ASSOCIATION BETWEEN TUMOR EGFR AND KRAS MUTATION STATUS AND CLINICAL OUTCOMES IN NSCLC PATIENTS RANDOMIZED TO SORAFENIB PLUS BEST SUPPORTIVE CARE (BSC) OR BSC ALONE: SUBANALYSIS OF THE PHASE III MISSION TRIAL


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Background: Tumor EGFR and KRas mutations are both predictive and prognostic biomarkers in patients with advanced NSCLC. We analyzed the correlation between these biomarkers and treatment outcomes in a phase III trial of 3rd/4th line sorafenib in patients with NSCLC.

Methods: The global, randomized, placebo-controlled MISSION trial enrolled 703 patients with advanced relapsed/refractory NSCLC of predominantly non-squamous histology. The primary study endpoint was overall survival (OS). EGFR and KRas mutations were analyzed in archival tumor samples and in circulating tumor DNA isolated from plasma.

Results: Tumor and/or plasma mutation data were available from 347 patients (49%). EGFR and KRas mutations were detected in 89 (26%) and 68 (20%) patients, respectively, and were well balanced between treatment arms. Analysis of the interaction between EGFR mutation status and treatment effect on survival suggested that patients with EGFR mutations (mEGFR) benefited from sorafenib, while those with wild-type EGFR (wtEGFR) did not (p = 0.023). Median OS was two-fold longer in mEGFR patients receiving sorafenib versus placebo (423 vs 197 days, HR 0.48, p = 0.002). There was no significant difference in OS between patients with wtEGFR receiving sorafenib or placebo (253 vs 256 days, HR 0.92, p = 0.559). An interaction was also seen between EGFR mutation status and the sorafenib effect on PFS (p = 0.015). Patients with mEGFR treated with sorafenib had better outcomes compared to placebo based on Cox regression analysis (HR 0.27, p < 0.001; median PFS 83 vs 42 days) than patients with wtEGFR (HR 0.62, p = 0.001; median PFS 82 vs 46 days). KRas mutation status was not predictive of sorafenib efficacy.

Conclusion: Post-hoc analyses of efficacy outcomes in MISSION suggest that advanced NSCLC patients with EGFR mutations may derive a survival benefit from receiving 3rd/4th line sorafenib. These results must be interpreted with caution due to the small, non-representative nature of the genetic biomarker subpopulation analyzed in this trial. Further prospective investigation may be warranted.

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breast cancer, early stage

PHARE TRIAL RESULTS COMPARING 6 TO 12 MONTHS OF TRASTUZUMAB IN ADJUVANT EARLY BREAST CANCER


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Background: Since 2005, One year trastuzumab (T) treatment has been providing survival benefit to patients with early breast cancer and HER2 overexpression.

However, the optimal duration of T has been debatable due to concerns forcardiac toxicity and results from the FinHer trial which showed that 9 weeks of T provided a similar magnitude of benefit than the 1-year treatment. The French National Cancer Institute (INCa) initiated an academic randomised non-inferiority trial aiming to compare a shorter T exposure of 6 months versus the standard 12 months. This trial, named PHARE for ‘Protocol for Herceptin’ as Adjuvant therapy with Reduced Exposure’ [NCT00381901] was approved by an independent ethics committee with regular planning meetings.

Methods

- Patients and methods: Patients with HER2+ early breast cancer who received at least 4 cycles of (neo-)adjuvant chemotherapy were eligible. Randomization 1:1 using a minimisation algorithm was stratified on concomitant or sequential T administration, to T every 3 weeks for 1 yr, 2 yrs, or observation.

- Results: Between 5/2006 and 7/2010, 3382 patients were randomised to 6 or 12 months of T following the IDMC recommendation for accrual interruption and extended follow-up. Disease and treatment characteristics were well balanced between the 2 arms: median age 55 years (range 21–86), median tumour size 20 mm (0–270), node involvement 45%, SBR grade III 56%, ER positive 58%, radiotherapy as indicated, to T every 3 weeks for 1 yr, 2 yrs, or observation.

- Conclusions: These results confirm that 1 yr of adjuvant T remains the standard of care for HER2-positive EBC pts. It is also reassuring that the significant improvement in DFS and OS persists over time and that the incidence of cardiac endpoints remains low at a median FU of 8 yrs.

Disclosures: X. Pivot: The study of the abstract has received funding and sponsorship from the French National Cancer Institute (INCa). All authors have declared no conflicts of interest.

HERA TRIAL: 2 YEARS VERSUS 1 YEAR OF TRASTUZUMAB AFTER ADJUVANT CHEMOTHERAPY IN WOMEN WITH HER2-POSITIVE EARLY BREAST CANCER AT 8 YEARS OF MEDIAN FOLLOW UP


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Background: One year (yr) of trastuzumab (T) significantly improves disease-free (DFS) and overall survival (OS) in patients with HER2-positive early breast cancer (EBC) and is considered the standard of care. HERA is the only randomized trial investigating whether longer duration of T can further improve efficacy outcome.

Materials and methods: HERA (BIG 01-01) is an international, multicenter, phase III randomized trial involving 5102 women with HER2-positive EBC. Pts were randomized, after completion of primary therapy [surgery, chemotherapy and radiotherapy as indicated], to T every 3 weeks for 1 yr, 2 yrs, or observation. This landmark efficacy analysis compares the outcome of pts randomized to either 2 yrs or 1 yr of T who were disease-free at 1 yr after randomization (N = 1553 for 2 yrs, and N = 1552 for 1 yr). The primary endpoint is DFS and secondary endpoints are OS and time to distant recurrence (TTDR). Updated efficacy analyses of the T arms vs. observation at 8-yrs of median follow-up (FU) are also presented.

Results: On 12 April 2012 HERA reached the target number of 725 DFS events needed for 80% power to detect a true hazard ratio (HR) of 0.80 for the comparison of 2 yrs vs. 1 yr of T. The unadjusted HR for an event in the 2-yr vs 1-yr T arms was 0.99 (95% CI 0.85-1.14; P = 0.8588), OS in the two arms was comparable [HR = 1.05 (95% CI 0.86-1.28; P = 0.6333)]. TTDR results were similar. The primary cardiac endpoint was comparable (96% vs. 83% for 2 yr and 1 yr arms, respectively), but the secondary cardiac endpoint** was higher in the 2-yr arm (7.1% vs. 4.10%). Importantly, the durable benefit in DFS and OS for both 1 yr and 2 yrs of T compared with observation remains stable at 8 yrs of median FU.

Discussion: These results confirm that 1 yr of adjuvant T remains the standard of care for HER2-positive EBC pts. It is also reassuring that the significant improvement in DFS and OS persists over time and that the incidence of cardiac endpoints remains low at a median FU of 8 yrs.

** Cardiac death or severe CHF (NYHA class III or IV, confirmed by a cardiologist, and a significant LVEF decrease)

Disclosures: M. Piccart: Roche - Genentech: Consultancy, honoraria M. Procter: Marion Proctor’s institution has received funding in relation to the HERA trial E. De Azambuja: I have received travel grant form Roche. I have received honoraria from Roche. H. Weber: Stock options from Roche, Employment from Roche L. Gianni: Roche: Advisory board, GSK: Advisory board C. Jackisch: Speakers Bureau Roche & GlaxoSmithKline D. Cameron: Personal and institutional reimbursement from Roche for advisory boards, consultancy and grants. M. Dowsett: Roche: Grant, advisory board, lecture fees J. Baselga: Advisory board memberships of Roche and GlaxoSmithKline. All other authors have declared no conflicts of interest.
1. Vaidya JS, Vyas JJ, Chinoy RF, Merchant N, Sharma OP, Mittra D, Joseph6, on behalf of the TARGIT trialists group1

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These data illustrate the danger of over-diagnosis and overtreatment of breast cancer: whole-organ analysis and clinical implications. 

Introduction: The TARGIT-A trial (n = 3451) has completed recruitment and the fresh analysis confirms that the risk-adjusted approach using targeted intra-operative radiotherapy (TARGIT) achieves local control that is non-inferior to conventional whole breast radiotherapy (EBRT).

Method: Patients could be randomised and receive TARGIT either at the time of the lumpectomy (‘pre-pathology stratum’), or afterwards as a second procedure (‘post-pathology stratum’). In the pre-pathology stratum, if protocol-defined adverse pathological features were found post-operatively, the whole breast was irradiated (avoiding boost) in addition to intra-operative radiotherapy. This analysis looks at the pattern of local recurrence (LR) in the pre-pathology stratum, 64% of whom were screen detected.

Results: The 5-year KM estimate of local recurrence outside the index quadrants was similar in the two randomised groups (TARGIT: 0.8% vs. EBRT 0.4%, p = 0.709). Subsequently we were able to derive a group of 498 patients who received no treatment to the ipsilateral breast beyond the index quadrant, only 2 of whom experienced a LR that was outside the index quadrant. If we assume that approximately 60% of these patients had occult disease outside the index quadrant [1], then we have 296 women with locally untreated occult foci of breast cancer that failed to progress following1923 woman-years exposure to risk.

Conclusion: These data illustrate the danger of over-diagnosis and overtreatment of subclinical breast cancer and together add further fuel to the debate on the harms versus benefits of mammographic screening.


Disclosure: M. Baum: Travel expenses and honoraria on occasions from Carl Zeiss Consultancy fees on a regular basis until last year J.S. Vaidya: Research grant from Photoelectron Corp (1996–99), and from Carl Zeiss for supporting data management and has subsequently received honoraria. Carl Zeiss also sponsored travel and accommodation for meetings of the international steering committee. F. Wenz: Carl Zeiss supports radiobiological research at the University Medical Center Mannheim. All other authors have declared no conflicts of interest.

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2.450 A PROSPECTIVE RANDOMIZED TRIAL EVALUATING GENE EXPRESSION ARRAYS TO SELECT NEOADJUVANT CHEMOTHERAPY REGIMEN FOR OPERABLE BREAST CANCER: FIRST REPORT OF THE REMAGUS04 TRIAL

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Background: DNA arrays allow quantifying gene expression at the whole genome level and could improve prediction of the benefit from a specific chemotherapy (CT). We have evaluated here whether DNA array could increase efficacy of neoadjuvant CT.

Patients and methods: This prospective randomized phase III trial compared the choice of a CT regimen based on DNA array to a standard CT. Pts with HER2 neg breast carcinoma not eligible for conserving surgery were included. DNA arrays (Affymetrix U133Av2) were performed within 15 days after frozen tumour biopsy. Only samples with >30% cancer cells, a RIN > 6 and a test array positive were eligible. DLD30 prediction score and topoisomerase 2A (TOP2A) level were calculated. Pts randomized to “genomic-driven” CT arm were allocated to 12 weekly paclitaxel then 4 FEC100 if DLD30+, to 4*FEC*4 + docetaxel (D) if TOP2A+/DLD30- and to 6 D/capecitabine (DC) if DLD30-/TOP2A-. Pts randomized to standard arm were treated with 4*FEC*4 +D. The trial, designed to include 300 pts, was stopped after a preplanned interim analysis showing < 2 pathological Complete Response (pCR) in the DC group.

Results: Overall 303 pts entered in the screening phase: 64 (21%) were not eligible for the main trial because of exclusion criteria, 60 (20%) presented less than 30% tumor cells in the sample and 37 (15%) presented a poor quality RNA. Overall, DNA array was feasible within 15 days in the context of daily practice in 59% of the pts. 142 pts entered in the clinical decision trial. 39% and 57% of the pts presented an ER-neg or high grade tumour. The overall pCR rate was 22%. No difference was observed between genomic driven arm and standard CT arm (pCR rates: 22 % and 21% respectively). DLD30+ score was associated with an increased likelihood of pCR (36% versus 3% for DLD30-). DLD30+ was associated with OR for pCR at 4.7 (0.87–35.9, p = 0.09) in a multivariate analysis. Additional unplanned retrospective analyses have shown that immune signature could improve prediction of pCR.

Conclusion: This is the first prospective trial showing that whole expression genome array is feasible in the context of daily practice, quantifies gene expression accurately and validates predictive value of DLD30 and immune signatures. Gene expression arrays could be a solution in the future to propose an all-in-one assay for personalized medicine.

Disclosure: All authors have declared no conflicts of interest.
The discrepancy between high pathological complete response (pCR) rate and low breast conserving surgery (BCS) following neoadjuvant therapy: analysis from the NeoALTTO trial (BIG 1-06)


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Background: The NeoALTTO trial showed that paclitaxel plus lapatinib and trastuzumab nearly doubles the rate of pCR compared to paclitaxel combined with either drug alone (51.3% vs 29.5% vs 24.7%). However, this high pCR rate did not translate into a higher rate of BCS, which was around 40% across the 3 arms. We investigated different factors that may have affected the choice of surgery.

Patients and methods: In the NeoALTTO trial, patients (pts) with HER2+ breast cancer were randomized to either trastuzumab, lapatinib or their combination concomitantly with paclitaxel prior to surgery. The primary endpoint was pCR, defined as the absence of invasive cancer in the breast at the time of surgery. Here, we investigated the association between achieving pCR, and type of surgery, age, histology, grade, tumor size, ER status, multicentricity, response to therapy and the country where the treatment was given.

Results: 429 pts were eligible for the analysis (26 have been excluded as they did not undergo breast surgery), of whom 160 (37%) achieved a pCR. 242 (57%) and 187 (43%) pts had mastectomy and BCS, respectively. Mastectomy was more frequent if the patient was < 50, if treated in developing country, if the tumor was multicentric, >5 cm, or ER-. All pts diagnosed with lobular cancer (n = 17) underwent mastectomy regardless of pCR. 68 pts had a radiological complete response, yet 36 of those (53%) were subjected to mastectomy (25 pts (70%) achieved a pCR). Of the 128 pts considered for BCS at screening, only 95 (74%) had a conservative surgery and rates were similar according to pCR status (79% in pCR vs. 72% in no pCR). Conversely, 30% of pts initially evaluated as inoperable or requiring mastectomy had a BCS.

Conclusion: Tumor characteristics prior to neoadjuvant therapy appeared to play a main role in deciding the type of surgery irrespective of response. This may deny a large fraction of women the chance of preserving their breast. These results should be taken into account in addressing the criteria for BCS after neoadjuvant therapy.

Disclosure: E. De Azambuja: advisory board from GSK; honoraria from Roche M. Piccart: Consulting/advisory role/honoraria from SanofiAventis, Amgen, Bayer, Bristol Myers Squibb, Roche, Glaxo Smith Kline, Boehringer, PharMar S. Di Cosimo: Speaker for GSK. All other authors have declared no conflicts of interest.
breast cancer, locally advanced and metastatic

LBA11

CEREBEL (EGF111438): AN OPEN LABEL RANDOMIZED PHASE III STUDY COMPARING THE INCIDENCE OF CNS METASTASES IN PATIENTS (PTS) WITH HER2+ METASTATIC BREAST CANCER (MBC), TREATED WITH LAPATINIB PLUS CAPECITABINE (LC) VERSUS TRASTUZUMAB PLUS CAPECITABINE (TC)

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Background: In HER2+ MBC, central nervous system (CNS) metastases (mets) occur in 28 – 43% of cases. Systemic therapies with potential to prevent or reduce CNS mets are of current interest. Based on lapatinib promising activity in CNS mets, CEREBEL evaluated the prophylactic impact on CNS mets incidence in HER2+ MBC pts treated with Lapatinib plus capecitabine (LC) in comparison to Trastuzumab plus capecitabine (TC).

Methods: CEREBEL was a multicenter study in HER2+ MBC pts without CNS mets at baseline, confirmed centrally by MRI. Prior treatment must include anthracyclines or taxanes in (neo)adjuvant or metastatic setting. Pts were randomized to LC (L-1250 mg daily + C-2000 mg/m2/day for 14 days [21-day cycle] or TC (T loading dose 8 mg/kg followed by 6 mg/kg q3weekly + C-2500 mg/m2/day for 14 days [21-day cycle]). Primary endpoint was incidence of CNS as first site of relapse. Secondary endpoints were progression free survival (PFS), overall survival (OS), CNS progression at any time, overall response rate (ORR), clinical benefit response rate, duration of response and safety.

Results: A pre-specified interim analysis (IA) including 475 pts was performed by an IDMC convened on June 2012. A total of 43% and 46% of pts had not received prior T in LC and TC arms, respectively. Adverse events were similar in both arms with the exception of diarrhoea, nausea and rash (higher with LC). The incidence of CNS metastasis as site of first relapse was 3% for LC versus 4% for TC (OR 0.75 (0.25, 2.20) in modified ITT population (N = 218 pts per arm). The median PFS was 6.6 and 8.0 months in LC and TC arms (HR 1.3; 95% CI: 1.0, 1.7) and median OS was 22.4 and 27.3 months (HR:1.3; 95% CI:1.07-2.32)(ITT)

Conclusions: Based on these results, the IDMC recommended study termination. Final results and updated survival data will be presented at ESMO with the 535 pts included in CEREBEL.

EudraCT number: 2008-00673-38

Disclosure: X. Pivot: I am consultant and I have received honorariums for the sponsor GSK. R. Allerton: Roche advisory board for use of Pertuzumab in breast cancer. R. Parikh: Employee of GSK M. DeSivio: Employee of GSK S. Santillana: Employees of GSK, Director Clinical Development R. Swaby: Employee of GSK. All other authors have declared no conflicts of interest.

LBA12

RESULTS FROM EMILIA, A PHASE 3 STUDY OF TRASTUZUMAB EMTANSINE (T-DM1) VS CAPECITABINE (X) AND LAPATINIB (L) IN LOCALLY ADVANCED OR METASTATIC BREAST CANCER (MBC)

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Background: T-DM1 is an antibody–drug conjugate incorporating the HER2– targeted antitumor properties of trastuzumab (T) with the cytotoxic activity of the microtubule inhibitor DM1, connected by a stable linker.

Methods: Patients (pts) with confirmed HER2+ MBC (IHC3+) and/or FISH+ and prior treatment with T and a taxane were randomized to T-DM1 (3.6 mg/kg IV q3w) or X (1000 mg/m2 bid, days 1–14 q3w) + L (1250 mg PO qd, days 1–21). Primary end points were progression-free survival (PFS) by independent review, overall survival (OS), and safety. An interim OS analysis occurred at the time of the final PFS analysis.

Results: 991 pts were enrolled; 978 received treatment. Median durations of follow-up were 12.9 (T-DM1) and 12.4 (XL) mos. Baseline demographics, prior therapy, and disease characteristics were balanced. PFS was significantly improved in T-DM1 compared with XL. Results of other study end points, including interim OS, were consistent with PFS. T-DM1 conferred a significant and clinically meaningful improvement in PFS compared with XL. The incidence rates of cardiac AEs and left ventricular dysfunction were low and similar in both arms.

Conclusions: T-DM1 conferred a significant and clinically meaningful improvement in PFS compared with X. Results of other study end points, including interim OS, safety, and key secondary end points, favor T-DM1 and establish its role as a potential new therapy for HER2+ MBC pts previously treated with T and a taxane.

Disclosure: S. Verma: *Compensated consultant/advisory relationship with Roche/GSK *Honoraria from GSK/Roche *Research funding from Genentech/Roche L. Gianni: Dr. Gianni was a compensated consultant/advisory relationship with Genentech/Roche. L. Kroop: Uncompensated consultant/advisory relationship with Novartis Research funding from Genentech/Roche J. Baselga: Compensated consultant/advisory relationship with Genentech/Roche M. Pegram: Compensated consultant/advisory relationship with Genentech/Roche Honoraria from Genentech/Roche V. Díaz:...
Background: Breast cancer includes large number of actionable genomic alterations. Each of these alterations characterizes individually a rare genomic entity. In the context of daily practice at the national level, and provide the first genomic landscape of breast cancer metastases. Final results of the genomic analysis (n = 428) and first results of treatment efficacy will be presented.

Disclosure: All authors have declared no conflicts of interest.

*Compensated consultant/advisory relationship with Genentech/Roche, Novartis, Sanofi, Amgen, Clovis, Pfizer, GK* Honoraria from Genentech/Roche, Novartis, Sanofi, Amgen, Clovis, Pfizer, GSK J. Guardely

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Background: A previous phase 1/2 trial of PANVAC, a poxviral based cancer vaccine, suggested clinical efficacy in some patients (pts) with breast and ovarian cancer and evidence of immunologic activity. Preclinical data showed DOC can modify tumor phenotype, making tumor cells more amenable to T-cell mediated killing. The goal was to determine if DOC and PANVAC could synergize and improve clinical outcomes compared with DOC alone.

Methods: This is an open-label randomized phase 2 multi-center trial designed to enroll 48 pts with metastatic breast cancer to receive DOC in combination with PANVAC (A) or alone (B). Cross-over was allowed so that pts randomized to B could receive the vaccine upon progression. Eligibility included ECOG performance status 1 and normal organ and immune function with no limits on previous lines of therapy, but pts may not have received DOC for metastatic disease. Her2+ pts on trastuzumab were allowed to continue trastuzumab on disease. Her2+ pts on trastuzumab were allowed to continue trastuzumab on

Results: Enrollment of 48 pts completed in February 2012 (A, n = 25; B, n = 23). Five pts remain on treatment (2 on A, 3 on B). Patient and tumor characteristics were well matched. Analysis through August 2, 2012 (median follow-up of 5.1 months for pts on study), indicates PFS is 6.6 vs. 3.8 months in A vs. B (p = 0.12, HR = 0.67, 95% CI: 0.34 to 1.31). Toxicity was similar in both arms. Immune analysis and correlation to pt clinical outcomes is ongoing.

Conclusion: This randomized study suggests the combination of PANVAC with DOC in metastatic breast cancer may provide a clinical benefit compared to DOC alone. The clear separation of the curves indicates potential benefit, which is not statistically significant, likely due to the small number of pts enrolled. This study was hypothesis generating and may provide both rationale and statistical assumptions for a larger definitive randomized study.

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**Table: LBA12**

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<th>T-DM1 n = 495</th>
<th>XL n = 496</th>
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<tbody>
<tr>
<td>PFS, median mos</td>
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<td>6.4</td>
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<td>6.5 (5.45, 7.16)</td>
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<td>HR (95% CI)</td>
<td>0.703 (0.602, 0.820)</td>
<td></td>
</tr>
</tbody>
</table>

**Table: LBA13-PR**

**ARRAY CGH AND DNA SEQUENCING TO PERSONALIZE THERAPY FOR METASTATIC BREAST CANCER: A PROSPECTIVE NATIONAL TRIAL (UNCANCER SAFIR-01)**

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**Background:** Breast cancer includes large number of actionable genomic alterations. Each of these alterations characterizes individually a rare genomic entity. In the present study, we have used array CGH (aCGH) and Sanger sequencing to direct patients to specific targeted agents. We report the first large prospective trial testing whole genome DNA approaches to identify actionable alterations and drive patients to specific targeted agents. This trial shows that whole genome approaches are feasible in the context of daily practice at the national level, and provide the first genomic landscape of breast cancer metastases.

**Methods:** This is an open-label randomized phase 2 multi-center trial designed to enroll 48 pts with metastatic breast cancer to receive DOC in combination with PANVAC (A) or alone (B). Cross-over was allowed so that pts randomized to B could receive the vaccine upon progression. Eligibility included ECOG performance status 1 and normal organ and immune function with no limits on previous lines of therapy, but pts may not have received DOC for metastatic disease. Her2+ pts on trastuzumab were allowed to continue trastuzumab on disease. Her2+ pts on trastuzumab were allowed to continue trastuzumab on

**Results:** Enrollment of 48 pts completed in February 2012 (A, n = 25; B, n = 23). Five pts remain on treatment (2 on A, 3 on B). Patient and tumor characteristics were well matched. Analysis through August 2, 2012 (median follow-up of 5.1 months for pts on study), indicates PFS is 6.6 vs. 3.8 months in A vs. B (p = 0.12, HR = 0.67, 95% CI: 0.34 to 1.31). Toxicity was similar in both arms. Immune analysis and correlation to pt clinical outcomes is ongoing.

**Conclusion:** This randomized study suggests the combination of PANVAC with DOC in metastatic breast cancer may provide a clinical benefit compared to DOC alone. The clear separation of the curves indicates potential benefit, which is not statistically significant, likely due to the small number of pts enrolled. This study was hypothesis generating and may provide both rationale and statistical assumptions for a larger definitive randomized study.

**Acknowledgements:** M. Bilusic, J. Kim, N.K. Singh, J. Hodge.

**Clinical trials.gov number:** NCT00179309.

**Disclosure:** J. Schlam: The Laboratory of Tumor Immunology and Biology, of which I am Lab Chief, has a Collaborative Research and Development Agreement with Bavarian Nordic. The LTIB’s research is funded by the Intramural Research Program, CCR, NCI, NIH. All other authors have declared no conflicts of interest.
CNS tumors

**LBA15** RANDOMIZED Multicenter Phase II Trial of Irinotecan and Bevacizumab as Neo-Adjuvant and Adjuvant to Temozolomide-Based Chemoradiation Versus Chemoradiation for Unresectable Glioblastoma (Definitive Results of the Temavir ANOCF Study)


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Background: The prognosis of unresectable glioblastoma (GBM) remains poor despite temozolomide (TMZ)-based chemoradiation. Activity of bevacizumab/irinotecan has been reported in recurrent GBM (Vardenburgh, 2007). We evaluate irinotecan (IRI) and bevacizumab (BVZ) as neo-adjuvant and adjuvant to TMZ-based chemoradiation for unresectable glioblastoma.

Method: Pts with de novo unresectable GBM, aged 18-70, and KPS > 50, and RPA class 5 were eligible. Experimental arm (A) consisted of neo-adjuvant BVZ 10 mg/kg and IRI 125 mg/m², every 2 wk for 4 cycles before radiotherapy (60 Gy in 30 fractions) with concurrent TMZ 75 mg/m²/day and BVZ every 2 wk. Adjuvant BVZ and IRI were given every 2 wk for 6 months. The control arm (B) consisted of concomitant TMZ, 75 mg/m²/during radiotherapy and 150-200 mg/m² for 5 d every 28 d for 6 months. Cross over were allowed at progression. The inclusion of 60 pts/arm was planned using Fleming’s 2 steps design aiming at an increase of PFS at 6 month (PFS6) from 50 % to 66 %, with unilateral alpha 5% and 80% power. Final analysis, including overall survival (OS), was performed 16 months after the end of inclusion.

Results: Patients (120) were included from April 2009 to January 2011. Clinical factors were well balanced between arms. Treatment-related serious adverse events were brain haemorrhages (3; 3 fatal), biliary or digestive perforation/infection (3, 1 fatal), thrombo-embolism (4, 0 fatal) in arm A, and brain or digestive perforation/infection (2, 2 fatal), pulmonary infection (1, no fatal), thrombo-embolism (2, 0 fatal), thrombo- and/or neutropenia (4, 0 fatal) in arm B. PFS at 6 and 12 months appears to be longer in arm A, but OS was similar in both arms (table).

<table>
<thead>
<tr>
<th>ARM (patients)</th>
<th>PFS 6 % [IC95, %]</th>
<th>PFS 12 % [IC95, %]</th>
<th>OS 6 % [IC95, %]</th>
<th>OS 12 % [IC95, %]</th>
</tr>
</thead>
</table>

Conclusion: Despite a trend to a better PFS at 6 and 12 month in the experimental arm, overall survival was not different between arms.

Disclosure: B. Chauffert: Bruno Chauffert was granted by Roche for travels and attending on several meetings about neuro-oncology. He did not receive any salary or indemnity for coordinating this trial. O. Chinot: Pr Olivier Chinot is the international coordinator of the AVACLIO trial that is sponsored by Roche. All other authors have declared no conflicts of interest.

**LBA16** ASSOCIATION OF MATRIX METALLOPROTEINASE 2 (MMP2) PLASMA LEVEL WITH RESPONSE AND SURVIVAL IN PATIENTS TREATED WITH BEVACIZUMAB FOR RECURRENT HIGH GRADE GLIOMA

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Background: Predictive marker of bevacizumab activity is an unmet medical need, while activity of this anti-VEGF Mab is reported to be heterogeneous, particularly in glioblastoma.

Objective: To identify circulating biomarker that predicts response to bevacizumab and outcome in recurrent high grade glioma (HGG).

Methods: Eleven angiogenic makers were analyzed, using ELISA, at baseline and one month apart from bevacizumab initiation in a first cohort of 26 HGG patients of our institution (cohort 1); Plasma marker dosages were correlated to objective response (RANO criterias), Progression-free survival (PFS), and overall survival (OS).

Correlations were validated in a separate cohort of 50 patients (Cohort 2). Markers analyses were performed in two other cohorts treated with cytotoxic agents up front (cohort 3 n = 20) or concomitant to radiotherapy (cohort 4 n = 24).

Results: In cohort 1, high MMP2 baseline level was associated to a probability of response of 83.3% versus 15.4% in case of low MMP2 level (p = 0.001). By univariate analyses, confirmed by multivariate analysis, MMP2 correlated with PFS (p = 0.007) and OS (p = 0.001), as decrease of plasmatic VEGF level (p = 0.038 for PFS and p = 0.013 for OS) and MMP9 level (PFS p = 0.016, OS p = 0.025). These results were confirmed with a similar magnitude in cohort 2 for MMP2 only (p < 0.0001 for response, p = 0.009 for PFS and p = 0.009 for OS). In cohort 3 and 4, no association was found between MMP2 and response, PFS, or OS.

Conclusions: Among patients with recurrent HGG treated with bevacizumab, but apparently not with cytotoxic agent, higher plasma MMP2 levels were associated with objective response, prolonged tumor control and survival. Further studies are needed to validate the predictive value of these/this biomarker(s) both with glioma and other cancers.

Disclosure: O. Chinot: Roche consultant. All other authors have declared no conflicts of interest.
COMPARISON OF DIAGNOSTIC AND TREATMENT DELAYS OF ADOLESCENT AND YOUNG ADULT BRAIN TUMOR PATIENTS WITH OLDER ADULT BRAIN TUMOR PATIENTS

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Background: Adolescent and young adult (AYA) cancer patients are confronted with obstacles and challenges related to their diagnosis and treatment compared to children and older adults. The aim of this study is to compare patient-related and healthcare system-related delays, from cancer symptom onset to diagnosis and treatment, between the AYA brain tumor patients and older adult brain tumor patients.

Material and methods: This study is based on a questionnaire conducted in 2010-2012 completed by AYA brain tumor patients diagnosed at the ages between 16 and 39 years and older adult brain tumor patients diagnosed at an average age of 59 years. Total delay (time from cancer symptom onset to treatment start) was calculated and divided into three stages (1) Patient delay: time from patient symptom onset until first health care contact date; (2) Health care system delay: time from first health care contact until diagnosis date; (3) Treatment delay: time from diagnosis date until first treatment. Median delay in days with interquartile interval (IQR) is the main outcome measure.

Results: For AYA brain tumor patients, we identify a median total delay of 169 (IQR 72-395) days, a median patient delay of 1 (0-78) days, a median health care system delay of 42 (5-203) days and a median treatment delay of 60 (35-92) days. For older adult brain tumor patients, we identify a median total delay of 176 (IQR 104-212) days, a median patient delay of 0 (0-14) days, a median health care system delay of 42 (21-63) days and a median treatment delay of 35 (21-63) days. Delays of all stages are longer in AYA brain tumor patients as compared to older adult brain tumor patients, and the findings of total delay and treatment delay are statistically significant (p = 0.013 and p = 0.048, respectively).

Conclusions: Health care system delay and treatment delay account for much of the delay from symptom onset to first treatment in both groups which indicates professional characteristics of frontline medical personnel may contribute to delay. Also, we have longer delays in AYA brain tumor patients. This suggests that AYA cancer patients as underserved patient population need to get more attention from healthcare professionals and the general community.

Disclosure: All authors have declared no conflicts of interest.

UPDATED RESULTS FROM A CANCER RESEARCH UK MULTI PEPTIDE VACCINE PLUS GM-CSF IN PATIENTS WITH NEWLY DIAGNOSED GliOBLASTOMA


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Background: IMA950 is a novel multi-peptide glioblastoma (GBM) specific vaccine that contains 11 HLA binding tumour associated peptides (TUMAPs), identified on human leukocyte antigen (HLA) surface receptors in primary human GBM tissue, and one viral (HBV) marker peptide. The TUMAPs are designed to activate TUMAP-specific CD8+ cytotoxic and CD4+ helper T lymphocytes, which then recognise cognate TUMAPs presented by GBM tumour cells and effect a targeted immune response.

Methods: Patients (pts) must be eligible for standard treatment of newly diagnosed GBM (maximal safe tumour resection, concomitant chemoradiotherapy (CRT) and adjuvant temozolomide (TMZ)) and be HLA A*02 positive with no history of autoimmune disease. Vaccination comprises IMA950 plus GM-CSF injected intradermally at 11 time points over a 24 week period. Up to 45 pts will be entered into one of two cohorts with similar schedules. In Cohort 1 vaccination begins 7 to 14 days prior to initial CRT; in Cohort 2 it begins at least 7 days post CRT and 28 days prior to adjuvant TMZ. Safety is assessed according to NCI CTCAE Version 4.0. Immune response is determined by HLA-multimer analysis of vaccine-induced Tcell response in PBMC samples. Secondary objectives include observation of any anti-tumour effects, measurement of pre-treatment regulatory T-cell levels and evaluation of the effect of steroid dose on observed T-cell responses.

Results: As of 21 May 12, 25 pts (12 in Cohort 1 and 13 in Cohort 2) have been recruited. Adverse events related to either IMA950 or GM-CSF have been restricted to minor injection site reactions, a single distant allergic rash and a case of isolated asymptomatic neutropenia. Eleven pts have been analysed for immune response with 10 showing a positive immune response, 2 having no response and 9 equivocal responses. Of the 9 pts who were evaluable (6 from Cohort 1 and 3 from Cohort 2) 8 assessed positive for IMA950 plus GM-CSF. Eleven pts have been analysed for immune response with 10 showing a positive immune response, 2 having no response and 9 equivocal responses. Of the 9 pts who were evaluable (6 from Cohort 1 and 3 from Cohort 2) 8 assessed positive for IMA950 plus GM-CSF. Eleven pts have been analysed for immune response with 10 showing a positive immune response, 2 having no response and 9 equivocal responses. Of the 9 pts who were evaluable (6 from Cohort 1 and 3 from Cohort 2) 8 assessed positive for IMA950 plus GM-CSF.

Conclusion: IMA950 plus GM-CSF given alongside standard treatment for GBM has been well tolerated to date and these results already give encouragement for further development of this vaccine.

Disclosure: H. Singh-Jasuja: Harpreet Singh-Jasuja is a Founder and the Chief Scientific Officer of Immatics Biotechnologies GmbH. He also has stock or ownership stakes to disclose. All other authors have declared no conflicts of interest.
A RANDOMIZED PHASE III STUDY EVALUATING THE CONTINUATION OF BEVACIZUMAB (BV) BEYOND PROGRESSION IN METASTATIC COLORECTAL CANCER (mCRC) PATIENTS (PTS) WHO RECEIVED BV AS PART OF FIRST-LINE TREATMENT: RESULTS OF THE BEBYP TRIAL BY THE GRUPO ONCOLÒGICO NORDEVEST (GONO)


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Introduction: Retrospective data suggested that the continuation of BV with second line chemotherapy (CT) beyond the progression to a first line treatment with BV was associated with improved survival.

Methods: This phase III study randomized pts with unresectable mCRC treated with BV plus first line CT (fluoropyrimidine, FOLFIRI, FOLOX4) to receive a second line CT with FOLFOX or if FOLFOX (depending on first-line chemotherapy) alone (arm A) or in combination with BV at 5 mg/Kg i.v. every 2 weeks (arm B). Pts were stratified according to center, PS (0 vs 1-2), disease free interval from the last administration of first line CT (≤ 3 months vs >3 months), second line regimen. The primary endpoint was progression-free survival (PFS). To detect a HR for PFS of 0.70 the trial was designed to randomize 262 pts. Considering that the AIO/AMG MIL1847 trial with a similar design demonstrated a very similar HR on 41-42% at 10 months, this study met its primary endpoint. After a median follow up of 18 months the number of events for PFS was 172 (93%); median PFS was 4.97 months for arm A and 6.77 months for arm B (HR = 0.65; 95% CI 0.48-0.89; unstratified log-rank test, p = 0.0062). Adjusted analysis for PFS taking into account stratification factors, age and sex confirmed the increased PFS for arm B (HR = 0.70; 95% CI 0.50-0.97; p = 0.032). The response rate was 18% for CT and 21% for BEV + CT (p = 0.71). The OS data are still immature with a number of events of 52 in arm A and 46 in arm B. The adverse event profile was consistent with previously reported data for BEV + CT.

Conclusions: This study demonstrates an increased PFS by continuing BV in second line beyond progression, the accrual was stopped on May 11th 2012.

Results: A total of 185 pts were randomized and 184 pts were included in the ITT analysis (1 pt randomized in error). Pts characteristics (arm A/arm B): number 92/92, gender M75%-F25%/M57%-F43%, median age 66 (38-75) years/62 (38-75) years, PS 0 ≤ 2 ≤ 3. The adverse event profile was consistent with previously reported data for BEV + CT.

Disclosure: A. Falcone: Research grant from Amgen, Merck and Roche. All other authors have declared no conflicts of interest.
LBA18  PHASE 3 CORRECT TRIAL OF REGORAFENIB IN METASTATIC COLORECTAL CANCER (mCRC): OVERALL SURVIVAL UPDATE

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Background: The CORRECT trial was conducted to evaluate the oral multikinase inhibitor regorafenib (REG) in patients (pts) with mCRC whose disease had progressed after all approved standard therapies. This trial met its primary endpoint—assessed at 3 months after last standard therapy, in pts (98.6%) compared with Caucasian pts (92.3%), and higher in pts with a baseline Eastern Cooperative Oncology Group (ECOG) score of 0 (97.0%) compared with pts with ECOG score of 1 (88.6%).

Methods: Enrollment criteria included documented mCRC and progression during ≤3 months after last standard therapy. Pts were randomized 2:1 to receive best supportive care plus either REG (160 mg od po) or placebo (PL) on a 3 weeks on/1 week off schedule. The primary endpoint was overall survival (OS). Secondary endpoints included progression-free survival (PFS), overall response rate, and disease control rate. Safety and quality of life were also evaluated.

Results: From May 2010 to March 2011, 760 pts were randomized (REG: 505; PL: 255). Baseline characteristics were balanced between the two arms. A descriptive updated analysis of OS was performed, based on a database cutoff of Nov 13, 2011 with 566 total events (97% of events originally required). In this analysis, the hazard ratio (HR, REG/PL) for OS was 0.79 (95% CI, 0.66-0.94, 1-sided p = 0.0038). Median OS was 6.4 months (95% CI, 5.8-7.0) in the REG arm vs 5.0 months (95% CI, 4.4-5.9) in the PL arm. OS rate at 6 and 12 months was 52.2% and 24.1% in the REG arm vs 43.1% and 17% in the PL arm, respectively. These data serve as an update to previously reported OS data from the earlier interim analysis based on 432 (74%) events, which showed a HR for OS of 0.77 (95% CI, 0.64-0.94, 1-sided p = 0.0052). Pts in the REG arm received an average of 78.9% of the planned dose, and pts in PL arm 90.2% of the planned dose. The mean treatment duration was 12.1 ± 9.7 wks (REG) and 7.8 ± 5.2 wks (PL), respectively. Incidence of treatment-emergent, REG-related adverse events was similar in subgroups by age, sex, renal function and hepatic function, whereas the incidence was higher in Asian pts (98.6%) compared with Caucasian pts (92.3%), and higher in pts with a baseline ECOG score of 0 (97.0%) compared with pts with ECOG score of 1 (88.6%).

Conclusions: This updated OS analysis demonstrated the robustness and consistency of the OS benefit of REG treatment over PL in pts with previously treated mCRC.
gastrointestinal tumors, non-colorectal

SEARCH: A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF SORAFENIB PLUS ERLOTINIB IN PATIENTS WITH HEPATOCELLULAR CARCINOMA (HCC)


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Background: Sorafenib is the only systemic agent to show statistically significant overall survival (OS) benefits in advanced HCC. Erlotinib is a direct and reversible EGFR tyrosine kinase inhibitor. Combining sorafenib and erlotinib in HCC patients may result in synergistic or additive antitumor effects.

Methods: Patients ≥ 18 years with advanced HCC, ECOG PS 0–1 and Child-Pugh class A and stratified by ECOG PS (0 vs 1), macroscopic vascular invasion and/or extraparenchymal spread (yes vs no), smoking status (current vs former vs never) and region (Americas vs Europe and South Africa vs Asia-Pacific), were randomised 1:1 to oral sorafenib 400 mg bid plus erlotinib 150 mg or sorafenib 400 mg bid plus placebo 150 mg qd. Treatment was on a continuous basis, with scans performed every 6 weeks. The primary endpoint was OS, with secondary endpoints including time to progression (TTP), disease control rate (DCR), and safety.

Results: Of 720 randomized patients, 362 received sorafenib plus erlotinib and 358 received sorafenib plus placebo. Median OS (95% vs 8.5 mo; HR 0.929; 95% CI 0.871–1.106, p = 0.204) and TTP (3.2 vs 4 mo; HR 1.135; 95% CI 0.944–1.366, p = 0.261) did not differ significantly in the two arms. There were no significant differences in OS or TTP between arms by region. The median daily doses of sorafenib in the sorafenib plus erlotinib and sorafenib plus placebo arms were 768 and 773 mg, respectively, while the median daily doses of erlotinib and placebo were 142 and 143 mg, respectively. DCR (43.9% vs 52.5%) and median treatment duration (2.8 vs 4 mo) were lower in the sorafenib plus erlotinib arm, while the percentage withdrawing after ≥1 treatment cycle was greater (34.0% vs 23.8%). Rates of treatment-emergent (≥ 80% received by 88% of pts. Exposure to X and P was balanced between treatment arms. Median duration of cetuximab treatment was 14.9 weeks with relative dose intensity ≥80% received by 88% of pts. Exposure to X and P was similar between treatment arms. PFS, OS and best overall response were similar between the treatment arms (Table) with comparable results for PFS and OS across subgroups. More grade 3/4 and serious adverse events were found in the XP + cetuximab vs XP arm (Table). Safety profiles were consistent with those known for these agents.

Conclusions: XP + cetuximab showed no benefit compared with XP alone in the first-line treatment of advanced gastric cancer. Further classification of this heterogeneous disease may be required before advances in patient treatment are to be made.

Efficacy analysis*

<table>
<thead>
<tr>
<th>XP + cetuximab</th>
<th>XP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>455</td>
</tr>
<tr>
<td>PFS (IRC)</td>
<td></td>
</tr>
<tr>
<td>Median, months [95% CI]</td>
<td>11.3 [10.4–11.8]</td>
</tr>
<tr>
<td>Stratified HR [95% CI]</td>
<td>1.004 [0.866–1.165]</td>
</tr>
<tr>
<td>Stratified log-rank p value</td>
<td>0.3158</td>
</tr>
</tbody>
</table>

Method: Stratification factors were disease status, prior esophago-gastrectomy, prior neo adjuvant/radiochemotherapy.

Conclusions: XP + cetuximab showed no benefit compared with XP alone in the first-line treatment of advanced gastric cancer. Further classification of this heterogeneous disease may be required before advances in patient treatment are to be made.

Disclosure: F. Lordick: Received research support from Merck Serono Y. Kang: Honoraria from Roche, consultant for Roche H. Goette: The author is an employee of Merck KGaA H. Melezinkova: The author is an employee of Merck KGaA. M. Moehler: The University of Mainz received financial support for translational research 2005–2009. The author received compensation for talks or advisory board work during the study. All other authors have declared no conflicts of interest.

Background: There is a high unmet clinical need for more efficacious treatment in advanced gastric cancer, which has a poor prognosis. In phase II studies, cetuximab, an EGFR antibody, + first-line fluoropyrimidine with irinotecan or platinum compounds showed promising activity. This open-label, randomized, controlled phase III study (EudraCT No: 2007-004219-75) investigated cetuximab and cisplatin +/− cetuximab in gastric and gastroesophageal junction cancer.

Methods: Patients (pts) were randomized (1:1) to 3-week cycles of twice daily (days 1–5) capecitabine (X, Xeloda) 1000 mg/m2 and iv cisplatin (P) 80 mg/m2 (day 1) + weekly cetuximab (day 1) 400 mg/m2 initial infusion followed by 250 mg/m2/week thereafter, or XP alone. The primary endpoint was progression-free survival (PFS) assessed by blinded independent review committee (IRC). Secondary endpoints included overall survival (OS), best overall response (ORR) and safety.

Results: Between June 2008 and December 2010, 904 pts from 25 countries were randomized: 455 to XP + cetuximab and 449 to XP alone. Most were male (74%), had stomach cancer (83%) and metastatic disease (97%). Baseline characteristics were balanced between treatment arms. Median duration of cetuximab treatment was 14.9 weeks with relative dose intensity ≥80% received by 88% of pts. Exposure to X and P was similar between treatment arms. PFS, OS and best overall response were similar between the treatment arms (Table). Grade 3/4 adverse events were similar between the two arms (Table). Grade 3/4 and serious adverse events were found in the XP + cetuximab vs XP arm (Table). Safety profiles were consistent with those known for these agents.

Conclusions: XP + cetuximab showed no benefit compared with XP alone in the first-line treatment of advanced gastric cancer. Further classification of this heterogeneous disease may be required before advances in patient treatment are to be made.

Background: There is a high unmet clinical need for more efficacious treatment in advanced gastric cancer, which has a poor prognosis. In phase II studies, cetuximab, an EGFR antibody, + first-line fluoropyrimidine with irinotecan or platinum compounds showed promising activity. This open-label, randomized, controlled phase III study (EudraCT No: 2007-004219-75) investigated cetuximab and cisplatin +/− cetuximab in gastric and gastroesophageal junction cancer.

Methods: Patients (pts) were randomized (1:1) to 3-week cycles of twice daily (days 1–5) capecitabine (X, Xeloda) 1000 mg/m2 and iv cisplatin (P) 80 mg/m2 (day 1) + weekly cetuximab (day 1) 400 mg/m2 initial infusion followed by 250 mg/m2/week thereafter, or XP alone. The primary endpoint was progression-free survival (PFS) assessed by blinded independent review committee (IRC). Secondary endpoints included overall survival (OS), best overall response (ORR) and safety.

Results: Between June 2008 and December 2010, 904 pts from 25 countries were randomized: 455 to XP + cetuximab and 449 to XP alone. Most were male (74%), had stomach cancer (83%) and metastatic disease (97%). Baseline characteristics were balanced between treatment arms. Median duration of cetuximab treatment was 14.9 weeks with relative dose intensity ≥80% received by 88% of pts. Exposure to X and P was similar between treatment arms. PFS, OS and best overall response were similar between the treatment arms (Table). Grade 3/4 adverse events were similar between the two arms (Table). Grade 3/4 and serious adverse events were found in the XP + cetuximab vs XP arm (Table). Safety profiles were consistent with those known for these agents.

Conclusions: XP + cetuximab showed no benefit compared with XP alone in the first-line treatment of advanced gastric cancer. Further classification of this heterogeneous disease may be required before advances in patient treatment are to be made.

Disclosure: F. Lordick: Received research support from Merck Serono Y. Kang: Honoraria from Roche, consultant for Roche H. Goette: The author is an employee of Merck KGaA H. Melezinkova: The author is an employee of Merck KGaA. M. Moehler: The University of Mainz received financial support for translational research 2005–2009. The author received compensation for talks or advisory board work during the study. All other authors have declared no conflicts of interest.
Background: S-1, an oral fluoropyrimidine, is used as a standard treatment for advanced and recurrent gastric cancer (AGC) in East Asia. A phase 3 multicenter study was performed in Japan and Korea to evaluate potential benefits of adding docetaxel to S-1 in patients with AGC. Results of this study were reported through planned analysis at ASCO GI 2011 (YH Kim, et al.). However an independent biostatistician pointed out that there was large number of censored cases led to insufficient number of events for proper analysis. According to the recommendations by the statistician, further follow up of survival status was performed to analyze the START trial properly.

Methods: Patients with unresectable or recurrent gastric cancer were randomly assigned to docetaxel plus S-1 (DS) or S-1 alone (S-1). The DS group received 40 mg/m² of docetaxel on day 1 intravenously and 80 mg/m² of S-1 on days 1 to 14 orally of a 21-day cycle. The primary endpoint was overall survival (OS) and the secondary endpoints were including progression-free survival (PFS) and response rate (RR).

Results: Of the 639 patients enrolled, 635 were eligible for analysis. The median survival time was 12.48 months in the DS group and 10.78 months in the S-1 group (p = 0.001). RR was 38.8% (32.8-45.2) in the DS group and 4.17 months in the S-1 group (p = 0.001).}

Disclosure:
K. Yoshida: Research fund from Chugai Pharmaceutical Co. Yakult Honsha, is a new treatment option for patients with untreated AGC. Adding docetaxel to S-1 significantly improved OS, PFS and RR, which was improved for gefitinib (p = 0.004).

Conclusion: Adding docetaxel to S-1 significantly improved OS, PFS and RR, which was improved for gefitinib. A phase II trial of the EGFR kinase inhibitor gefitinib showed good tolerance with 11% partial responses and a trend towards improved survival (Ferry et al. Clin Cancer Res 2007, 13: 5869-75). Four other phase II trials showed objective responses with gefitinib or erlotinib. Cancer Research UK funded this pivotal phase III trial with free study drug provided by Astra Zeneca UK. This trial is investigating the correlation of benefit with biomarkers. Significant safety concerns emerged. PS is a highly significant prognostic factor for OS in the DS group and 26.8% (21.6-32.6) in the S-1 group (p = 0.004). As for adverse events, neutropenia was more frequent in the DS group and one patient died by Grade 4 thrombocytopenia in the DS group.

Disclosure: K. Yoshida: Research fund from Chugai Pharmaceutical Co. Yakult Honsha, Taiho Pharmaceutical Co. All other authors have declared no conflicts of interest.

Disclosure:
K. Yoshida: Research fund from Chugai Pharmaceutical Co. Yakult Honsha, Taiho Pharmaceutical Co. All other authors have declared no conflicts of interest.

Disclosure: All authors have declared no conflicts of interest.

Disclosure: D.R. Ferry: Consultant role for Astra Zeneca Honoraria from Astra Zeneca Research funding from Astra Zeneca M. Harrison: Wife has shares in Astra Zeneca. Otherwise no conflicts of interest A. Chatterjee: Received and honoraria for a presentation on gefitinib, otherwise no conflicts of interest. A. Garcia-Alonso: A consultant/advisory role for Roche. otherwise no conflicts of interest. J. Jankowski: Consultant to AstraZeneca. No other conflicts of interest. R.D. Petty: Consultant for Roche and Astra Zeneca (compensated) Honoraria from Roche and Pfizer Research funding from Roche. All other authors have declared no conflicts of interest.
Background: Pazopanib and sunitinib are oral multi-kinase angiogenesis inhibitors that have shown progression-free survival (PFS) benefit for mRCC patients in clinical trials (NEJM 2007;356:115; JCO 2009;29:475). The COMPARZ study (NCT00720941) was designed to provide a direct comparison of efficacy, safety, and tolerability of pazopanib and sunitinib.

Methods: A total of 1110 treatment-naïve patients with clear cell mRCC and measurable disease were randomized 1:1 to pazopanib 800 mg QD continuous dosing or sunitinib 50 mg QD in 6-week cycles (4 weeks on followed by 2 weeks off). Primary endpoint was PFS. Based on a planned 631 PFS events by independent review committee (IRC) the study had 80% power to detect non-inferiority of pazopanib to sunitinib where the non-inferiority margin was chosen to exclude a difference of >25% in the hazards. Key secondary endpoints included overall survival (OS), overall response rate (ORR), adverse events (AEs), and quality of life (QoL).

Results: Patient characteristics were balanced. The upper bound of the 95% CI for PFS by IRC was <1.25, indicating pazopanib is non-inferior to sunitinib. Differences in 11 of 14 QoL domains were small but statistically significant, all favoring pazopanib.

Conclusions: Pazopanib has similar efficacy to sunitinib with a differentiated safety and QoL profile.

Table: LBA8_PR

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<th>Sunitinib N = 553</th>
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<td>ORR (IRC)</td>
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Disclosures: R.E. Hutson: Research Funding: GlaxoSmithKline >10,000 US dollars Research Funding: Pfizer VS. Paid Consultancy: Pfizer <10,000 US dollars.
Background: Bevacizumab (BEV) + interferon alfa (IFN), as well as temsirolimus (TEM), have demonstrated clinical activity as 1st-line treatment of patients (pts) with metastatic renal cell carcinoma (mRCC). Based on initial data of combination therapy with TEM + BEV, a phase IbII trial was undertaken.

Methods: This global phase IbII, randomized, open-label, multicenter trial compared TEM + BEV and IFN + BEV as 1st-line treatment for pts with predominantly clear cell mRCC. Eligible pts, stratified by MSKCC prognostic risk and nephrectomy status, were randomized (1:1) to receive either TEM (25 mg intravenously [IV] weekly) + BEV (10 mg/kg IV every 2 weeks), or IFN (9 MU subcutaneously 3 times weekly) + BEV (10 mg/kg IV every 2 weeks). Dose reductions were allowed for TEM and IFN, but not for BEV. The study was designed to detect a 30% improvement in progression-free survival (PFS) by independent central review (primary end point) with 80% power while maintaining a significance level of 2.5% in a 1-sided stratified log-rank test.

Results: From April 2008 to October 2010, 791 pts were enrolled from 131 sites in 29 countries; 480 received TEM + BEV and 391 received IFN + BEV. Baseline demographics were balanced. Mean age was 58y, 70% were male, and 83% were white (Asian, 12%). At data cutoff for final analysis (April 19, 2012), 489 pts had independently assessed PFS events; 409 had died. Median PFS with TEM + BEV was 9.1 mo (95% confidence interval [CI]: 8.1, 10.2) vs 9.3 mo with IFN + BEV (95% CI: 9.0, 11.2); hazard ratio [HR] = 1.07 (95% CI: 0.89, 1.26; 1-sided P value = 0.759). Median OS was 25.8 mo (95% CI: 21.1, 30.7) for the TEM + BEV group and 25.5 mo (95% CI: 22.4, 30.8) for the IFN + BEV group; HR = 1.04 (95% CI: 0.85, 1.26; 1-sided P value = 0.638). Safety data were consistent with known profiles of these agents. In the TEM + BEV arm, pneumonitis frequency was lower than expected (1%). Grade ≥3 mucosal inflammation, stomatitis, hyperphosphatemia, hyperglycemia, and hypercholesterolemia were more common with TEM + BEV (P < 0.001); grade ≥3 neutropenia was more common with IFN + BEV (P < 0.001).

Conclusions: TEM + BEV was not superior to IFN + BEV as 1st-line therapy for pts with clear cell mRCC.

Disclosure: B.J. Rini: Research funding and consulting from Pfizer Inc. J. Bellmunt: Consultancy and board membership for Pfizer Inc. and Roche (compensated) J. Clancy: An employee of Pfizer during the study of this article, but is no longer employed by Pfizer Inc. Owsns stocks of Pfizer Inc. K. Wang: Employee and owns stock of Pfizer Inc. A. Niethammer: Employee and owns stock of Pfizer Inc. B. Escudier: Advisory role with Pfizer Inc. Honorarium received, compensated

Background: Temsirolimus (TEM) demonstrated an overall survival (OS) benefit vs interferon alfa in previously untreated patients (pts) with advanced renal cell carcinoma (RCC) and poor prognostic features. The efficacy of temsirolimus after VEGF inhibitor therapy is not known. This multicenter, randomized, open-label phase 3 trial compared the efficacy and safety of TEM vs sorafenib (SOR) in pts with metastatic RCC (mRCC) who failed prior sunitinib therapy.

Methods: RCC pts with disease progression after 1st-line sunitinib therapy and VEGF inhibitor therapy is not known. This multicenter, randomized, open-label phase 3 trial compared the efficacy and safety of TEM vs sorafenib (SOR) in pts with metastatic RCC (mRCC) who failed prior sunitinib therapy.

Results: From Sept 2007 to March 2011, 112 sites in 20 countries enrolled 512 pts; 259 received TEM and 253 received SOR. Baseline demographics were balanced. Mean age was 60 y, 75% were male, and 67% were white (Asian, 17%). Histology was clear cell in 422 pts, non-clear cell in 90 pts. At data cutoff for final analysis (May 2012), 389 pts had independently assessed PFS events; 351 pts had died. Median PFS with TEM was 4.28 mo (95% confidence interval [CI]: 4.01, 5.43) and 16.64 mo (95% CI: 13.55, 18.72) with SOR; HR = 1.07; 2-sided P value = 0.1933. Median OS for the TEM group was 12.27 mo (95% CI: 10.13, 14.80) for the SOR group; 16.64 mo (95% CI: 13.55, 18.72); HR = 1.31 (95% CI: 1.05, 1.63; 2-sided P value = 0.0144). The most common adverse events (all grade, all cause) with TEM were rash, fatigue, diarrhea, anemia, and hyperglycemia; with SOR, they were diarrhea, rash, hand-foot syndrome, and decreased appetite.

Conclusions: TEM did not show superiority to SOR in the primary end point (OS [independent]) or in the secondary end point of OS. Safety data were as expected for both agents. Further evaluation is needed to define the optimal sequence after prior sunitinib in advanced RCC pts.

Disclosure: This study was sponsored by Pfizer Inc. T. Hutson: Dr. Hutson is a Study Investigator for Pfizer Inc. B. Escudier: Advisory role for Aven, Bayer, GSK, Novartis, Pfizer Inc G.A. Bjarnason: Has received honoraria for talks given, support for travel to meetings and advisory boards, and funding for investigator initiated trials from Pfizer Inc. P. Senico: Employee and stock owner of Pfizer Inc. A. Niethammer: Employee and stock owner of Pfizer Inc. D. Lu: Employee and stock owner of Pfizer Inc S. Harinaran: Employee and stock owner of Pfizer Inc. R.J. Motzer: Research Funding and Consultancy with Pfizer Inc. All other authors have declared no conflicts of interest.
Derivation and Validation of Blood mRNA Expression Signatures to Stratify Castration-Resistant Prostate Cancer Patients and Predict Poor Outcome


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Background: Biomarkers are urgently required to dissect prostate cancer (PrCa) inter-patient disease heterogeneity to improve treatment and accelerate drug development. We analyzed blood mRNA expression arrays to identify metastatic castration resistant PrCa (CRPC) with poorer outcome.

Methods: Whole blood was collected into PAXgene tubes from CRPC patients and PrCa patients selected for active surveillance (AS). In stage I (derivation test set) 69 CRPC patients were used as cases and 31 AS patients as controls; in stage II (validation set) 70 CRPC patients were evaluated. Whole blood RNA from patients in stage I was hybridised to Affymetrix U133plus2 microarrays. Expression profiles were analysed using Bayesian Latent Process Decomposition (LPD) to identify RNA expression profiles associated with CRPC subgroups and prognosis. A reduced gene signature was then derived using Random Forest algorithm and later verified (stage I) and validated (stage II) by qRT-PCR studies. All p values were corrected for false discovery rate.

Results: LPD analyses of the mRNA expression data divided the evaluable patients in stage I (n = 94) into 4 groups. LPD1 and LPD2 consisted almost entirely of CRPC patients (15/31; 12/21) vs controls (AS patients). LPD1 group patients had features of worse prognosis CRPC and poorer overall survival (OS) than CRPC patients in other LPD groups (p = 0.00907). A 9 gene signature (TERF2IP, TMCC2, SNCA, GABARAPL2, RIO3K, TFDP1, HMBS, SLC4A1, STOM) classified patients into this LPD1 group with a very low misclassification rate (1.2%). After verification of the signature by qRT-PCR, LPD1 membership was associated with worse OS in the derivation CRPC cohort (10.7 vs 25.6 months, p = 0.00001). Importantly, the prognostic value of this signature was confirmed in the validation CRPC cohort, where LPD1 membership was also associated to poor OS (9.2 vs 21.6 months, p = 0.001), and remained an independent prognostic factor in multivariable analyses for both cohorts. The LPD1 signature was associated with bone marrow disruption (mobilization of early erythroid cells) and decreased immune response.

Conclusion: Gene expression signatures derived from whole Blood genome profiling identify CRPC patients with very poor outcomes.

Disclosure: All authors have declared no conflicts of interest.

A Phase 3 Study to Evaluate the Efficacy and Safety of Docetaxel and Prednisone (DP) with or Without Lenalidomide (LEN) in Patients with Castrate-Resistant Prostate Cancer (CRPC): The MAINSAIL Trial


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Introduction: LEN, an antiangiogenic and immunomodulatory agent, was active and well tolerated as a single agent and in combination with DP in phase 1/2 trials in CRPC. This phase 3, multicenter, randomized, double-blind, placebo (PBO)-controlled study evaluated the efficacy and safety of LEN versus PBO in combination with DP as first-line treatment for CRPC.

Methods: Chemotherapy naïve patients with progressive metastatic CRPC were randomized to the LEN + DP arm (oral [p.o.] LEN 25 mg/day on days 1-14 of each 21-day cycle) or the PBO + DP arm (PBO in the same schedule). In both arms, docetaxel was administered intravenously at 75 mg/m2 on day 1 of each cycle, and prednisone was dosed at 5 mg p.o. twice daily. Primary endpoint was overall survival (OS) and secondary endpoints were progression-free survival (PFS), objective response rate, and safety. Patient enrollment was completed in Nov 2011 with a total of 1059 patients randomized. The data analysis results were based on the cut-off date of 13, 2012.

Results: 533 patients were randomized in the LEN + DP and 526 patients in the PBO + DP arm. The arms were well balanced; mean age was 69 years and ECOG PS scores were 0 in 48.1% and 1 in 47.5% of patients. Median number of cycles administered was 6 and 8 in the LEN + DP and PBO + DP arms, respectively. The most common grade ≥ 3 adverse events in the LEN + DP arm included neutropenia (22%), febrile neutropenia (12%), neutropenic sepsis (3%). Vascular events grade > 3 were reported in 7.4% of patients in the LEN + DP arm versus 4.4% in the PBO + DP arm. No increased mortality due to toxicity was seen. Median OS and PFS was 77 and 45 weeks in the LEN + DP arm, compared to median not reached (p = 0.0017) and 46 weeks (p = 0.0187), in the PBO + DP arm, respectively. Hazard ratio (LEN over PBO) is 1.53 (95% CI = 1.17 to 2.00) for OS and 1.32 (95% CI = 1.05 to 1.66) for PFS.

Conclusions: The addition of LEN to DP did not improve OS in patients with CRPC and was associated with greater toxicity. Shorter treatment duration, lower dose intensity and earlier treatment discontinuation might have contributed to this lack of benefit. Studies to explain the poorer outcome of the LEN arm are underway.

Disclosure: D.P. Petrylak: Advisory board: Amgen, Bayer, Pfizer, Ferring, Millenium, Novartis, Dendreon, Johnson and Johnson, GlaxoSmithKline. Corporate sponsored research: Celgene, Dendreon, Sanofi, Pfizer, AstraZeneca, GlaxoSmithKline, Rogensen institute, Boehringer Ingelheim. K. Fizazi: Participation to advisory boards for Sanofi-Aventis and Celgene C.N. Sternberg: Honoraria: Johnson + Johnson, Astellas, Amgen and Sanofi-Aventis Research funding. Cougar J. Bellmunt: Consultancy and adboard contribution for Celgene and Sanofi (compensated). D. Barton: Celgene employee and stock owner U. Jungnelius: Celgene Corporation: Company employee S. Li: Statistician working at Celgene. I have Celgene stock options as a regular employee. A. Fandi: Celgene employee and stock owner U. Jungnelius: Celgene Corporation: Company employee S. Li: Statistician working at Celgene. I have Celgene stock options as a regular employee. N. Vogelzang: Member of the MAINSAIL steering committee, did not receive direct funds from Celgene for conducting the research as it was conducted thru US Oncology/McKesson. Honoraria from Celgene for lectures. Salary compensation from US Oncology Research All other authors have declared no conflicts of interest.
ARADES TRIAL: A FIRST-IN-MAN, OPEN-LABEL, PHASE I/II SAFETY, PHARMACOKINETIC, AND PROOF-OF-CONCEPT STUDY OF ODM-201 IN PATIENTS (PTS) WITH PROGRESSIVE METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (MCRPC)

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Background: CRPC is characterized by persistent, high level androgen receptor (AR) expression and resistance to conventional antiandrogens such as bicalutamide. ODM-201 is a novel, new generation, AR antagonist that does not, unlike other antiandrogens, enter brain in nonclinical models, and that lacks the partial agonist activity seen with bicalutamide in the setting of AR overexpression. Unlike bicalutamide, ODM-201 inhibits AR function by blocking nuclear translocation, and has no agonist activity when AR is overexpressed.

Methods: A first-in-man, multi-center Phase I/II dose-escalation trial in progressive mCRPC pts with and without prior chemotherapy was started in March 2011 to assess safety, pharmacokinetics, and anti-tumor effects. ODM-201 was administered orally, twice daily with food. In the study, three to six pts were to be enrolled per dose-escalation cohort on the preplanned doses of 100, 200, 300, 500, 700 and 900 mg twice daily. Once the safety of an administered dose was established, next dose level was administered, and pts with previous dose level were allowed to continue treatment until progression or intolerable adverse event (AE).

Results: The dose-escalation part of the study is still ongoing at 700 mg × 2 dose level. In 21 treated pts, ODM-201 has been well-tolerated to date, with no significant treatment emerged AEs. The most common AEs were asthenia, nausea and diarrhea. A PSA response (defined as ≥ 50% PSA decrease) was obtained in 13 (87%) of 15 patients currently evaluable at 12-weeks. All 6 docetaxel-pretreated pts had a PSA decrease at 12-weeks. All evaluable pts so far achieved a partial response or remained stable according to RECIST criteria at 12-weeks. The pharmacokinetics is linear in dose range 100 - 300 mg × 2 and the steady state is reached at day 8.

Conclusions: ODM-201, a uniquely designed AR antagonist, showed good tolerability and high anti-cancer activity in pts with mCRPC, including docetaxel-pretreated pts, in this Phase I/II trial. Expansion of Phase II trial has started in June 2012. ARADES trial is sponsored by Orion Corporation Orion Pharma and Endo Pharmaceuticals. NCT01317641.

Disclosure: C. Massard: The author is investigator in Orion Corporation sponsored clinical trial NCT01317641. N. James: The author is investigator in Orion Corporation sponsored clinical trial NCT01317641. S. Culine: The author is investigator in Orion Corporation sponsored clinical trial NCT01317641. R. Jones: The author is investigator in Orion Corporation sponsored clinical trial NCT01317641. A. Vuorela: The author is employee in Orion Corporation NCT01317641. M. Mustonen: The author is employee in Orion Corporation NCT01317641. K. Fizazi: The author is principal investigator in Orion Corporation sponsored clinical trial NCT01317641. The author is member of ODM-201 Advisory Board of Orion Corporation Orion Pharma and Endo Pharmaceuticals.
Background: AURELIA is the first trial to compare BEV + CT vs CT in PT-resistant recurrent OC. The hazard ratio (HR) for progression-free survival (PFS) by RECIST (primary endpoint) in the overall population was 0.48 (95% CI 0.38-0.60; p < 0.001). We report exploratory analyses according to selected CT.

Methods: Eligible patients (pts) had OC that had progressed <6 mo after ≥4 cycles of PT-based therapy. Pts with refractory OC, history of bowel obstruction or >2 prior anticancer regimens were ineligible. Investigators chose single-agent CT (PAC 80 mg/m² d1, 8, 15 & 22 q4w; PLD 40 mg/m² d1 q4w; or TOP 4 mg/m² d1, 8 & 15 q4w or 1.25 mg/m² d1 q4w) for each pt before randomisation to CT (until progression, unacceptable toxicity or withdrawal of consent).

Results: Between Oct 2009 and Apr 2011, 361 pts were randomised. Baseline characteristics, CT exposure and efficacy are summarised below.

Conclusion: In PT-resistant OC, the improvement in PFS and ORR gained by adding BEV to single-agent CT was observed across all CT cohorts. Increased CT exposure of PT-based therapy. Pts with refractory OC, history of bowel obstruction or >2 prior anticancer regimens were ineligible. Investigators chose single-agent CT (PAC 80 mg/m² d1, 8, 15 & 22 q4w; PLD 40 mg/m² d1 q4w; or TOP 4 mg/m² d1, 8 & 15 q4w or 1.25 mg/m² d1 q5 w) for each pt before randomisation to CT (until progression, unacceptable toxicity or withdrawal of consent).

Results: Between Oct 2009 and Apr 2011, 361 pts were randomised. Baseline characteristics, CT exposure and efficacy are summarised below.

Conclusion: In PT-resistant OC, the improvement in PFS and ORR gained by adding BEV to single-agent CT was observed across all CT cohorts. Increased CT exposure associated with prolonged PFS accounts for some increase in cumulative CT toxicity.

Background: PM01183 is a new anticancer agent, acting through minor groove DNA-binding against a wide range of ovarian cancer cell lines and orthotopic models, including several platinum-resistant. The first step of a randomized phase II trial is reported here.

Methods: Between Dec 11 and Feb 12, 22 platinum-resistant or refractory ovarian cancer patients (pts) with less than 3 prior chemotherapy (CT) lines for advanced disease, adequate major organ function and performance status (ECOG) 0-2 were included in the exploratory first stage of this study. The primary endpoint was confirmed response rate (either by RECIST v1.1 or by Rustin criteria). At least two confirmed responses (by either criterion) were required to proceed to the second stage. This study was reviewed and approved by each institutional IRBs and ECs, as well as by the Spanish and French health authorities.

Results: Median age was 59 years (35–77), median ECOG was 1 (0–2.5); 68% and 7 (16%) pts received 1 or 2 prior CT lines for advanced disease, respectively. Six pts were platinum-refractory (no response to last platinum-containing CT) and 16 were platinum-resistant (platinum-free interval < 6 months). All patients (n = 22) were evaluable for efficacy. 6 pts responded (two by Rustin and four by RECIST) for an ORR: 27% (95% CI: 11%–50%) with 1 radiological CR. Only six patients (27%) had progressed at the first evaluation. Thus, overall disease control rate was 73%. As most patients are still ongoing, it is therefore too early to evaluate both quality and/or duration of response. The preliminary toxicity profile observed confirms prior phase 1 results, with myelosuppression, nausea/vomiting despite adequate prophylaxis, and fatigue being the most common drug-related toxicity. No drug related deaths have been reported.

Conclusions: PM01183 is tolerable and has a very promising activity in platinum-resistant/refractory ovarian cancer patients. The second stage started in Apr 2012 and 60 additional patients will be randomized to PM01183 or topotecan, in order to confirm the initial results. Updated results will be presented during the meeting.

Disclosure: C. Fernández: PharmaMar membership. All other authors have declared no conflicts of interest.

Table: LBA26

<table>
<thead>
<tr>
<th>PAC (N = 115)</th>
<th>PLD (N = 126)</th>
<th>TOP (N = 120)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT (N = 55)</td>
<td>BEV + CT (N = 60)</td>
<td>CT (N = 64)</td>
</tr>
<tr>
<td>Median age, y</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>FIGO stage III/IV, %</td>
<td>87</td>
<td>80</td>
</tr>
<tr>
<td>PT-free interval &lt;3 mo, %</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>Median no. of CT cycles (range)</td>
<td>4 (1–15)</td>
<td>6 (1–13)</td>
</tr>
<tr>
<td>PFS Events, %</td>
<td>89</td>
<td>62</td>
</tr>
<tr>
<td>Median, mo</td>
<td>3.9</td>
<td>10.4</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.46 (0.30–0.71)</td>
<td>0.57 (0.39–0.83)</td>
</tr>
<tr>
<td>ORR, %</td>
<td>28.8</td>
<td>51.7</td>
</tr>
<tr>
<td>Difference (95% CI)</td>
<td>22.9 (3.9–41.8)</td>
<td>10.4 (2.4–23.2)</td>
</tr>
</tbody>
</table>

*Not stratified ORR = overall response rate (RECIST and/or CA-125) BEV + CT was associated with a higher incidence of grade ≥2 peripheral sensory neuropathy in the PAC cohort (35% vs 22% with CT), grade ≥2 hand-foot syndrome in the PLD cohort (27% vs 14%) and grade ≥2 hypertension and proteinuria in the PAC and PLD but not the TOP cohort. Grade ≥3 abdominal pain, vomiting and fatigue were more common with CT than BEV + CT in all cohorts.*
A great proportion of FA patients reaches adulthood and become at risk for developing secondary malignancies. In 2009, the High Risk and Cancer Prevention Unit (HRCPU) at Hospital Vall d’Hebron started a follow-up program for adolescents and adult patients with FA. The goal was to advocate for prevention measures to reduce cancer risk, and coordinate a multidisciplinary surveillance for different neoplasms. During annual HRCPU visits, FA patients undergo a complete anamnesis and receive health education. The surveillance program includes: hematological follow up with hemograms and bone marrow aspiration; examination for head and neck lesions by an otolaryngologist; detailed examination of the oral cavity by a maxillofacial specialist; semestral gynecologic examinations for women with annual cervical cytology testing and breast examination. Finally, HPV vaccination is encouraged. Since 2009, 14 FA patients have been enrolled in our follow-up program. Overall, 50% were women, and median age was 22 years (14-32). Their mean age at diagnosis of FA was 6.5 years, 57% belonged to FANCA group and 57% underwent a bone marrow transplantation (BMT). Follow up has ranged from 1 month to 3 years, 70% of patients have adhered properly with the program and 83% of women have received HPV vaccination. So far, 4 patients (29%) have been diagnosed with a malignant tumor and another two with a premalignant lesion. Premalignant lesions were found in the oral cavity (hyperplasia with mild dysplasia of the tongue) and gynecological (squamous intraepithelial lesion of the cervix CIN1). From those diagnosed with cancer, two of them had head and neck tumors. One was a lingual squamous cell carcinoma pT2N1M0 diagnosed at 24 years which recurred at 4 years and the patient died at age 30. The patient had received a BMT at age 8. The other one was a squamous cell carcinoma of the epiglottis pT4N1M0 diagnosed at 32 years in a patient with mosaicism. The third and fourth patients have developed several basal cell carcinomas in the jaw and back since age 21 and both had undergone BMT at 7 and 8 years. Head and neck tumors are frequent neoplasms in young adults with FA, regardless prior BMT. We need to reinforce surveillance and prevention strategies to reduce the risk of malignancies in these locations.

Disclosure: All authors have declared no conflicts of interest.
melanoma and other skin tumors


Introduction: Dabrafenib (D) combined with trametinib (T) shows enhanced activity in BRAF V600-mutated cancer cell lines and xenograft models compared with either drug alone. Preclinically, D + T delays resistance and prevents BRAF-induced proliferative skin lesions. Safety and efficacy of D + T were evaluated in a four-arm Phase I–2 study. Safety and efficacy from Part C, the randomised study of D + T vs D are presented.

Methods: BRAF (D) + MEK (T) inhibition-naive pts (≥18 yrs; RECIST measurable disease were randomised 1:1:1 to D-150 mg BID (D mono), D-150 mg BID + T-1 mg QD (150/1), D-150 mg BID + T-2 mg QD (150/2), crossover allowed after progression. Primary endpoints were progression free survival (PFS), response rate (RR) and duration of response (DoR); secondary endpoints included overall survival (OS) and safety.

Results: Pts (n = 162) baseline characteristics were balanced across the three arms. Investigator assessed median PFS for 150/2 was 5.8 vs 150/1 (p = 0.03). Median DoR was 10.5 mo for 150/2 vs 6.8 mo for D mono. 12-mo OS rate was 79% for 150/2 vs 70% for D mono despite crossover of 43 (80%) pts to 150/2; median OS has not been reached. Pyrexia (71% vs 26%) and chills (38% vs 17%) were the most common adverse events (AEs) leading to dose reduction (35% vs 4%) and interruption (42% vs 6%) in 150/2 vs D mono, respectively. Most common grade ≥3 AEs in 150/2 were neutropenia (11%) and hyponatremia (7%) compared to D mono. Local recurrence incidence of skin lesions was observed in 15% of pts with baseline skin lesions, including cuSCC (7% vs 19%), skin papilloma (4% vs 15%) and hyperkeratosis (9% vs 3%).

Conclusions: D + T provided a statistically significant and clinically meaningful improvement in PFS and DoR compared to D mono in pts with BRAF V600 mutation-positive MM. The data is consistent to Part B reported with D + T. Increased incidence and severity of pyrexia and local recurrence of skin lesions are observed with D + T compared to D mono. Phase 3 studies are ongoing.

Disclosure: G.V. Long: Has participated in advisory boards for GlaxoSmithKline, Bristol Myers Squibb and Roche. Has received research funding and honoraria from Roche, J.A. Sosman: Has received research funding from GlaxoSmithKline. J.S. Weber: Has participated in advisory boards for, and has received honoraria from, GlaxoSmithKline. K.T. Flaherty: Has acted as a data safety monitoring board member and consulted (uncompensated) for, and has received research funding from, GlaxoSmithKline. J.R. Infante: Has participated in an advisory board for GlaxoSmithKline. O. Hamid: Has acted as a consultant (uncompensated) for GlaxoSmithKline. Has received research funding from Bristol Myers Squibb. L. K. Pavlick: Has acted as a consultant and speaker at the Zelboraf World Wide launch conference. A. Daud: Has participated in Genentech advisory boards and been part of the speakers bureau for Genentech. T.F. Gajewski: I participated in a Roche advisory board last year. I. Puzanov: Advisory board, speaker at the Zelboraf World Wide launch conference. M.S.L. Tseng: I am a full time employee of Genentech. I. Chi: I am a full time employee of Genentech. N.W. Choo: I am a full time employee of Genentech. G. McArthur: Research support Pfizer, Novartis & Millennium
PROOF OF CONCEPT OF GENE THERAPY USING PLASMID AMEP IN DISSEMINATED MELANOMA: SAFETY AND EFFICACY RESULTS OF A PHASE I FIRST-IN-MAN STUDY

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Background: AMEP (for Antiangiogenic MEtargidin Peptide) is a novel anti-cancer agent with proven anti-proliferative and anti-angiogenic properties by binding of αvβ3 and α5β1 integrins. Electrotransfer designates the use of electric pulses (electroporation) to transfer plasmid DNA into tissues, and is an attractive alternative to viral gene therapy. This study investigated safety and tolerability of intratumoral plasmid AMEP electrotransfer into cutaneous metastatic melanoma. Secondary objectives were efficacy and pharmacokinetics.

Patients and methods: Five pts with disseminated melanoma without further treatment options (median age 62 y, AJCC III/IV, ECOG status ≤2) were treated at two dose levels (1 and 2 mg DNA) in a phase I study. In each patient, two cutaneous lesions were identified (one treated, one control). Under local anaesthesia, at day 1 and day 8, plasmid AMEP was injected intratumourally followed by electrotransfer with needle electrodes. Pts were monitored weekly until day 29, and at day 64. At day 29 local efficacy was assessed by measuring both lesions and post-treatment biopsies were obtained for determination of AMEP mRNA levels by RT-QPCR. Pharmacokinetic evaluation of plasmid AMEP by QPCR was performed on plasma and urine.

Results: The 5 pts received the 2 planned injections. Minimal systemic toxicity was observed including transient fever (1 pt) and transitory increase in C-Reactive Protein (2 pts). Local toxicity after injection was reported as mild. No related serious adverse events were seen. AMEP mRNA was found in 3 of 5 treated lesions and none of control lesions. Plasmid AMEP was detected in plasma in 4 of 5 pts, but not in urine. At day 29, all 5 treated lesions were stable in diameter, whereas 4 of 5 control lesions increased over 20 %. Response was not observed in any distant lesions.

Conclusion: This first-in-man study on electrotransfer of plasmid AMEP into cutaneous melanoma tumours shows local efficacy, efficiency of the DNA transfer method as well as an excellent safety profile. Further studies using the intramuscular route will evaluate whether a systemic efficacy of plasmid AMEP could be obtained using this transfer method.

Disclosure: C. Bouquet: Employee and stockholder at BioAlliance Pharma, who sponsored the study. B. Vasseur: Employee at BioAlliance Pharma, who sponsored the study. P. Attali: Employee and stockholder at BioAlliance Pharma who sponsored the study. All other authors have declared no conflicts of interest.
Background: Chromosomal rearrangements of anaplastic lymphoma kinase (ALK) are associated with marked clinical responses to crizotinib, an orally available ALK inhibitor targeting ALK. This global randomized phase III study compared the efficacy and safety of crizotinib (C) with standard chemotherapy (pemetrexed or docetaxel [P/D]) as 2nd-line therapy for patients (pts) with advanced ALK+ NSCLC.

Methods: Between Feb 2010 and Feb 2012, 347 pts with stage IIIB/IV ALK+ NSCLC (pemetrexed or docetaxel [P/D]) as 2nd-line therapy for patients (pts) with previously treated with 1 prior platinum-based regimen were randomized to receive chemotherapy. Pts received E monotherapy 150 mg daily (Arm A) or E 150 mg from chemotherapy E was continued as a daily regimen until PD. Primary endpoint is progression-free survival (PFS). Secondary endpoints include toxicity and overall survival (OS). Subgroup analysis for the SQ and NSQ was preplanned. The study was designed with 80% power to detect a 33% decrease in the hazard of progression as primary endpoint was not significantly different between arms.

Results: The study met its primary objective by demonstrating the superiority of C vs P/D (median cycles started 11 vs 4).

Conclusions: for C vs P/D (median cycles started 11 vs 4).


A randomized phase II study comparing erlotinib (E) versus E alternating with chemotherapy in relapsed non-small cell lung cancer (NSCLC) patients. The NVALT10 study

Introduction: Epidermal growth factor receptor tyrosine kinase inhibitors (TKIs) administered concurrently with chemotherapy did not improve outcome. However, in preclinical models and early phase non-comparative studies pharmacodynamic separation of chemotherapy and TKIs did show a synergistic effect.

Methods: A randomized open label phase II study was performed in pts with advanced NSCLC who had progressed on or following first-line platinum containing chemotherapy. Pts received E monotherapy 150 mg daily (Arm A) or E 150 mg from day 2 to 16 of the 21 day cycle during 4 cycles of docetaxel for squamous (SQ) or pemetrexed for non-squamous (NSQ) pts (Arm B). After completion of chemotherapy E was continued as a daily regimen until PD. Primary endpoint is progression-free survival (PFS). Secondary endpoints include toxicity and overall survival (OS). Subgroup analysis for the SQ and NSQ was preplanned. The study was designed with 80% power to detect a 33% decrease in the hazard of progression.

Results: Between March 2009 and December 2011, 231 patients were randomized, 115 in arm A (42 SQ, 73 NSQ) and 116 in arm B (35 SQ, 81 NSQ). The adjusted HR for PFS for all patients is 0.80 (95% CI 0.60 - 1.00), p = 0.12. Toxicity gr 3+ occurred in 9% (arm A) and 24% (arm B), most frequent rash (7 vs 15%, resp). Febrile neutropenia was 0 vs 6%, resp. C was significantly improved in the combination arm and was restricted to non squamous histology.

Conclusion: PFS as primary endpoint was not significantly different between arms. OS was significantly improved in the combination arm and was restricted to non squamous histology.

Disclosure: All authors have declared no conflicts of interest.

Table: LBA29

<table>
<thead>
<tr>
<th>All patients</th>
<th>Squamous</th>
<th>Non squamous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mono</td>
<td>Combi</td>
<td>Mono</td>
</tr>
<tr>
<td>male/female(%)</td>
<td>65/35</td>
<td>63/37</td>
</tr>
<tr>
<td>age (med. range)</td>
<td>64 (38-81)</td>
<td>63 (40-81)</td>
</tr>
<tr>
<td>ECOG PS 0/1/2 (%)</td>
<td>34/58/8</td>
<td>43/50/8</td>
</tr>
<tr>
<td>PFS months (median; 95% CI)</td>
<td>4.9 (4.2-6.3)</td>
<td>6.1 (4.8-7.9)</td>
</tr>
<tr>
<td>OS months (median; 95% CI)</td>
<td>5.5 (4.5-8.5)</td>
<td>7.8 (6.5-10.4)</td>
</tr>
</tbody>
</table>

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ELUNG: A MULTICENTER, RANDOMIZED PHASE IIIB TRIAL OF “STANDARD” PLATINUM DOUBLETS PLUS CETUXIMAB (CET) AS FIRST-LINE TREATMENT OF RECURRENT OR ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

L.S. Schwartzberg1, K. Tauer1, J. Atkins2, K. Sivarajan3, V. Patel4, B. Bastos5, C. Langer1, M.A. Socinski6, D.R. Spigel7
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Background: CET added to platinum doublet chemotherapy (chemo) improves survival in advanced NSCLC (Parker R, et al. Lancet 2009). However, the optimal chemo combination with CET is not established for either squamous cell (SQ) or non-squamous (NSQ) histology.

Methods: eLung was an open-label randomized phase II study in SQ & NSQ cohorts of patients (pts) with advanced NSCLC. Pts with NSQ were randomized to 1 of 3 treatment arms: cisplatin or carboplatin + either gemcitabine (PG) or pemetrexed (PPm) + CET (130) 10.6 (8.0-14.5) NSQ 47.3 (39.1-57.1) NSQ
† CBPc + CET (233) 9.5 (7.0-12.5)* 9.6 (7.9-11.5)
‡ PPm + CET (130) 10.6 (8.0-14.5)* N/A 47.3 (39.1-57.1) N/A
† CBPc + CET (233) 9.5 (7.0-12.5)* 9.6 (7.9-11.5)
‡ PPm + CET (130) 10.6 (8.0-14.5)* N/A 47.3 (39.1-57.1) N/A

Results: Between 12/08 and 5/11, 601 stage IIIb/IV chemo naive pts (399 NSQ and 202 SQ) were randomized from 97 centers. Baseline demographics in NSQ/SQ cohorts: male 62/55%, median (range) age 67 (45-89)/67 (35-86), 81/83% Caucasian, 13.9%/8% African-American, 0.5%/1.0% Asian, stage IIIb 7.2%/4.5%, ECOG PS 0, 67/60%. Median OS & 1-year survival are shown in Table 1. Grade 3/4 AE's in > 5% of pts included rash (8%), neuropenia (26%), thrombocytopenia (24%), anemia (11%), hypomagnesemia (5%), hypokalemia (5%), fatigue (8%), dehydration (5%) and dyspnea (5%). In exploratory analysis pts with grade > 3 rash had median OS of 14.0 months vs. 9.4 for lesser grade rash (P = 0.031).

Conclusions: No new safety signals for platinum doublets + CET were identified. There were no significant differences in outcome by chemo regimen. NSQ patients receiving chemo + CET have improved survival compared to SQ patients.

Disclosure: L.S. Schwartzberg: research support from Eli Lilly and BMS B. Bastos: Eli Lilly advisory board participation C. Langer: Eli Lilly advisory board participation M.A. Socinski: research support from Eli Lilly. All other authors have declared no conflicts of interest.

Table: LBA30

<table>
<thead>
<tr>
<th>Arm (N)</th>
<th>Median OS in months (95% CI)</th>
<th>1-year survival % (95% CI)</th>
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<tbody>
<tr>
<td></td>
<td>NSQ</td>
<td>SQ</td>
</tr>
<tr>
<td>PG + CET (236)</td>
<td>9.3 (7.3-12.2)*</td>
<td>7.1 (5.9-9.5)*</td>
</tr>
<tr>
<td>CBPc + CET (233)</td>
<td>9.5 (7.0-12.5)*</td>
<td>9.6 (7.9-11.5)</td>
</tr>
<tr>
<td>PPm + CET (130)</td>
<td>10.6 (8.0-14.5)*</td>
<td>N/A</td>
</tr>
<tr>
<td>Chemo + CET (599)</td>
<td>9.9 (8.3-11.4)*</td>
<td>8.7 (7.4-10.1)*</td>
</tr>
</tbody>
</table>

* † Log-Rank-p-value = 0.1863 Log-Rank-p-value = 0.2570 \( K \) Log-Rank-p-value = 0.0082

LBA31

CONCOMITANT ACTIONABLE MUTATIONS AND OVERALL SURVIVAL (OS) IN EGFR-MUTANT NON- SMALL-CELL LUNG CANCER (NSCLC) PATIENTS (P) INCLUDED IN THE EURTAC TRIAL: EGFR L858R, EGFR T790M, TP53 R273H AND EML4-ALK (V3)

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Background: At the final cutoff of April 2012, in the randomized phase III EURTAC trial, erlotinib improved progression-free survival (PFS) in comparison with chemotherapy as first-line treatment in European p with EGFR-mutation-positive NSCLC (HR, 0.34; P < 0.0001). No differences were observed in overall survival (OS) (22.9 vs 20.8 months [m]).

Methods: We have assessed EGFR T790M and TP53 mutations, the EML4-ALK translocation and BIM mRNA expression in pretreatment tumor samples of 95 p from the EURTAC trial and correlated our findings with outcome.

Results: Concomitant T790M was found in 37.89%, TP53 in 24.21% and EML4-ALK in 15.8% of p. BIM expression was low or intermediate in 55.8% of p and high in 31.6%, 86.7% of the 45 p receiving chemotherapy had crossed over to receive EGFR TKIs at the time of progression. In p treated with erlotinib, overall response rates (ORR) were 87.5% in p with high BIM expression and 34.6% in p with low/intermediate BIM. ORR in the chemotherapy group were 11.1 and 14.2, respectively (P = 0.0002). Among p in the erlotinib group without T790M mutations, ORR was 100% for p with high BIM expression vs 35.2% for p with low/intermediate BIM levels (P = 0.01). In the multivariate analysis, only erlotinib (HR, 0.36; P < 0.0001) and high BIM expression (HR, 0.55; P = 0.03) were markers of longer PFS. OS for p with T790M mutations was 40.1 m in p with high BIM expression and 15.4 m in p with low/intermediate BIM levels (P = 0.04). In the multivariate analysis, including T790M, TP53 and EML4-ALK, only high BIM expression emerged as a marker of longer OS (HR, 0.47; P = 0.02).

Conclusions: Our results can lead to the design of studies of treatment based on the presence of the EGFR T790M mutation and BIM expression levels. We are currently designing a clinical trial based on our findings.

Disclosure: All authors have declared no conflicts of interest.
MONOTHERAPY ADMINISTRATION OF SORAFENIB IN PATIENTS WITH NON-SMALL CELL LUNG CANCER: PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED MISSION TRIAL

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Background: Sorafenib monotherapy showed activity in a randomized discontinuation phase II trial of patients with advanced NSCLC who failed 2–3 chemotherapy regimens (ECOG 2501). The Phase III MISSION trial assessed whether 3rd- or 4th-line treatment with sorafenib plus best supportive care (BSC) would improve overall survival (OS), relative to placebo plus BSC, in patients with advanced relapsed/refractory NSCLC of predominantly non-squamous histology.

Methods: Eligible patients were randomized 1:1 to oral sorafenib (S) 400 mg bid or placebo (P) and stratified by geographic region, number of prior lines of treatment, brain metastases, and prior anti-EGFR therapy. The primary endpoint was OS; secondary endpoints included progression-free survival (PFS), time to progression (TTP), overall response rate (ORR), disease control rate (DCR), and safety; endpoints were tested with one-sided significance level of 0.025.

Results: A total of 703 patients were randomized (S = 350; P = 353). Baseline demographic factors and prior treatments were generally balanced, with minor imbalances (S vs P) in female gender (47% vs 41%) and never smokers (46% vs 38%). Fewer patients received post-progression therapy in the S arm (44%) than in the P arm (56%). Assessment of OS was based on a total of 579 events (S = 285; P = 294). Median OS was similar in the two groups (248 vs 253 vs; HR 0.99, p = 0.4687), whereas median PFS (84 vs 43 vs; HR 0.61; p < 0.0001), TTP (89 vs 43 vs; HR 0.54; p = 0.001) were significantly longer and dose reductions (35% vs 6%) and dose interruptions (52% vs 19%) were higher in the S group. Rates of all (99% vs 91%) and serious (39% vs 32%) adverse events were higher in the S group.

Conclusion: The phase III MISSION trial did not meet its primary endpoint of improving OS as 3rd- or 4th-line treatment in patients with advanced NSCLC. Sorafenib treatment significantly enhanced PFS, TTP, ORR, and DCR compared to BSC alone. Safety and tolerability data were as expected. Supported by Bayer HealthCare Pharmaceuticals and Onyx Pharmaceuticals.

Disclosure: L. Paz-Ares: Luis Paz-Ares has received honoraria from Bayer HealthCare Pharmaceuticals, Lilly, Roche and Pfizer V. Hirsh: Member of the steering committee for the MISSION trial.

FORTIS-M, A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE 3 STUDY OF ORAL TALTACOFERRIN ALFA WITH BEST SUPPORTIVE CARE IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER FOLLOWING TWO OR MORE PRIOR REGIMENS- BY THE FORTIS-M STUDY GROUP

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Background: Taltacoferrin alfa (TLF) is an oral Dendritic Cell Mediated Immuno-Activator (DCMI). Based on positive results in two randomized phase II trials in NSCLC, we conducted a phase III study of TLF versus placebo for advanced NSCLC following ≥2 prior systemic therapy regimens (NCT00707304).

Methods: Inclusion criteria were: age >18 years; failure ≥2 prior systemic regimens (received 1 platinum-based regimen); presence of measurable disease; ECOG performance status 0–2; and life expectancy >12 weeks. Patients were randomly assigned (2:1) to receive TLF (1.5 g oral solution) or placebo, each with best supportive care, for a maximum of five 14-week cycles (12 weeks on/2 weeks off). The primary endpoint was overall survival (OS). Secondary endpoints included 6-month and 1-year survival rates, progression-free survival (PFS), objective response rate, and objective disease control rate (DCR), complete or partial response or stable disease. The primary endpoint was analyzed using a stratified log rank test with a 2-sided significance level of 0.05.

Results: A total of 742 patients (TLF = 497, placebo = 245) were enrolled between November 2008 and March 2011 at 163 centers worldwide. Median age was 62 years for TLF and 63 years for placebo; 90% of patients in each group had Stage IV disease; and 56.5% of TLF patients and 58.4% of placebo patients had received ≥3 prior regimens. The median OS for TLF was 7.49 months versus 7.66 months for placebo (HR 1.04, P = 0.6602), and the respective values for PFS were 1.68 and 1.64 months (HR 0.99, P = 0.8829). The DCR was 37.6% for TLF and 38.4% for placebo (P = 0.8336). 87.3% of patients in the TLF arm experienced an adverse event (AEs), 86.0% in the placebo arm; 34% and 36% of patients had Grade 3–4 AEs in the TLF arm, 35.5% in the placebo arm; and those for serious AEs were 43.7% and 41.7%. Discontinuations due to AEs occurred for 14.5% of TLF patients vs 15.7% for placebo.

Conclusions: TLF plus best supportive care did not extend OS or PFS vs placebo plus best supportive care in patients with advanced NSCLC. Oral TLF had a safety profile comparable to that for placebo.

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THE GALAXY TRIAL (NCT01348126): A RANDOMIZED IIB/III STUDY OF GANETESPIB (STA-9090) IN COMBINATION WITH DOCETAXEL VERSUS DOCETAXEL ALONE AS SECOND LINE THERAPY IN PATIENTS WITH STAGE IIIB OR IV NSCLC


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Background: Inhibition of Hsp90, a key molecular chaperone required for activation of many oncoproteins, can lead to cancer cell death. Ganetespib (G) is a resorcinolic 2nd generation Hsp90 inhibitor that has shown single agent activity in pretreated patients with advanced NSCLC harboring the ELM4-ALK rearrangement and KRAS mutations. Combination of G with docetaxel (D) results in synergistic activity in NSCLC xenografts and was well tolerated in a Phase I study.

Methods: The GALAXY trial is an international, randomized Phase IIB/III study. The Phase IIB stage (N = 300) evaluates treatment with G plus D vs. D alone in 2nd line advanced NSCLC patients. Co-primary endpoints are PFS in the high LDH adenocarcinoma population and PFS in patients with mKRAS tumors. Main secondary endpoints include PFS and OS in adenocarcinoma patients, ORR, disease control rate, and clinical activity in genetically profiled subpopulations. All patients receive D 75 mg/m^2 on day 1 of a three-week treatment cycle; combination arm patients receive G 150 mg/m^2 on day 1 and day 15 in addition.

Results: As of April 2012, just over half of the 300 planned patients were enrolled. Baseline characteristics were balanced. Tumor tissue was obtained in ~90% of patients. In the combination arm, 1-4% of patients had transient Gr 3\4 GI and liver toxicities; Gr 1\2 ocular toxicities were observed in <3% of patients. The overall safety profile of the combination is comparable to docetaxel single agent. An early signal of activity was observed in two pre-specified patient populations. Results from a planned interim analysis in early September, including efficacy results in subpopulations, will be presented at the meeting.

Conclusions: Ganetespib in combination with docetaxel was well tolerated by patients with advanced NSCLC. Encouraging signals of activity in pre-specified patient populations have been observed.

Disclosure: C. Manegold: Author has served on advisory board meetings to Synta Pharmaceuticals. R. Rosell: Author has served on advisory board meetings to Synta Pharmaceuticals. V. Vukovic: Author is an employee of Synta Pharmaceuticals. I. El-Hariry: Author is an employee of Synta Pharmaceuticals. F. Teofilovici: Author is an employee of Synta Pharmaceuticals. A. Enke: Author is an employee of Synta Pharmaceuticals. D.A. Fennell: Author has served on scientific advisory board meetings for Synta Pharmaceuticals. All other authors have declared no conflicts of interest.
oncology and public health

1371P.PR VENOUS THROMBOEMBOLISM (VTE) IN BREAST AND PROSTATE CANCER PATIENTS RECEIVING CHEMOTHERAPY – A REAL WORLD ANALYSIS OF RISK AND ECONOMIC BURDEN

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Background: Breast and prostate cancer represent the most frequent cancers among women and men, respectively in US. These patients are at an increased risk of VTE, and chemotherapy is an additional risk factor. Rates of VTE vary by cancer type, stage and time from chemotherapy initiation. This study explores rates of VTE after chemotherapy.

Methods: The US IMPACT® claims database was used to retrospectively identify patients with breast and prostate cancer initiating chemotherapy between 1/1/05 and 12/31/08. Index date was defined as the first day of chemotherapy after cancer diagnosis. Patients with ≥ 12 months of continuous medical coverage prior to index date and ≥3.5 months during follow-up were included. Patients with prior VTE within 12 months, major bleeding within 3 months, or anticoagulant treatment within 2 weeks of index date were excluded. Baseline characteristics and healthcare costs (pharmacy, inpatient, emergency room, and outpatient costs) were assessed at 1 year pre index. Incidence of VTE was assessed at 3.5 and 12 months post index and costs at 1 year post index.

Results: 34,144 patients were identified. Both groups had comparable demographic distribution. Risk of VTE 3.5 months after chemotherapy initiation was 3.9% for breast cancer and 3.6% for prostate cancer patients. Prostate cancer patients who developed VTE within 12 months post index had comparable healthcare costs at baseline ($29,373) to those without VTE ($24,595). However, during 1 year post index, costs in VTE patients were significantly higher ($80,583) than in those without VTE ($39,102) driven by inpatient and outpatient costs. A similar pattern was observed for breast cancer patients. The table below shows baseline characteristics, costs and VTE risk in patients.

Conclusions: Risk of VTE 3.5 months after chemo initiation is about 4% for two major cancer types and almost doubles at 12 months. VTE is also associated with major cancer types and almost doubles at 12 months. VTE is also associated with increased economic burden.

Disclosure: All authors have declared no conflicts of interest.

1418PD.PR QUANTIFYING THE BURDEN OF CAREGIVING FOR PATIENTS WITH CANCER IN EUROPE

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Background: It is recognized that cancer imposes a burden both on patients and on those who provide care for them, but the extent of this burden compared to non-caregivers is unknown.

Methods: Data were obtained from the 2010 EU National Health and Wellness Survey (NHWS), a self-administered online survey of adults in France, Germany, Italy, Spain, and the United Kingdom (n = 57,865). Stratified random sampling matched the NHWS with each country’s demographic composition. Respondents who reported providing care for a patient with cancer (called informal “caregivers”) were compared with respondents not providing care (“non-caregivers”) on health status (from the Short Form (SF)-12 and SF-6D health utility measure), work impairment from the Work Productivity and Activity Impairment (WPAI) questionnaire, diagnosed comorbid illness, and self-reported healthcare resource use. Regression models were used to predict health outcomes as a function of caregiving vs. non-caregiving, controlling for demographics, health risk behaviors, and Charlson Comorbidity Index.

Results: Adjusting for covariates, caregivers (n = 847) reported significantly worse health status than non-caregivers (n = 52,127) (physical: -1.32 points; mental: -3.21 points; health utilities: -0.043 points, all p < .001), and during the last week higher mean levels of absenteeism (8.39% vs. 4.76%), overall work impairment (26.43% vs. 18.09%) and activity impairment (28.85% vs. 21.91%) (all p < .001). In addition, caregivers reported more mean healthcare provider visits (6.53 vs. 4.89, p < .001), emergency room visits (0.26 vs. 0.16, p = .002) and hospitalizations (0.19 vs. 0.10, p = .003) during the last 6 months. Caregivers had greater likelihood than non-caregivers of being diagnosed with depression (OR = 1.455), anxiety (OR = 1.972), insomnia (OR = 1.945), migraine (OR = 1.697), and gastrointestinal problems (OR = 1.644) (all p < .001).

Conclusion: Cancer caregivers experience a significantly higher burden than non-caregivers, adding to the already high societal cost of cancer. Special attention to caregivers should be given based on their pivotal role in maintaining the health and well-being of patients with cancer, fulfilling a need not addressed by the healthcare system.

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MODERATE ALCOHOL INTAKE AND CANCER: THE ROLE OF UNDER-REPORTING

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Background: There is consensus that heavy alcohol drinking is related to increased risk of several cancer types. However, the role of light-moderate drinking and the existence of a threshold amount of alcohol for risk are less clear.

Methods: We explored possible underreporting among moderate drinkers in a cohort study of 129,987 persons. From baseline in 1978-85 through 2008 cancer was diagnosed in 15,080 persons. Cox proportional hazard models were controlled for age, sex, ethnicity, smoking, education, and body mass index. Alcohol was studied categorically, with lifelong abstainers as referent. We studied risk of any cancer and of a composite of 5 types with alcohol-associated risk in this cohort (upper airway digestive, liver, breast, lung, colo-rectal). We stratified moderate drinking categories (<1 and 1-2 drinks per day) into persons suspected of under-reporting (“suspect”) and those not suspected (“not suspect”). The “suspect” group either reported heavier intake at some other time or had an alcohol-related diagnosis (out-patient, in-patient, or death) at any time.

Results: The relative risks (RR) and 95% confidence intervals (CI) among the alcohol categories for any cancer were: exdrinkers = 1.17 (1.07-1.27, p < 0.001), <1 drink per day = 1.05 (1.00-1.09, p = 0.04), 1-2 drinks per day = 1.09 (1.04-1.14, p < 0.001), and ≥3 drinks per day = 1.16 (1.09 = 1.24, p < 0.001). Relationships of light-moderate drinking (<3 drinks per day) were similar in men, women, whites, blacks, Asians, never smokers, persons diagnosed within or after 10 years. For all persons reporting 1-2 drinks per day, the RR of cancer among "suspect" was 1.14 (1.04-1.25, p = 0.004) and for "non-suspect it was 1.00 (0.89-1.11). For those reporting <1 drink per day the RR for “suspect” was 1.17 (1.06-1.28, p = 0.001); for “non-suspect it was 1.00 (0.90-1.09). For the alcohol-related composite the RR(CI) among “suspect” persons reporting 1-2 drinks per day was 1.41 (1.23-1.62) and for “not suspect persons it was 1.06 (0.89-1.25), while at < 1 drink per day the RR for “suspect” was 1.39 (1.21-1.59, p< 0.00) and for “non-suspect” it was 1.03 (0.90-1.18).

Conclusions: We conclude that apparent increased risk of cancer among light-moderate drinkers is substantially due to underreporting of intake.

Disclosure: All authors have declared no conflicts of interest.
Prevention and screening

POOR KNOWLEDGE OF RISK FACTORS FOR CANCER AMONGST GENERAL PUBLIC & HEALTH CARE PROFESSIONALS

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Background: Knowledge of cancer risk factors has rarely been studied in Ireland. An understanding of this can help inform cancer prevention programs.

Methods: An 48 question online survey was used to assess knowledge.

Results: 748 people took part, 126 (17%) were Health Care Professionals (HCP). Mean age was 37yrs. 80% of public and 78% of HCP were concerned about developing cancer, however 15% of public believed if cancer was in their family there was nothing they could do about personal risk. 20% of public and 10% of HCP did not know risk increases with age. 90% of both groups believe that genetics 'strongly' increases risk, 79% of public and 73% of HCP reporting that >10% of cancers are inherited. The top 5 risk factors listed were: smoking 87%, diet 76%, alcohol 42%, genetics 47%, and environment 31%. Only 32% of public and 41% of HCP were aware that obesity is a risk factor. 33% of public and 24% of HCP did not think the location of fat was important. 78% of HCP were unaware abdominal fat can cause inflammation and secrete substances implicated in cancer development. 94% of respondents believe stress is a risk factor and 68% believed cell phones increase risk. 35% thought 'detox' diets and 61% believed organic food reduced risk. The following were thought to increase risk: Aerosols (71%), cleaning agents (73%), cooking methods (68%), processed meat (86%), food irradiation (77%), and genetically modified food (81%). The majority were aware that berries, green tea, vegetables and physical activity (30mins/d) can reduce risk. Only 33% of public and 35% of HCP knew that frozen vegetables/fruit are as good as fresh, 40% of public and 28% of HCP were unaware that red meat is a risk factor, and 46% did not know salt can increase risk. 51% of public and 54% of HCP believed that a daily multivitamin is protective, and 24% of public and 20% of HCP thought they should be consumed daily. 29% of public and 24% of HCP believed wearing a tight bra increases risk of breast cancer, and 48% of public and 41% of HCP believed a blow to the breast can increase risk.

Conclusions: A sizable portion of public and HCP are misinformed about cancer risk. Most are aware of classic risk factors but many overestimate risk attributable to genetics, environment, stress, and underestimate age, obesity and sunlight. One in 6 members of public believes lifetime risk of cancer is non-modifiable.

Disclosure: All authors have declared no conflicts of interest.
RESULTS OF A RANDOMISED PHASE III TRIAL (EORTC 62012) OF SINGLE AGENT DOXORUBICIN VERSUS DOXORUBICIN PLUS IFOSFAMIDE AS FIRST LINE CHEMOTHERAPY FOR PATIENTS WITH ADVANCED OR METASTATIC SOFT TISSUE SARCOMA: A SURVIVAL STUDY

BY THE EORTC SOFT TISSUE AND BONE SARCOMA GROUP

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The EORTC 62012 trial was initiated to address concerns that previous studies comparing single agent doxorubicin (D) versus (vs) doxorubicin plus ifosfamide (I) in soft tissue sarcomas (STS) had used suboptimal doses of I. Non-randomised data suggested that a higher dose of I could increase response rate and progression free survival (PFS).

Methods: Patients (pts) with locally advanced or metastatic, grade 2 or 3 STS aged up to 60 yrs, were randomised to receive either single agent D (75 mg/m²) or D (75 mg/m²) with I (10 g/m² over 4 days with mesna and pegfilgrastim) as first-line treatment. Randomisation was stratified by performance status (0 or 1), age (< / ≥ 50 yrs), presence or absence of liver metastases and histological grade (grade 2 vs 3). Pts were treated every 3 wks till progression or max. 6 cycles. The primary endpoint was overall survival (OS).

Results: 455 pts from 38 centres were randomised to D (n = 228) or D-I (n = 227). With median follow-up of 56 months, OS at 1 yr was slightly greater with D-I at 60% (95.5% CI 53 – 66) vs 51% (95.5% CI 44 – 58) with D alone, but the difference was not statistically significant (HR 0.82, 95% CI 0.66 – 1.01, stratified log rank test p = 0.061). No difference was seen in the 2-yr OS rate which was 31% (95.5%CI 25 – 38) for D-I vs 28% (95.5%CI 22 – 34) for D. Median PFS was significantly increased at 7.4 months (95% CI 6.6 – 8.3) for D-I vs 4.6 months (95% CI 2.9 – 5.6) for D (HR 0.72, 95% CI 0.59 – 0.88, stratified log rank test p = 0.002). Responses were CR: D = 1, D-I = 4; PR: D = 30 (13.2%), D-I = 56 (24.7%); SD: D = 105 (46.1%), D-I = 114 (50.2%). Febrile neutropenia was more common with D-I (45.9% vs 13.6%) as was anaemia (35.3% vs 4.6%).

Conclusions: The lack of a significant improvement in OS does not support the routine use of this intensive combination of D + I for STS in the palliative setting. The higher response rate suggests that D-I might be justified in selected pts age <60 if tumour shrinkage is critical, but it is significantly more toxic. D remains the gold standard for comparative studies of first line chemotherapy in metastatic STS.

Disclosure: All authors have declared no conflicts of interest.
Background: Whether an anticoagulant prophylaxis is needed for patients with cancer with a central venous catheter is a highly controversial subject. We designed a study to compare different prophylactic strategies over 3 months of treatment.

Patients and methods: We performed a phase III prospective, randomized trial. After the insertion of a central venous access device, consecutive outpatients with local nodes or metastatic invasion, and planned chemotherapy were randomized to no anticoagulant prophylaxis, low molecular weight heparin (LMWH: dalteparine 2500 IU, nadroparine 2850 IU, or enoxaparine 4000 IU, once daily), or warfarin 1 mg/day. Treatments were given over the first 3 months. Doppler ultrasound and venographies were performed on days 1 and 90 or sooner in case of clinical presumption of thrombosis.

Results: A total of 420 patients were randomized and 407 were evaluable. Forty-two catheter-related deep-vein thromboses (DVT) occurred (10.3%), 20 in those with no anticoagulant prophylaxis, low molecular weight heparin (LMWH: dalteparine 2500 IU, nadroparine 2850 IU, or enoxaparine 4000 IU, once daily), or warfarin 1 mg/day. Treatments were given over the first 3 months. Doppler ultrasound and venographies were performed on days 1 and 90 or sooner in case of clinical presumption of thrombosis.

Conclusions: Prophylaxis showed a benefit regarding catheter-related and non-catheter-related DVT with no increase in serious side effects.

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HPV biology and implications in gynecological malignancies

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The “high-risk” types of human papillomaviruses (HPV), in particular PV 16 and 18 are responsible for the development of almost all cases of cervical cancer, for a substantial fraction of other malignant anogenital tumors (penis, vulva and perianum) and for a proportion of head and neck cancer. The natural history of HPV infections and immunization experiments in animals with their respective papillomaviruses (e.g. the canine oral papillomavirus) clearly revealed the involvement of the immune system in controlling the viral infections and the diseases associated therewith. Antibodies appear to be the key molecules in preventing of an infection whereas mostly T cells and cytokines are involved in controlling virus persistence and progression towards malignancy. During the natural course of infection human papillomaviruses are not particularly immunogenic since their biology makes them barely “visible” by the immune system (infection is confined to the epithelium) but also since it has acquired the ability to actively suppress certain immune functions. This is in remarkable contrast to the strong immune response induced by i.m. immunization with virus particles when they become exposed to and interact directly with circulating antigen presenting cells. There is mounting awareness about the mechanisms of these interactions.

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The following abstracts have been withdrawn from the ESMO 2012 congress abstract book and program

- NOTCH AND DLL4 EXPRESSION IN BEVACIZUMAB-TREATED COLON CANCER PATIENTS
- PHASE II STUDY OF S-1 PLUS LEUCOVORIN (1 WEEK TREATMENT REGIMEN FOLLOWED BY 1 WEEK REST PERIOD) IN PATIENTS WITH UNTREATED METASTATIC COLORECTAL CANCER IN JAPAN AND CHINA: COMPARING RESULTS OF EACH COUNTRY AND UPDATING OVERALL SURVIVAL
- RETROSPECTIVE ANALYSIS OF PATHOLOGICAL RESPONSE IN COLORECTAL CANCER LIVER METASTASES FOLLOWING TREATMENT WITH BEVACIZUMAB: UPDATED FINDINGS
- BASELINE CEA SERUM LEVELS PREDICT THE EFFICACY OF BEVACIZUMAB-BASED TREATMENT IN ADVANCED COLORECTAL CANCER