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OPPORTUNITIES AND CHALLENGES IN CANCER R&D

HIGHLIGHTS FROM THE SOCIETY OF MEDICINES RESEARCH SYMPOSIUM, HELD JUNE 5, 2015 – THE BEATSON INSTITUTE, GLASGOW, UK

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SUMMARY

Despite major efforts to tackle cancer, it is still a leading cause of death worldwide that places tremendous health and economic burden on societies. Given this, developing new approaches to attack tumors continues to be a key area of research for both academia and industry. This 1-day Society for Medicines Research Symposium hosted by the Cancer Research UK Beatson Institute, Glasgow, U.K. and sponsored by The Cancer Research UK Centre for Drug Development was organized by Wendy Alderton, Ruth Lock, James Ritchie and Peter Weber. The meeting discussed key challenges and opportunities from early research through to clinical development in oncology. It focussed on new advances in cancer therapy and brought together a panel of international speakers to spotlight the recent emergence of rationally designed targeted drugs, combination therapies and effective immunotherapies based on a deeper understanding of cancer genomics and host/tumor interactions.

Key words: ATR inhibitors – Immune-mediated therapy – IMCgp100 – VX-970 – Selumetinib

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40 YEARS OF DRUG DISCOVERY – HIGHS AND LOWS, AND LESSONS LEARNED

Herbie Newell, Professor of Cancer Therapeutics at the Northern Institute for Cancer Research, Newcastle University gave an introduction to cancer drug discovery and development, starting during World War I with the serendipitous discovery that soldiers exposed to nitrogen mustards had very few white blood cells. It was subsequently demonstrated that nitrogen mustard derivatives could kill cancer cells and the era of cancer chemotherapy began. By the early 1970s several classes of chemotherapeutic agents had been developed including alkylating agents, topoisomerase inhibitors, antimetabolites and tubulin binding agents. Although providing major advances in the treatment of cancer patients these drugs were universally toxic and had very poor selectivity toward tumor cells. The focus of the following 20 years, leading up to the era of targeted agents in the 1990s, was the development of less toxic, more targeted chemotherapy analogues which led to breakthroughs such as **carboplatin**. Professor Newell described how as a Ph.D. student he

was involved with the discovery and development of carboplatin, which has significantly less hematological toxicity but equivalent potency to cisplatin, and how he was lucky enough to be at the bedside of the first patient to be treated with the drug—an experience he described as both inspiring and humbling.

The 1990s heralded the era of molecular oncology led by the discovery of **imatinib** (Glivec®, Novartis) which showed remarkable potency in chronic myeloid leukemia patients whose tumors are Philadelphia chromosome translocation positive. During the same time period at the University of Newcastle, Professor Newell was involved in developing agents, using a structural-based approach for the first time, that targeted part of the cellular DNA repair machinery known as poly(ADP-ribose) polymerase (PARP). The rationale underlying the development of PARP inhibitors was that of enhancing the activity of chemo- and radiotherapy by reducing the tumor cells' ability to repair damage induced by cancer therapy leading to increased cell death. An additional unforeseen benefit of inhibiting PARP is that of 'synthetic lethality'—having single agent activity in tumors which have defects in additional DNA repair machinery, such as *BRCA1* and *BRCA2* mutations, that are required for homologous recombination repair. The PARP inhibitor program led to the eventual discovery of **rucaparib** (licensed to Clovis Pharmaceuticals) which has shown remarkable response rates of up to 70% in *BRCA*-related ovarian cancer in clinical trials. Rucaparib has received breakthrough designation by the FDA and is expected to be approved during 2016. Professor Newell also highlighted a second drug discovery program that targeted fibroblast growth factor receptors (FGFR), a family of receptor kinases that have been shown to be important in several cancers either via mutation and/or overexpression. Collaboration between the University of Newcastle and Astex Pharmaceuticals, using fragment-based drug discovery, has successfully led to the development of a highly potent pan-FGFR inhibitor (**JNJ-42756493**) which is showing clinical activity in patients with tumors that have FGFR amplification, mutations or translocations.

Even though targeted cancer therapies have been successfully developed, there still remain many challenges in the discovery and development of these agents, several of which were highlighted by Professor Newell: identification and validation of novel targets; exploitation of 'undruggable' targets; defining rational combinations; tackling drug resistance and the development of biomarkers to enable hypothesis-based testing and decision making in early phase clinical trials. Pediatric cancers were specifically highlighted as an area requiring improvement, despite their treatment being an apparent success story with almost 80% of children diagnosed with cancer today surviving for 5 years. However, essentially all drugs currently forming the standard of care for these children are cytotoxics developed during the 1940s to 1970s. Given this, the long-term side effects are significant and represent an urgent unmet need for less toxic but just as effective replacement therapies. Professor Newell concluded by giving his perspective on what the management of cancer may look like in the future and the lessons he had learned from 40 years in drug discovery (Table I).

CHALLENGING TARGETS IN CANCER DRUG DISCOVERY

Professor Martin Drysdale, Head of Drug Discovery Programme at The Beatson Institute for Cancer Research, CR-UK, Glasgow, gave an overview of two projects, fascin and KRAS, currently being prosecuted within the Drug Discovery Programme at the Cancer Research UK Beatson Institute. The use of weak binding 'fragments' of molecules is now recognized as an efficient and robust method of hit identification in the drug discovery process. The two projects described highlighted the successful targeting of protein–protein interactions using fragment-based methods of hit identification coupled with structure-based compound evolution.

Table I. *Vision of a Cancer Cure and Lessons Learned from 40 years of anticancer drug discovery (courtesy of Professor Herbie Newell).*

Vision of a "Cancer Cure"
Genetic analysis at birth to predict lifetime risk.
Lifestyle advice and chemoprevention to minimize any risk.
Screening using a multitude of techniques to facilitate early detection.
If cancer develops then surgery and curative personalized therapy with extensive use of prognostic and predictive biomarkers as well as imaging technologies.
Lessons learned
People in positions of responsibility are capable of making bad decisions.
"When a distinguished but elderly scientist states that something is possible, he is almost certainly right. When he states that something is impossible, he is very probably wrong" (Arthur C. Clarke).
Cancer drug discovery and development is at its most impressive when potent and specific molecules are used in genetically defined experiments.
"Anticancer agents based on an elegant working hypothesis are sometimes successful in the clinic however; the way they act is often nothing to do with the working hypothesis" (Tom Connors).
Successful drug discovery is a multidisciplinary team game that requires symbiotic academic/commercial partnerships, in which people are as important as the science and technologies.

Fascins are actin binding proteins that cross link filamentous actin into parallel bundles, and are required for membrane protusion, cell motility and extracellular matrix degradation. The activity of fascin proteins is regulated by protein kinase Cα and RhoGTPases. Fascin-1 is highly overexpressed in numerous cancer types, is low or absent in normal epithelia and is prognostic for poor outcome, particularly in pancreatic cancer. Fascin knockdown reduces tumor cell invasion and proliferation. Fascin proteins are composed of four β trefoil domains and are amenable to a structural biology approach due to multiple fragment-complex structures having been solved, which reveal four distinct fragment binding sites. Single point mutagenesis studies (1) have identified the area around Site 1 as a 'druggable' pocket containing functionally important residues that inhibit fascin function upon mutation. While Site 2 appeared to be a very hydrophobic site with scope for efficient ligand binding, but with apparently no nearby functionally important residues. A fragment library and surface plasmon resonance (SPR) screening campaign using 500 compounds yielded a 6% hit rate. A biophysically based optimization strategy was employed including SPR binding, compound aggregation, solubility and nuclear magnetic resonance (NMR) binding evaluation, followed by X-ray crystallography and an agarose gel-based actin bundling activity biochemical assay. This strategy of structure-based design yielded 200- to 1,000-fold improvements from the original hits to a Site 1 lead with a K_D of 2.7 μM and a biochemical functional assay IC_{50} of 23 μM; and a Site 2 'induced pocket binder lead with a K_D of 0.85 μM and a biochemical functional assay IC_{50} of 1.1 μM. This project has generated 250 small molecule/fascin crystal structures to dates and has employed a first-of-its-kind robust biochemical screening assay for fascin/actin binding.

The second project described by Professor Drysdale was KRAS, which functions as a guanosine diphosphate-guanosine-5'-triphosphate (GTP)-regulated binary switch, and is one of the most frequently mutated oncogenes associated with 16% of all cancers and the majority of pancreatic cancers. The critical role of mutant KRAS in driving oncogenesis is supported by several genetically engineered mouse model studies. Mutant KRAS is in the constitutively active GTP bound form and is insensitive to inactivation. KRAS has long been regarded as an 'undruggable' target, however, there have been recent successes in the last 3 years with a number of publications on KRAS inhibitors including irreversible inhibitors and those arising from fragment-based structural approaches. SPR screening of a fragment library of 1,000 compounds yielded 16 validated hits. After intensive optimization of the crystallography conditions the project eventually obtained 42 small molecule X-ray crystal structures and employed biophysical approaches alongside KRAS nucleotide exchange assays. This strategy has successfully resulted in two chemical series where the K_D for NMR binding of the leads has been improved from 630 μM to > 1000 μM down to < 10 μM. The KRAS nucleotide exchange assay EC_{50} values determined were 64-70 μM with acceptable clogD and solubility.

DISCOVERY AND CHARACTERIZATION OF ATR INHIBITORS FOR THE TREATMENT OF CANCER

Dr. Juan-Miguel Jimenez, Head of Chemistry UK, Vertex Pharmaceuticals, gave an account of Vertex's drug discovery project which has successfully produced potent and selective inhibitors of ataxia telangiectasia mutated and Rad3-related (ATR) kinase. This project has culminated in several drug candidates entering phase I clinical trials.

DNA-damaging agents, such as cisplatin, or ionizing radiation currently represent the cornerstone for the treatment of cancer. However, such agents typically provide only modest benefit for many patients due to the presence of highly effective cellular processes for surveillance and repair of DNA damage. ATR is a key mediator in one cellular process that responds to replication stress to avoid dangerous double strand DNA breaks. Replication stress can be induced by a wide range of DNA-damaging agents and thus inhibition of ATR was expected to sensitize cells to such agents. A high-throughput screen against recombinant ATR using a kinase focused library yielded hits of modest potency and cellular activity, but encouraging selectivity against related kinases; ataxia telangiectasia mutated (ATM) and DNA-dependent protein kinase (2). Optimization of these hits by rational design yielded **VE-821**, which was then used as a tool compound to probe target biology. VE-821 has a K_i of 0.013 μM for ATR, > 100-fold selectivity against 50 kinases and an IC_{50} of 0.8 μM in a cellular ATR assay (2). Cellular studies using VE-821 showed that ATR inhibition potentiates the toxicity of multiple classes of DNA-damaging agents (cisplatin, camptothecin, gemcitabine, etoposide) in some cancer cells but not noncancer cells, which undergo reversible cytostasis (3). This noncancer cell tolerance was attributed to compensatory signaling through an overlapping double strand break surveillance and repair pathway mediated by the ATR homolog ATM and its principle substrate p53. This compensatory pathway is commonly defective in cancer cells. Accordingly, cell studies showed that cells lacking either ATM or p53, through depletion or inhibition, were highly sensitive to the ATR inhibitor when treated with DNA-damaging agents such as cisplatin. VE-821 was also shown to potentiate ionizing radiation and reverse hypoxia radiation resistance in MiaPaca pancreatic cancer cells (4). Further optimization to improve the potency and drug-like properties of the chemical series yielded **VX-970**, the clinical candidate. VX-970, when dosed at 60 mg/kg orally q.d. 4 days on 3 days off with cisplatin 1 mg/kg weekly in a non-small cell lung cancer patient-derived mouse xenograft, markedly improved tumor response to cisplatin (5). The combination was well tolerated and VX-970 efficacy was shown to correlate with biomarker responses in tumors (inhibition of Chk1 phosphorylation and accumulation of the DNA damage marker phosphor-H2AX). Combinations of VX-970 and gemcitabine, irinotecan or ionizing radiation were efficacious in xenograft models and tolerated well with no significant body weight loss. VX-970 is currently in phase I clinical studies in combination with gemcitabine, cisplatin, carboplatin and as a single agent.

IMMUNE-MEDIATED THERAPY FOR CANCER: PRECLINICAL ASSESSMENT OF IMMUNOBIOLOGY AND COMBINATION ACTIVITY

Dr. Robert Wilkinson, Director, Oncology Research at MedImmune, U.K. described the approach MedImmune has taken to identify effective combination therapies that restore the immune response to cancer. In his introduction, Dr. Wilkinson outlined how cancer cells are believed to overcome immune surveillance by promoting mechanisms to evade the immune system. The concept of harnessing a patient's own immune system to combat cancer can be traced back

over a century ago to the pioneering work of William Coley, who noted the apparent relationship between infection and cancer regressions in some patients. Coley used dead bacteria (Coley's toxins) to treat some patients with inoperable tumors. However, it took until the 1990s until a number of novel agents entered the clinic to specifically target immune cell modulation pathways, in particular in T cells. The first of these drugs to be approved in 2011 was the anti-cytotoxic T-lymphocyte protein 4 (CTLA-4) antibody **ipilimumab** (Yervoy®, Bristol-Myers Squibb) for the treatment of unresectable or metastatic melanoma. This was recently followed by antibodies against programmed cell death protein 1 (PD-1), namely **pembrolizumab** (Keytruda®, Merck & Co.) and **nivolumab** (Opdivo®, Bristol-Myers Squibb). Clinical data with other immune-mediated therapies (IMTs), for example MedImmune's anti-OX40 antibody and anti-programmed cell death 1 ligand 1 (PD-L1) antibody (**durvalumab**, MEDI-4736), further highlight the potential of therapies that target immune evasion pathways. However, while these agents are able to produce long-lasting responses in cancer patients, the response rate as monotherapies tends to be low. A key goal is now to develop combination therapies, either between different IMTs or between IMTs and conventional therapies, to increase the responder population. In order to select the best combination partners, a greater understanding is needed as to how therapies affect the immune system both directly, through effects on leukocytes, and indirectly, through effects on tumor immunogenicity and induction of tumor cell death.

Dr. Wilkinson used two examples to outline how MedImmune uses a rational approach to achieve effective combinations of different agents in preclinical models: combinations of IMTs with radiotherapy and with a mitogen-activated protein kinase kinase (MEK) inhibitor. MedImmune collaborated with the University of Manchester to investigate the potential for combination between anti-PD-L1 and radiotherapy (6). The low-dose fractionated radiotherapy of mouse syngeneic tumors led to an increase in PD-L1 expression on cancer cells and leukocyte infiltration into the tumor. Combination of radiotherapy with anti-PD-1 or -PD-L1 antibodies caused a significant increase in tumor growth inhibition compared to radiotherapy alone. A systematic analysis showed that PD-L1 expression was dependent on the presence of infiltrating $CD8^+$ T cells, but not NK cells or $CD4^+$ lymphocytes. Consequently, depletion of $CD8^+$ cells led to ablation of synergy between anti-PD-L1- and radiotherapy. The gained mechanistic understanding from these experiments can form the basis of a clinical strategy to improve anti-tumor response in patients.

In the second example Dr. Wilkinson explained how a mechanistic approach ("SyngenOmic") was utilized to understand the scope of MEK inhibitor/IMT combination. MedImmune's team created a large panel of syngeneic tumor models and profiled them in detail using genetic, transcriptomic and proteomic tools to characterize tumor lines in vitro, implanted tumors and lymphatic organs. In addition, the immune cell status of tumor-bearing animals was determined using IHC and FACS analysis. Tumor models were then ranked according to antigenicity and occurrence of different intratumor leukocyte populations ('hot' vs. 'cold' tumors). As an example, while syngeneic 4T1 tumors contained low levels of NK and $CD8^+$ cells, levels in CT26 tumors were high. The SyngenOmic panel was now used to understand the effect MEK inhibition could have on various components of the immune response and how such an effect could influence combination therapy with IMTs. Initial in vitro experiments showed that **selumetinib** (AZD-6244, AstraZeneca), a MEK 1/2 inhibitor, caused inhibition of T-cell proliferation, which could antagonize immunotherapy. On antigen-presenting cells however, selumetinib treatment caused increased surface presentation of immuno-stimulating ligands. Similarly, selumetinib treatment of CT-26 cells in vitro triggered upregulation of MHC1 complex but decreased the expression of PD-L1. Finally, an optimized combination of selumetinib and anti-PD-L1 led to additivity in vivo demonstrating that a PD analysis of immune effects can drive the rationale for MEK/anti-PD-L1 combination therapy.

Dr. Wilkinson closed his talk with a positive outlook on IMT/IMT combinations: preclinical data suggest a strong synergy with anti-CTLA-4, anti-PD-1 as well as anti-OX40 antibodies, and trials with MedImmune's anti-OX40-antibody **MEDI-6469** in combination with MEDI-4736 and Pfizer's **tremelimumab** (anti-CTLA-4-IgG2) are currently ongoing. Finally, proof of concept for IMT/IMT combinations has recently been provided in a phase III trial in advanced melanoma where a combination of nivolumab and ipilimumab treatment increased patient response significantly compared to monotherapy alone.

CANCER EVOLUTION AND DRUG DEVELOPMENT

Professor Charles Swanton of The Francis Crick Institute and University College London Hospital, London, U.K. opened his presentation by highlighting the current mismatch between cost and benefit of cancer drug therapy. Between 2002 and 2012, of 71 anti-cancer drugs approved by the FDA including 52 targeted medicines, the median overall survival benefit was 2.1 months, balanced against an estimated USD 10,000 per month on therapy at a cost of USD 2.7 million per life year saved (7). Thus, precision medicine strategies are not dramatically improving outcomes commensurate with their price and as such are not sustainable in Europe. New approaches to cancer therapy are required but in order to try to achieve this we need to better understand the mechanisms driving cancer evolution since despite advances in genomic technologies, most advanced solid tumors remain incurable and resistant to treatments currently used. In addition, identification of robust clinical biomarkers for disease progression remains problematic due to intratumor heterogeneity.

Comprehensive genomic analysis of cancers has shown that i) each tumor contains an individual assortment of multiple genomic aberrations few of which are shared between patients with the same histopathological tumor subtype and ii) these anomalies appear to vary both spatially and temporally within the tumor. Molecular evidence has shown that tumors do not evolve in a consistent linear manner, but evolve in a branched fashion resulting in "intratumor heterogeneity". Such heterogeneity results in co-existing cancer cell subclones, which can further show heterogeneity at the cellular level. Branched evolution results in tumor diversity and has been shown in clear cell renal cell carcinoma where 65% of mutations are heterogeneous and not present in every tumor biopsy. Drivers of mutations can be subclonal (and hence missed by single biopsy sampling) and combinations of subclonal drivers can be distinct from patient to patient (8).

Professor Swanton discussed how intratumor heterogeneity and

tumor sampling bias, resulting from single biopsy-driven biomarker discovery and validation approaches, can miss potential drivers of progression in a patient's cancer and might start to explain why there have been difficulties when looking for robust clinical biomarkers and hence finding truly curative cancer therapies. Research in his lab has shown that the more biopsies you collect from a given tumor, the more driver events you will find, with many more than two to three driver events possible in heterogeneous cancers. Such heterogeneity has been shown to have implications for drug response, as highlighted by everolimus therapy a treatment for advanced recurrent kidney cancer. Everolimus inhibits the tumor growth and prevents the protein mammalian target of rapamycin (mTOR) from functioning properly. Following 6 weeks of everolimus treatment it was found that there was evidence of differential mTOR activity across different regions of the tumor, such that mTOR was active in all but one primary region and not active in metastases. This was found to be due to a heterogeneous kinase domain mutation (L243IP) that confers constitutive mTOR activation.

Professor Swanton explained how branched evolution of tumor growth can be likened to Darwin's "tree of life". The first set of genetic changes that initiate the tumor can be defined as the "trunk" and are present in every cell. As a tumor grows and cells acquire new genetic changes it becomes more diverse and groups of cells with different genetic changes can be likened to the many "branches" of the tree. Such branched genetic events can be present in some cancer cells but not others. Understanding of "trunk" drivers and monitoring subclonal driver events during branched evolution in order to define drug resistance mechanisms could provide new opportunities in clinical trial and cancer drug development.

Despite striking heterogeneity within individual tumors, parallel evolution of subclones, with distinct somatic events occurring in the same gene, signal transduction pathway or protein complex, occurs across multiple malignancies and suggests constraints to tumor evolution that might be therapeutically exploitable. Examples were given of genetic heterogeneity potentially affecting the same signaling pathways (PI3K, phosphatase and tensin homolog [PTEN] and mTOR) and parallel evolution of neurogenic locus notch homolog protein 1 (Notch 1) in esophageal adenocarcinoma. Professor Swanton discussed in detail the drivers of tumor heterogeneity (genomic doubling, DNA replication stress, APOBEC DNA editing proteins, cytotoxics) and some can appear to change during the disease course that contribute to the temporally distinct origins of cancer driver events. Genome doubling, occurring early or late in tumor evolution, exacerbates chromosomal instability contributing to intercellular heterogeneity and poor outcome. Variegated phenotypes, resulting from intratumoral genetic heterogeneity and the emergence of new subclones at relapse, are likely to have important implications for developing novel targeted therapies and for preventing the emergence of drug resistance. The finding of subclonal driver events is likely to limit the efficacy or targeted monotherapies, suggesting the need for new approaches to drug development (early detection and screening before heterogeneity has taken place and pre-emptive treatment strategies) and clinical trial design.

Two clinical trials, TRACERx and DARWIN, aimed at deciphering the relevance of subclonal driver events to therapeutic outcome and exploiting tumor heterogeneity through immune-based approaches, were discussed. TRACERx (Tracking Lung Cancer Evolution through therapy/Rx) aims to better understand how lung cancers change over time, adapt to treatment, become resistant and evolve in real time in patients over the course of their disease. TRACERx is a GBP 14 million investment by Cancer Research UK and a national collaboration between six clinical centers and four centers of scientific expertise (9). Researchers will analyze how the genetic changes inside lung cancers of more than 850 patients change over time, from their point of diagnosis and throughout their treatment. Understanding where the lethal subclone derives from and what drives it to metastasize and adapt to its new environment, will allow researchers to better understand how to use current cancer therapies and how to ultimately develop new therapies that prevent those lethal tumors from metastasizing.

The DARWIN trial (Deciphering Anti-tumor Response With INtratumor Heterogeneity) aims to assess whether targeting a clonally dominant driver event results in improved progression-free survival (PFS) outcomes relative to targeting the same driver event when it is present subclonally. In addition, studies will monitor the subclonal dynamics through therapy and during the acquisition of drug resistance (10).

In conclusion, precision medicine therapies require an understanding of the cancer-causing processes behind the genetic signature of mutations, as well as an appreciation of the extent to which these are found heterogeneously in cancer cells during tumor evolution (11). In contrast to current reactive clinical approaches, pre-emptive treatment strategies will require early detection and screening before heterogeneity has taken place.

BENCH-TO-BEDSIDE APPLICATIONS OF CLINICAL PHARMACOLOGY IN ONCOLOGY DRUG DEVELOPMENT

Dr. Karthik Venkatakrishnan, Senior Director of Clinical Pharmacology, Takeda, U.S., opened his presentation by highlighting some of the unique features of oncology drug development. These were described as:

i) Availability of nonclinical xenograft models of antitumor activity, providing opportunities for pharmacokinetic (PK)/pharmacodynamic (PD)/efficacy modeling, but there are challenges in precise translation to clinical disease setting.

ii) First-in-human studies in cancer patient populations provide the opportunity to get an early read on potential for antitumor activity and PD characterization in tumor tissue, but there are challenges of PK variability in cancer patients and the need to manage risk for drug–drug interactions (DDIs).

iii) Opportunity to confirm target engagement, pathway modulation and terminal outcomes at the cellular/biochemical levels in tumor tissue, but there are challenges with small sample sizes and single time point PD data.

iv) Challenges with use of exposure–PD relationship to guide dose selection as the linkage between PD effect and clinical efficacy is often unknown.

v) Classical cytotoxic paradigm doses at the maximum tolerated dose (MTD), although this may not be appropriate for targeted agents since dose ranging is unfortunately uncommon in phase II.

Table II. *Key questions faced by clinical pharmacologists in oncology drug development.*

Stage	Question
Entry into humans	What is (are) the optimal schedule(s) of dosing in phase I?
	How do we manage risk for DDIs in a cancer patient FIH study?
	At what time post-dose should tumor biopsies be done for PD measurement?
Phase I	If a dosing schedule change is needed due to clinical toxicity, how may alternate schedules be prioritized?
	Is there a risk for clinically meaningful DDI between selected combination partners?
End of phase I	Is the MTD/RP2D expected to provide adequate target modulation in tumor?
	From the tested schedules in phase I, which is optimal for the POC study?
	How can the RP2D be selected from equally tolerable dose pairs (e.g., a+B vs. A+b) for a novel-novel combination program?
End of phase II	Does the selected dose for phase III provide an optimum benefit-risk balance?
	What is the POS for achieving the desired phase III efficacy outcomes?
	Can Asia be seamlessly integrated at the same dose into a global phase III trial?
Phase III and beyond	What is the optimal dose/regimen for patients with renal or hepatic impairment?
	What is the risk management guidance for drug–drug interactions in product labeling?

DDI, drug–drug interactions; FIH, first in human; PD, pharmacodynamics; MTD, maximum tolerated dose; RP2D, recommended phase II dose; POC, proof of concept; POS, probability of success.

Dr. Venkatakrishnan then went on to discuss some of the key questions faced by clinical pharmacologists in oncology drug development (Table II) (12).

He further described the application of translational and clinical pharmacology across the clinical drug development continuum in oncology drug development, to optimize benefit–risk through selection of appropriate doses and dosing schedules across clinical contexts of use. He emphasized the value of understanding exposure–effect relationships in preclinical models as well as in early clinical development for PD and safety endpoints to guide understanding of a bioactive and tolerable dose/exposure range and therapeutic index for future clinical development of cancer therapies. In addition, Dr. Venkatakrishnan described the value of understanding sources of PK variability and the potential implications for phase I dose-finding studies through the use of stochastic simulations. Other highlights of his presentation included approaches to manage risks for DDIs in clinical development based on bench to bedside translation of drug metabolism (13); and the importance of population PK and exposure–safety modeling in informing understanding of the impact of ethnic/regional sources of variability for globalization of clinical development to include Asia at the appropriate dose.

A PHASE I STUDY OF IMCGP100: DURABLE RESPONSES WITH A NOVEL FIRST-IN-CLASS IMMUNOTHERAPY FOR ADVANCED MELANOMA

Dr. Namir Hassan, Director of Translational Research & Development, Immunocore Ltd, U.K., opened his presentation by introducing Immunocore's proprietary ImmTAC platform, which is based on anti-cancer monoclonal T-cell receptors (TCRs) fused to an anti-CD3 scFv effector function (14). This technology yields bispecific molecules that recognize specific peptides bound to the MHC complex and activate a highly potent and specific T-cell response to destroy cancer cells. This technology falls into the class of cancer immunotherapy agents; however, as opposed to antibody-based technologies it targets both cell surface and intracellular proteins as long as they are presented as part of the HLA-peptide antigen complex. ImmTACs bind to antigens on cancer cells with picomolar affinity through their TCR component. The low-affinity anti-CD3 part then recruits T cells towards cancer cells, leading to the formation of immune synapses, the release of lytic granules from T cells and apoptosis of the targeted cancer cells. Dr. Hassan showed a movie of an in vitro experiment where a mixed culture of MAGE-antigen presenting A375 cells, HLA-A1-only presenting cells and unstimulated $CD8^+$ T cells were treated with an ImmTAC against MAGE. Over time the MAGE-specific ImmTAC caused activation of T cells that specifically killed MAGE-presenting A375 cells without affecting HLA-A1-only (antigen negative) presenting cells, demonstrating the selectivity of the approach.

In the second part of his presentation, Dr. Hassan outlined the properties of **IMCgp100**, Immunocore's most advanced clinical candidate. This first-in-class ImmTAC recognizes the 280-288 amino acid fragment of gp100, a tumor-associated antigen frequently presented by melanoma cells. The TCR fragment has an affinity (K_D) of 23 pM, and a residence half-life of ~24 h. Plasma clearance is ~7 h in

humans. In in vitro experiments IMCgp100 was shown to direct T cells to kill gp100-positive melanoma cells, even if these display low antigen copies (15). Using IMCgp100, peripheral blood mononuclear cells from melanoma patients and a Mel624 melanoma cell line it was found that, while tumor cell killing remained effective, time to maximum killing was dependent on donor.

IMCgp100 is currently in phase I/IIa trials in the U.K. and U.S. against advanced malignant melanoma (unresectable stage III and stage IV). During phase I dose-escalation of a weekly schedule, cohorts of three patients were enrolled in a standard 3+3 design. Dose levels, starting at 5 ng/kg, were initially increased by tripling of dose in the absence of toxicity, moving to smaller increments according to safety and PK profiles. Dose-limiting toxicities were observed at doses ≥ 405 ng/kg and presented as grade 3 or 4 hypotension, associated with rash, fever or edema that were found to be reversible and self-correcting. These events are considered to be caused by IMCgp100 on-target mechanism driven due to the expression of gp100 on melanocytes in the skin. The MTD was defined as 600 ng/kg which was transitioned to a flat absolute dose of 50 µg. An expanded cohort is currently accruing at the MTD, and no further grade 3 or 4 hypotension has been observed in expansion patients to date. The plan is to dose about 10 patients to observe efficacy and safety with the aim to retrieve biopsies from 6 patients. A second dose escalation has been initiated to determine MTD, toxicity and potential activity of a daily x 4 q3w schedule. In this study, initiated with a dose of 10 µg, a cohort to receive 40 µg daily is currently recruiting. One patient from a cohort receiving 20 µg, who was previously refractory to pembrolizumab, showed a partial response (PR) (–40%), with PFS greater than 5 months and a duration of response (DoR) > 4 months at the time of analysis (June 2015).

In the subsequent part of his presentation Dr. Hassan outlined findings from the 50 µg weekly dosing schedule related to efficacy. This expansion cohort consisted of 16 melanoma patients with grade IV and one patient with grade IIIB disease. A total of 65% of patients had previously received ≥ 2 prior systemic therapies, including ipilimumab (56%), Raf inhibitors (29%) and anti-PD-1 or other immunotherapies (19%). Three patients were shown to be gp100 negative by immunohistochemistry. Three PRs and one complete response (CR) were observed by RECIST 1.1. criteria; two of these patients (PRs) are still on treatment for more than 2 years, a third patient, refractory to prior treatment with ipilimumab, showed a DoR of 5.9 months and a PFS of 9 months. The fourth response (CR) showed a DoR of 7 months and a PFS of 12 months. Interestingly, these latter responses occurred in ocular melanoma patients, a rare and hard-to-treat subtype that differs from cutaneous melanoma. There are no FDA-approved drugs for this subgroup and recent successes in cutaneous melanoma agents have not transferred to the ocular subgroup of patients. Responses were also noted in various visceral metastases, including lesions in lung, liver, lymphatic systems and soft tissues. A summary of all patients treated with a weekly dose of IMCgp100 (n = 38), including those treated just once during dose escalation, shows that 270 ng/kg is the lowest dose with clear evidence of clinical activity.

In conclusion, IMCgp100 is well tolerated and has led to durable PRs in 4 melanoma patients from a cohort of 17 treated with the weekly MTD dosing regimen. Further evaluation of IMCgp100 will include combination studies with checkpoint inhibitors MEDI-4736 (anti-PD-L1) and/or tremelimumab (anti-CTLA-4) with evidence gained from PD assessments in this study.

DEVELOPING RADIOTHERAPY COMBINATIONS FOR ONCOLOGY INDICATIONS

Dr. Hazel Jones, Head of Combination Therapies at Cancer Research UK Centre for Drug Development and Dr. Glen Clack, Senior Medical Director, Oncology Innovative Medicine Unit, AstraZeneca, spoke jointly on radiotherapy combinations. Advances in imaging and computational technology has led to significant improvements in delivery of radiotherapy to patients by minimizing damage to normal tissue while maximizing the dose delivered to the tumor. Although considered curative in many settings there is still a need to improve the efficacy of radiotherapy, which could be achieved by combination with agents known to improve efficacy based on preclinical data. For example, vascular endothelial growth factor (VEGF) inhibitors can mature tumor vasculature and reduce hypoxia which is a key mechanism of resistance to radiotherapy. Despite this potential, Dr. Clack described the reasons behind barriers that are perceived in some quarters of the pharmaceutical industry, when considering combining their drugs with radiotherapy (described in more detail in 16). The key issues include: challenges of translating preclinical data to clinic and lack of clinically relevant model systems, dearth of funding sources and selection of agents of interest, difficulties in determining the optimal sequence of combining with radiation (and potentially chemotherapy), monitoring of phase I clinical safety beyond the normal 28-day window and long-term adverse events, lengthy development timelines and unclear registration endpoints and commercial challenges such as short treatment cycles leading to a low return on investment. In order to address at least some of these challenges, a workshop was held by the U.S. National Cancer Institute to identify the key opportunities and challenges inherent to developing molecularly targeted agents with radiation (17).

Dr. Hazel Jones then discussed how Cancer Research UK (CR-UK) has established the Experimental Cancer Medicines Centre (ECMC) Combinations Alliance—an initiative established by the CR-UK Centre for Drug Development (CDD)—with the key aim of increasing novel combination treatment options for cancer patients, including radiotherapy drug combinations (18). The ECMC Combinations Alliance now has a portfolio of 15 trials, including 4 with radiotherapy with 7 participating industrial partners (http://www.ecmcnetwork.org.uk/our-portfolio). The Alliance supports preclinical combinations and has established a preclinical radiotherapy–drug combinations consortium RaDCom (19) with UK National Cancer Research Institute Clinical and Translational Radiotherapy working group (CTRad). RaDCom advises and collaborates with industry to ensure the development and delivery of appropriate preclinical data to support phase I radiotherapy combination clinical trials. Critically, demonstration of preclinical rationale for the combination is a prerequisite for entry into the Combinations Alliance and a quarter of the clinical portfolio is currently radiotherapy–drug combination studies. A good example includes the DREAM trial, which is a combination of a VEGF receptor and a MEK inhibitor alongside chemoradiotherapy in rectal carcinoma. In addition to being well tolerated,

early signs of clinical efficacy have been demonstrated. RaDCom is also working with the CTRad and industry to map out a route to registration for these studies.

DISCLOSURES

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