34th International Conference

Advances in the Applications of Monoclonal Antibodies in Clinical Oncology and Symposium on Neuro-Oncology

Grecian Park Hotel, Konnos Bay, Cyprus

12- 14 June 2017

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Anastasis Biotec Ltd

PROGRAMME

Day 1 Monday 12th June 2017

9.00-9.30 **Registration**

9.30-9.35 Welcome **Agamemnon Epenetos**

SESSION 1 Chairperson: Sir Walter F Bodmer

9.35-10.00 Klaus Bosslet Therapharm GmbH, Germany

ASCO 2017: Clinical progress and mechanistic learnings

Within the last 20 years progress in cancer therapy was mainly driven by drugs which interfere with signalling pathways in tumour cells, endothelial cells and,most recently , immune cells.

Signalling inhibition can be achieved by various mechanistic approaches:

1: Ligand neutralization avoiding receptor activation (dimerization) and blockade of ligand driven signalling.

2: Direct binding to receptors blocking receptor dimerization and cross talk on the same tumour cell.

3: Interference with receptors and their ligands on immune cells (T-cells) and tumour cells.

Already, several drugs working according to the above mentioned mechanisms have been approved and are having a significant impact on cancer patients survival.

This update highlights some of the progress achieved with clinical development candidates as presented at ASC0 2017. I will focus on :

- The progress in the field of immuno-oncology (interference of T-cells with cancer cells) as well as innovative approaches in signalling.

- Clinical studies with immune check point inhibitors, used as single agents and/or in combination with other drugs with different modes of actions .

10.00-10.20 Mahendra Deonarain, Antikor Biopharma & Imperial College London ,UK.

Antibody-Drug Conjugates: What's on the horizon ?

The concept of Antibody Drug Conjugates (ADCs) is practically as old as Antibodies themselves and having been though several technology cycles, there are only two approved products. What can we expect in the near future from all the refinements in conjugation chemistry and payload potency ? Can we achieve the therapeutic window that has bee so lacking from current generation technologies. An outline of current and next-generation ADCs will be given looking forward to new potential products for difficult to treat solid tumours.

10.20-10.40 Jens Hoffmann, Maria Stecklum, Annika Wulf-Goldenberg, Bernadette Brzezicha, Iduna Fichtner, EPO Experimental Pharmacology & Oncology Berlin-Buch GmbH, Berlin, Germany.

Preclinical "humanized" tumour models for the characterization of functional antibodies and drug conjugates

The evaluation of functional antibodies for antitumour immune therapy is still a challenge for the preclinical research as the classical syngeneic tumour models are of limited translational value and patient-derived human tumour xenograft models (PDX) could only be grafted on immunodeficient animals. Translational research however, urgently needs models for identification of clinically relevant biomarkers and defining rational combination strategies. Human patient-derived xenografts (PDX) from different tumour indications transplanted on immunodeficient mice have not shown strong predictive value in drug development programs.

To overcome the current constraints our aim is the development of PDX models in mice with a functional human immune system. This strategy should allow to implement the highly predictable PDX in a functional human immune environment to study drug efficacy and safety .

We reconstituted a human immune system in mice by engrafting human hematopoietic stem cells in immunodeficient mice. We have demonstrated the engraftment of a full set of human immune cells, including T cells, B cells, NK cells, monocytes and dendritic cells.

When the human immune system is developed, we then establish patient-derived xenografts in these humanized mice.

To test the functionality of the human immune cells, mice were treated with checkpoint inhibitors ipilimumab and nivolumab. Checkpoint inhibitors alone or in

combination led to a minor tumour growth delay and an increased number of activated T-cells in the blood and in the tumour.
Thus this humanized PDX model can enable appropriate preclinical studies on tumour immune biology, evaluation of new immune therapies and combinations, as well as the identification and validation of biomarkers for tumour immunotherapy.

10.40-11.00 Walter Bodmer ,Weatherall Institute of Molecular Medicine, Department of Oncology, University of Oxford, UK

Some thoughts on a programme for cancer immunotherapy

I will outline my personal view of a strategy for a cancer immunotherapy programme. It would have two major components, one based on a variety of engineered monoclonal antibodies, including T-cell bispecific antibodies, and the other based on enhancing the adaptive immune response to cancers. In both cases combinations with check point inhibitors would play an important but not overriding role. I would not include cellular based therapies or antibody drug conjugates.
I will illustrate approaches to in vitro testing of bispecific antibodies and their combination with check point inhibitors through some results obtained in our laboratory by Djamila Ouaret. I will also emphasise the need for new approaches to immunisation for boosting the adaptive immune response to cancers and the need to develop in vitro models for investigating the immune response.

11.00-11.30 Coffee Break

SESSION 2 Chairperson: Klaus Bosslet

11.30- 11.50
Alex Duncan, Chief Technology Officer
Agenus Inc, Lexington USA

Approaches to Generating and Improving Response Rates to Cancer Immunotherapy with Combinations

Agenus has assembled a suite of different antibody discovery technologies to isolate and test antibody drug candidates as immune checkpoint modulators. In addition 'omic technologies have been employed to transform an autologous cancer vaccine, derived from patient tumour, into a recombinant neoantigen specific vaccine platform. Examples will be presented how the combination of CPMs with individualized cancer specific vaccines could increase patient response rates and provide durable outcomes for those with cancer.

11.50-12.10 Djamila Ouaret, Weatherall Institute of Molecular Medicine and Department of Oncology, Oxford University, UK

Predicting response to anti-IGF1R therapy using a panel of colorectal cancer cell lines

Initial trials using therapies targeting the type 1 insulin like growth factor receptor (IGF1R) have been disappointing for the treatment of colorectal cancer (CRC) emphasising the importance of identifying biomarkers to predict response to anti-IGF1R therapies. In this study, we have investigated the response to OSI906, a tyrosine kinase inhibitor and the monoclonal antibody Figitumumab, in a large panel of CRC cell lines. This panel is extremely well characterized at the biological and molecular level, therefore allowing association between anti-IGF1R therapy response, gene mutations and gene expression.

Our results clearly show that mutations in *PIK3CA* exon 9 and 20 are associated with resistance to OSI906 and Figitumumab. Interestingly, in a subset of PIK3CA wild-type cell lines refractory to OSI906 treatment, we have tested the efficacy of a

combination to a pan-Akt inhibitor based on evidence that the AKT pathway was upregulated in these cell lines. This combination resulted in synergistic effects on cell lines characterised by a *KRAS* wild-type, a high expression of the cell surface protein CD24 and Akt-dependant GSK-3β phosphorylation.

Thus, these findings suggest for the first time an important role of the PI3K/Akt signaling pathway in the response to OSI906 in CRC. Furthermore, we have identified *PIK3CA* mutations as a biomarker for anti-IGF-1R therapy resistance in CRC. Our study also indicates that the co-targeting of IGF1R and AKT pathways could be a novel therapeutic approach for the treatment of CRC in a genetically and molecularly defined subgroup of tumours.

Taken together, our data provide strong evidence of a genetic profile for selecting patients who should benefit from OSI906 treatment in future clinical settings, either in monotherapy or in combination to an AKT inhibitor

12.10-12.30 Nelson Castellanos Rios , Associate Consultant | Business & Technology Solutions (BTS) ,Capgemini, UK.

The Project Life Cycle

The project life cycle varies across different industries. All projects have a beginning, an end and various stages of advancement, referred to as life cycle phases. In recent years, life cycle management has become a dominant area for debate in project management, recognising its value is vital to increasing efficiency and concluding a project successfully.

The project life cycle will typically encompass five main stages, feasibility, initiation, planning, execution and close-out. There are various Project Management methodologies available that can be applied to manage each phase. In the session we will go through the different methodologies and tools available for each phase; emphasising budgeting, forecasting, planning and RAID

management. This will provide a concise framework to help understand the Project Management activities, what tools are available throughout the project lifespan and how to successfully start, track and complete a project within the defined time scale and budget.

12.30-2.30pm Lunch Break

2.30- 3.30 pm Open Air workshop Chairpersons : Sir Walter Bodmer, Alexander Duncan
Immuno-Oncology , Today and tomorrow

Day 2 13 June 2017

Session 3
Chairperson Kerry Chester

Neuro- Oncology Symposium

9.00-9.30 Paul Mulholland, UCL, London, UK .

Immunotherapy for glioma patients

Glioblastoma is the most common form of primary brain cancer. Prognosis for newly diagnosed patients is less than one year. Recent clinical trials have all failed to show improved survival. It is becoming clear that there is a complex relationship between glioblastoma, its immune micro-environment and the interaction with the systemic immune system which can be targeted as treatment.

Different forms of Immunotherapy are in various stages of development for the treatment of glioblastoma, including dendritic cell therapy, peptide vaccination and immune check point inhibitors. This session will review the status of immunotherapy in glioblastoma and the potential to treat other gliomas.

9.30- 10.00 Thomas Carter, Clinical Research Fellow, UCL Cancer Institute/University College London Hospital, London , UK

Nanomedicine for Hyperthermia in Glioblastoma

Despite advances in other tumour types, prognosis for glioblastoma remains poor with a median survival of just over one year following diagnosis. Following surgical resection, patients receive radiotherapy and temozolomide chemotherapy but the majority of patients relapse following this treatment. There is currently no standard second line therapy. Immunotherapy is a promising area of research in glioblastoma, and there are number of ongoing trials investigating both immune checkpoint inhibitors and tumour vaccines.

Hyperthermia therapy can initiate sub-lethal cellular damage and may even generate 'in-situ anti-tumour vaccination' using temperatures of between 43-45**°**C; temperatures which non-cancerous cells can often withstand. The main challenge in hyperthermia therapy has been generating localised heat specifically within tumours, and one solution to this is through the use of superparamagnetic iron-oxide nanoparticles (SPIONs), which can be localised within tumours and activated using an externally applied magnetic field to release energy in the form of heat; a process known as alternating magnetic hyperthermia (AMF).

Understanding the biological response to SPION treatment is pivotal for clinical translation. Towards this, we have recently demonstrated that AMF is capable of initiating a specific, localised, heat-shock protein response in an *in-vivo* model of glioblastoma, along with a transient inhibition of tumour growth. Furthermore we have generated evidence that AMF can initiate an anti-tumour immune response. This response is characterised by an influx of activated cytotoxic T-cells following treatment along with an increase in proliferating regulatory T-cells. These results

suggest that AMF could act as an *in-situ* tumour vaccine and work synergistically with treatments designed to inhibit the immunosuppressive effects of regulatory T-cells such as immune checkpoint inhibitors.

10.00-10.30 Shimobi Onuoha, Autolus Ltd, UK

Targeting T-Cell Receptor β-Constant Domain for Immunotherapy of T-Cell Malignancies.

T-cell lymphomas are an aggressive group of cancers. The outcome is poor, and unlike B cell cancers there are no effective immunotherapies. Chimeric Antigen Receptor (CAR) T-cells targeting pan-B-cell antigens such as CD19 is acceptable since deletion of the normal B-cell compartment is surprisingly well tolerated and can be mitigated by administration of pooled immunoglobulin. In contrast, targeting a pan-T-cell antigen to treat T-cell cancers would result in depletion of the entire normal T-cell compartment, resulting in profound immunosuppression that cannot be mitigated. We have identified a CAR target that allows targeting of a T-cell lymphoma in its entirety but spares approximately half of the normal T-cell compartment. Here, we present data describing the development and pre-clinical characterisation of the CAR.

10.30-11.30 Coffee break

11.30-12.00 John Anderson , UCL Great Ormond Street Institute of Child Health, UK.

Modulating chimeric antigen receptors to fine tune sensitivity and specificity

Tumour immunotherapy has come to the fore, fuelled by impressive clinical responses to checkpoint inhibitor antibodies in a range of adult malignancies, and by the success of CAR T cells targeting adult and paediatric B cell malignancies. Clearly, if appropriately fine-tuned, the immune system has the capability to seek out and destroy cancer. Studies in paediatric solid cancers have not so far shown the therapeutic potential checkpoint inhibitors described in adults cancers and this may reflect fewer tumour associated antigens or different immune evasion

mechanisms. One potential approach to overcome these limitations will be combine interventions to undermine immune evasion mechanisms with engineered T cell adoptive transfer.

12.00- 12.30 Kathleen Birley, UCL Great Ormond Street Institute of Child Health, UK.

Developing Antibodies against B7-H3 as a Target for Cancer Treatment

Introduction

B7-H3 is a transmembrane protein present in a wide variety of childhood and adult cancers including neuroblastoma and diffuse intrinsic pontine glioma but relatively absent from healthy tissue. It acts as a ligand for an unidentified receptor and although its actions remain poorly understood, current evidence supports a role in immune inhibition and oncogenesis. We aim to develop antibodies against B7-H3 as target for cancer therapy in children.

Methods

3 mice were immunised with a B7-H3-Fc fusion protein. The mice were sacrificed and splenic mRNA used to develop a phage display library in the pHEN phagemid. Panning of this library was carried out against B7-H3 immobilised in immunotubes or on beads. Phage producing ScFvs (single chain variable fragments) showing positive binding against B7-H3 were selected for further evaluation.

Results

The 3 immunised mice showed positive seroconversion against a range of B7-H3 isoforms. Analysis of the library demonstrated it was of adequate size and quality for ScFv production. ScFvs showing positive binding to B7-H3 have been selected for further testing.

Discussion

ScFvs which display positive binding to B7-H3 have been identified. These can be used to develop a variety of different immunotherapies. Although mortality associated with children's cancer is improving, several types of tumours, including

CNS tumours, continue to have a poor prognosis and the morbidity associated with current therapy remains high. It is hoped that immunotherapy against specific targets such as B7-H3 will lead to novel treatment and improved survival for these patients.

12.30-1.00 Christoph Goletz, Berlin, Germany.

Glyco-engineering of an anti-PD-L1 antibody

The PD-1/PD-L1 axis plays a central role in suppression of anti-tumour immunity. Blocking the axis by targeting PD-L1 with monoclonal antibodies is a promising and already clinically approved approach to treat cancer patients. Glyco-engineering technology can be used to optimize different properties of monoclonal antibodies, for example their bioactivity. Using the human expression platform GlycoExpress™ we generated two differently glycosylated anti-PD-L1 antibodies: an anti-PD-L1 antibody bearing core fucosylated *N*-glycans in its Fc part and a fucose-reduced counterpart. The two glycosylation variants were compared to a non-glycosylated commercially available anti-PD-L1 antibody in various assays. PD-L1 and FcγR binding of the different variants were assessed using ELISA, flow cytometry and bead-based AlphaScreen technology. Mixed lymphocyte reactions were performed to compare their capacity to induce T cell activation. The systematic comparison of anti-PD-L1 antibody glycosylation variants with different Fc-mediated potencies demonstrates that our glyco-optimization approach has the potential to improve the therapeutic benefit of anti-PD-L1 antibodies.

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1.00-2.30 Lunch break

2.30 -3.30 Open Air workshop Chairpersons : Kerry Chester, John Anderson
What the future holds for Neuro-oncology

Day 3 14 June 2017

Session 4 Chairperson: Aleksandra Filipovic

9.00- 9.30 Niki Agnanti , Ioannina University, Greece.

The Pathologist's contribution to cancer research and clinical practice

Pathology acts as a bridge between Clinical Medicine and Basic Sciences, particularly regarding Oncology. In every-day practice, cancer diagnosis depends on macroscopical and microscopical examination. Pathologists decide on the type, grade and stage of the tumour. Furthermore, identification of genetic alterations, such as DNA mutations, chromosomal aberrations, epigenetic modifications, altered protein-protein interactions are important both in the making diagnosis, treatment and prognosis. Two of the commonest carcinomas are those of breast and colon. In recent years molecular studies have changed the way these cancers are perceived. Molecular classification of breast cancer based on complex patterns of gene expression, provides a link between the molecular biology of breast cancer and the behaviour of cancer cells in the intrinsic subtypes. Although it is clear that traditional histological evaluation of breast cancer is of important value, the actual complexity of the disease cannot be fully understood without taking under consideration of breast cancer genome and proteome. It is expected that histological and molecular taxonomy would be integrated for a better management of breast cancer.

Regarding colorectal adenocarcinoma, besides the traditional pathway to carcinogenesis (adenoma-carcinoma sequence, implication of APC, KRAS, DCC, SMAD2/4, p53 mutations and chromosomal instability) a new serrated pathway has been recently reported. This is a distinct and separate pathway involving BRAF, KRAS mutations, GpG-island methylation and MSI (microsatellite instability).

As Precision Oncology and Therapeutics are beginning to be based on particular molecular characteristics of each neoplasm, the availability of these tests for all patients is an issue of great interest and importance.

9.30-10.00 Claudio Sustmann, Roche Innovation Center Munich, Germany.

Antibody engineering in drug discovery & development at Roche

Bispecific antibodies are an important drug class in oncology but also beyond. Identification of the best candidates for a certain application is a challenging task. These aspects as well as selected examples of Roche development candidates will be in focus of the presentation. In particular, application of the IgG-like bispecific CrossMab technology in different disease areas will be addressed.

10.00 -10.30 Enrique Miranda Rota, UCL, UK

Developing Antibody-Based Treatments for Cervical Cancer

Cervical cancer is the 13th most common cancer in women, with a higher incidence in young women (25 to 39 years of age). Despite recent development of HPV vaccines, not all cancers are HPV-derived and a large percentage of women have not been vaccinated; as a result, nearly a 1000 women died from the disease every year. Current treatments consist on surgery, internal radiotherapy and classical chemotherapy combinations and lack targeting properties that could improve payload delivery specifically to the tumour. Based on histological examination of biopsies from cervical cancer patients, we observed that over 80% of cervical

cancers expressed CEA and/or integrin $\alpha_v\beta_6$. In addition, the expression of these proteins showed a spatially-exclusive pattern that could affect the outcome of therapies based solely on a single target. Hence, we designed antibodies targeting both CEA and/or $\alpha_v\beta_6$ by insertion of an integrin-binding peptide into critical regions of an anti-CEA antibody. This novel antibody retained CEA binding while exhibiting additional nanomolar affinity to $\alpha_v\beta_6$ and could target both CEA and $\alpha_v\beta_6$ expressing tumour cells. Their development as antibody-drug conjugates will be discussed.

10.30 -11.30 Coffee Break

Session 5 Chairperson: Agamemnon Epenetos

11.30 -12.00 Jenny Thirlway, Glythera Ltd, UK .

Assessing the therapeutic efficacy of a broad range of novel toxins conjugated using the stable, non-maleimide, technology of PermaLink®.

Antibody Drug Conjugates (ADCs) are an emerging class of targeted therapeutics with the potential to improve therapeutic index over traditional chemotherapy. By combining the targeting power of antibodies with the cell killing capability of potent cytotoxic molecules, it is possible to kill cancer cells more effectively whilst reducing debilitating side effects.

Glythera's PermaLink® technology has been validated in a range of ADC models and demonstrated improved stability, efficacy and tolerability profiles. Using these important differentiators Glythera has accessed a portfolio of toxins with known and novel modes of action and has completed the three part ADC jigsaw by additionally accessing novel antibodies through its partners.

12.00-12.30 Mahendra Deonarain, G.Yahioglu I. Stamati ,

Antikor Biopharma & Imperial College London , UK.

Fragment Antibody Drug Conjugates (FDCs): Specifically designed oncology therapeutics for solid tumours.

There are over 60 ADCs in clinical development, around half against solid tumours. All of these are based on whole antibody formats which are known to penetrate solid tumours slowly. A number of developers are investigating smaller formats of ADCs with faster tumour penetration properties. Antikor have developed FDCs based on their OptiLink technology where single-chain Fvs can be engineered to carry up to 10 cytotoxic payloads but still retain favourable pharmacokinetic and pharmacodynamic properties. Here we will present compelling data to show that FDCs can specifically address the treatment of solid tumours in a way that conventional ADCs have been unable to.

12.30-1.00 Aleksandra Filipovic , ICL and Puretech , UK and USA.

Puretech model of bringing life to science: venture creation of breakthrough academic science

Pure Tech Health is a modern biopharmaceutical company focused on the adaptive systems of the human body, including the immune system, the central nervous system and the enteric nervous system in the gut. Pure Tech Health has a pipeline of clinical and pivotal stage product candidates that target major chronic diseases.

1.00 Farewell