Poster Board #1

The Role of the Clinical Trials Translational Lab in the New Era of Clinical Trials

Sharon Halperin[1], Menucha Jurkowicz[1], Sivan Liberman[2], Jonathan Weidenfeld[3], Iris Barshack[3], Aviram Nissan[4], Aliza Ackerstein[1], Talia Golan[1], Raanan Berger[1]

[1]*Oncology Institute, Sheba Medical Center, Israel*
[2]*Radiology department, Sheba Medical Center, Israel*
[3]*Pathology Institute, Sheba Medical Center, Israel*
[4]*Surgical Oncology, Sheba Medical Center, Israel*

Background
Drug development in oncology is shifting from a one size fits all towards a more personalized, biomarker-driven approach. In order to facilitate this important shift, tissue acquisition from research biopsies and biological sampling requirements are crucial for exploring the impact of novel agents and retrospective analysis of biomarkers. In recent years, there has been an increased demand for high quality archival and fresh tumor tissue in oncology clinical trials for patient driven correlative studies. The clinical trial translational lab supports all biological sample requirements and assures strict quality control to streamline the process.

Objectives
to ensure that all biological samples required by the protocols are of the highest quality possible.

Methods
Standard operation procedures have been defined including: -The Translational Lab staff review protocols to assess the feasibility of the specific requirements and are present at trial initiations ensuring that samples are being processed according to the protocol. -The translational lab staff coordinates procedures with dedicated interventional radiologists and surgeons. Lab personnel are present at all trial related procedures in order to inform the radiologists/surgeons of the specific requirements for each trial, obtain high quantity and quality samples requirements. -The translational lab is also responsible for archival tissue. Dedicated pathologists assess all newly obtained biopsies. The pathologists determine the tumor cell percentage and count the number of malignant cells in an expeditious time frame. -The lab handles all other biological samples including blood, urine, fecal and buccal samples. The lab is capable of performing all necessary processing methods including PBMCs separation, DNA/RNA extraction and can support pre-clinical models such as in-vivo work.

Conclusion In the new era of oncology clinical trials, our translational lab offers an important platform to support all clinical trials and their requirements including pre-clinical models, investigator initiated trials, retrospective analysis of samples and correlative studies.

Poster Board #2

The Application of Data Analytics to Clinical Trial Research in the Precision Medicine Era

Jack London

Sidney Kimmel Cancer Center, Thomas Jefferson University, USA

Background

Unsystematic design and deployment of clinical trials results in many studies needing time-consuming and costly amendments, and possibly failing to satisfy accrual requirements. Evidence exists that a data-driven approach to designing and deploying clinical trials can lead to more efficient and productive trials. With this approach, real-world patient clinical data are analyzed to assess potential cohort sizes. With targeted therapy studies often including eligibility criteria (e.g., genomic characteristics) that result in small cohorts, analysis of data from multiple healthcare organizations (HCOs) is necessary to design and deploy productive multi-site trials.

Objective

Apply data-driven procedures to clinical trial design and deployment.

Methods

A data analytical approach to clinical research has been implemented at Thomas Jefferson University's Sidney Kimmel Cancer Center (SKCC) in Philadelphia (USA). This includes a research data warehouse of patient data, and our participation in the TriNetX Global Health Research Network. The TriNetX platform allows for data visualization and analysis for study hypothesis generation, or cohort size assessment for proposed trials, and data sharing and collaboration with other TriNetX members. The network has 60 healthcare organization members from 10 countries (including Germany, Israel, Italy, UK, US, Singapore), along with 16 global industry (pharma/CRO) members. Data includes patient demographics, diagnoses, procedures, medications, labs, and importantly for precision medicine, genomic test results. Data sources include electronic medical record systems and cancer registries (necessary for oncology trials), and data extracted from text reports. All shared data are compliant with data privacy regulations.

Results

SKCC researchers have access to data on 2.9 million Jefferson patients having 130 million clinical observations (including genomic test results on 396 genes having 10,862 mutations), as well as collaborations with other TriNetX members.

Conclusion

The design and deployment of precision medicine targeted trials can be more efficient and productive by the application of a data analytical approach.

Poster Board #3

Analysis of Frequently Mutated Genes in Advanced Colorectal Cancer

Francesca De Nicola[1], Frauke Goeman[1], Matteo Pallocca[1], Francesca Sperati[1], Laura Pizzuti[1], Elisa Melucci[1], Beatrice Casini[1], Carla Azzurra Amoreo[1], Enzo Gallo[1], Maria Grazia Diodoro[1], Simonetta Buglioni[1], Marco Mazzotta[2], Patrizia Vici[1], Domenico Sergi[1], Luigi Di Lauro[1], Maddalena Barba[1], Edoardo Pescarmona[1], **Gennaro Ciliberto**[1], Ruggero De Maria[3], Maurizio Fanciulli[1], Marcello Maugeri-Saccà[1]

[1]*Medical Oncology/Pathology, Regina Elena National Cancer Institute, Italy*
[2]*Medical Oncology Unit, Policlinico Sant'Andrea, Italy*
[3]*Institute of General Pathology, Catholic University of the Sacred Heart, Italy*

Background: Genomic technologies are reshaping the molecular landscape of colorectal cancer (CRC), revealing that oncogenic driver mutations coexist with still underappreciated genetic events.

Objective: We hypothesized that mutational analysis of CRC-linked genes may provide novel information on the connection between genetically-deregulated pathways and clinical outcomes. Patients and methods: We performed next-generation sequencing (NGS) analysis of 16 recurrently mutated genes in CRC exploiting tissue specimens from 98 advanced CRC patients (pts) who received first-line chemotherapy between September 2000 and September 2016. We focused on 16 genes altering the following pathways: WNT (AMER1, APC, CTNNB1, FBXW7, SOX9, TCF7L2), TGF-β (ACVR1B, SMAD2, SMAD4), PI3K (PIK3CA and PTEN), RAS/MAPK (BRAF, MAP3K21, KRAS, NRAS) and cell-cycle/apoptosis (TP53).

Results: Median age at diagnosis was 61.6 years. The ECOG Performance Status was 0 in 47 pts (48%). Fifty-five pts (56.1%) had left CRC, and 52 pts (53.1%) had only one metastatic site. In the first-line setting, 20 pts (20.4%) received chemotherapy plus cetuximab, 19 pts (19.4%) received chemotherapy plus bevacizumab, and 59 pts (60.2%) were treated with chemotherapy alone. In the present cohort, 29 pts (29.6%) underwent surgery for metastatic disease. NGS analysis showed a mutation frequencies comparable to those reported by independent investigators: ACVR1B 1%, AMER1 7%, APC 53%, BRAF 6%, CTNNB1 5%, FBXW7 21%, KRAS 58%, MAP3K21 17%, NRAS 8%, PIK3CA 33%, PTEN 20%, SMAD2 8%, SMAD4 12%, SOX9 11%, TCF7L2 8%, and TP53 65%.

Conclusions: Our results are consistent with those reported in other datasets by independent research groups. Further analyses in an expanded case series are ongoing to identify genomic predictors of survival outcomes.

Keywords: Next-generation sequencing, advanced colorectal cancer, frequently mutated genes.

Poster Board #4

Efficacy and Effectiveness of Checkpoint Inhibitors in Randomized Clinical Trials (RCTs) and in Real World Evidence (RWE): The case of Ipilimumab (IPI)

Diana Giannarelli[1], Michele Milella[1], Sabrina Vari[2], Stefano Molica[3], Emilio Bria[4]

[1]*Biostatistics and Medical Oncology 1, Regina Elena National Cancer Institute, Italy*
[2]*Barts Cancer Institute, St. Bartholomew's Hospital, UK*
[3]*Department of Hematology-Oncology, Azienda Ospedaliera Pugliese-Ciaccio, Italy*
[4]*Medical Oncology, Azienda Ospedaliera Universitaria Integrata, University of Verona, Italy*

Background: The effectiveness of licensed drugs in RWE (observational, generally prospective studies, mainly Expanded Access Programs, EAPs) is expected to be lower than in RCTs, since entry criteria significantly differ in the different settings. Moreover, the overall safety profile will likely be different, considering that RWE include larger patients' samples with longer follow-up.

Objective: To evaluate differences in efficacy and effectiveness between registration RCTs and RWE. Methods: A systematic review including registration RCTs and RWE (EAPs, other), evaluating Overall Survival, Progression-Free Survival (OS, PFS), and Immune-Related Adverse Events (IRAEs) of IPI in advanced melanoma was accomplished.

Results: Median OS and PFS for IPI were 10.1 months and 2.9 months, respectively, in the registration trial (MDX010-20); IRAEs rate of any grade and grade 3-4 were reported in 61% and in 15% of patients. With regard to RWE, 25 articles/abstracts were retrieved, including >4000 patients who received IPI. Median OS ranged between 5.2 and 11.7 months, with a median of 7.5 months; median PFS was very homogeneous: 3 months (range 2.6 to 4.1 months). The median rate of patients treated with 4 IPI cycles was 63% (59%-73%). The toxicity profile was the most variable outcome: IRAE rates of any grade and grade 3-4 s were in the range of 17%-100% and 6%-55%, respectively.

Conclusions: These data indicate that the performance of IPI in different clinical contexts (RCTs vs. RWE) may differ according to the different patients' entry criteria. While patients included in RCTs are constantly monitored for safety, patients in RWE (more closely resembling the daily clinical practice) are less intensively monitored. On the other hand, less experienced centers (which are usually included in EAP programs) might face unexpected toxicities, thus overestimating IRAEs. On the other hand, rare side effects might be missed in RCTs and become evident in larger patient populations.
Keywords: Randomized clinical trials, Real world evidence, Ipilimumab, Advanced melanoma, Efficacy, Toxicity.

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Poster Board #5

ATM loss of protein as a biomarker for DNA damage repair deficiency in pancreatic ductal adenocarcinoma

Sharon Halperin[1], Michael Schvimer[2], Chani Stossel[1], Maria Raitses Gurevich[1], Dikla Atias[1], Yulia Glick[1], Roni Borshtein[1], Raanan Berger[1], Talia Golan[1]

[1]*Oncology Institute, Sheba Medical Center, Israel*
[2]*Pathology Institute, Sheba Medical Center, Israel*

Background
Approximately 15% of PDAC tumors display DNA damage repair (DDR) deficiency. Germline BRCA (gBRCA) mutation serves as a robust biomarker for the DDR deficiency. A subset of patients displays a similar clinical phenotype but lack the gBRCA mutation. Identification of these BRCA-like subset of patients remains a challenge and an alternative approach may include DDR functional assays. Here we suggest loss of the ATM protein as one of the biomarkers for the identification of the DDR deficiency signature in PDAC.

Methods
Patients were identified from the Sheba pancreatic cancer database based on strong family/personal history of BRCA- associated cancers or a durable response to platinum containing regimens or harboring germline/somatic mutations in the DNA-repair pathway (excluding gBRCA mutation). Archival FFPE blocks of primary tumors/metastatic lesions were used to explore ATM protein expression by IHC. Nuclear staining was regarded as positive. Tumor infiltrating lymphocytes served as an internal positive control. ATM loss was defined as less than10% neoplastic nuclear staining at any intensity in the presence of positive lymphocytes staining.

Results
We identified 53 patients with DDR deficiency phenotype between from our database. 47% were diagnosed at stage I/II and 53% stage IV. In the subgroup of patients with DDR deficiency phenotype, 55% displayed a family history of BRCA-associated cancers, 19% had a personal history of malignancy and 23% had known mutation in DNA-repair pathway. 23/53 identified subjects have been analyzed to date. We identified 52% loss of ATM in the analyzed group.

Conclusion
Loss of ATM in an unselected PDAC population is 12%. Our data demonstrate that 52% of the highly selected subgroup of PDAC patients was found to have loss of ATM protein expression, suggesting it to be one of the biomarker for DDR signature. Identification of these patients, based on ATM protein expression profile may lead to personalized treatment options.

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Poster Board #6

Genetic Background Modulates Angiogenic Potential in Preclinical Models of Colorectal Cancer (CRC)

Fabiana Conciatori[1,2], Chiara Bazzichetto[1,2], Italia Falcone[1], Isabella Sperduti[1], Francesco Cognetti[1], **Michele Milella**[1], Ludovica Ciuffreda[1]

[1]*Medical Oncology 1, Regina Elena National Cancer Institute, Italy*
[2]*Oncology, University of Rome La Sapienza, Italy*

Background: Genetic aberrations, such as BRAFV600E and PTEN-loss, portend rapid tumor progression, treatment resistance, and overall impaired survival; on the other hand, tumor-stroma interactions are also a crucial determinants of tumor progression.

Objective: Here we hypothesize that tumor genetic background may influence the surrounding microenvironment, through the production of chemokines and pro-angiogenic factors in CRC models. Methods: Production of Interleukin (IL)-6, IL-8, and vascular endothelial growth factor (VEGF) was determined by ELISA under standardized culture conditions in a panel of 29 CRC cell lines with different genetic backgrounds (KRAS, BRAF, PI3K, and PTEN). Modulation of cytokine production after exposure to selective inhibitors of the BRAF/MEK/ERK and PI3K/AKT/mTOR pathways was assessed.

Results: BRAFV600E, and to a lesser extent PTEN loss, were significantly associated with the production of higher levels of IL-8 ($p=0.004$; $p=0.05$), whereas the other genetic alterations tested (RAS, PI3K) had no effect on IL-8 production. CRC cell lines BRAFV600E and PTEN-loss expressed the highest levels of IL-8 and a ROC curve-based prediction algorithm based on these two mutations had 68 % accuracy in predicting IL-8 production ($p=0.002$). On the other hand, IL-6 was almost never detected and VEGF levels correlated with KRAS mutational status. IL-8 is tightly controlled by activation of the MEK/ERK pathway, as MEK and ERK inhibitors profoundly suppressed its production regardless of the genetic background; the selective BRAF inhibitor downregulated IL-8 only in BRAFV600E contexts, but upregulated its production in parallel with ERK phosphorylation in BRAF-wt CRC cells. The PI3K/mTOR inhibitor had no effect on IL-8 production.

Conclusions: In CRC models BRAF mutations and PTEN-loss result in high levels of IL-8 production; differential modulation of IL-8 after pharmacological treatments highlights the need to correlate molecularly defined subclasses of CRC with a specific chemokine/immunologic profile(s), as they could differentially benefit from specific signaling inhibitors.

Poster Board #7

Dissecting Response to Targeted Agents in Preclinical Model of Colorectal Cancer (CRC): Role of the Microenvironment

Chiara Bazzichetto[1,2], Fabiana Conciatori[1,2], Italia Falcone[1], Francesco Cognetti[1], Ludovica Ciuffreda[1], **Michele Milella**[1]

[1]*Medical Oncology 1, Regina Elena National Cancer Institute, Italy*
[2]*Oncology, University of Rome La Sapienza, Italy*

Background: Identification of molecular mechanisms of action and putative biomarkers is crucial to the successful development of new therapeutic strategies, but clinical development of combinations of targeted agents is often hampered failure to prospectively identify patients at the highest chance of benefit; this is due, at least in part, to the fact that preclinical experiments often do not reflect the in vivo situation, since tissue and cellular architecture is lost in the in vitro experiment.

Objective: Our group has recently demonstrated the synergistic nature of combined MAPK/PI3K inhibition selectively in PTEN-loss, but not in PTEN-competent tumor cells; the aim of this study is to set-up multicellular culture models to uncover the molecular mechanisms by which stromal/endothelial cells modulate the response to signaling inhibitors and to identify potential therapeutic targets. Methods: We monitored the effects of MEK and PI3K/mTOR inhibitors on isogenic CRC cell lines differing for PTEN status (HCT116 and HCT116 PTEN-/-), in the presence or absence of stromal fibroblasts or fibroblast/endothelial cell conditioned medium (CM); moreover, we evaluated pathway activation and analysed the cytokine/chemokine profile.

Results: The response to MEKi seems to be mostly dependent on the genetic background of tumour cells, while the response to PI3K/mTOR double inhibitor is mainly influenced by microenvironmental interactions, in opposite ways depending on PTEN status. Combination treatment is synergistic in PTEN-competent tumor cell lines under direct co-culture conditions. CM from different types of stromal cells similarly affected the response of CRC cell lines to signalling inhibitors, possibly due to similar profiles of cytokine/chemokine production in stromal cell.

Conclusions: Stromal cells differentially affected response of CRC to agents targeting the MAPK and PI3K pathways; such effects varied depending on the genetic background of the tumor cell (PTEN-competent/ PTEN-loss) and on the modality of tumor stroma interaction (direct cell contact or soluble factors).

Keywords: PTEN; microenvironment; co-culture; cytokine/chemokine.

Poster Board #8

Inflammatory Parameters Modulated by 6 Weeks of Physical Training in Gastrointestinal Cancer

Ana Flávia Pessoa[1], Simone Stone[2], Katrin Radloff[1], Raquel Galvão[1], Joyce de Cassia Rosa[3], Ariene Murari[3], Paula Leme[1], Emídio Matos-Neto[4], Luis Henrique Andrade[1], Rodolfo Marinho[1], Fernanda Formiga[5], Fang Chia Bin[5], Flávio Tokeshi[3], Ana Paula Lepique[2], Alessandro Laviano[6], Maurizio Muscaritoli[6], José Pinhata Otoch[3], Paulo Sérgio Alcantara[3], Marília Seelaender[1,3]

[1]*Cell and Developmental Biology Department, Institute of Biomedical Sciences University of São Paulo - ICB/USP, Brazil*
[2]*Immunology Department, Institute of Biomedical Sciences University of São Paulo - ICB/USP, Brazil*
[3]*Department of Surgery, FMUSP - Medicine College of the University of São Paulo, Brazil*
[4]*Departament of Physical Education, Federal University of Piaui, Brazil*
[5]*Department of Surgery of Irmandade, Irmandade da Santa Casa de Misericórdia de São Paulo, Brazil*
[6]*Department of Clinical Medicine, Sapienza University of Rome, Italy*

Background: There is consensus that physical exercise can be employed as an adjuvant therapy in several diseases or even reduce the risk of cancer by stimulation of the immune system; yet the underlying mechanisms are not completely elucidated. We hypothesize that a individually designed program of physical physical exercise may induce anti-inflammatory profile in circulating immune cells such as MDSCs (Myeloid Derived Suppressor Cells) in patients with gastrointestinal cancer and systemic inflammation. **Aim:** to evaluate the effect of physical training on blood MDSCs and serum chemokines in gastrointestinal cancer patients. **Methods:** This study was approved as clinical trial U1111-1140-7773 by the ethics committees of the Biomedical Sciences Institute (CEP 788/07) and the University Hospital (CEP 752/07, SISNEP CAAE: 0031.0.198.019.07). The treadmill training protocol was performed before surgery for tumor excision, for 6 weeks. Intensity samples were collected at three times points, 1st (baseline), 3rd and 6th week of training to evaluate the protein expression of TNF- α; CCL2, CCL-3 and CXCL-10 by Multiplex Magpix®. MDSC inter and high subpopulations were classified using flow cytometry and a gating strategy concerning the intensity of CD11b+ labeling. **Results:** MDSC subpopulations inter (30%) and high (43%) in the 1st week changed after 6 weeks of training as observed in increased MDSC-inter (68%) and decreased MDSC-high (21%) populations. At baseline, pro-inflammatory TNF-α as well as antitumoral CXCL10 were negatively correlated with the MDSC-inter fraction while this correlation was not observed in weeks 3 and 6. The serum concentration of chemoattractants CCL2 and CCL3 was higher in the 1st week when compared with weeks 3 and 6, while CXCL10 content was higher after the training period. **Conclusion:** Our results demonstrated that the 6-week training protocol was able to change the systemic inflammatory parameters that contribute to worsen prognosis in gastrointestinal cancer. Patients presented overall reduction in systemic inflammation (PCR) and cessation of cancer-associated weight loss.

Poster Board #9

Influence of Anemia on Cognitive Functions in Cancer Patients

Duska Petranovic

Hematology, Clinical Hospital Center Rijeka, Croatia

Background: There is growing evidence of cognitive impairment in cancer pts and anemia could be one of the possible factor that thave an impact.

Objectives: Aim of the study was to examine the influence of anemia and malignant disease on cognition 1. Is there correlation of anemia and/or cancer with cognitive functions? 2. Is it possible to improve cognition by correcting anemia?

Patients and Methods: Four hundred adult pts controled in Clinical Hospital center Rijeka, Croatia were included in the study and selected in four groups (100 pts in each) according two variables: anemia and therapy naive malignancies: Group 1- pts with cancer and anemia, Group 2- pts with cancer without anemia, Group 3- anemic pts without cancer and Group 4- healthy controls. Third independent variable was cognition measured two times: T1- basal and T2 - after one month. Anemic pts received therapy for anemia in that period. Cognition was assessed by the Complex Reactiometer Drenovac (CRD) in 7 domaines: convergent inductive thinking, spatial visualisation, visual orientation, maze learning/memory, complex psychomotoric reaction and simple reaction to sound and light.

Results: Hemoglobin level was in positive correlation with all cognitive abilities. Cognition Group 1 were the worst among all groups, improved significantly ($p<0,0001$) after correction of anemia but never achieved results of other groups. When statistically partialized, anemia showed more impact on cognition than age, gender and education (beta-0,458,$p<0,000$). Two sided variance analysis showed that anemia and cancer had additive negative effect on cognition.

Conclusion: Anemia is significantly correlated with cognitive disfunctions. Correction of anemia could enhance cognition and thus inprove QoL esspecially in cancer pts.

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Poster Board #10

A Phase Ib Study of Durvalumab (MEDI4736) in Combination with Savolitinib in Patients with Metastatic Renal Cell Carcinoma

S Vari[1], B Szabados[1], A GomezdeLiano[1], K Mousa[2], L Rammazzo[2], A Prendergast[2], T Powles[1]

[1]*Barts Health NHS Trust, Barts Cancer Institute, Queen Mary University of London, UK*
[2]*Central Coordination Centre for Experimental Cancer Medicine, Barts Cancer Institute, Queen Mary University of London, UK*

Background: Anti-PD-L1 and CTLA-4 antibodies are associated with clinical benefit in mRCC. MET dysregulation plays an important role in papillary RCC pathogenesis and is a mechanism of resistance against TKIs in ccRCC. Pre-clinical data suggests benefit in dual MET plus PD-L1 inhibition. The phase Ib part of this trial was designed to determine the RP2D of savolitinib (c-Met kinase inhibitor) and durvalumab (PD-L1 mAb) when given in combination (NCT028195996).

Methods: International, investigator led phase Ib/IIa study with a dose de-escalation (3+3) part in patients with metastatic renal cell cancer (irrespective of PD-L1 and MET alteration status). Dose level 0 (600mg OD savolitinib and 1500mg Q4wk durvalumab) and -1A (400mg OD savolitinib and 1500mg Q4wk durvalumab) were investigated. Patients received a 28 day cycle of savolitinib before commencing durvalumab treatment on day 1 of cycle 2. Treatment given until PD (RECIST v1.1) or intolerable toxicity. Primary endpoint was DLTs over a 2 month period. Secondary endpoints included PK and safety (CTCAE v4.03).

Results: 6 evaluable patients enrolled at dose level 0 with no reported DLTs. Median age 46 years (25-59), median ECOG 1. ccRCC (n=4), papillary cell (n=2). All 6 patients had Intermediate Heng risk score. 3 ccRCC patients had 3 previous lines of therapy and 1 ccRCC received 1 prior therapy. 1 papillary cell patient entered with no prior lines of therapy and 1 received 4 prior lines. Worst reported toxicity related to IMP was fatigue G2-3 (n=2). Other toxicities: G1-2 pain (n=3), G2 Caugh (n=1), G2 diarrhoea (n=1), G1 gastritis (n=1), G1 nausea (n=2), G2 Peripheral edema (n=2), Rash G2 (n=1), G1 transaminitis (n=1), PPE G2 (n=1). Two AESIs were reported, gastritis G1 and G3 numbness. At 12 weeks best response by RECIST v1.1 was SD (n=4).

Conclusions: Based on DLTs and cumulative toxicity, dose level 0 was selected as the RP2D for the expansion phase. Dose level -1A was not investigated. Adverse events were in keeping with established single agent safety profiles. The expansion phase is open to recruitment in the UK and Spain and is investigating two cohort populations. mccRCC or sarcomatoid RCC patients (n=156) randomised (1:1:1:1) to savolitinib alone, durvalumab alone, savolitinib plus durvalumab or tremelimumab and durvalumab followed by durvalumab alone. Metastatic papillary patients (n=39) receive durvalumab plus savolitinib. A biomarker enrichment phase in tumours positive for MET or PD-L1 alterations may be investigated.

Poster Board #11

Capturing dynamic lymphocyte infiltration induced by immunotherapy, using a personalized *ex-vivo* human tumor platform, CANscript™

Munisha Smalley[1], Basavaraja U Shanthappa[1], Hans Gertje[1], Mark Lawson[1], Baraneedharan Ulaganathan[1], Allen Thayakumar[1], Laura Maciejko[1], D.C. Doval[2], Anurag Mehta[2], Raanan Berger[3], Padhma Radhakrishnan[1], Pradip Majumder[1], Aaron Goldman[1]

[1]Integrative Immuno-Oncology Center, Mitra Biotech, Woburn, MA 01801, USA
[2]Rajiv Gandhi Cancer Institute, New Delhi, India
[3]Sackler Medical School, Tel Aviv University, Sheba, Israel

Background: The presence and activity of lymphocytes within the tumor is critical for clinical response to cancer immunotherapy, such as immune checkpoint blockade. Tumors with poor T-cell inflamed phenotypes, often referred to as a 'cold' tumor, is associated with modest clinical response. High baseline infiltration of effector T-cell lymphocytes is considered 'hot', and patients are predicted to respond more favorably to treatment. However, patient-to-patient response and durability remains highly variable. There is an urgent gap in available methods to study lymphocyte infiltration, trafficking and spatial heterogeneity induced by different cancer immunotherapies in individual patients. Moreover, there is a poor correlation between therapy-induced lymphocyte infiltration with clinical response, which could be shaped using personalized approaches to therapy.

Methods: Here, we used CANscript™, an *ex-vivo* human tumor model that recapitulates and preserves the native, patient-autologous tumor microenvironment, including autologous patient-derived peripheral blood mononucleated cells (PBMC). Utilizing tissue from breast cancer patients classified as either 'cold' (N=5) or 'hot' (N=5), we studied lymphocyte infiltration under pressure of a-PD-1 immune checkpoint blockade (pembrolizumab) over a 72h time course. Using fluorescent labelling and flow cytometric analysis we characterized infiltrating lymphocytes, studying the role of T-cell repertoires under different environmental and immunotherapy pressures. We coupled these analyses with multiplex immunohistochemistry (CD3+, CD4+, CD8+) to map spatial heterogeneity of tumor cells and lymphocytes before and after treatment, *ex vivo*.

Results: We determined that immune checkpoint blockade induced unique patterns of migration and infiltration of effector T-cells (Teff) and T-regulatory (Treg) cells in 'hot' vs 'cold' tumors. Furthermore, we determined that, in some instances, 'cold' tumors can be driven towards a 'hot' phenotype characterized by trafficking of active immune lymphocytes following treatment, which corresponded to differential ratio of Teff to Treg compared to baseline.

Concluding remarks: Taken together, these data demonstrate the utility of CANscript™ as a platform to characterize response to immunotherapy in a spatial context, providing insight into the migratory patterns of immune cell subsets at the individual patient level. Such an advance in our preclinical methods to study immuno-modulators may help guide treatment decisions for clinicians while simultaneously functioning as a platform to study and discover mechanisms of clinical efficacy for emerging drug combinations.

Poster Board #12

Assessment of the Pharmacokinetics, Pharmacodynamics and Tolerability of Recombinant (Expressed by Pichia Pastoris) Human Serum Albumin/Human Granulocyte Colony Stimulating Factor Fusion Protein in Healthy Subjects

Jiang Bo

GCP, Qi junyuan, China

Objective: This study was performed to investigate the pharmacokinetics (PK), pharmacodynamics (PD) and tolerability of a novel recombinant (expressed by Pichia pastoris) human serum albumin/human granulocyte-colony stimulating factor fusion protein (GW003) in healthy volunteers. **Methods:** Twenty-six healthy Chinese volunteers randomly received a single subcutaneous (SC) GW003 injection at a dose of 150 (n=4), 300 (n=6), 500 (n=8), 650 (n=8) μg/kg. Safety and tolerability were evaluated by monitoring adverse events, laboratory parameters, electrocardiography (ECG). Blood sample were collected up to 21 days after injection. The absolute neutrophil count (ANC) and CD34+ cell counts were the PD markers. **Results:** After GW003 administration, 4 different pharmacokinetic phases were identified, indicating target-mediated drug disposition (TMDD) for the elimination of GW003, which was slowed down as the dose was increased. **Conclusion:** The study showed a non-linear TMDD of GW003. Compared with the similar drugs, the peak time of pharmacodynamics of GW003 was delayed by peak time of serum drug concentration. GW003 at 150–650 µg/kg was well tolerated in healthy Chinese subjects.

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Poster Board #13

A Comparison Between Different Locations of Censoring: A Simulation Study

Ehsan Rezaei-Darzi[1], Ameneh Ebrahim Valojerdi[2], Seyedeh Maryam Sadati[3], Sahar Pedram[3]

[1]*Non-Communicable Diseases Research Center, Endocrinology and Metabolism Population Sciences Institute, Tehran University of Medical Sciences, Iran*
[2]*Department of Biostatistics, School of Public Health, Iran University of Medical Sciences, Iran*
[3]*Department of Clinical Pharmacy, Faculty of Pharmacy, Tehran University of Medical Sciences, Iran*

Background: In many oncology trials, time to event is an outcome of interest. These events could be death or disease progression, which may not occur during the study for all patients. Some patients will be censored due to Loss-to-follow-up, competing risk and not occurring event until the end of study. In real clinical trials of cancer, censors may be performed because of investigator non-compliance, short time of study or incident of severe adverse event. Furthermore, location of censoring might increase potential bias, which may affect estimates of Hazard Ratio (HR). The aim of this study is comparison of censoring during the study period and at the end of the study.

Objective: Comparing different locations of censoring for estimating HR in these mentioned scenarios.

Method: A simulation method was conducted to sample survival times from a Weibull distribution. A total of 1000 observations were replicated 1000 times to illustrate censoring effects for these two scenarios. Firstly, the researchers assumed that 40% censoring will occur at the end of study. Secondly, 40% censoring during the study was assumed. More specifically, 30% censoring occurred before the last time and 10% in the terminal phase. Bias and coverage are reported as two measurements for assessing treatment effect estimate. The researchers also calculated percentiles 2.5% and 97.5% for comparing HRs.

Results: Bias and coverage values for both strategies were close together with a slight difference in favor of the first view (0.0005, 95.3%) vs. (0.0009, 94.7%). The results indicated that 95% uncertainty for HRs crossed each other with a high percent overlap.

Conclusion: Statistical analyses declared that the location of censoring time (during the study or at the end of the study) is not determinative in HR results.

Poster Board #14

Preclinical Study for Advancement of Intravesical Chemotherapeutic Efficacy in Urothelial Carcinoma of Urinary Bladder: A New Step Taken to Explore Autophagy Potential

Shrawan K Singh[1], Rani Ojha[1], Navjit Gill[2], Smita Pattanaik[2], Ravimohan Mavuduru[1], Nandita Kakkar[3], Amanjit Bal[3]

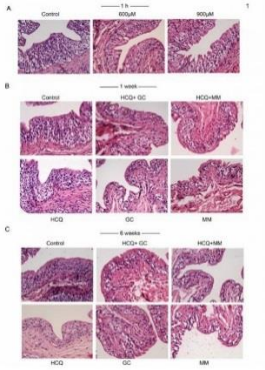
[1]*Urology, PGIMER, Chandigarh, India*
[2]*Pharmacology, PGIMER, Chandigarh, India*
[3]*Histopathology, PGIMER, Chandigarh, India*

Background: Ex-vivo study has shown that Chloroquine**/**Hydroxychloroquine (HCQ) is a potent blocker of autophagy and can enhance tumour cell killing when administered with chemotherapeutic agents. This animal experimental study evaluated the bladder mucosal changes on intravesical administration of HCQ along with chemotherapeutic agents.

Methods: The study was conducted in two phases on normal Wistar female rats (N=66, 6-7 weeks old, weight- 200–300g). The urinary bladder was catheterized using 18g cannula. In phase one a total of 16 rats were treated with two different concentrations of HCQ; 600 µM and 900 µM ; 8 in each group for one hour. The rats were scarified and bladder harvested for histopathology. In second phase, 50 rats were administered with intravesical HCQ (600 µM either alone or in combination with gemcitabine (GC) or mitomycin (MM) once in a week for six weeks. Rats were scarified at one, two, four and 6 weeks and bladder was harvested and for histological examination. Effect of intravescial thrapy on bladder mucosa was studied using H&E staining. For control group, normal female rats were treated with saline. The study was approved by Institute Animal Ethics Committee.

Results: Morphology of Urothelium was not affected with HCQ at both 600 µM and 900µM doses than as compared to saline (control)) **(Fig 1A)**. Rats treated with MM or GC alone showed marked inflammatory response with the passage of time, however, in combination with GC or MM for 1 to 6 weeks , these rat bladders did not show any additional effect infiltration of inflammatory cells **(Fig 1B, C)**.

Conclusions: HCQ with or without gemcitabine or mitomycin was safe and well-tolerated. The finding of present work may be extrapolated for intravesical treatment of superficial bladder cancer in humans.



Poster Board #15

A Randomized Controlled Trial of Ready to Use Therapeutic Food (RUTF) For Moderate/Severe Acute Malnourished Indian Children with Cancer

Sneha Tandon[2], Brijesh Arora[1], Maya Prasad[1], Shripad Banavali[1], Gaurav Narula[1], Meera Gadge[1], Alka Jadhav[3]

[1]*Paediatric oncology, Tata Memorial Centre, India*
[2]*Paediatric haematology/oncology, Great Ormond Street Hospital, UK*
[3]*Paediatrics, Sion Hospital, India*

Background: Children with cancer are at increased risk of malnutrition.Early nutrition intervention helps to maintain weight, lean body mass, improved treatment tolerance and QOL.RUTF, with higher recovery rates in pilot studies has brought a paradigm shift in the management of malnutrition.This pioneer trial evaluated the effectiveness of RUTF in prevention of malignancy related weight loss, improvement of micro/macronutrient status, treatment tolerance and QOL.

Methods: 70 children (5-15 yrs) with hematolymphoid and solid tumors were enrolled post the appetite test. Randomization into 1:1 using a computerized table and stratification by type of malignancy. Nutritional status (weight, height ,BMI ,MUAC ,TSF), biochemial analysis, DEXA scan, HRQOL, treatment tolerance evaluated at baseline, 6 weeks and 3 months into study and 6 months follow-up for anthropometry and treatment tolerance.

Results: Seventy newly diagnosed MAM/SAM children with cancer with median age 9 years (range,5-15), M:F 3:1 were randomized into RUTF (37) :control(33) arms. Median protein and calorie intake as well as weight gain at 6 weeks(2.6kg vs.2 kg) was higher in the RUTF arm compared to controls on standard dietary care. At 6 weeks there was significant reduction of MAM/SAM children ((16 vs. 23, $p<0.05$))with increment of lean mass in the RUTF arm vs. controls. Vitamin B12 and folate deficiency (33%), vitamin D(63%), 56% and 96% had copper and zinc deficiency respectively, which improved in the RUTF arm. Children on RUTF experienced significant reduction in the episodes of febrile neutropenia(18.9% vs. 30.3%, $p=0.06$), protocol delays(2.7% vs 30.3%, $p<0.05$), grade 3 /4 neutropenia (40.54% vs. 66.7% ,$p<0.05$),thrombocytopenia(21.6% vs. 30.3%, $p<0.05$) and anemia(18.9% vs. 36.36%, $p>0.05$) beyond 6 weeks. Mean HRQOL scores were better in the RUTF arm at baseline, 6 weeks and 3 months.

Conclusion: RUTF is cost-effective in improving nutritional status resulting in higher weight and lean body mass which translates into improved treatment tolerance and QOL.