P5. PERSONALIZED CARE IN CLINICAL PRACTICE

P5.01

PERSONALIZED MEDICINE FOR PATIENTS WITH ADVANCED CANCER IN THE PHASE I PROGRAM: VALIDATION ANALYSIS

A.M. Tsimberidou, D.S. Hong, J.J. Wheler, Y. Ye, S. Fu, S.A. Piha-Paul, A. Naing, G.S. Falchook, F. Janku, K. Aldape, S. Wen, D. Berry, R. Kurzrock

1MD Anderson Cancer Center, Houston, TX, USA
2West Virginia University Health Science Center, Morgantown, WV, USA
3UCSD Moores Cancer Center, San Diego, CA, USA

Background: We have previously published that targeted agents matched with tumor molecular aberrations are associated with improved treatment outcomes in patients with one molecular aberration in their tumor compared to the standard approach (Tsimberidou et al, Clin Cancer Res. 2012 18(22):6373-83). To validate these results, we analyzed additional patients treated in our clinic with the same therapeutic approach from 3/2011 to 2/2012.

Methods: Tumor molecular analysis was performed at MD Anderson (CLIA; PCR-based sequencing, IHC, FISH). Patients were treated with matched therapy, when available.

Results: Overall, 379 additional patients (median no. of prior therapies, 3) with any tumor type and 1 molecular aberration were treated. Tumor types were as follows: colorectal cancer 21.9%, melanoma 9.0%, lung 11.6%, ovarian 9.2%, head and neck 5.8%, breast 9.0%, thyroid 3.4%, endometrial 3.7%, sarcoma 2.6%, renal 1.8% and other cancers 22%. Proportions of aberrations were as follows: PIK3CA 11.5%, AKT 3%, PTEN 23.9%, KRAS 35.4%, NRAS 9.9%, BRAF 17%, EGFR 13%, MET 7.4%, GNAQ 3.3%, KIT 5.1%, and HER2 12.9%. Results are shown in the table. In multivariate analyses, matched therapy was an independent factor predicting response (p=.015) and longer TTF (P=.0003); and it was associated with a trend towards longer survival (p=.07).

Conclusions: These results from additional patients confirm our previously published data and continue to support use of a personalized molecular approach for patients with cancer. Complete molecular profiling to understand resistance mechanisms and new targeted agents are needed.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Matched (n=143)</th>
<th>Non-matched (n=236)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR+PR</td>
<td>12%</td>
<td>5%</td>
<td>.023</td>
</tr>
<tr>
<td>SD 6 months</td>
<td>16%</td>
<td>12%</td>
<td></td>
</tr>
<tr>
<td>CR+PR+ SD 6 months</td>
<td>28%</td>
<td>17%</td>
<td>.021</td>
</tr>
<tr>
<td>PFS, months (95% CI)</td>
<td>3.9 (3.4-5.0)</td>
<td>2.2 (2.0-2.8)</td>
<td>.001</td>
</tr>
<tr>
<td>FFS, months (95% CI)</td>
<td>3.5 (2.8-4.1)</td>
<td>2.0 (1.8-2.2)</td>
<td>.0003</td>
</tr>
<tr>
<td>Overall survival, months (95% CI)</td>
<td>11.4 (9.3-17.3)</td>
<td>8.6 (7.5-10.4)</td>
<td>.04</td>
</tr>
</tbody>
</table>
T200: AN INTEGRATED PLATFORM FOR PERSONALIZED CANCER THERAPY
The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Introduction: The fast progress of the next generation sequencing technology is leading us to enter the era of personalized cancer therapy. We establish an integrated platform called T200 to perform ultradepth sequencing and detect genomic aberrations in individual patients, where T200 represents targeting 202 cancer associated genes that are mutated in various cancers. Our goal was to detect mutations in individual patients and determine the clinical relevance of next generation sequencing information at MD Anderson.

Materials and Methods: DNA from matched patient blood and tumor tissue were captured using Nimblegen SeqCap and sequenced on Illumina HiSeq2000. On average, we achieved over 500X coverage of all selected exons in each gene, providing technical and statistical strength for mutation detection. A computational pipeline was implemented for mutation detection. The raw reads were mapped to the hg19 reference genome. Duplicate reads were removed. VarScan2 [1] was applied to call somatic, germline and loss of heterozygosity SNVs and short indels. Copy number variation is also reported if there was significant gain/loss on an exon. Various tools were applied to annotate the functional consequence of the SNVs. Specifically, CanDrA (Mao et al, submitted) was applied to predict if an SNV is driver or passenger event. This pipeline is also applicable to whole-exome sequencing data.

Results: In total, 668 patient genomes have been sequenced and analyzed on the T200 platform. Mutations at 5% allele frequency or above were compared to CMS46, an Ion Torrent based hotspot sequencing platform. We achieved almost 100% sensitivity (only 1 out of the 325 CMS46 reported somatic SNVs was missed by T200).

Discussion: We have established an integrated platform T200 to detect mutations with almost 100% sensitivity. Ongoing work includes i) the detection of multi-nucleotide variants, ii) analysis of clonal evolution of the SNVs, iii) more accurate calculation of allele frequencies by correcting sequencing errors and by combining the copy number variation influences on SNV sites.

Acute myeloid leukemia (AML) is a genetically heterogeneous disease characterized by significant clonal evolution during disease progression. It is critical to understand clonal diversity and evolution during tumor progression and drug resistance in order to tailor curative therapies for the multiple AML subclones in a patient. In this study, we applied next-generation sequencing to follow clonal progression of adult AML during treatment with novel targeted drugs. These drugs were selected based on ex-vivo drug sensitivity and resistance testing (DSRT) with a comprehensive set of 300 cancer drugs on patient cells (Pemovska et al, manuscript, 2013). Short-term complete clinical responses were seen in 3/6 chemorefractory patients treated in a compassionate setting based on DSRT results. Sequencing of pre and post-relapse samples indicated clonal evolution and emergence of new subclones. Treatment of one such AML patient with a combination of dasatinib-sunitinib-temsirolimus led to the selection of an AML clone carrying ETV6-NTRK3 fusion. DSRT of relapse sample indicated addiction to IGF1R signalling, compatible with genetic changes emerging after treatment. Thus, effective treatment for AML will require therapeutic targeting of not only the major clone, but also inhibition of multiple pre-existing subclones. Therefore, we are now testing a) whether such rare clones can be detected before therapy, and b) whether therapeutic cocktails inhibiting such clones could be designed to improve patient therapies. Proof of concept experiments were carried out in AML cell-lines (MV4-11 and THP1) treated with targeted drugs. Analogous to clonal heterogeneity, we mixed two cell-lines in varying proportions and treated them with quizartinib, to which MV4-11 cells are sensitive, and THP1 are resistant. The effect of drug on each cell-line in mixture is quantitatively measured using cytotoxicity assays and amplicon sequencing of drug treated cells. Based on this assay, we were able to establish the sensitivity of the assay for detecting rare clones and test how combination of drugs inhibiting both cell-lines work. We hope this unique approach of combining genomics, ex-vivo drug testing and patient monitoring in a time-dependent manner to track clonal evolution in-vivo will help us design effective drug combinatorial strategies, thereby improving the treatment of AML patients.
IMPLEMENTATION OF INDIVIDUALIZED PROGNOSTIC COUNSELLING IN HEAD AND NECK ONCOLOGY
Erasmus Medical Centre, Rotterdam, The Netherlands

Background: In the Netherlands, about 2700 new patients with head and neck squamous cell carcinoma (HNSCC) are diagnosed annually. In majority of cases, treatment consists of surgery, radiotherapy, chemotherapy and combinations of these modalities. All types of treatment are associated with high morbidity, sometimes compromising vital functions. Accurate counselling for treatment options, survival rates and quality of life is therefore important. Without knowledge of a reliable individual prognosis, the patient and doctor both will tend to choose treatment according to protocol-based advices by a multidisciplinary team, which is usually the most extensive treatment. Extensive treatment is often associated with major morbidity. Especially in these patients, the balance between survival and quality of life could be improved by choosing a less aggressive and non-protocol based treatment. Our hypothesis is that a change to individualized prognostic counselling leads to less decisional conflict, less extensive treatment, and an improved quality of life in patients with HNSCC.

Methods: In a prospective clinical trial with sequential cohorts we want to investigate the influence of prognostic counselling in patients with HNSCC. For this purpose we developed dedicated software packages incorporating a prognostic model, in which an individualized prognosis for each patient with HNSCC can be calculated (OncologIQ). Besides localisation and TNM-classification of the tumor, patient characteristics such as gender, age, medical history and comorbidity are taken into account. The outcome of this calculation is expressed in a time-bound percentage (as for example 5-year survival rate), applicable for that specific patient. This prognostic model is internally and externally validated. Newly diagnosed patients with HNSCC at ErasmusMC, with a curative intent, will be included. Prognosis will be communicated using absolute percentages visually supported by graphics. Questionnaires on decisional conflict and quality of life will be taken to measure outcomes.

Conclusion: In our opinion individualized prognostic counselling, using unique patient characteristics, will support informed values based decisions, and therefore will lead to improved communication and quality of life. With the implementation of our innovative prognostic model, OncologIQ, in clinical practice for patients with HNSCC, we aim to improve communication and quality of life: in other words, true personalized medicine.
CIRCULATING CELL-FREE DNA: IMPORTANCE OF PRE-ANALYTICAL PARAMETERS

S. El Messaoudi, F. Mouliere, A.R. Thierry
Institut de Recherche en Cancérologie de Montpellier IRCM-INSERM U896, Montpellier, France

Despite the growing interest in circulating cell-free DNA (ccfDNA) analysis in oncology, few studies on sample handling have been reported and no analytical consensus is available. The lack of consistency between the various protocols for sample handling and the techniques used for ccfDNA analysis is one of the major obstacles to translating ccfDNA analysis to the patient’s bedside. Although this point is highlighted regularly in the published reviews on ccfDNA analysis, no standard operating procedure currently exists. We focused our work for more than 8 years on the origins and structures of ccfDNA [1,2,3]. Important observations lead us to design methods to sensitively and specifically quantify ccfDNA especially in plasma of colorectal cancer patients. For instance, we can simultaneously determine total ccfDNA concentration, ccfDNA fragmentation; mutation detection and mutation load and implement clinical studies [4]. We studied the preanalytical parameters potentially affecting ccfDNA concentration and fragmentation at each preanalytical step from blood drawing to the storage of ccfDNA extracts. Based on these data, we proposed to determine the optimal preanalytical protocols for ccfDNA analysis and ultimately, define a guideline for the translation of ccfDNA analysis in routine clinical laboratories [5]. Thanks to our robust preanalytical guideline and Intplex, our refined allele-specific quantitative PCR designed specifically to accurately analyze tumor-derived ccfDNA in blood; we obtained unprecedented results from a blinded clinical study directly comparing KRAS/BRAF mutational status determined by colorectal tumor section analysis to mutational status determined by plasma ccfDNA analysis [4] in a cohort of 106 metastatic colorectal cancer patients. Our study reveals a sensitivity of 94% and a specificity of 98%. Altogether, these data reveals that preanalytical handling of samples warrant the quality and success of clinical studies in this field and largely contribute to the translation of ccfDNA analysis from bench to bedside.

MOLECULAR ANALYSIS OF NEO-ADJUVANT PLATINUM IN TRIPLE NEGATIVE BREAST CANCER
M.D. Pegram¹, I.M. Reis², B. Issac², J. Leone², S. Rodgers², C. Gomez², J. Wright², R. Larrieux², K. Ellison³, J. Hurley²
¹Stanford University, Stanford, CA, USA
²University of Miami, Miami, FL, USA
³Almac DX, Craigavon, United Kingdom

Purpose: Triple negative breast cancers (TNBC) compose about 15% of breast cancers (BC). They have a poor prognosis and, in contrast to ER+ BC and HER2+ BC, there are no targeted therapeutic options. The aim of this study was to define a gene expression profile that correlates with pathologic complete response (pCR) in patients with TNBC treated with neoadjuvant platinum-based chemotherapy.

Patients and Methods: This is a retrospective study of one hundred forty four women with TNBC treated with neoadjuvant platinum-containing chemotherapy for locally advanced breast cancer at the University of Miami between January 1, 1999 and January 1, 2011. The medical record was reviewed to obtain data on clinical characteristics, including ethnicity, race, age, clinical stage, treatment regimen and vital status. Tissue blocks were obtained and mRNA extracts were subjected to transcript expression microarray analysis (Almac Diagnostics XcelTM microarray platform containing 110961 probes). This study was approved by the University of Miami IRB.

Results: All patients had locally advanced breast cancer with at least one of the following features at presentation: T3, T4, N2, N3. The mean tumor size was 9.4 cm. The clinical T stage at presentation was: 1.4% T1, 8.3% T2, 52.8% T3, 37.5% T4 (19.4% T4d). The nodal status by physical exam at presentation was: 23% N0, 37.5% N1, 34% N2, and 5.5% N3. pCR in breast and axilla was seen in 31%. Projected PFS and OS by Kaplan-Meier analysis were 55% and 59% at 7 years. Cisplatin-containing regimens offered a survival advantage over carboplatin regimens for both PFS (p=0.007) and OS (p=0.018). Node positivity was the most important predictor of survival. Hierarchical clustering visualized on heatmap showed clear separation between pCR and no pCR. The top 10 enriched pathways from MetaCore analysis included seven differentially expressed genes: MAPK14, SOD2, PIK3AP1, DOCK9, DOCK11, FANCD2 and DAPP1.

Conclusion: Cisplatin/docetaxel neoadjuvant therapy was well tolerated and effective in locally advanced TNBC. The responders had a distinctive genetic signature based on microarray profile. Application of this gene signature to independent validation cohorts of TNBC treated with platinum is ongoing to determine its ability to predict response and clinical outcome.
MOLECULAR STRATIFICATION IDENTIFIES EXCEPTIONAL RESPONDERS TO THERAPY FOR PANCREATIC CANCER

D.K. Chang¹, M. Pajic², N. Waddell³, J. Morton⁴, K.S. Kassahn⁵, A.L. Johns⁵, D.K. Miller³, J. Wu², M.J. Cowley⁷, H. Wasan⁵, E.A. Musgrove², J.V. Pearson³, O. Sansom⁴, S.M. Grimmond³, A.V. Biankin¹

¹University of Glasgow, Bearsden, United Kingdom
²Garvan Institute of Medical Research, Sydney, Australia
³University of Queensland, Brisbane, Australia
⁴Beatson Institute for Cancer Research, Glasgow, United Kingdom
⁵Imperial College Healthcare NHS Trust, London, United Kingdom

Background: Our increasing appreciation of the genomic heterogeneity of cancer suggests that the failure of definitive clinical trials to demonstrate efficacy in many instances is potentially due to the low proportion of responsive phenotypes. Developing genotype-guided approaches to therapy may improve outcomes for pancreatic cancer and many other molecularly heterogeneous malignancies with poor survival rates.

Methods: We used a combined phenotype-to-genotype (P2G) and genotype-to-phenotype (G2P) approach to identify therapies associated with exceptional responses in patients, patient-derived xenografts and genetically engineered mouse models.

Results: A combination of tissue based and genomic assays including next-generation sequencing identified 19 candidate actionable molecular phenotypes with available therapeutics. Outliers that express high levels of molecules involved in gemcitabine activity (hENT1, hCNT1 and hCNT3) demonstrate significant responses to gemcitabine therapy. Similarly, tumours with pan-genomic instability respond to treatment with DNA damaging agents. Response to trastuzumab for HER2 amplified PC and emerging therapies such as nab-paclitaxel are associated with exceptional responses. This molecular phenotype-based stratification was associated with a median survival of 21 months and an exceptional response rate of 60% for metastatic disease.

Conclusions: This proof of concept study suggests that although these actionable phenotypes are individually small, the cumulative efficacy of using a stratified approach may be beneficial, and potentially be required to overcome the challenge of molecular heterogeneity that hampers therapeutic advances in many cancer types.

(Table for this abstract on next page)
## Actionable molecular phenotypes in pancreatic ductal adenocarcinoma

<table>
<thead>
<tr>
<th>Actionable Phenotype</th>
<th>Therapeutic</th>
<th>Rationale</th>
<th>Molecular Characterization</th>
<th>Number of outliers per total examined (Methodology)</th>
<th>Overall Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine + Aliskiren</td>
<td>Gemcitabine</td>
<td>Phase III clinical trial data</td>
<td>High HER1, HER2, CNOT11</td>
<td>13/8 (mRNA array)</td>
<td>14%</td>
</tr>
<tr>
<td>DDR deficient</td>
<td>Platinum; MMC; PARI</td>
<td>Case reports; Clinical Trial Signals</td>
<td>Genoaumixus</td>
<td>19/4 (WGS)</td>
<td>30%</td>
</tr>
<tr>
<td>nab-paclitaxel resistant</td>
<td>nab-paclitaxel</td>
<td>Clinical Trial: preclinical models</td>
<td>SPARC expression</td>
<td>4/99 (NGS)</td>
<td>4%</td>
</tr>
<tr>
<td>5-FU Responsive</td>
<td>5-Fluorouracil, Capecitabine</td>
<td>Phase II Clinical Trials</td>
<td>Unknown</td>
<td>6/54 (IUC)</td>
<td>11%</td>
</tr>
<tr>
<td>Anti-EGFR Resistant</td>
<td>Erlotinib</td>
<td>Phase II clinical trial data (PA3)</td>
<td>KRAS wt Epithelial signature</td>
<td>6/121 (NGS)</td>
<td>5%</td>
</tr>
<tr>
<td>Anti-HER2 Responsive</td>
<td>Trastuzumab</td>
<td>Repurposing</td>
<td>HER2 amplification</td>
<td>104/85 (IHC)</td>
<td>2%</td>
</tr>
<tr>
<td>Hedgehog</td>
<td>SMO inhibitors</td>
<td>Preclinical studies</td>
<td>HH pathway mutations</td>
<td>4/8 (NGS)</td>
<td>4%</td>
</tr>
<tr>
<td>STK11/PRK11 null</td>
<td>mTOR inhibitors</td>
<td>Repurposing</td>
<td>Loss of STK11/PRK11 expression</td>
<td>2/72 (IHC)</td>
<td>3%</td>
</tr>
<tr>
<td>PTEN null / PI3K activated</td>
<td>mTOR inhibitor</td>
<td>Repurposing</td>
<td>Loss of PTEN expression</td>
<td>20/172 (IHC)</td>
<td>12%</td>
</tr>
<tr>
<td>MET Amplified</td>
<td>MET inhibitors</td>
<td>Repurposing</td>
<td>MET Amplification</td>
<td>1/5 (IHC)</td>
<td>2%</td>
</tr>
<tr>
<td>ROKC Amplified</td>
<td>Hasudil</td>
<td>Repurposing</td>
<td>ROKC amplification</td>
<td>11/8 (CNV)</td>
<td>12%</td>
</tr>
<tr>
<td>FGFR2 Amplified</td>
<td>FGFR inhibitor</td>
<td>Preclinical studies</td>
<td>FGFR2 Amplification</td>
<td>1/4 (NGS)</td>
<td>2%</td>
</tr>
<tr>
<td>CSGK Amplified</td>
<td>CSGK inhibitors</td>
<td>Preclinical studies</td>
<td>CSGK Amplification</td>
<td>1/48 (NGS)</td>
<td>2%</td>
</tr>
<tr>
<td>PKC-mediated</td>
<td>PKC inhibitors</td>
<td>Preclinical studies</td>
<td>PKCAmplification</td>
<td>1/48 (NGS)</td>
<td>2%</td>
</tr>
<tr>
<td>MAPK3A mutated</td>
<td>Suntrabib</td>
<td>Repurposing</td>
<td>MAPK3A amplification</td>
<td>1/48 (NGS)</td>
<td>2%</td>
</tr>
<tr>
<td>KIT mutated</td>
<td>Imatinib</td>
<td>Repurposing</td>
<td>KIT overexpression, KIT mutation</td>
<td>1/48 (IHC)</td>
<td>2%</td>
</tr>
<tr>
<td>MZS-like</td>
<td>S-AZA</td>
<td>Repurposing</td>
<td>Chromatin modifier mutations</td>
<td>8/8 (NGS)</td>
<td>9%</td>
</tr>
<tr>
<td>EML4 ALK Fusion</td>
<td>Crizotinib</td>
<td>Repurposing</td>
<td>Translocation: EML4 ALK Fusion</td>
<td>3/48 (NGS)</td>
<td>0%</td>
</tr>
</tbody>
</table>
P5.08

THE PRIME NETWORK: FORWARDING BIOMARKER DISCOVERIES FOR PROSTATE CANCER INTO THE CLINICAL SETTING

Q. Nguyen^1, S. Ackland^2, R. Balleine^3, A. Biankin^1, D. Catchpoole^4, L. Chantrill^1, S. Clarke^5, S. Crossing^6, A. Defazio^7, H. Gurney^2, M. Links^8, G. Mann^8, P. Moscato^2, M. Murray^9, C. Nath^4, D. Richardson^8, M. Robotin^10, R. Scott^2, L. Horvath^11

^1The Garvan Institute of Medical Research/The Kinghorn Cancer Centre, Darlinghurst, NSW, Australia
^2Hunter Medical Research Institute, Newcastle, NSW, Australia
^3Westmead Hospital, Westmead, NSW, Australia
^4The Children’s Hospital at Westmead, Westmead nsw, Australia
^5Royal North Shore Hospital, St Leonards, NSW, Australia
^6Cancer Voices NSW, Sydney, NSW, Australia
^7St George Hospital, St George, NSW, Australia
^8Westmead Millennium Institute, Westmead, NSW, Australia
^9University of Sydney, Sydney, NSW, Australia
^10Cancer Council NSW, Sydney, NSW, Australia
^11Royal Prince Alfred Hospital, Camperdown, NSW, Australia

Introduction: The PRIMe (Pharmacogenomic Research for Individualised Medicine) network was established to accelerate the conduct of pharmacogenomic research and to assist in implementing findings into the clinical setting. In this example of PRIMe’s progress, an existing single site study investigating Glutathione-S-transferase Pi (GSTPi) as a potential biomarker for response to chemotherapy for castrate resistant prostate cancer was validated in half the time that would otherwise be required, by adopting of the study into the network.

Aim: To establish a dedicated clinical trials network to accelerate the conduct of cancer related pharmacogenomic research.

Method: A grant from the Cancer Council NSW and support from Cancer Voices NSW enabled PRIMe to open five clinical sites that has allowed cancer patients to be recruited into various investigator driven pharmacogenomic studies. The GSTPi study is one of such studies adopted by PRIMe. The GSTPi study required an independent validation cohort to confirm that GSTPi was a suitable predictor for response to chemotherapy. GSTPi is an enzyme that is known to be highly expressed in various cancer types including prostate. Response to chemotherapy can be predicted by determining the extent of GSTPi expression prior to and following the first round of chemotherapy. Under PRIMe, the study grew from a single site study to a multicentre study, enabling it to recruit more patients within a shorter timeframe.

Results: The validation cohort required a population of 50 patients. Prior to PRIMe (May 2010), five patients were eligible to be included. Following PRIMe, an additional 23 patients were recruited from the original study site and 28 patients from the other PRIMe sites. Overall, 56 patients were included on the cohort within 29 months (Recruitment rate: 0.8 patient/month vs 1.0 patient/month, respectively).

Conclusion: The GSTPi study was able to validate GSTPi as a predictor of response to chemotherapy and the results are being prepared for publication. PRIMe was able to increase the recruitment rate and reduce the recruitment time by adopting the study as a multicentre study. PRIMe continues to conduct and seek studies in other cancers and invites expression of interest to join the network.
TREATMENT OF HER2-POSITIVE RECURRENT BREAST CANCER (BC) AFTER ADJUVANT TRASTUZUMAB (ADJT): A GROWING MEDICAL ISSUE HARDLY ADDRESSED IN CLINICAL TRIALS

S. Di Cosimo1, D. Serpico2, L. Porcu3, G. Fanetti2, M. Leonardo2, V. Torri3, F. de Braud2

1Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy
2Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy
3Department of Oncology, Istituto di Ricerche Farmacologiche “Mario Negri”, IRCC, Milan, Italy

Background: About 15% of pts treated with AdjT relapse. These pts were not included in initial trials for HER2-positive recurrent BC. Therefore, we planned a cross-sectional study to address their clinical presentation and therapeutic outcome.

Methods: We reviewed the medical charts of HER2-positive BC pts relapsing on AdjT admitted at the National Cancer Institute-Milan. Fisher’s exact test was used for contingency tables, long-rank for survival distribution; p<0.05 was considered statistically significant. Data were matched with literature.

Results: Forty pts with prior AdjT were identified in the first 2013 quarter. Median age was 47.4 (22.1-76.3) years; 67.5% of pts had stage III; 93% neo-/adj anthracycline±taxane; 55% hormonotherapy. Median time to relapse (TTR) was 23.5 (5.2-108.5) months (mos). Median AdjT cycles were 15 (2-18) and 18 (6-19) in pts relapsing during and after AdjT. Lung, liver and bone metastases occurred in 32.5%, 27.5% and 32.5% of cases. T was the 1st line in 77.5% of pts. After a median follow-up of 21.3 (0.6-98.6) mos, 29 pts (72.5%) progressed. Median time to progression (TTP) was 12.7 (9.0-15.3) mos, response rate (RR) 61%. Pts relapsing during AdjT had a shorter TTP than pts relapsing after AdjT, 9.2 (95%CI:3.9-13.3) vs 15 mos (95%CI:9.1-27.9), p=0.048. T was the 2nd line in 65.5% of pts; RR 51%. We reviewed 8 registrational trials for HER2-positive recurrent BC. Pts with prior AdjT represented 0.9-11.7% of study-population in just 5 trials. No trials included pts relapsing during AdjT. Compared to pts of the above trials, our pts were more likely to have locally-advanced BC at diagnosis and neo-/adj chemotherapy.

Conclusions: This study supports the use of anti-HER2 beyond progression for pts with prior AdjT. The anti-tumor activity of T was consistent across 1st, 2nd line and with literature. This data should be interpreted with caution, as the cross-sectional design may have favored the inclusion of pts at good prognosis. Notwithstanding the above, we found that pts relapsing during AdjT had a decreased TTP. These pts are excluded from trials whilst deserve immediate attention for individualized therapy. Data collection continues and an update will be provide at the meeting.
Background. Rapid progress in identifying the most effective treatments and understanding in whom treatments work and do not work depends on possibilities to identify moderators of treatment outcome. We defined the blind man’s bluff as a statistical procedure in which a model aims at selecting and identifying patients with unknown moderators of treatment outcome or unknown prognosis factors. We have developed a non-parametric and robust method leading to better results than logistic regression [1,2], called ROP (Regression OPtimized). Moreover ROP allows selecting 2 clusters among the overall sample which have the highest and lowest probabilities, respectively, to be identified with such moderators or prognosis factors. A comparative screening of these patients identified using ROP will maximize the probability to discover interesting moderators of treatment outcome or novel prognosis factors.

Materials and methods. Public data concerning prostate cancer (www.agrocampus-ouest.fr) were used. Prognostic factors for the grade were blinded for performing the analyses using the ROP model. The ROP model was asked to select 2 clusters from the overall sample. Nine internal validation procedures were compared to logistic models [3].

Results. Among the 32 patients identified at risk using ROP, 16 (50%) had a high grade, while there were only 4 (19%) patients with high grade among the 21 patients not identified at risk (p=0.04, exact test Fisher). ROP allowed personalizing regression coefficients for each variable and for each patient. In addition, ROP had the lowest Brier score and the highest Youden Index in validation samples compared to logistic regression.

Conclusions. Other data were analyzed, including clinical trials, and all confirmed the effectiveness of ROP to identify subgroups or interesting clusters, particularly for identifying unknown moderators of treatment outcome. Changes in regression coefficients between each patient allow better understanding how each prognosis factor works for each patient. The results obtained using the ROP model seem very promising to select the patients for whom treatments will be the more efficient, and to help direct the research on unknown prognosis factors or moderators of treatment outcome.

AN INDIVIDUALIZED TREATMENT PROTOCOL FOR SOLID TUMORS: THE EXACT TRIAL
G.P. Prager¹, R.M. Mader¹, F. Wrba¹, A. von Haeseler², S. Thurner¹, R. Hanel¹, C. Zielinski¹
¹Medical University of Vienna, Vienna, Austria
²University of Vienna, Vienna, Austria

Background: Currently introduced novel targeted agents in the treatment of cancer are approved for defined subtypes of cancer rather than for an individually diagnosed druggable target or for an entire signaling pathway. To improve existing therapeutic strategies, there is increasing evidence of benefit by extension of treatment protocols focusing at molecular profile-based treatment decisions. To generate a scientific rationale for an individualized treatment approach, the current protocol was designed.

Aim. We aim to prospectively validate treatment benefit of an individualized treatment concept based on molecular profiling from paraffin-embedded tumor tissue sections obtained by real time biopsy.

Methods: Patients with refractory metastatic cancer without any standard treatment options according to NCCN guidelines and/or local guidelines can be included. Potential therapeutic targets in individual patients’ tumor sections will be evaluated via a fully informative genomic tumor profile that analyses DNA via ultrahigh multiplex PCR. Suggested treatment benefit will be evaluated to reject the null hypothesis, which is defined as follows: ≤ 40 % of this patient population have a progression free survival (PFS) ratio of ≥ 1.0. Thus, the individual patient serves as his own control for outcome parameters. The alternative proportion P1 (PFS ratio > 1.0) is set at least to 55% using a one-sided exact binomial test at a significance level of 0.0250. The null hypothesis, i.e. no benefit by using this strategy, can be rejected, if at least 30 out of 55 patients treated show a PFS ratio > 1.0. A potential correlation between overall response rate, PFS or overall survival will be assessed by RECIST criteria and evaluated as secondary end points.

Conclusions: This prospective translational study evaluates an individualized treatment concept based on prospective biomarkers assessed in a real-time biopsy for patients with treatment-refractory cancer.
P5.12

SHIVA - RANDOMIZED PHASE II TRIAL COMPARING THERAPY BASED ON TUMOR MOLECULAR PROFILING VERSUS CONVENTIONAL THERAPY IN REFRACTORY CANCER PATIENTS

C. Le Tourneau1, E. Mitry1, A. Goncalves3, N. Isambert3, C. Gavoille6, O. Tredan5, J-P. Delord6, M. Camponèse, V. Servois1, O. Mariani1, A. Vincent-Salomon1, D. Gentien1, T. Rio-Frio1, N. Servant1, N. Romejons, I. Bieche, O. Delattre1, X. Paoletti1, M. Kamal1

1Institut Curie, Paris, France
2Institut Paoli-Calmettes, Marseille, France
3Centre Georges-François Leclerc, Dijon, France
4Centre Alexis Vautrin, Nancy, France
5Centre Leon Berard, Lyon, France
6Institut Claudius Regaud, Toulouse, France
7Centre Rene Gauducheau, Nantes, France

Background: Two recent studies suggest that a histology-independent approach consisting in selecting molecularly targeted agents based on the molecular profile of patients' tumors improves patients' outcome [1,2].

Patients and Methods: The SHIVA trial is a multicentric randomized proof-of-concept phase II trial comparing molecularly targeted therapy based on tumor molecular profiling versus conventional therapy in patients with any type of refractory cancer. The primary endpoint is PFS. The molecular profile performed on a mandatory biopsy includes the assessment of: 1) hot spots mutations using the AmpliSeq cancer panel on Ion Torrent/ PGMLife Technologies; 2) gene copy number alterations using Cytoscan HD/Affymetrix; and 3) expression of estrogen, progesterone and androgen receptors by immunohistochemistry on formalin-fixed sample. The algorithm used by a Molecular Biology Board (MBB) to guide treatment in the experimental arm is presented in the Table. A cross-over is proposed at disease progression.

Results: Between 10/2012 and 04/2013, 143 patients have been included in the study. Results of the feasibility part are available for the first 53 patients at the time of the abstract submission. Biopsy was performed in 50 out of 53 patients (94%). Median time between the biopsy and the MBB was 26 days [range: 14-42]. Mutations, gene copy number alterations and IHC profile were obtained in 32 (64%), 34 (68%) and 45 (90%) patients, respectively. A molecular abnormality leading to randomization was present in 21 patients (42%).

Conclusions: The establishment of a comprehensive tumor molecular profile is safe, feasible and compatible with clinical practice.

EXOME SEQUENCING IDENTIFIES A SOMATIC VARIATION IN TEKT4 BEFORE AND AFTER TAXANE-CONTAINING NEOADJUVANT CHEMOTHERAPY IN BREAST CANCER
K.D. Yu¹, Y.Z. Jiang², Z.M. Shao²
¹Cancer Center and Cancer Institute, Fudan University, Shanghai, China
²Cancer Center and Cancer Institute, Shanghai Medical College, Fudan University, Shanghai, China

Purpose. It is of great importance to illustrate the drug-resistance mechanisms of breast cancer and identify resistance pathways that can be exploited for therapeutic selection. The changed gene expression profiles of breast cancer under neoadjuvant chemotherapy have been described. However, the comparison of exomes and genomes of pre- and post-treatment samples remains elusive. We designed the experiment to test the hypothesis that significant mutational evolution of breast cancer might occur during taxane-containing neoadjuvant chemotherapy.

Methods. We performed an exome sequencing to examine the exomes (100-fold coverage) of one paired samples (pre-treatment tumor biopsies and post-treatment tumors). We sequenced a basal-like breast tumor genomic DNA obtained before and after neoadjuvant chemotherapy and their matched normal breast tissues. The identified loci were further validated in a larger sample size. We subsequently investigated the biological functions and clinical significance of the somatic variation.

Results. Compared with pre-treatment biopsies, analysis of whole-exome sequence data identified a somatic variation in TEKT4, which codes a constitutive protein of microtubules in cilia, flagella, basal bodies and centrioles. The difference in frequency of that variant (before and after taxane-containing neoadjuvant chemotherapy) is 25% in an independent extension cohort of 84 paired samples of different molecular subtypes. We investigated the relationship between TEKT mutation and adaptive drug resistance of taxane. When treated with paclitaxel, breast cancer cells overexpressing mutant TEKT4 displayed lower cyclin dependent kinase 1-cyclin B1 activity and weaker Mcl-1/Bcl-xL phosphorylation than their counterparts, which promoted cell survival and resulted in paclitaxel resistance. Furthermore, the acquired TEKT4 mutation after neoadjuvant chemotherapy predicted poorer pathologic complete remission rates and worse prognosis of patients, which is further validated in an additional cohort of 253 patients who received taxane-containing adjuvant chemotherapy.

Conclusion. Our data reveal that a significant evolution might occur during chemotherapy and result in acquired chemoresistance. TEKT4 probably contributes to taxane resistance. Further experimental studies and prospective researches are warranted.