

WIN 2018 SYMPOSIUM - MEETING REPORT

by Dr Lisa Hutchinson, PhD

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INTRODUCTION

WIN is a global organization on personalized cancer medicine and its mission is to transform clinical practice and significantly improve survival and quality of life for patients with cancer. WIN has members from 21 countries and four continents involving 31 academic centres, as well as nine industry entities and three cancer organizations. The 2018 conference celebrated the continuation of Chairman Emeritus John Mendelsohn's legacy. Richard L. Schilsky is the new WIN Chairman and Josep Taberero is the Vice Chairman and Chair of the Scientific Advisory Board. Razelle Kurzrock is Head of the Clinical Trials Committee and Vladimir Lazar is the Founder of WIN and Chief Scientific and Operating Officer. Brian Leyland-Jones is the Director of Fundraising. Amir Onn is Head of Standard Operating Procedures and Repository Committee. Apostolia-Maria Tsimberidou is Head of the WIN Membership Committee, and Catherine Bresson is Director of the Operational Team.

In the first 6 to 7 years, WIN initiated something exciting, but now it has started to reach its goals and produce some promising clinical trial results. Although the start point was focused on understanding cancer using DNA analysis (genomics), RNA is very complex and reveals a lot about the disease (transcriptomics), and so WIN has undertaken transcriptomic assessment within its core scientific outputs. WIN is committed to solving the research problems of today and providing the solutions for tomorrow. In a video presentation, John Mendelsohn commented that while we have made great strides in understanding cancer, we know about 10% of what we need to know. John complimented Richard L. Schilsky as the new Chairman, as he has taken on a scientific managerial role at an important juncture in WIN's history. John Mendelsohn ended with words of wisdom "if something new happens we need to get busy in figuring out why!"

MAKING CANCER HISTORY ALL TOGETHER

In the first session, Dr Stephen Hahn highlighted that to improve outcomes in cancer research, it is important to overcome some of the key challenges. These hurdles include identifying and validating biomarkers that inform on the use of combination therapy, which require a strong rationale, the need to sequence tumours in exquisite detail, and developing strategies to avoid the toxicities associated with treatment. Decision support tools and the mechanisms of capturing sensitivity and resistance information are important data that should be shared.

In the IMPACT study, 3,743 patients had molecular testing and more than one alteration was revealed. Of these, 711 were matched to targeted therapy, but 45% of patients were not matched. The study showed that overall response rates and outcomes were improved for patients who were matched to therapy versus those who were not. Progression-free survival (PFS) and overall survival were double in those who received matched therapy (15%) versus those who did not (7%). Matched therapy was an independent factor that predicted survival for patients treated with PI3K and mTOR therapy. Precision medicine uses targeted therapies, immunotherapy and other strategies to target the specific biological alterations in tumours. It is necessary, however, to understand tumour biology and the immune environment for personalized medicine to achieve its fullest potential.

The Institute for Personalized Cancer Therapy (IPCT) at the MD Anderson have set goals to create a platform for the integration of genetic analysis and clinical data (personalizedcancertherapy.org). WIN celebrates the commitment and collaborative spirit on the vision to share data relating to combination therapy. WIN is a not-for-profit clinical research organization operating in a structured framework through a cooperative agreement. It has expertise in leading clinical investigators from over 30 academic centres, which was a fitting example to open the 2018 conference, which celebrates 10 years since the WIN Consortium was founded.

WIN TRIALS: LESSONS LEARNED AND NEW OPPORTUNITIES

As part of the armamentarium of WIN, we know that assessing genomics is the tip of the iceberg in metaphorical terms of what defines cancer. The recently reported WINTHER trial, which applies the WINTHER algorithm, is a big step in the broader need to assess transcriptomics.

In the WINTHER trial, RNA-expression profiling was introduced for decision making, in addition to DNA sequencing – this trial is momentous as is the first time that prospective decision making has been made on the basis of RNA expression in the history of any cancer clinical trial. An important practical consideration of the WINTHER trial was procurement of both tumour and matched normal tissue biopsy samples. The WINTHER trial demonstrated that dual biopsy is feasible, and that a large number of patients received personalized therapies and derived clinical benefit, despite extensive treatment with prior therapies.

The lessons learned included the need to switch from freshly frozen biopsies to formalin-fixed paraffin embedded (FFPE) samples in the future and integrating both DNA and RNA results within a same algorithm (in the WIN new trial SPRING, an integrative algorithm is being tested – the SIMS (simplified interventional mapping system) algorithm. In this opening session, the SPRING_01 trial was summarised: it will test the switch from assessing monotherapies (assessed in the WINTHER trial) to combination therapies for stage IV non-small-cell lung cancer (NSCLC). The SPRING_01 trial is a proof-of-concept trial that is assessing safety and efficacy of triplet therapy in the first-line setting for patients with advanced or metastatic NSCLC.

BOOSTER TRIAL: NEW BLOOD BIOMARKERS FOR NSCLC

Dr Amir Omn discussed the WIN Consortium BOOSTER (Biomarkers in Oncology for Overall Survival and Therapeutic Efficacy Repository) trial for the identification of blood biomarkers for early detection and monitoring the course of disease. Lung cancer is the most common cancer and number one cancer killer. The number of new cases diagnosed worldwide (1.8 million) is similar to the number who die with the disease globally (1.6 million). This very common disease is very heterogeneous: the incidence of adenocarcinoma and squamous-cell carcinoma differs in different regions. Even the most common type of lung cancer (NSCLC) is genomically very diverse, with survival rates that vary depending on the types of mutational alteration. Squamous cancers have an overall poorer survival compared with adenocarcinoma histology.

To date, imaging studies to detect NSCLC have had limited success. In the National Lung Screening Trial (NLST) programme, which was initiated to detect early-stage lung cancers in high-risk individuals (smokers), there was an overall reduction in lung-cancer related death in the computed tomography (CT)-detected group. In the trial, although 26,000 cases underwent annual thoracic low-dose CT, and 25% of these patients had ‘positive’ findings, 98% of these were not cancer! Therefore, it was determined that 350 CTs were needed to detect one patient with lung cancer. In the implementation lung screening trial of the Veterans Health Administration study, only 60% of patients that qualified for the trial agreed to participate, and in only 60% of cases was a nodule detected. Thus, there is a need for additional technologies. Since CT scans are not that successful in detecting cancer, a blood-based biomarker approach is underway to detect and localize surgically resectable cancers.

Liquid biopsy assessment will be used to diagnose, assess response and follow up, and provide insights on tumour evolution as well as monitoring minimal residual disease. How will BOOSTER make a difference? The cancer community needs an effective global platform to validate biomarker candidates and increase the likelihood of identifying a panel of efficacious markers. Through the BOOSTER trial, WIN will offer a factory for biomarker validation. The objective is to reach over 4,000 fully characterised stage I lung cancer patients across Europe, USA, China, Korea, India, Jordan and Israel in a large repository. It will provide an open platform to any institution or company within or outside WIN, enabling identification and validation of panels of several biomarkers as well as offering a global resource.

TRIPLET THERAPY IN FIRST LINE FOR LUNG CANCER

There is an unmet need in lung cancer because only 14% of patients with stage IIIA survive 5 years and this survival statistic drops to 1% when the cancer has spread to other locations. Sadly, more than 60% of NSCLC cases are detected in the advanced stage. Razelle Kurzrock, lead investigator of the ongoing SPRING trial, discussed the SPRING_01 proof-of-concept study that is exploring the effects and efficacy of triplet therapy in advanced or metastatic NSCLC with the aid of integrated genomics and transcriptomics to match patients to a three-drug combination.

The SPRING_01 (Survival Prolongation by Rationale Innovative Genomics) trial is the first study of a series of trials intended to test triplet drug combinations, which emulates the approach used in the treatment of AIDs and also for some leukaemias where triple therapy has been very successful. Genomics are only part of the tumour story: transcriptomics, proteins and epigenetic factors are equally important in the overall picture of how to tackle cancer. New approaches tested in the SPRING_01 trial were patient assessment using the WIN SIMS (simplified interventional mapping system) integrative algorithm, as well as sampling dual tumour and normal tissue from each patient. The WIN trial developed the SIMS algorithm technology with the overarching goal to match patients to optimal drug combinations. The SPRING trials will be assessing DNA and RNA to deploy triplet drug combinations, especially where the preclinical evidence is robust.

RNA from normal tissue has lots of variability from patient to patient. Thus, it made sense to determine the relative difference between the normal and tumour tissue from each patient. The SIMS algorithm provides a level of activity of 24 druggable intervention points and uses a score of 1 to 10 for activation. Following patient consent, biopsies of the tumour and normal tissue were taken from patients with stage III or IV NSCLC, and next-generation sequencing (NGS) was applied to assess DNA anomalies, as well as RNA differential expression between tumour and normal tissue. Patients eligible for this study included those who did not have a classic *EGFR*, *ALK*, *ROS* mutation or MET exon 14 skipping. For the phase 1, patients who had received a maximum of two previous treatment lines and needed off-label therapies were eligible. For the phase II, only patients without prior therapy in the metastatic setting were eligible – this is unprecedented because most trials assess new therapy combinations in subsequent lines.

Assessment of safety of the combination and activity parameters (including response rate (RR) according to RECIST 1.1 criteria, duration of response, PFS, overall survival), as well as a retrospective assessment of SIMS algorithm's ability to predict clinical outcomes, were end points in the trial. In addition, any safety issues in relation to performing biopsies in normal and tumour tissue and drug combination were assessed. Triple therapy is possible and many other SPRING trials are being planned.

The WIN Consortium has been a 10-year journey to build a global translational research network that has vision, passion, energy, commitment, leadership and also takes risks. WIN has now completed its first proof-of-concept, innovative trial WINTHER and the SPRING_01 triple therapy trial is enrolling patients. WIN is planning other innovative trials, such as BOOSTER and MERCURY (discussed later). The changes in therapy lines that cancer patients are treated with, and the direction of research have culminated in an inflection point in which we can hope to see real progress in transformative trials for patients with early-stage, advanced or metastatic cancer.

WINTHER TRIAL: MATCHED BIOPSIES, THE NEW NORM

The International WINTHER trial uses genomics and transcriptomic analysis in patients with a variety of advanced cancers. The WINTHER trial is the first international trial conducted in France, Spain, Israel, Canada and the USA, in the hope of increasing the number of patients receiving personalized therapy based on analysis of either DNA or RNA from matched normal and tumour tissue. The trial included two arms: the first analysed DNA and patients were matched to therapy on the basis of the actionable genomic alterations. If not, patients were enrolled on another arm, which was transcriptomic-oriented and used the WINTHER algorithm assessment of RNA for matching patients with a suitable therapy.

Crucially, in the transcriptomic arm, tumour and matched normal tissue samples were assessed, as it is difficult to know RNA levels that faithfully reflect the tumour without matched normal tissue as a control. The WINTHER team used matched normal tissue and tumour samples to determine differential gene-expression profiling. This approach enabled control of individual RNA and highlighted the expression variability. For instance, if VEGFA

expression was high in the tumour tissue it was not deemed relevant if its expression was also elevated in normal tissue. The study showed that normal gene and RNA expression varies considerably from patient to patient. Thus, it is important for the non-cancer tissue levels to be elucidated for comparison.

Dr Kurzrock emphasised that to coordinate and share knowledge effectively, weekly meetings were held to review NGS reports from Foundation One to reveal actionable alterations and RNA reports presenting a list of drugs scored according to their estimated efficacy for each individual patient. If no oncogenic match was available, patients were treated with therapies based on their RNA results. Therapeutic decision making was also based on factors such as drug availability, clinical trial availability and the patient's co-morbidities. The final decision for treatment was made by the treating physicians. A blinded post-hoc analysis was also performed using a matched score to judge the quality of therapy matched based on the drug given to patients by the treating physicians.

In total, 303 patients were enrolled, with the most common cancer being from the gastrointestinal tract. 107 patients were treated. The trial results have been summarized in a manuscript that is currently under peer-review and the paper will be available soon. Nevertheless, we can already confirm that the use of dual biopsies was feasible and without any major adverse events, and that more patients were treated in a personalized manner thanks to using RNA information.

TAPUR—BUILDING A GLOBAL DATA-SHARING PLATFORM

Dr Richard L. Schilsky reiterated that many patients with advanced cancer often have no standard treatment options. Genomic profiling can reveal actionable opportunities, but often it is not possible to have access to a suitable drug. If a drug is given off-label, who pays? Also, how can we learn from treating patients who are not in a trial who are treated off-label? This situation promoted the creation of TAPUR (Targeted Agent and Profiling Utilization Registry), which aims to learn from the real-world practice of prescribing targeted drugs to patients with advanced cancer whose tumours harbour a genomic variant known to be a suitable target for a specific targeted agent, and for oncologists to be educated about the implementation of precision medicine in clinical practice.

It was necessary to make this initiate prospective and provision of drugs for free. For instance, it was possible to describe the anti-tumour activity and toxicity of targeted anticancer drugs for B-cell non-Hodgkin lymphoma and multiple myeloma for patients with no standard therapeutic options. Patients had to have adequate organ function and a Karnofsky performance status between 0–2. Results were available from FISH, IHC, PCR, NGS and whole-exome sequencing genomic testing in CLIA certified lab testing located in the New York state. Patients who received matched therapy were assessed for safety and efficacy outcomes. The Data Monitoring Committee reviewed response rates of patients and the data had to align with specific matching rules.

So far, an impressive 68% of cases have been matched. The trial used a Simon two-stage design and unlike most trials, this had a general eligibility format. To date, over 1,350 patients have been registered, with 959 enrolled at 113 centres in 20 USA states. Many patients have been enrolled according to a drug that could be matched to their tumour, such as palbociclib, olaparib, sunitinib, pembrolizumab, temsirolimus, cetuximab and erlotinib. Colorectal cancer is the most common organ site, followed by breast and lung cancer. The trial shows the enormous diversity of human cancers. The TAPUR trial has an expanded and closed cohort.

Challenges of conducting this trial included determining the profiling strategy, ensuring the match rules to designate therapy according to the tumour profile were adhered to, defining cohorts and building a team infrastructure, as well as clinical site training on the protocols and matching rules. In the Netherlands, the Drug re-Utilization Protocol (DRUP) study has been initiated and has so far registered 590 patients, and enrolled 237 patients. In a similar vein, the Canadian Profiling and Targeted Agent Utilization (CAPTUR) trial launched in October 2017 and is recruiting at four sites in Canada October 2017. The benefits of the TAPUR trials are that patients get a drug that is matched to their tumour genomic profile. Physicians can be guided on the interpretation of genomic test results, as well as off-label use. Furthermore, pharmaceutical companies and payers have the benefit of receiving data derived from this approach and can learn from the outcomes. Finally, regulatory bodies have access to important data on the extent of outcomes on real-world data and this can inform prospectively on future big data personalized cancer medicine trials.

NCI PRECISION ONCOLOGY PERSPECTIVE

Dr James Doroshow from the National Cancer Institute (NCI) began by explaining that there is disconnect between the theory of precision medicine and the challenges in practice. For instance, many preclinical models are inadequate for assessing molecular targeted agents, as it is not possible to have a precise measure of target engagement and downstream effectors of therapy response. Although immunotherapy agents have provided great successes in oncology, the predictors of activity to immunotherapy are inexact, and there is insufficient information to standardize data collection and tissue acquisition, which is an unresolved issue for combination therapy. There is not a lot of evidence that combination therapies are synergistic or effective compared with sequential single agent therapy. How can this situation be improved?

The NCI set about establishing the Patient-Derived Models Repository (PDMR), which collects tissues, has produced 3D cultures and 2D and organoid cultures, as well as capturing live tumour imaging from NCI centres. Currently, there are 154 patient-derived tumour models (PDX), and a further 300 will be released over the coming year. Each model has patient limited medical history, representative PDX histology images, whole-exome sequencing and RNA sequencing as well as genetic ancestry assessment. Specimens include samples from patients with primary and metastatic disease, and data can be collected from treatment naïve or heavily pretreated patients with cancer. The repository includes soft-tissue sarcomas and under-represented populations, including 700 cancer-associated fibroblast cell lines. There is also a PDX preclinical trial in support of NCI clinical trials.

Dr Doroshow explained how The Canine Precision Medicine Consortium has initiated early trials to evaluate targeted agents and immunotherapies in spontaneous malignancies in dogs, which should inform on human malignancies. For instance, a phase I trial of a topoisomerase 1 inhibitor is being tested in spontaneous canine lymphoma showing encouraging data in which superior 80% response rates were observed, and this is now being studied in the clinic. The challenges to precision oncology in the clinic are numerous. One such challenge is that there is inadequate preclinical modelling for molecular targeted agents, immuno-oncology agents and combination therapies. The imprecise ability to measure target engagement and downstream effectors of therapeutic response is also an issue. There is insufficient support for standardization of data collection, tissue acquisition, and correlates of sensitivity and resistance.

How can we conduct early clinical trials more effectively in light of these issues? The NCI addressed this by developing an Early Phase Clinical Trials Network comprised of pharmacokinetic core data, a bio-repository data cloud, enhanced specimen collection, clinical lab network, cancer immune monitoring, novel immunopharmacodynamic assays, and PDX resistance and sensitivity network, all of which dovetail to sites conducting phase I and II clinical testing. This initiative has started to gather data on predictors of response and activity for immunotherapies. The NCI have developed novel immunopharmacodynamic assays from interrogating the NCI clinical trials data archive, which has 850,000 specimens on 60,000 patients to establish a national cancer biobank to longitudinally assess biospecimens (blood and tumour samples) from newly diagnosed and recurrent disease patients. The high quality in clinically annotated specimens and pilot study of 150 matched pretreated and some treated and progressive specimens, collectively provide an impressive resource.

This infrastructure enables a model of drug sensitivity and resistance, which revealed a 'long tail' in the alterations from these patients. They have started to define regressive phenotypes and some unusual tumour histologies, and this has informed on novel precision oncology clinical trial designs that also link with NCI-MATCH and other trials. In the future, there is the possibility that over 100,000 cancer patients will have NGS in the next few years based on CMS management decisions. This information will inform treatment and will be shared to help validate advances in molecular tumour characterisation in the clinic, assisted by multiple pathway analysis and rapid improvements in proteomics.

BEYOND STANDARD OF CARE: PRECISION ONCOLOGY NEXT STEPS

Dr Josep Tabernero, the President of the European Society for Medical Oncology (ESMO) described how ESMO has over 18,000 members representing 150 countries. Membership has increased by a staggering 215% since 2009, and it has a reciprocal membership with 50 national oncology societies that include 25 committees with over 500 experts in the faculty. Notable examples include Sustainable Cancer Care that oversees the Cancer Medicines Committee for inexpensive essential cancer medicines.

There is also the Cancer Medicines Working Group and its full committee that oversees accessibility to essential and relatively inexpensive drugs, and how to overcome the drug shortages of these agents. The other area this Group is overseeing is access to expensive innovative cancer medicines, which vary considerably across countries. Furthermore, ESMO provides tailored educational materials for oncologists to ensure an improved framework exists to adapted value-based reimbursement models in different geographic locations in the hope that it will help more patients receive adequate drugs on time.

Existing models in oncology tend to favour expensive agents. However, it is important to safeguard academic clinical cancer research for excellence. Many cancer trials are driven by academic-based researchers, with 65% supported by government funding—CAREFOR (Clinical Academic Cancer Research Forum) as one such example. ESMO works with many organizations, such as IARC, Rare Cancers Group and the Oncology Working Party. The potential approval of drugs based on single arm studies is very important for rare tumours and for precision medicine. ESMO has also been promoting other actions at the level of policy in collaboration with the European Union, the European Commission and the European Medicines Agency.

Non-commercial sponsored trials as well as public policy driven activities are areas that ESMO is not only supporting, but hopes to provide innovative solutions to ensure that policy, academia and industry can learn from one another. Dr Tabernero explained that we have entered a new era of genomic and transcriptomic driven precision oncology. For instance, pembrolizumab is approved for tumours with high microsatellite instability (MSI-high). PD-1 and PD-L1 status, the inflammatory microenvironment, neoantigen load and the mutational tumour burden are all used to stratify patients most likely to respond to PD-1 checkpoint inhibitor therapy. Different trials are based on the molecular profile of the tumour and plasma samples together with companion diagnostics and a clinically annotated database. The type of trial and treatment deployed depends on the levels of actionability. This is highlighted by 2,240 cancer combination immunotherapy trials and the role for classic versus adaptive randomized trial designs. In metastatic colorectal cancer, diagnostic biopsy and biomarker assessment revealed BRAF, KRAS, PI3K and other mutational profiles that indicated the type of drug and how patients can receive treatments beyond the typical standard of care. These examples all point to how the standard of care can be improved or more precisely determined through precision oncology efforts.

EU FRAMEWORK PROGRAMMES FOR RESEARCH AND INNOVATION

Cancer is a global health priority and Dr Cornelius Schmalz reminded us that there are several challenges in the healthcare landscape. Many innovative agents are in the pipeline and the EU framework hopes to lead on personalized medicine to provide better health for all. The digital potential is huge and will help to address health and global challenges. Importantly, 90% of this framework is funded trans-nationally. Horizon Europe has invested €100 billion for research and innovation from 2021 to 2027. This will strengthen EU science and technology to deliver on ultimate priorities and supplement the socioeconomic model and add value. An additional €4.1 billion will be invested and Horizon Europe promotes open science as well as the global challenge of industry competitive and open innovation.

To enhance the impact of research, €3 billion of further funding will be made available, and visible research and innovation missions are being initiated to reinforce openness and extended association partnerships. It represents a contractual arrangement and is co-funded from institutionalized channels based on long-term dimension and high integration. Sustainability of social health-care systems is another area the EU is focusing on. The EU has enabled six areas of intervention: health in life course, non-communicable diseases (NCDs) and rare diseases, environmental and social health determinants, infectious diseases, tools for technology, and digital solutions and healthcare systems.

An earlier and more accurate diagnosis for cancer and other NCDs is needed, as well as prevention and screening. Currently, the EU supports so many projects that this can disperse or fragment funding. Bold, inspirational and wide societal relevance is where new focus will become evident. Ambitious but realistic goals are needed, together with cross-disciplinary research and innovation, and priority will be given to cross-sector areas utilizing bottom-up solutions. For instance, 10.5 million people in Europe are affected by dementia and they are aiming to reduce this by 50% by 2030. ⁷

OPPORTUNITIES OF 21st CENTURY SYSTEMS MEDICINE HEALTHCARE

Dr Leroy Hood explained there are new opportunities in precision cancer. Although the assays to measure genomic bases have increased in dimensionality, they reveal a small part of the issue. Personal dense dynamic data (PD3) represents the future. Dr Hood has participated personally in seven paradigm shifts in biology and medicine. In the 1970s he brought engineering to biology showing it was possible to generate high-throughput data and accumulate big data. In 1998, the human genome sequencing project began, which enabled access to human genomic variability data and how to coordinate this with disease assessment. In the 1990s, the whole genome automated sequencer was devised and the ability to analyse proteins, which spanned cross-disciplinary biology. In 2000, Dr Hood set up the Institute of Systems Biology (ISB), recognizing that a new institution needed to be created to fully harness these innovations. The conceptualization of systems medicine and P4 healthcare occurred from 2000 to 2004. The two thrusts of healthcare — disease and wellness — had not been recognized previously, as 98% of knowledge is on disease with less than 2% on wellness. Billions of quantitative data measurements for wellness were mapped in 2013. In 2017, the 108 Pioneers Wellness study was published, showing dense phenotyping through personalized dynamic data clouds could be generated and used to provide health improvements in individuals who were presymptomatic but transitioning into disease.

In the 108 Pioneers study, personalized data including whole genome sequences, clinical tests, metabolomes, proteomes, and microbiomes at three time points — and daily activity tracking — were generated over a 9-month period to produce a digital database of actionable opportunities. Each month, scientific wellness coaches presented actionable possibilities to each of the 108 pioneers. Overall, there was 72% compliance and longitudinal data was captured. This was successful in improving the health of all individuals who participated. Personalized data clouds have transformed many aspects of biomarker and drug discovery, which prompted Arivale to be created in 2015 to bring wellness to the consumer, which has extended to dense dynamic data capture on 4,000 pioneers.

To date, more than 60 wellness to disease transitions have been identified and more than 20 for cancer. Personalized, dense, dynamic data clouds are able to probe the dark matter of disease at an unparalleled resolution. Statistical correlations and insights for 3,500 correlations have been revealed. The dynamic and statistical correlations are different for each disease state transition. The ISB has identified over 70 multi-omic functional communities (modules) in the correlation network. For example, the cholesterol community is one of 70 communities with 14 correlations. Thymic and vitamin E patterns, for example, correlated positively with cholesterol. Systems Medicine and Big Data is hypothesis-generating and correlates can be connected in a cyclical pattern.

The ISB have started to determine the disease risk based on this multi-omic data for over 127 diseases, and these individuals have been followed to identify the earliest transitions into disease. State transitions reveal metabolites, clinical chemistries and protein expression levels that diverge with age and provide metrics of wellness. The ISB has captured these data for a decade. Any given age of an individual relates to where the individual lies in the biological versus chronological age correlation. Thus, a measure of wellness for each individual can be produced. A 59-year old woman with pancreatic cancer had over 10,000 analytes and the ISB assessed how this correlated in relation to other individuals. One protein was an outlier, the Notch receptor protein, which was correlated to a disease perturbed network that was pre-diagnostic; the ISB team have examined over 1,000 individuals in this manner. It is now possible to build computational systems for truly personalized disease diagnostics, and thereby define wellness states from the cohort, by identifying divergent values for each individual network at each blood draw.

Functional analysis of individual divergences was detected before diagnosis. This information was used to reverse chronic diseases, which Dr Hood emphasized should be at the front end of healthcare systems by assessing well people or individuals undergoing transitions. Biological disease perturbations were detected in the blood 13 weeks before clinical signs. For over 4,000 individuals, a wellness to disease transition map has been constructed, which can optimize wellness. Individualized, $n = 1$ experiments should be the new approach to follow disease, and such an approach would save billions of dollars in the longer term. In the future, it will be possible to predict outcomes for patients, which represents a translational pillar.

Wellness and early transition points for Alzheimer's disease have been mapped and some preclinical data look very promising. ISB are assessing breast cancer survivor wellness.

20th century medicine was based on germ theory, chemistry, physiology, pathology, physics, and understanding disease. Ultimately, a 'find it and fix it' approach. 21st century medicine differs from 20th century medicine as it is interested in wellness and wellness to disease transitions. It is predictive, preventive, personalized and participatory (P4). 21st century medicine encompasses systems medicine, P4 healthcare, scientific wellness, proteomics and genomics, digital self measurements, the microbiome and integrated data analysis – collectively, a systems-based approach to understanding wellness, diseases, and their transitions. There are three contributions of systems biology to systems medicine: first, dense dynamic, personalized data clouds; second, dynamic disease-perturbed biological networks; and third, systems-driven technologies and strategies that have heralded P4 medicine.

The integration of Systems Biology, Digital Health, Big Data and Analytics, as well as Social Wellness will help to demystify disease, improve health, reverse illness, and will reduce healthcare costs. Scientific wellness will also decrease the incidence of cancer. Dense phenotyping will identify the analyte outliers; it is predicted that proteins will be superior to nucleic acid biomarkers to understanding disease. Molecular organ-specific blood proteins are powerful diagnostic reagents for organ disease. It will be possible to screen billions of natural compounds and develop synthetic agents for intervention. Within a few years, integrating healthcare records will help stratify patients. Cancer is not a tumour of the cell *per se* but the individual response to the presence of neoplastic cells. We are approaching a systems-driven technologies and strategies era to enable novel approaches to cancer. The data generation from 21st century medicine is unbiased, and assay costs will soon be 10% of what they are now. Once you get such data it is possible to reduce the dimension of diagnostics!

COMBINATIONS TO OVERCOME DRUG RESISTANCE

Dr Yosef Yarden reminded conference attendees that complex systems use genome duplication. The evolution of biological systems—from simple to complex genomes—shows that chromosome duplication is apparent. Networks are trained to resist common perturbations; they show extreme fragility to uncommon attacks. While networks expand, rich nodes become richer to build robust networks. If the central node is attacked, essentially this is the lethality principle. Targeting a central hub may fail a network (termed hub addiction). Networks are trained to overcome one perturbation at a time. Thus, monotherapy represents an approach where resistance develops even though good specific targeted drugs are available. Resistance is due to secondary mutations (for instance, *EGFR* double mutant cell lines are resistance to further *EGFR* therapy). This does not work in mice owing to feedback regulation via hyper-phosphorylation of the receptor. One possibility is to use combination receptor inhibition. Interestingly, dual therapy did not work, but triple therapy prevented *EGFR* activation, and these results have been mirrored *in vivo*.

Dr Yarden discussed osimertinib and resistance to third-generation tyrosine kinase inhibitors (TKIs). If *HER2* or *MET* is overexpressed in the presence of *KRAS* and *HRAS* aberrations, there is emergence of a third mutation. TKIs can impair cell survival by inducing apoptosis. When three monoclonal antibodies (moAbs) are used, it induces cell senescence but not cell death. By using osimertinib with three other moAbs, relapse was prevented in NSCLC animal models. Anti-*EGFR* upregulates *HER2* and *HER3*, thus inducing compensatory feedback. Is it possible to reduce the complexity of drug combinations? Since combining drugs can translate to stronger adverse events, could using a TKI at a sub-therapeutic dose (5% of the full dose) replace a third moAb? In initial studies this approach seemed to work, and treatment was stopped after 3 weeks and only after 2 months did tumour progression return in animal model studies. Combining two moAbs and osimertinib is effective, but requires further investigation.

A potential advantage of two moAbs and osimertinib is increased apoptosis because it blocks the evasion pathways. Resistance mechanisms occur through *AXL* and *MET* kinases. Second-line treatment with two moAbs and osimertinib showed that all tumours were eliminated in mouse models. The tumours did not return provided continuous treatment was used. Thus, biological networks resist single perturbation, but are fragile when two or more drugs are used. Antibodies and TKIs differ in their mechanism of action and are synergistic. In the future, there will be many approvals of moAb combinations. Combination therapy will tackle drug resistance but will also increase toxicity. Thus, combining moAbs with TKIs holds promise for *EGFR*-positive lung cancer. It is unclear whether blocking the *EGFR* pathway vertically with a TKI and moAb necessitates a double moAb approach.

EARLY CANCERS — ARCHIVE IMPORTANCE

Surgeons who want to do translational science are very focused with regard to what they are studying and have prospective collection systems that allow them complete control over their specimens. If they encounter limitations they often overcome this by collaboration with other surgeons. They need to be willing to share their resources. Without robust databases and matching specimen archives the potential for novel solutions to various research questions will be limited.

Dr Harvey Pass cautioned that we are usually very focused with regard to what we can say. We need to know our limits, which to some extent have been overcome by collaboration. Surgeons should not stop operating and in fact need to recruit more surgeons. Many questions are not answered without robust databases and the need for matched specimens. There are issues with archives and their representation.

Elite archives depict the type of disease progression (local or systemic) and include detailed notes on how occurrence influence patient survival. The IASLC (International Association for the Study of Lung Cancer) staging archive can be sorted by size. The type of resection (wedge or segment) can be recorded along with details of multipanel genes to determine whether the original blood draw can inform on prognosis. Before embarking on any type of prognostic or diagnostic biomarker discovery, the patient cohorts approximate clinical demographics and intermediate endpoints described in the literature. In summary, standard operating procedures must be used consistently, and importantly archives and databases cannot be siloed.

MOVING THE TREATMENT SETTING DIAL EARLIER

To expedite the 10 to 15 year knowledge cycle, Dr Laura Esserman gave an overview of breast cancer and explained that in the past, breast cancer was treated in a 'one size fits all' way. This is true in surgery and radiation as well as prevention, in terms of more not necessarily being better. For example, dose minimizations can decrease toxicity and treatments could be better tailored to patients. This is especially true in surgery, when we consider radical mastectomy and how this has changed to less radical (breast conserving) surgery, and when one considers how less-intensive therapy radiation and systemic therapy can provide equal efficacy. Dr Esserman discussed the timeline of lumpectomy and radiotherapy, the use of taxanes, tamoxifen and more contemporary agents. Despite a tailored dose and sequence, many women suffer overdiagnosis and overtreatment.

Screening always overdiagnoses and this is often not driven by physicians who are risk adverse. Patients want better outcomes. Biology trumps stage! Dr Esserman explained that a rise in ductal carcinoma *in situ* (DCIS) was not correlated with an increase in metastasis. All the changes made in the past 50 years have been without the field realizing that the disease has changed. Cancer is evolving and so must treatment. In the context of this evolution, screening has changed the spectrum and distribution of tumours. Lots of tests are available (such as MammaPrint, Oncotype DX, PAM 50) as well as the genomic grade index. We need to be at the forefront to ensure better outcomes. More is just more, not necessarily better in treatment terms. The rationale that early detection saves lives assumes everyone is at equal risk, when they are not. If this were true, we would expect a drop in mortality, which has not occurred. Essentially there is indolent disease, slowly progressing disease and rapid progression.

We need to rethink screening. Evidence suggests ultra low cancers exist and we have an opportunity to improve our approach to prevention, screening and treatment. We should invest in better biomarkers, and recognize that screening increases the chances of detecting indolent lesion of epithelial origin (IDLE) tumours. Is there a molecular definition of indolent? Using the 70-gene signature of MammaPrint, it was possible to decipher a good and poor signature dichotomy in which the separation of ultra-low risk versus low risk versus high risk patients was possible. We do not want to find DCIS in trials because if this has no consequence, there is no point in finding it. In the 8th edition of the AJCC cancer staging, the clinical data indicate a paradigm shift in which trials support giving less therapy. For example, the benefit of radiotherapy depends on recurrence risk. Personalized screening with a risk prediction model is a way to personalize breast cancer risk. Predictive risk, and early risk settings might determine whether to give chemotherapy first. Lessons from treating chronic myeloid leukaemia show we can now cure most tumours in the accelerated but not in the blast phase of the disease.

Some women at risk of breast cancer are not cured by surgery alone and the order of surgery and systemic therapy has an impact on survival. Pathologic complete response can be used to screen metastatic disease. But, who has indolent, early or late disease? Who can we safely ignore? How can we get patients to complete response as early as possible? Dr Esserman discussed how surgery could be used as a tool to see how therapy is working. For instance, if no T cells are present, response to treatment is unlikely. We should let go of therapies that no longer add value. New effective therapies can replace older toxic treatments. When trials show less is more, we should embrace this.

Precision Medicine is how to personalize. After 50 years of doing trials we understand the basis of breast cancer biology rather than chasing huge therapy advances for all cancers. Is there a more efficient way to learn this? How do we move to the next level? N of 1 is a biological test, but can we learn from dense phenotyping discussed by Dr Hood? Any cancer is susceptible to these multi-dimensional analyses and we can optimize using dense dynamic assessment – in other words, an individual response. For instance, it does not make sense to test the whole population with mammography. We need to integrate biology to all aspects of the screening, diagnostic, prognostic and treatment paradigms. In essence, we are testing the idea of risk screening and personalised screening. Screening can be very helpful if used in the early high-risk setting rather than to screen those with metastatic disease.

CHALLENGE OF COMBINATION THERAPIES IN BIOMARKER-DRIVEN PRECISION ONCOLOGY

Dr Jean-Francois Martini (Pfizer) discussed ALK-positive NSCLC. His discussion focused on lorlatinib, which is a third-generation ALK inhibitor that has clinically meaningful activity against lung tumours and brain metastases in a range of patients with ALK-positive and ROS1-positive advanced NSCLC. A companion diagnostic is also being developed. Lorlatinib has a much greater potency than crizotinib, and a phase I/II study of the drug in 54 patients was promising. By understanding the mutations that occurred in patients whose tumours became resistant to crizotinib and other ALK inhibitors, medicinal chemists were able to design a molecule with the potential to overcome that resistance and inhibit ALK, despite these secondary mutations.

Critically, patients with brain metastases were allowed to enrol in the ongoing trials assessing lorlatinib. Adverse events were hypercholesterolemia and raised triglycerides. ALK kinase domain mutations were detected in previously treated patients with ALK-positive alterations. In total, 21% of patients had one or more ALK kinase domain mutations. There was good concordance between fresh and archived tissue and blood samples. The best overall responses were durable and post-crizotinib PFS rates in patients treated with lorlatinib were encouraging. Interestingly, if patients had been previously treated with chemotherapy, it would not have been possible to observe the results owing to a lack of sampling.

Patients who had an ALK and EGFR mutations did twice as well as those without these mutations. Thus, it was possible to stratify responses according to the mutational profile, and such mutations could serve as useful biomarkers of response to lorlatinib. In patients with brain metastases and prior crizotinib therapy, response rates were good. Avelumab, an anti-PD-1 monoclonal antibody, was also combined with lorlatinib, but this result was somewhat disappointing. In total, 52% of patients had 30% tumour shrinkage and the response was quick. In heavily pretreated patients, avelumab and lorlatinib provided a 46% overall response rate, which was similar to lorlatinib alone. Ongoing studies are underway to test various lorlatinib combinations in the preclinical setting and phase I trials.

MYPATHWAY: NOVEL MULTIPLE BASKET PRECISION ONCOLOGY TRIAL

Dr Mary Beattie started her presentation with key questions about trial design, such as why should we study approved drugs in non-approved tumours? What are efficient and effective ways to perform such studies? The molecular alterations that define a tumour may be as relevant as the histopathology that was historically used to classify a tumour and determine treatment options. Basket study designs potentially broaden the population of patients eligible to receive drugs. The design offers efficiency by enabling multiple tumour types to be studied simultaneously, to test possible signs of drug activity and assess rare cancers. For clinicians and patients access to drugs that would not otherwise have been available is offered as well as clinical trial evidence.

The rationale of tumour testing is to reduce driver molecular alterations and provide new treatment options and trial designs. As cancers evolve the molecular alterations change when re-treating patients compared with historical or untreated patients. This opens options via basket trials, as they allow many diverse tumour types and alterations to be studied at the same time. Applying a Simon two-stage design, the sample size dictates how and when to stop therapy owing to a lack of efficacy. A common control group is needed. In some cases, randomization is not ethical or feasible and so randomized blinded evidence is not possible.

All mutations are not created equal and in the MyPathway trial clinicians could match many drugs according to the molecular profile of the patient. Many patients derived 30–70% overall response rates, reasonable duration of responses and high clinical benefit rates. Some activity was noted for agents in non-approved tumour types. In various *HER2*-amplified tumours of different origin, some response rates and clinical benefit rates were observed. Targeted therapy can be effective in multiple tumour types, and both the molecular alteration and tumour type matter. The overarching protocol allows for basket groups or therapies to be added or closed. In the future, such studies can improve therapy options for patients, provide meaningful data in rare cancers, or an innovative study design and biomarker exploration can be applied to validate blood or tissue biomarkers, and improve access and evaluation of drugs.

PRECISION CAR T-CELL THERAPEUTICS

Dr Carl June started his Keynote lecture by explaining that synthetic biology can be used to overcome tolerance by creating bi-specific CAR T cells. Second-generation CAR T-cell therapy examples that target the CD19 cells include axicabtagene ciloleucel and tisagenlecleucel. The first CAR T-cell infusion was given on 21 July 2010 to a child with chronic lymphocytic leukaemia (CLL), in which the patient's tumour cells were taken and genetically engineered to express the tumour antigen, expanded *ex vivo* and then re-infused back in the same patient so that their own immune system would recognize and destroy the tumour. Patients treated with this therapy obtained long-term T-cell persistence.

Characterisation of the CAR T cells in CLL patients revealed that the CAR T cells from those with a complete response were enriched in memory-related genes including IL-6 and STAT3 signatures. CAR T cells from non-responding patients had upregulation of genes involved in effector differentiation, glycolysis, T-cell exhaustion and apoptosis. CD27+PD-1- CD8+ CAR T cells expressing high levels of IL-6 receptor were associated with therapeutic response and tumour control. The poster child success story of this treatment was captured on the front of *Time* magazine. That patient is still in remission, and had previously relapsed on three different chemotherapies.

Tocilizumab is an IL-6 receptor antagonist and is used in rheumatoid arthritis and juvenile idiopathic arthritis as well as Castleman's disease. As a monthly treatment it has rare adverse effects and is efficient in trafficking of T cells to the central nervous system. Modelling of pharmacodynamics of the drug, which is 'live' showed that some T cells die and some become memory cells. Unlike a traditional drug, no relationship was detected between the dose of tisagenlecleucel and the C_{max} or any other parameter. However, C_{max} was associated with more severe cytokine-release syndrome. Long-term persistence and expression of CTL-019 was a predictive biomarker that correlated with remission in CLL. In one patient, delayed tumour lysis syndrome was noted and severe fever was observed 45 days following CAR T-cell infusion, which correlated with a rapid massive expansion of clonal CAR T cells. However, all blasts disappeared and at 4 years post-therapy, patients are still in remission.

Dr June then explained that TET2 enzymes belong to the dioxygenase superfamily of proteins, and mutations and loss of function alterations are common in haematological malignancies. Remarkably, the progeny of a single CD8+ induced by CAR T-cell therapy was capable of removing more than 1kg of tumour! This striking observations prompted the question: can the lowest effective single dose of CAR T cell therapy be a single cell? In essence, they can and since *TET* mutations increase haematopoietic stem cell renewal or 'stemness', this might be exploited for future clinical benefit.

Can CAR T cells have a role in solid tumours? In pancreatic patients, responses were seen in the metastases but not the primary lesions. Armoured CARs (next-generation CAR therapies) are also progressing.

In prostate cancer, PMSA is expressed and functions in glutamate and folate metabolism. PMSA expression increases with advancing tumour stage and grade. TGF- β is a checkpoint inhibitor, which is expressed highly in the tumour microenvironment. High levels of TGF- β in prostate tumours likely reduce anti-tumour activity of PSMA CAR T cells. A PSMA-armoured CAR T cell has been designed and the PMCA-TGF β -BRDN CAR T cells are resistant to exhaustion. A clinical phase I trial is open and recruiting patients with prostate cancer. There are various challenges to the manufacturing and healthcare management aspects of engineered T-cell therapies. The manufacturing costs need to change as this is a very expensive therapy. Central manufacturing of CAR T cells is happening and numerous combinational cancer immunotherapy possibilities look promising.

IMMUNOTHERAPIES TURNING COLD INTO HOT TUMOURS

Dr Jean-Charles Soria (MedImmune) pointed out that despite advances with checkpoint blockade inhibitors there is still room for much improvement with anti-tumour immune response. Only 20% or lower responses are typically seen, although sometimes this is higher but responses might be short-lived. Patients usually have no anti-tumour immunity at baseline because T cells are exhausted and this issue needs addressing in the clinic. By attacking the anti-tumour microenvironment this might provide clues.

The tumour microenvironment is suppressive and illustrates ineffective antitumour immunity. Thus, Dr Soria discussed turning 'cold' tumours into 'hot' tumours. Oncolytic viruses, innate agonists and monoclonal conjugates offer possibilities. Some have responses to immuno-oncology therapy and some are insensitive and show a lack of response. Oncolytic viruses and antibody drug conjugates (ADCs) combined with dendritic cells could provide benefits. It is possible to prime a new response using oncolytic viruses. Newcastle disease virus (NDV) combined with GMSF and oncolytic viruses can reduce T-cell recruitment and activation. Thus, these early data indicate the feasibility of inducing immunologic cell death and neoantigen spread. Synergistic effects are seen when combined with standard of care.

Dr Soria asked if destroying tumour cells that are resistant to standard of care therapy can be considered? Using talimogene laherparepvec it was possible to derive an abscopal effect. There are various oncolytic viruses at different stages of development. Viral engineering has overcome many of the hurdles. NDV GM-CSF kills a large number of cancer cell clones and has active antitumour immunity and overcomes immunosuppression. This agent has potent antitumour activity in immune-competent mouse models. It is possible to prime new responses with ADCs, as these can induce immunogenic cell death and dendritic cell maturation. Two payloads are constructed and a critical role for CD8 T cells was revealed by ADC therapy. There are differential effects of warheads on immune response.

In the latter section, the synergistic activity of ADCs with checkpoint inhibitor combinations was described. There are 27 ADC-immuno-oncology combinations and using these agents it is possible to prime new responses with innate agonists. One example is CD40, which is a master regulator of humoral and innate immunity. CD40 has an important role in activating both aspects of the immune system and the latest compound, MED15083, enables dendritic cell activation and maturation, and activates antigen-presenting cells to enhance the immune effects. It also repolarizes the myelosuppressive tumour microenvironment or M2 phenotype. This compound has now entered the clinic and has robust preclinical data, and further clinical results in the future are eagerly awaited.

ADVANCES IN IMMUNOTHERAPY PRECISION ONCOLOGY APPROACHES

The use of biomarkers and diagnostic tests to determine therapy is an extremely ripe area of research. Dr Eric Rubin (Merck) explained that an increased use of diagnostic tests has been employed to see if there is benefit from pembrolizumab for monotherapy and combination therapy management. No test is perfect but some tests are useful. Companion diagnostics are increasingly used to select therapy options; however, diagnostic development typically lags behind therapeutics, which creates science and regulatory complexity. PD1 and PD-L1 serve as potential mechanistic-based precision biomarkers, based on tumour PD-L1 expression.

Other examples include tumour inflammation, determined by PD-L1 expression, and tumour antigenicity that reveals microsatellite instability, DNA mismatch repair and tumour mutational burden, which can be used to determine which patients are likely to respond to PD-1 based therapy. Predictive biomarkers have been important for several pembrolizumab approvals. For example, the utility of 22C3 immunohistochemistry (IHC) assay for pembrolizumab in NSCLC. This led to the approval of pembrolizumab for the first-line treatment of patients with biomarker positive tumours, as the median overall survival was 30 months for pembrolizumab versus 14.2 months for chemotherapy.

Biomarkers can also be used to expand the benefit of the population that benefits. For example, in the KEYNOTE-189 trial, the risk of death using chemotherapy alone was halved when pembrolizumab was combined with chemotherapy. In 2017, pembrolizumab was approved for the treatment of solid paediatric and adult solid tumours with microsatellite instability or mismatch repair deficiency regardless of tumour site or histology. Biomarkers related to tumour antigenicity have been used to decipher treatment with immunotherapy. DNA error-prone repair is carried out by the mismatch repair (MMR) proteins: MLH1, MSH2, MSH6, and PMS2. If these proteins do not repair DNA they result in a microsatellite instability high phenotype, which is susceptible to anti-PD-1 agents, and MMR deficiency caused by mutations in these genes are ideal candidates for pembrolizumab.

In colorectal cancer and non-colorectal tumours, patients with MMR deficiency derived a striking response from pembrolizumab, but responses were not seen in those with competent MMR. MSI-high phenotype is unique in its immunobiology. High mutational load also generally respond to immune checkpoint blockade regardless of tumour histology, which led to the approval of this agent in a tissue agnostic setting. Although multiple assays are being developed for several immunotherapy agents, and the evaluation of tumour mutational burden, the increased complexity of companion diagnostics and multiple assays being developed make direct comparisons complex because different scores and approaches are used with different assays. The clonal diversity of tumour mutational burden is another complex issue that needs further investigation. Another opportunity lies in cancer vaccines. Using NGS techniques to fully sequence a patient's tumour, it is possible to identify mutations and using an algorithmic approach to predict which mutations would result in an immunogenic antigen as a basis to construct an RNA-based vaccine. The use of combined pembrolizumab and vaccine could help target the immune system towards relevant neoantigens to enhance personalized therapy.

EARLY DEVELOPMENT IN ONCOLOGY – WHERE ARE WE?

Dr Giorgio Massimini from Merck KGaA, Darmstadt, posed the question that while the classic trial approach of enrolling patients with advanced disease in phase I trials made sense because they have no other therapy options and determining the maximum tolerated dose was appropriate for cytotoxic agents, this approach may no longer be valid for newer therapies. More trials now consider endpoints other than safety in phase I to determine the recommended phase II dose (RP2D). For example, the oral selective c-Met inhibitor tepotinib was assessed in advanced solid tumours in the phase I setting. The trial explored safety, biomarkers and RP2D that was not the maximum tolerated dose. Thus, safety and pharmacodynamics and demonstration of target inhibition are becoming more relevant, and the scope of early development is changing from safety to exploring efficacy in selected populations, when appropriate.

Expansion cohorts are becoming more popular in phase II trials owing to a better understanding of the biology of the disease. Moreover, targeting specific cancer cell subsets that harbour the target is now the direction of travel. Heterogeneity means that single therapy is rarely effective. Multiple combinations are being explored that are almost limitless, so assessment in combinatory phase I and II is required. Despite efforts to expedite the development of trial combination testing, studies can be cumbersome and linked to maximum tolerated dose. Expanding phase I of each combination of drugs in an exploratory cohort can result in larger assessment. Although an early phase trial to test multiple patients' cohorts can be successful, such as in the case of pimasertib, many challenges remain. For instance, pimasertib, which inhibits phospho S6, a biomarker of p70 inhibition kinase, gave a false impression of target inhibition owing to limited sample availability and technical difficulties with the assay.

Most clinical trials have high attrition rates, with many not meeting their primary end point owing to a lack of efficacy or lack of ability to prolong life over the standard of care. Thus, WIN and Merck KGaA are exploring a new trial design (MERCURY) to test drugs alone or in combinations based on the known targets and safety profiles of drugs. The unique features of the WIN MERCURY trial is to include dual normal and matched tumour samples based on DNA and transcriptomic analysis and use WIN algorithms to match the patient's tumour biology to the most appropriate drug or combination. A Simon two-stage design will be applied with limited number of patients enrolled in each target match cohort. Cohorts will be stopped for futility or expanded according to response. It is hoped this will raise the bar for entry into phase III testing. The next-generation trials will look at target inhibition, safety and clinical outcome by essentially combining phase I and II trial approaches to create a pre-competitive space to test drugs or combinations in different pathologies.

PATIENTS DRIVING PROGRESS

In the way that cancer treatment and our understanding of the disease has evolved, so too has patient advocacy. Dr Ellen Sigal from the Friends of Cancer Research explained how traditionally, the patient voice was not considered, but that gradually over time, this has now taken on a much more central and integral part of the psyche of cancer. From sponsored walks to the National Pancreatic Cancer Advocacy Day that themed “Nothing About Us, Without Us”, are just two examples of how far the journey has progressed. There are opportunities for patients to be involved with the drug development process, from the drug discovery and preclinical early stages right through to post-marketing surveillance. The patient perspective is powerful! Patients want to question things from the relevance of the trial to their disease, data privacy to access to drugs and the options available if a patient does not wish to be randomized. While science may provide the most useful way to organize empirical, reproducible data, this information is very limited without human emotions. A Washington-based Think Tank and Advocacy organization are now driving policy, science, regulation and advocacy to enhance life-saving treatments for patients. Partnerships have been forged with academic research centres, professional societies, industry, and advocacy organizations. Patients concerns that need solutions include the timing of drug approvals, clinical trial design limitations, and the efficient regulation of cancer drugs.

Why should patients have to wait years for drugs to show significant clinical activity early in development? This question can be part answered by patient participation and advocacy opportunities to condense the drug development process. For instance, the FDA worked with advocacy organizations to bring about breakthrough therapy designation, which was signed into law in 2012 in the USA. Ultimately, faster drug approvals equates to faster access to life-saving drugs. In some instances, this has shaved years off the drug development process, especially in cancer. As Jeff Allen (CEO of Friends of Cancer Research) laments “Clinical trials should be serving patients, not patients serving clinical trials”.

Patient advocacy involvement in the LUNG-MAP Master Protocol exemplifies major progress for patients, as it employs a dynamic study design, allows all histologies of lung cancer to be included and multiple drugs can be selected based on the tumour genomic profile, which leads to accelerated approval or expedites phase III trial testing. The Friends of Cancer Research are focused on finding opportunities to consolidate regulatory approaches to the clinical evaluation of cancer treatments. In summary, we need to persuade audacious ideas that are meaningful to patients even if they are not as clean and tidy as we expect.

PATIENT ACCESS TO PRECISION ONCOLOGY

Professor Francesco De Lorenzo representing the European Cancer Patient Coalition (ECPC) summarised the scale of the organization, which is a large, 430-member umbrella organization that includes over 46 countries from within and outside the EU. The vision of the ECPC is to ensure all European patients with cancer have timely and affordable access to the best treatment and care available throughout their life. Policy makers, doctors, researchers and industry need to recognize cancer patients as co-creators of their own health. Crucially, ECPC increases the vital role of patients, and their role in good governance, policy, capacity building and research.

As personalized medicine is the future, we need the best treatments according to medical history, physiological status and molecular considerations. Genetic testing can boost survival and avoid toxic treatments; however, there are also barriers to innovative medicine.

Patient stratification according to biological factors does not take into consideration personal preferences. Personalized medicine is a relatively young field, which requires us to adapt the way we design trials. Trials rarely consider lifestyle factors and there is a delay between advances in research and parallel innovation in healthcare, and access to best treatments. How can patients access innovation? For instance, the time delay in HER2-positive patients accessing trastuzumab was 2 to 10 years after its approval. Around 5,000 patients per year are denied access to life-saving treatments. There is also an East–West divide, as one survey showed that 70% of patients in Western Europe were treated with innovative medicines, whereas in Eastern Europe only 10% of patients had access to therapies recommended in European guidelines. True value-based healthcare should be assessed not only as a ratio of outcomes to cost, but clinical efficacy and value of treatments, as well as clinical benefit, quality of life and social aspects. Healthcare delivery systems often do not interact effectively, which delays timely diagnosis and treatment. The ECPC succeeded in working successfully with the European Commission to develop a proposal for health technology assessment (HTA) cooperation. Access to innovative drugs is a component of health coverage, but the dynamics of drug development and approval are counterproductive. Health technology assessment needs a more harmonized approach, so the European Commission set plans across member states involving 56 public bodies in 27 European countries. This initiative strengthens regulatory cooperation to accelerate clinical assessments and improve access to medicines. Nonetheless, the division of resource between medicine, hospitals and devices through silos of budgets and separate responsibilities can prevent the true potential of these organizations working together. There are also biomarker testing challenges across Europe that create many challenges. These include accessibility and genetic testing that varies from country to country and administrative burdens can cause delays and long waiting times as there is little organization between hospitals to perform tests. Also some countries are not reimbursed and only 23% of European doctors felt their patients were kept fully informed about biomarker testing. The ECPC called for more progress to be made towards a more harmonised and efficient regulatory framework. It is calling for increased access, decreased waiting times, high quality biomarker testing, and awareness campaigns to increase biomarker literacy. Numerous activities have been initiated to achieve these aims including the creation of the Innovation Partnership Action Against Cancer (iPAAC). This enterprise is

developing guidelines on successful integrity of genomics and healthcare systems, as well as access to biomarker testing. Similarly, the Joint Action on Cancer Control (CANCON) was a common effort between representatives of 17 EU member states co-funded by the European Commission to create guidelines for harmonisation of national cancer plans. The ECPC was a vital partner in this joint action to embed equity within cancer prevention, align policies and adopt a health equity impact assessment framework.

IMPLEMENTING PRECISION MEDICINE: IMPACT CLINICAL TRIAL

Dr Apostolia-Maria Tsimberidou explained that treating and selecting therapies based on the molecular analysis of the tumour is expected to improve outcomes compared with standard approach. Some patients with rare or incurable cancers or who had exhausted other options were enrolled on the phase I Initiative for Molecular Profiling in Advanced Cancer Therapy (IMPACT), which assesses up to 50 genes. Treatment is matched to targeted therapy if available, and if not they have non-matched standard therapy. Overall, 3,743 patients were recruited between 2007 and 2013; overall 54% had an alteration that could be matched to a therapy, and 46% were not matched. Stable disease (18% versus 14%) and objective response (16% versus 4%) were higher for those matched to therapy. The disease control rate, PFS and overall survival were greater in patients matched to therapy than non-matched.

Non-matched therapy was an independent risk factor for a shorter survival (hazard ratio 1.30). Overall, 3-year overall survival was higher (15%) in the therapy matched group versus non-matched (7%) group. Matched therapy was an independent predictor of a longer survival in multivariate analysis. Those with *PI3K* and *AKT* mutations had inferior outcomes compared with other alterations. A prognostic score for overall survival was developed that included molecular pathway abnormalities.

Precision medicine in cancer requires a detailed understanding of tumour biology including immune features that drive carcinogenesis. Importantly, access to testing and effective drugs is needed.

In 2011, a prominent article was published in the *Wall Street Journal* highlighted that a major shift on the war on cancer had occurred, owing to many more patients responding to therapies if the agents used targeted specific molecular alterations in the tumour compared with those receiving unmatched therapies. An article in the *Economist* in the same year proclaimed that if personalized medicine is to reach its full potential, it should be used earlier on in trials. This would not only speed up trials but could also save millions of dollars in the process. We don't use the therapies early enough, as they are always first tested on advanced metastatic disease.

The IMPACT2 randomized trial evaluating molecular profiling and targeted agents in the metastatic setting tested whether patients achieved a longer PFS than those patients not selected based on analysis of tumour alterations. Copy number variations and fusion variants were assessed. *BRAF* mutations, for example, were shown to be important in thyroid cancer. Mutational burden and overall response rate to PD-1 and PD-L1 inhibition in selected tumour types was assessed. This revealed immune markers that were able to predict responses to immunotherapy. High antigenicity was one such marker. Other biomarkers of interest being pursued are NGS in tumours and cell-free DNA analyses and looking at PD-L1 and MSI status. Tumour mutational load and individual markers for specific aspects are also important. Multiple alterations, complex molecular networks, along with epigenetic changes can be identified in individual patients. Such markers should be integrated into clinical practice to select the optimal therapy. However, as the complexity of biomarkers is increasing, an infrastructure that uses artificial intelligence to help integrate all available patient data to perform algorithmic analysis is needed. It is hoped this will result in optimal drug selection, and faster, more effective therapies to be given to more patients.

'GREATEST HITS' OF PRECISION ONCOLOGY – NEWSROOM VIEW

Bernadette Toner gave a tantalizing talk: she started by explaining the role of GenomeWeb, which is to bring scientific advances to practitioners and cover all aspects of advances in the genomic field to academic researchers, pharma, R&D, diagnostic developers,

manufacturers via a journalist approach. As an independent publishing company, founded in 1997, its main coverage is on gene sequencing. In 2011, the precision medicine was first used. If we think of greatest hits in music terms, the output is notable by record sales, visibility and air play. How can this be applied to precision oncology? Stratified oncology, which represents one tissue type, one marker, one drug is not the same as precision oncology, which is any tissue type, multiple markers and the 'best' drugs.

For instance, trastuzumab brought in \$7 billion in revenue in 2017, and 20% of breast cancer patients are HER2-positive. It is possible to focus on the drug centric end of a 'hit' in terms of revenue for many targeted therapy examples. But, what defines a 'hit'? Is it drug sales, patient eligibility, number of patients treated, outcome endpoints, patient quality of life, cost-effectiveness or some other measure of value? Are measurements of success the same for stratified versus precision oncology? How can the community move from a drug-centric model of success to one that is more process focused? As fewer patients are treated overall in light of precision oncology, how can one measure success in the 'long tail'? Defining value for precision oncology is a key challenge. Another issue is defining the promise of precision oncology. While success stories have been much publicised, it is important not to propagate the perception that precision oncology has reached a point where such benefit can be offered with any reasonable likelihood or frequency. While molecular profiling opens some opportunities most patients with solid tumours will not be meaningfully benefited by NGS at this time.

It is important to be aware of the anecdote. Regardless of how moving some stories are, they are not representative of the population at large. There has been an appearance of progress, but this does not always equate with success. Anecdotal stories are a problem as patients can be misled by press stories. If one person benefits, is it less than considering the whole population size that might derive the benefit? Will healthcare see value in sequencing all patients to find the few who will benefit? There is a delivery system issue. What is the largest possible number we can diagnose and treat without increasing the costs overall? Enter value-based genomics. There is a lack of data on precision controlled trials and value will take more time to access. Currently, we do not take into consideration how many people have been sequenced to get an actionable result. News must provide context and impact on all stories.

By the time patient eligibility, tissue sampling, sequencing, analysis pipeline, drug matching criteria and access to drugs are taken into account, the reduction funnel illustrates the benefits to date for precision oncology are for few patients.

There is an increasing complexity for oncologists and a mismatch between adoption and perception. This situation is not helped by different criteria and terminologies have been used to explain how patients were treated. If confusion arises for the experts it is even more baffling for community oncologists who are removed from the research scene. For example, Genentech surveyed oncologists and showed that 12% of doctors offer next-generation sequencing to around half of patients, but that most do not offer it at all, and any feel that genomic testing is over promoted. This has prompted patients to create support or advocacy groups, which can create trends in the field and also pose challenge for media. How can we communicate success, and ensure that stakeholders have all the information they need to honestly evaluate the progress that has been made in the field? We should not follow a drug-centric model, and we need to improve most of the steps in the process. Poor quality tissue is also an issue, as is assessment of RNA, epigenome and the microbiome. These aspects need to be optimal for drug decision support, but it is hoped this situation will improve with more data in the future.

Lisa Hutchinson, PhD

Member of the WIN Symposium Organizing Committee