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IMMUNO-ONCOLOGY: THE NEXT GENERATION OF BREAKTHROUGH THERAPIES

HIGHLIGHTS FROM THE SOCIETY FOR MEDICINES RESEARCH SYMPOSIUM, HELD ON 21ST JUNE 2019 AT ST. HILDA'S COLLEGE, OXFORD

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SUMMARY

The approval of immune checkpoint inhibitors has revolutionised cancer therapy. Even so, there remains an urgent need to find treatments for patients that do not respond to or are not eligible to receive this class of drugs. Given this, many more innovative approaches are now being developed to re-direct the immune system towards tumour cells, ranging from small molecules and novel biologics to cell therapies and gene therapy approaches. The aim of the one-day meeting was to bring together renowned experts from academia and industry to discuss the latest immunotherapy advances and highlight how these discoveries form the basis of novel drugs that are designed to target key immunology pathways and transform the lives of cancer patients. This meeting was aimed at students and practicing professionals from academia and industry looking to gain an understanding of the pathological mechanisms at play within immune-oncology and their targeting in discovery and development of novel immunotherapies.

This symposium was held at St.Hilda’s College, Cowley Place, Oxford, OX4 1DY, UK and sponsored by AstraZeneca.

Session 1: Introduction to novel immunotherapies and T-cell targets

Sifting the surfeit of novel immunotherapies: a phase 1 triallist's view

The first presentation of the day was given by Professor Mark Middleton, University of Oxford, who outlined the challenges of developing new immune-oncology agents. In particular, he highlighted that despite the revolutionary impact of immune checkpoint inhibitors in the treatment of melanoma, non-small cell lung cancer and other tumours, the majority of cancer patients do not stand to benefit from immunotherapy. Professor Middleton noted that most common tumour types have largely proved refractory to this approach and even in sensitive cancers only a minority of those patients treated derive benefit. This has driven a wave of clinical trials evaluating novel agents designed to overcome what we understand to be the key obstacles to successful treatment or seeking to identify new indications for existing immunotherapies. In addition, the potential approaches to be tested far outstrip the available patient population for clinical studies and there is no agreed basis for identifying or prioritising the most promising drugs or targets.

Professor Middleton went on to emphasise that mechanistic understanding, incorporating both biological and clinical end points, is required to better develop new treatments. He emphasised that results need to be interpreted within the context of the tumour immunology of the patient population, which if not specified in the protocol, might be skewed towards particular groups such as microsatellite stable colorectal cancer or checkpoint inhibitor refractory patients. The tools available to researchers are improving all the time and although analyses are not cheap they represent a tiny fraction of the cost of phase 1 clinical studies.

Professor Middleton proposed five key factors for improving the success of testing drugs in phase 1 studies, namely testing agents in potentially curable (earlier stage) patients,

acquisition and detailed analysis of tumour and normal tissue, linking changes to potential surrogate tissue markers, understanding the biological effects of dosing and the ability to explain clinical results in other clinical studies.

Whilst many patients have achieved clinical benefit with immuno-oncology therapies such as Ipilimumab, Pembrolizumab and Nivolumab, Professor Middleton explained that many patients do not benefit from these treatments including 40 to 70% of patients with potentially sensitive diseases, people whose tumours are growing too fast, patients with breast, prostate and colorectal cancer, people with brain metastases and patients with autoimmune conditions or organ transplants.

Professor Middleton outlined four factors that determine sensitivity to immunotherapy namely, mutational burden, tumour sensitivity to immune effects (e.g. MHC expression and IFNγ sensitivity, exhaustion markers), checkpoint expression and immune cell infiltrate (e.g. intratumoural T cells).

In the last part of his presentation Professor Middleton gave an example of the ImmTAC (immune mobilising monoclonal T-cell receptor against cancer) molecule Tebentafusp which binds a gp100 peptide presented by HLA-A2 on tumour cells. Mechanistic results from clinical studies suggest that patients with the greatest increase in CXCL10 have greater tumour shrinkage and longer survival.

New T-cell Receptor Targets by dissection of successful cancer immunotherapy

The next presentation was given by Professor Andrew Sewell from University of Cardiff. He outlined that over 20% of melanoma patients that have been refractory to other treatments undergo complete lasting remission after adoptive cell transfer of tumour-infiltrating

lymphocytes (TILs). Dissection of these extraordinary successes by examining the dominant tumour-reactive T-cell clonotypes in the TIL infusion product and patient blood after 'cure' has revealed some surprising, exciting new HLA-restricted and non-HLA restricted T-cell targets that are expressed by many other tumour types. Several of the new broadly expressed HLA-restricted cancer epitopes were unexpected as the proteins they derive from are thought to be expressed in some healthy cell types. In some cases, patients received billions of activated T-cells with these specificities within their TIL infusion product that persist in the blood years after complete remission and large populations of such cells can be found in other remission patients. These data suggest that targeting these new epitopes is safe. The Sewell group have also used a whole genome CRISPR forward genetic screening to identify the cancer-specific ligands recognised by 'HLA-agnostic' T cells. Professor Sewell described how such ligands, and the T-cell receptors that recognise them, could be used to build therapies for most cancers in all individuals as they circumvent the hurdle of only a minority of patients having any given HLA type.

Professor Sewell also demonstrated how altered peptide ligands could be used to skew T-cell responses towards effective T-cell clonotypes identified in patients successfully treated with TIL therapy. This approach was used to induce T-cell lines from the blood of patients with several types of cancer. These altered peptide ligand-induced T-cell lines were shown to be far more effective at killing autologous tumour lines than lines induced by the natural peptide ligand. In Professor Sewell's opinion, new approaches to cancer vaccination that focus on the *quality* of the response induced at the clonotypic level rather than the *quantity* of the response could revolutionise future prospects for successful cancer vaccination.

Session 2: TCR-based therapies

Advancing the ImmTAC TCR-Based Bi-specific Biologic Platform: Preclinical data on the next clinical ImmTAC molecule

Dr. Joseph Dukes from Immunocore Ltd continued on the theme of T-cell receptors (TCRs) and gave an overview of Immunocore's ImmTAC technology. ImmTAC molecules are a novel class of biologics that consist of a soluble TCR-based targeting domain and an anti-CD3 effector domain. Utilising TCRs as targeting domains provides access to potentially clean and cancer- or tissue-specific targets due to recognition of Class I MHC molecules. The TCRs are highly selective against peptide-HLA complexes presented by cancer cells and affinity matured to picomolar affinity. The mode of action of these molecules consists of binding of the TCR–domain to cancer cells and redirection of polyclonal T-cells via the anti-CD3 fragment. Recruited T-cells will then form an immunological synapse and destroy target tumour cells. Notably, ImmTACs can redirect T-cells even if these are not specific for the target in question. To select tumour-specific targets Immunocore has a large database of MS-validated peptide epitopes from normal and cancer cells. As ImmTACs are human-specific, selectivity and safety screens are done using a fully human *in vitro* approach using cell and tissue models (1).

In the second part of his talk Dr. Dukes outlined the key data and status of Immunocore's leading clinical molecules. He began with Tebentafusp (IMCgp100), the most advanced drug that is currently in pivotal registrational clinical studies for metastatic uveal melanoma. Importantly, this molecule has provided clinical proof-of-concept (PoC) for the ImmTAC platform with evidence for clinical activity and potential patient benefit in uveal and cutaneous melanoma. The activity in ocular melanoma is particularly noteworthy as this hard-to-treat

cancer type is insensitive to checkpoint inhibitors and has a low mutational burden. Two further ImmTAC molecules, directed against tumours positive for NY-ESO-1 (IMCnyeso, partnered with GSK) and MAGE-A4 (IMC-C103C, partnered with Genentech) are in Phase I clinical development stage. Due to the much broader tumour expression profile of these targets Immunocore expects applicability in a wide range of cancers. Dr. Dukes concluded that Immunocore has now built a strong emerging pipeline for internal and partnered programs to enter the clinic in oncology as well as in infectious and autoimmune diseases.

Session 3: Small molecule approaches

Going beyond combinations, bi-specific and bi-functional approaches in IO

Dr Tilo Senger (Development Program Lead in Oncology/Immuno-oncology) eloquently described aspects of Merck KGaA's research in an excellent talk. He began by presenting the options for addressing the challenges that face the immuno-oncology development community. Dr Senger then outlined Merck KGaA's twin paradigm of developing bifunctionals/bispecifics with strong rationale of superiority vs. combinations of two compounds for the same targets and advancing effective partnerships with academia/biotech/pharma to maximise resource and permit the integration of emerging technologies. His talk centred on three development programs that featured different aspects of these paradigms.

Firstly, studies around the investigational tumour-targeting immunocytokine M9241 (NHS-IL12) (2) were described. This work was conducted in partnership with the National Cancer Institute at Bethesda, USA. Preclinical data were presented demonstrating that the activity of Avelumab (anti-PD-L1) is increased in combination with NHS-IL12 (3). Treatment with NHS-IL12 also led to increased PD-L1 expression in mouse tumours, induction of tumour-infiltrating lymphocyte infiltration in EMT6 and MC38 murine models and increased proliferation and activation of tumour-associated macrophages, T-cells and NK-cells was observed. Indeed, this program has reached an exciting stage; a phase 1b, open-label, dose-escalation trial (JAVELIN study design) of NHS-IL12 and Avelumab treatment of advanced solid tumours, with sequential assignment of expansion cohorts, is underway and primary data are expected in January 2020.

Dr Senger then discussed approaches to targeting Indoleamine 2,3-dioxygenase 1 (IDO1) and tryptophan 2,3-dioxygenase 2 (TDO2), key players in establishing immune resistance in tumours and catalysing the commitment step of the kynurenine pathway (4). The profile of M4112, a dual IDO1/TDO2 inhibitor, was highlighted which offers an opportunity for differentiation; IDO1 and TDO2 have distinct natural expression sites and are upregulated on different tumour cells. Interesting results from a recent AACR Meeting disclosure (5) on clinical responses in a M4112 dose finding trial and unexpected pharmacodynamics effects in plasma (limited decrease of kynurenine on day 1 then returning to baseline levels by day 15) were presented. Further investigation is currently underway.

Dr Senger's third case study described the discovery of an innovative first-in-class bifunctional molecule (Bintrafusp alfa/M7824) in partnership with GSK. It is hoped that this TGF-β plus PD-L1 targeting bifunctional fusion protein will overcome poorly addressable tumour biology; M7824 exhibits stronger anti-tumour activity to co-administration of TGF-β trap and anti-PD-L1 in pre-clinical models (6). He showed promising data that indicated durable responses across all PD-L1 expression levels in a phase 1/2 non-small cell lung cancer (NSCLC) trial and marked responses in a phase 1 human papillomavirus-associated cancer trial. The Merck-GSK Alliance is currently evaluating the potential of M7824 to treat difficult-to-treat cancers such as unresectable NSCLC, biliary tract cancer and others, with results keenly anticipated.

Small molecule approaches to immune oncology

To set the scene for his engaging talk, Dr Simon Barry (Senior Principal Scientist and Small Molecule Immune-oncology lead at AstraZeneca, Cambridge) stated that the immune-oncology community is aiming to build on the foundation of PD1/L1 and CTLA4 (7). Also, driving effective anti-tumour T-cell immune responses may be accomplished by targeting the tumour microenvironment (to reverse immunosuppression) or tumour cells (to enhance immune engagement) or by enhancing immune priming and sustaining T-cell activation.

Dr Barry described the fact that targeting PI3Kα/δ(using AZD8835) appeared to be superior in his team's hands than targeting PI3Kδ alone (using PI-3065) for driving immune-dependent anti-tumour activity in a CT-26 syngeneic model (8). The question of whether inhibitors of the PI3K pathway have positive or negative effects on the anti-tumour

immune response was also addressed with the demonstration that PI3Kδ inhibitors dosed intermittently are more active in mouse syngeneic models than when dosed continuously (8). He also emphasised that transient suppression of PI3K-δ regulatory T cells was associated with the anti-tumour response following intermittent dosing but sustained elevation of CD8+ Tcells was achieved (8). Moving on to the evaluation of mTORC1/2, results were shown that Vistusertib and α-CTLA4 checkpoint blockade promotes immune anti-tumour responses in the CT26 model (9). In addition, Vistusertib/α-CTLA4 combination promotes a non-exhausted, Th1 effector response plus the activity of checkpoint inhibitors α-CTLA4, α-PD1 and α-PDL1 is all enhanced with Vistusertib (mTORC1/2) treatment in MC38 tumours (9).

Another interesting feature of this presentation involved the hypothesis of using unformulated next generation (Gen 2.5) antisense oligonucleotides (ASOs) to degrade mRNA of the transcription factor FOXP3 in order to provide anti-cancer benefit. Dr. Barry shared results of a collaboration between AstraZeneca and Ionis demonstrating that mouse FOXP3 ASOs promote potent FOXP3 downregulation in primary regulatory T-cells and deliver monotherapy efficacy in ID8-VEGF and A20 syngeneic models (dosing 50mg/kg BIW from d1 post-implantation). Gratifyingly, the immune changes induced by mouse FOXP3 ASOs are localised to the tumour (A20 mouse model), rather than the spleen, and FOXP3 ASO/PDx combination augments the depth of anti-tumour response. Modulation of STAT3 is known to be a global regulator of the tumour microenvironment (10) and Dr. Barry proceeded to show that downregulation of STAT3 by the ASO AZD9150 enhances PD-L1 inhibitor efficacy in the CT26 model. Collaborative efforts indicate that AZD9150 provides early evidence of clinical activity (11) in diffuse large B-cell lymphoma and lung cancer and

in combination with durvalumab (PD-L1 inhibitor) for the treatment of head and neck squamous cell carcinoma.

Specific tumour metabolites are thought to play a pivotal role in regulating T-cell function. Adenosine signaling also offers a therapeutic opportunity by tackling the immune suppressive tumour microenvironment. Dr. Barry shared data for the A2AR inhibitor AZD4635's (licensed from Heptares) ability to potently reverse adenosine mediated suppression of CD8+ T-cell activity and reduce tumour volume in combination with anti-PD-L1 monoclonal antibody in MC38 and MCA205 models. Targeting lactate transport offers yet another potential therapeutic approach (12). For example, the MCT4 inhibitor AZD0095 exhibits efficacy at 30mg/kg oral dosing BID in a MC38 MCT1 knockout model in combination with checkpoint inhibitors using various mass spectrometry techniques including MS imaging tumour cell lactate sequestration caused by AZD0095 has been analysed and the associated increased infiltration of immune cells to be imaged by mass cytometry.

Tumour genetics are likely to be important regulators of the response to immunotherapy. Loss of the phosphatase and tensin homolog PTEN promotes resistance to T cell-mediated immunotherapy (12). Dr Barry informed the meeting that PTEN-mediated immune resistance may be reversed by administration of the PI3Kbeta inhibitor GSK2636771. Similarly, in the context of BRCA mutation positive anti-tumour activity of the PARP inhibitor Olaparib (AZD2281) is achieved combination with anti-PD-L1 in a BRCA mutant syngeneic model.

The talk concluded with an impressive overview of the challenges facing the immune-oncology field. While there remains a sizeable opportunity around tumour-targeted combinations, Dr. Barry pointed out that non-clinical disease models remain suboptimal for effective decision-making, signals beyond the backbone therapy are currently limited and that increasing response rate in each disease segment is problematic. We are entering an exciting season in immune-oncology treatment with features associated with response emerging in some settings.

Session 4: Vaccines and gene therapy

Targeted immunotherapy for pre-invasive human papillomavirus disease

Professor Lucy Dorrell (Head of Translational Medicine - Infectious Diseases at Immunocore and Professor of Immunology at the Nuffield Department of Medicine within the University of Oxford) gave an insightful presentation into the progress that her team and collaborators have made in developing therapeutic vaccines for high risk (oncogenic) human papillomaviruses (hrHPV). hrHPV are responsible for a substantial disease burden globally, comprising virtually all cervical cancers and a high proportion of anogenital and head and neck cancers (14). Importantly, cervical cancer is the second leading cause of cancer death in women living in low/middle income countries, where access to cervical screening and prophylactic vaccines is limited (15). Globally, it is predicted that 600,000 women will be diagnosed in 2020, rising to 1.3 million a year in 2069, mainly due to the increasing size and average age of the population (15).

Therapeutic vaccination is a highly attractive, feasible and non-invasive approach to eliminating persistent hrHPV infection and cervical intraepithelial neoplasia (CIN) (16). Professor Dorrell and her team at Oxford have led the development of a potent heterologous viral vector “prime-boost” platform (a replication-defective chimpanzee adenovirus, ChAdOx1 (16), and modified vaccinia Ankara, MVA (17) to deliver a unique, bioinformatically designed HPV immunogen. '5GHPV3' comprises sequences from the 6 early proteins that are conserved across 5 high-risk genotypes including HPV16 and HPV18. In mouse models, they detected high frequencies of polyfunctional CD8+ and CD4+ T cells specific for 5GHPV3 in both the circulation and the cervix following systemic administration of viral vectored 5GHPV3 vaccines. HPV-specific T cells persisted for at least 6 weeks and were targeted to all early proteins in outbred mice.

In parallel, Professor Dorrell’s team are also conducting a prospective observational longitudinal study to explore the immunological correlates of viral clearance and persistence in women with current or prior hrHPV infection. One hundred and forty-five women aged 16-55 years have been recruited to date, with nearly half completing one year of follow-up to date. Up to 20% women had detectable T-cell responses to reference early protein sequences from HPV16 and HPV52, the majority of whom also made responses to 5GHPV3-derived peptides. This data confirmed the relevance of their immunogen sequence to natural hrHPV control.

Professor Dorrell concluded by stating that, based on their encouraging preclinical data, GMP manufacture and preclinical toxicology of their vaccines is underway in preparation for a proof-of-concept clinical trial in women with low-grade cervical HPV lesions. In addition, this vaccine technology has potential application to other populations including HIV+ patients and other HPV driven diseases.

Systemic delivery of localized combination immuno-gene therapy within the tumour microenvironment

Dr David Krige (Director of Translational Medicine, PsiOxus Therapeutics) gave an excellent overview of the novel and versatile oncolytic adenoviral vector platform for the selective systemic delivery of tumour-specific immuno-gene therapy (T-SIGn) that has been established by PsiOxus Therapeutics.

The platform was developed using a directed evolution process that involved passaging a very large randomly created library of chimeric adenoviruses repeatedly on human carcinoma cells, selecting for the most potent tumour killing viruses and then back-selecting these for lack of activity against normal human cells. The most potent of these were then screened against human carcinoma cells in the presence of fresh human blood to ensure stability and therefore suitability for intravenous systemic delivery. This resulted in the final selection of a viral vector known as Enadenotucirev (EnAd), which forms the basis of the platform (19). EnAd consists of an Ad11 capsid, to which there is low pre-existing immunity, a chimeric Ad11/Ad3 E2B region and deletions in E3 and E4orf4. In preclinical models, EnAd has demonstrated broad spectrum, potent anti-tumour activity and tumour selective replication. In cancer patients, EnAd has displayed a predictable and manageable safety profile following systemic (IV) dosing (20) as well as virus delivery and selective replication in tumour cell (21).

The deletions in the genome provide space for the insertion of multiple custom transgenes under the control of the virus major late promoter, allowing the EnAd vector to be armed while maintaining its tumour selective properties – “T-SIGn” viruses. Given that the encoded therapeutics are expressed from the virus major late promoter, products are only made in cells supporting virus replication, i.e. tumour cells. T-SIGn genome modification produces no changes to the structural properties of the virus particles, and several different therapeutic transgene payloads can be encoded within a single virus without impacting virus or payload production levels (up to 5, with a cloning capacity of approximately 3kb). This approach has several advantages, including:

- Intravenous systemic delivery of the viral vector but local production of biologics within tumour tissues, thereby enhancing local effects in the tumour microenvironment while minimizing systemic toxicities
- The use of novel therapeutic approaches for molecules with poor PK or which are poorly tolerated when dosed systemically.

A pipeline of T-SIGn candidates, differentiated by mechanism and targeted patient populations, are in both preclinical and clinical development. Dr Krige gave an overview of two such products; NG-641 (expressing fibroblast activating protein (FAP)-targeting bispecific T-cell activator (FAP-TAc), CXCL9, CXCL10 and IFNα transgenes), and NG-350A (anti-CD40 agonist antibody).

Extensive preclinical data were presented demonstrating that NG-641 has the desired anti-tumour properties including the ability to induce rapid activation of T-cells and killing of stromal fibroblasts, and to promote the selective T-cell mediated killing of FAP+ fibroblasts by infected tumour cells in primary malignant cell cultures leading to decreased TGFβ levels. Because in cold tumours the activity of FAP-TAc alone may be limited by insufficient T cells,

NG-641 includes CXCL9 and -10 to induce the migration of T cells and IFNα to drive innate immune cell (e.g. dendritic cell) activation and T-cell priming. A wide-ranging translational strategy for clinical trials has been developed which will use multiple different experimental methods, designed to investigate virus delivery to, and transgene expression within, tumours (proof of mechanism), the immune effects of virus/transgene (proof of principle and pharmacodynamic readouts) and potential predictive biomarkers.

The second T-SIGn candidate presented by Dr. Krige (NG-350A) has already reached the clinic and is currently in a multi-centre, open-label, first-in-human Phase I trial (NCT03852511). The study was initiated in February 2019 and will examine safety, tolerability and preliminary efficacy of NG-350A together with virus kinetics, immunogenicity and other pharmacodynamic effects in patients with advanced or metastatic epithelial tumours. The Phase IA dose escalation phase will investigate NG-350A given to patients by IV infusion on Day 1, 3 and 5. A parallel cohort will be given a single dose of NG-350A by intra-tumoral injection on Day 1 to provide an opportunity to perform translational research. Phase IB of the study, using the recommended dose from Phase IA, will investigate efficacy in up to three separate IV dosed cohorts of patients with epithelial tumour types.

In summary, PsiOxus have developed a platform that allows selective systemic delivery of tumour-specific immuno-gene therapy (T-SIGn) combinations locally within tumour tissues, thereby providing a route for “gene therapy” of cancer. They have a pipeline of candidates, differentiated by mechanism and targeted patient populations, which are in preclinical and clinical development.

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