-mediated Cytotoxicity via MHC Class I-related Chain A/ B in Human Breast Cancer Cells

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Background: HER2 and HER3 are frequently expressed in several types of cancer including breast cancer and their over-expression is associated with poor prognosis. HER2 targeting therapies are already in clinical practice since more than a decade and therapies targeting HER3 are in clinical trials. The role of HER2-HER3 signaling in tumour escape from the host immune system is however poorly understood. We previously reported that the HER2 oncogene down-regulated the expression of MHC class I, resulting in a phenotype promoting tumour escape from adaptive immunity. Here we demonstrate that HER2-HER3 signaling in breast cancer cell lines increases the expression of MHC class I-related chain A and B (MICA/B) molecules of the NK group 2 member D (NKG2D) ligand in breast cancer cell lines, resulting in enhanced sensitivity to NK cell-mediated recognition.
Material and Methods: A possible influence of HER2-HER3 signaling on MICA/B expression in human breast cancer cell lines (MDA-MB231, MDA-MB453, and T47D) was investigated. In order to assess the effect of blocking the HER2-HER3 signaling pathway, cells were either treated with siRNA of HER2 or HER3 or with inhibitors of the HER2-HER3 signaling pathways. To assess the consequences of HER2-HER3 activation, cells were either transfected with the HER3 oncogene or stimulated with the HER3 ligand NRG1-beta. NK cell-mediated cytotoxicity against tumour cells was assessed using ^{51}Cr release assay.
Results: The siRNA-mediated silencing of HER3 down-regulated MICA/B expression while transfection with a plasmid expressing the HER3 oncogene enhanced MICA/B in cell lines with high and low HER3 expression respectively. Treatment of HER3 positive tumour cells with the HER3 ligand NRG1-beta enhanced MICA/B. Among the major pathways activated by HER2-HER3 signaling, the expression of MICA/B was mainly regulated by the PI3K pathway. As expected, HER2-HER3 signaling-regulated MICA/B induced NK cell cytotoxicity in a NKG2D dependent manner.
Conclusions: We conclude that while signaling via the HER2-HER3 pathway may lead to decreased sensitivity to CTL mediated tumour elimination, this may instead lead to an enhanced recognition of the innate immune system mediated via MICA/B.

5005 ORAL

Exploratory Subgroup Analysis of the TAMRAD Phase 2 GINECO Trial Comparing Tamoxifen (TAM) Plus Everolimus (RAD) With TAM Alone in Patients With Hormone-receptor-positive, HER2-negative Metastatic Breast Cancer (mBC) With Prior Exposure to Aromatase Inhibitors (AIs): Implication for Research Strategies

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Background: In patients with mBC, resistance to hormonal therapy may be associated with activation of the PI3K/Akt pathway. RAD is an oral inhibitor of mammalian target of rapamycin (mTOR). In the previously reported TAMRAD phase 2 trial (N = 111), patients with prior exposure to AIs were randomized to receive TAM + RAD (TAM, 20 mg/d; RAD, 10 mg/d) or TAM alone (20 mg/d). Median time to progression (TTP) was 4.5 months with TAM and 8.6 months with TAM + RAD (hazard ratio [HR] = 0.53; 95% CI: 0.35–0.81). To gain insight as to which patient population may benefit the most from this strategy, unplanned exploratory subgroup analysis of this trial was performed.
Materials and Methods: HRs for TTP with TAM + RAD vs TAM alone were analyzed according to primary vs secondary hormone resistance, which was the study's only stratification variable besides the study site. Patients with primary hormone resistance were defined as having relapsed during adjuvant AI or <6 months after AI in the metastatic setting. Patients with secondary hormone resistance were defined as those who relapsed $\geqslant$6 months after adjuvant AI or responded for >6 months to AI in the metastatic setting. In addition, this analysis included the following factors: presence of liver or lung metastasis and TAM or previous chemotherapy for metastatic disease.
Results: Patients with secondary hormone resistance (n = 56) had an HR for TTP of 0.38 (95% CI: 0.21–0.71), whereas those with primary hormone resistance (n = 54) had a much smaller gain from the association (HR = 0.74; 95% CI: 0.42−1.3). HR for improvement in TTP in favor of the TAM + RAD arm was similar to the global HR in all other subgroups.
Conclusions: Patients with secondary hormone resistance may benefit more from the TAM + RAD combination than patients with primary hormone resistance. This result may have important implications for future clinical trial design.
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5006 ORAL

Eribulin Mesylate EMBRACE Study − Survival Analysis Excluding Patients Re-challenged With Therapies of the Same Class

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Background: Eribulin mesylate (Halaven™), a non-taxane microtubule dynamics inhibitor with a novel mode of action, has demonstrated prolonged overall survival (OS) in heavily pretreated patients (pts) with metastatic breast cancer (MBC) (EMBRACE study; NTC00388726; trial completed; sponsored by Eisai Ltd). It has been suggested that pts receiving treatment of physician's choice (TPC) may be less likely to gain benefit if they receive therapy with a class of agent they had previously been treated with (re-challenge), thereby favoring eribulin. This analysis excludes re-challenged pts in the TPC arm, allowing assessment of eribulin vs agents given for the first time. Eribulin vs re-challenged pts only was also assessed.
Methods: Pts (N = 762; 508 eribulin, 254 TPC) with locally recurrent or MBC who had received 2−5 prior chemotherapy regimens ($\geqslant$2 for advanced disease), including an anthracycline and a taxane (unless contraindicated) were randomized 2:1 to receive either eribulin mesylate 1.4 mg/m^2 2−5