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11th International Congress on Targeted Anticancer Therapies (TAT)

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SUMMARY

The 11th International Congress on Targeted Anticancer Therapies (TAT) was held in Paris for the second time under the presidency of Professor Jean-Charles Soria, Institut Gustave Roussy, Villejuif, France. The TAT Congress was co-sponsored by the Amsterdam-based NDDO Education Foundation and European Society for Medical Oncology (ESMO). NDDO is the primary organizer of all meetings in the TAT congress series, which aims to disseminate findings from experimental and clinical studies on the prevention and treatment of different types of cancer. ESMO is the foremost European professional organization committed to advancing the specialty of medical oncology and promoting a multidisciplinary approach to cancer treatment. The TAT Congress is also sponsored by the USA National Cancer Institute (NCI)/Center for Cancer Research, which is the world's largest organisation dedicated to cancer research.

The TAT 2013 Congress was attended by over 500 delegates from 46 countries, primarily from Europe (about 65%), but also from Australia, Canada, the United States and, for the first time, China was represented. The quality of the scientific programme and interesting topics covered this year drew the highest number of participants ever recorded. Many areas of intriguing early-phase clinical and translational research on dozens of new targets and targeted agents for cancer treatment were covered. As before, this year's TAT program featured a number of previously unreported findings from phase 1 trials.

INTRODUCTION

The TAT 2013 programme consisted of 12 consecutive plenary sessions held during the three-day conference. The Congress was planned without parallel sessions, allowing all participants to be able

to attend each of the 61 lectures presented by leading experts in the field of clinical cancer research and drug development. The NDDO Honorary Award Lecture, a key element of all TAT meetings, was presented during the opening ceremony in the first plenary session by Dr. Jean-Pierre Armand from Paris, France, who was awarded the TAT - NDDO Lifetime Achievement Award in recognition of his work which focused on the discovery and development of better anticancer medicine and pioneered the development of several anticancer drugs now commonly used in clinical practice. The lecture was entitled "Phase 1, a Critical Step for Cancer Drug Development" and stressed the importance of the phase I clinical study in drug development, which makes it possible to predict the potential clinical development of drugs. He emphasised that bringing new drugs to clinical practice requires a close collaboration between physicians and biotech companies, giving doctors the opportunity to work with the production capacity of the drug industry is the key to facilitating more rapid development of anticancer drugs. For this reason, Dr. Armand has created a complex in Toulouse where hospital facilities and the pharmaceutical industry coexist in the same place.

NEW IMMUNE CHECKPOINTS AS DRUG TARGETS

Plenary session 2 opened with the Keynote lecture on the role of the immune system as a potential target for the development of anticancer drugs and was delivered by Dr. Michael B. Atkins, of the Georgetown-Lombardi Comprehensive Cancer Center in Washington, DC, USA who presented an overview of immune checkpoints. He emphasized checkpoints which may be targeted for treatment and have allowed the recent development of new anticancer drugs such as ipilimumab, a new immunotherapy option, particularly for patients with metastatic melanoma. He also discussed numerous vaccine approaches in melanoma and other cancers that have yielded a low rate of clinical response, even though the induction of specific T cells could be detected in the peripheral blood. This observation has prompted several investigators to investigate the tumour microenvironment for biologic correlates to tumour response versus resistance. Evidence is beginning to emerge suggesting that distinct subsets of tumours may exist that reflect distinct categories of immune escape. Lack of chemokine-mediated trafficking, poor innate immune cell activation and the presence of specific immune suppressive mechanisms can be found to characterise subsets of tumours. Multiple immune suppressive mechanisms that may inhibit T cell function in the cancer context have been described.

Currently, immune checkpoints are being evaluated as targets for the development of four novel drugs. In particular, it has been noted that tumours may contain high levels of transcripts of programmed cell death-1 ligand 1 (PD-L1), a ligand for the PD-1 inhibitory receptor expressed on activated T cells. Early phase clinical trials are ongoing to block PD-1/PD-L1 interactions; specifically, neutralizing monoclonal antibodies (mABs) against either PD-1 or PD-L1 are being tested. Daniel Chen, from Genentech, in South San Francisco, USA discussed the clinical development of

MPDL3280A, an IgG4 monoclonal antibody targeting PD-L1. Results of phase 1 clinical studies indicate that the drug has a good safety profile.

Two monoclonal antibodies targeting PD-L1, MK-3475 and nivolumab are in clinical trials. Dr. Alexander Eggermont, Institut Gustave Roussy, Villejuif, France reported phase I data for MK-3475, a humanized anti-PD1. MK3475 has shown evidence of antitumour activity in patients with metastatic melanoma where a response rate of 51% was demonstrated. An update on nivolumab, a fully humanized monoclonal antibody against PD-1 was provided by David Feltquate, Bristol-Myers Squibb, Princeton, NJ, USA. Nivolumab showed antitumour activity in 304 heavily pretreated patients who demonstrated durable clinical benefit in melanoma, non-small cell lung cancer (NSCLC), and renal cell carcinoma. Drug-related adverse events of special interest (AEOSI) included colitis, hepatitis, hypophysitis, nephritis and thyroiditis. These findings support the importance of the PD-1 pathway in cancer therapy across multiple histologies and a phase III trial with nivolumab has been started.

James Smothers, GlaxoSmithKline, Collegeville, PA, USA discussed another novel agent targeting PD-1, AMP-224, which is an Fc-fused PD-L2 that can bind PD-1 on the surface of T cells. AMP-224 has a differentiated mode of action from PD-L1 antibodies that may demonstrate a different clinical profile.

DRUGS TARGETING THE RAS/RAF/MEK PATHWAY

A plenary session of great interest was on drugs targeting the RAS/RAF/MEK pathway. This session opened with an educational lecture entitled "the RAS-MAPK Pathway" given by Dr. Ji Luo of the NCI, Bethesda, Maryland, USA that updated information on the RAS/RAF/MEK/ERK signalling pathway, which is constitutively activated in several cancers and leads to uncontrolled cell proliferation, resistance to apoptosis and associates with a more aggressive neoplastic phenotype of breast cancer. Signalling alterations in this pathway may occur due to mutations of BRAF and RAS gene family members; mutations in KRAS are associated with resistance to epidermal growth factor receptor (EGFR) inhibitors. Dr. Luo also reported on drugs targeting RAF kinases in BRAF and KRAS mutant cancers, such as inhibitors of RAF (vemurafenib, dabrafenib, sorafenib, regorafenib) and MEK (trametinib, selumetinib). MEK inhibitors showed improved progression-free survival (PFS) in patients with melanoma and BRAF mutations and also demonstrated improved PFS in patients with lung tumours who were selected for mutant KRAS; however MEK inhibitors lacked efficacy in unselected patients.

KRAS mutations occur in approximately 25% of lung adenocarcinomas and are associated with a decreased response to EGFR tyrosine kinase inhibitors such as erlotinib and with worse survival.

Until very recently RAS had not been successfully targeted therapeutically in NSCLC. However, Dr. Corey A. Carter of NCI, Bethesda, Maryland, USA, presented findings from a prospective phase II clinical trial that tested selumetinib, a MEK inhibitor, with and without erlotinib in patients with advanced KRAS mutation-positive NSCLC. Selumetinib as monotherapy showed a response rate of 5% and, in combination with erlotinib, showed similar activity as reported for monotherapy erlotinib in patients with advanced NSCLC who did not have a known RAS mutation. MEK inhibitors have thus emerged as an important drug class to consider for these patients. These data are still experimental, and a pending phase III trial will provide more insight.

Dr. Anthony Tolcher, START, San Antonio, TX, USA reported on dual combinations of agents that involve MEK inhibition. Often two signalling pathways, the RAS/RAF/MEK and PI3K/AKT/mTOR pathways, are co-activated in tumours. Two strategies that may be effective for KRAS mutation-positive NSCLC are currently being tested in clinical trials: 1) concurrently targeting the MAPK and AKT/PI3K pathways by using inhibitors of MEK and mTOR inhibitors, respectively and 2) concurrently targeting the MEK and EGFR pathways, using selumetinib and erlotinib in combination. Another important pathway activated in cancer is the PI3K/AKT/mTOR signalling pathway. Preclinical evidence suggests a cross-talk between the two pathways and preclinical data suggest that antitumour activity by AKT inhibition can be abrogated by activating RAS mutations. Similarly, activation of the PI3K and AKT decreases activity of inhibitors of the RAS/RAF/MEK pathway. These data support the hypothesis that combined inhibition will enhance antitumour activity. A remarkable example of tumour shrinkage was shown following treatment with MEK and AKT inhibitors in a woman with triple negative breast cancer who had BRAF amplification as determined by genome sequencing. Unfortunately the preclinical assumptions do not always translate to clinical practice; results from phase I clinical trials of a combination of MEK and PI3K/AKT/mTOR inhibitors have shown that this association is not feasible due to toxicity that is predominant at low dose levels preventing the achievement of an effective therapeutic dose.

PHASE I STUDIES, COMPLETED OR IN PROGRESS

Plenary session 3 was devoted to clinical phase I trials and reports on the efficacy and tolerability of new anticancer drugs.

Galeterone (OK-001) is a small molecule in clinical development for the treatment of castration-resistant prostate cancer (CRPC), an advanced form of prostate cancer that occurs when the disease progresses after treatment with androgen deprivation therapy. Galeterone disrupts androgen receptor (AR) signalling, the key driver of CRPC, via a novel triple mechanism of action; it selectively inhibits CYP17-lyase to prevent testosterone synthesis, antagonizes testosterone binding to the AR and degrades the AR protein. Data were reported by Adrian Senderowicz, Tokia Pharmaceuticals,

Cambridge, MA, USA who presented findings from a phase I proof-of-concept study, ARMOR1, showing that galeterone was well-tolerated with minimal side effects and demonstrated clinical activity in patients with CRPC. In early efficacy tests, 49% of patients had prostate specific antigen (PSA) reductions of 30% or more; 11 of these patients had reductions of 50% or more. Reduction of PSA levels by 30% or more is considered to be quite good in a phase I dose-finding trial. Based on these results, galeterone is currently being evaluated in patients with CRPC in a phase II study, ARMOR2.

Inactivation of p53 by mutation or indirect mechanisms confers increased resistance to conventional chemotherapeutic drugs. Therefore, mutant p53-carrying tumours constitute a major therapeutic challenge, making mutated p53 an attractive target for novel cancer treatment, and several strategies for therapeutic reactivation of p53 have been developed. APR-017 (PRIMA-1) and its methylated form APR-246 (PRIMA-1MET) are first-in-class drugs that were identified in a screen for small molecules that selectively induce apoptosis in cancer cells with mutant p53. Dr. Klas Wiman, Karolinska Institute, Stockholm, Sweden discussed APR-246, which is the first drug of this class that has reached a clinical phase. A phase I/II dose-escalation safety study of APR-246 in patients with refractory haematological malignancies or prostate cancer has been conducted that showed that APR-246 is safe and has a favourable pharmacokinetic profile. APR-246 also demonstrated biologic effects, including activation of the p53 pathway in tumour cells during drug exposure in vivo, as well as examples of clinical effects. Clinical protocols with extended exposures to the drug as well as protocols with combination therapies are currently under development.

Akt functions as a pivotal junction in the phosphatidylinositol 3-kinase (PI3K) cell survival pathway. In cancer, Akt activity is frequently elevated due to multiple mechanisms that include loss of function of the PTEN tumour suppressor gene and mutations of the PIK3CA gene. Akt acts as a key survival kinase in many cancers. Dr. Rhoda Molife, Royal Marsden Hospital, Sutton, UK reported on GDC-0068, a novel, highly selective oral ATP-competitive inhibitor designed to bind to the 3 isoforms of Akt. The safety and tolerability of GDC-0068 in combination with docetaxel (Arm A) or mFOLFOX6 (Arm B) was evaluated in a phase I trial. GDC-0068 combined with chemotherapies showed evidence of anti-tumour activity in multiple tumour types. GDC-0068 with docetaxel or mFOLFOX6, was safe and well-tolerated with a recommended phase II dose of 600 mg (od) given for 14 days with docetaxel or on a 7 days on, 7 days off schedule with FOLFOX. A global phase II study testing mFOLFOX6 plus GDC-0068 versus mFOLFOX6 plus placebo in metastatic gastric cancer is being initiated.

Data were also presented by Dr. Dirk Strumberg, Marienhospital, Herne, Germany from a phase I trial of the drug Atu027, a liposomal formulation of small interfering RNA (SIRNA) directed against the protein kinase N3 (PKN3), which is a downstream effector of the PI3K pathway. The data showed that the drug was well tolerated and clinically safe, with moderate side effects, such as fatigue and hyperlipasemia. Furthermore, Atu027 also demonstrated clinical efficacy in patients with advanced

solid cancers who achieved stabilization of the disease.

DNA methylation is an epigenetic event found in many tumours, which regulates the expression of genes important in carcinogenesis. Dr. Michele Maio, Instituti Toscano Tumori, Sienna, Italy discussed several hypomethylating agents that have demonstrated efficacy in haematological malignancies such as acute myeloid leukaemia (AML) and myelodysplastic syndromes (MDS). SGI-110 is a second-generation novel hypomethylating drug that is produced by the chemical modification of decitabine that prevents deamination, which results in more rapid elimination. SGI-110 is being evaluated in a first-in-human phase I-II clinical trial in patients with intermediate or high-risk MDS and AML. Data from this trial have demonstrated a differentiated pharmacokinetic profile resulting in an extended half-life following exposure to decitabine as delivered by subcutaneous SGI-110. Excellent hypomethylation was achieved with higher doses in the daily regimen up to the biologically effective dose. Treatment was well tolerated by most patients with the most common drug-related adverse events being myelosuppression and grade 1 injection site pain. Major responses were observed in relapsed/refractory AML when adequate hypomethylation was achieved.

Dr. Eric Deutsch, Institut Gustav Roussy, Villejuif, France presented findings from a phase I trial of RAD001 (everolimus), an inhibitor of mammalian target of rapamycin (mTOR), in combination with radiotherapy in NSCLC. The results demonstrate good tolerability and efficacy. On the basis of these results, the recommended phase II dosage for everolimus is 50mg/week in combination with standard radiotherapy followed by chemotherapy.

WHOLE GENOME SEQUENCING IN PATIENT SELECTION FOR TARGETED THERAPIES

In addition to discussing new drugs and targets, Plenary session 4 of the TAT 2013 programme addressed emerging issues in cancer drug development, such as the use of whole-genome sequencing in patient selection for targeted therapies and the value and limitations of preclinical models in drug discovery and development. In particular, the problem of tumour heterogeneity, discussed by Dr. Emile Voest, UMC Utrecht, Utrecht, The Netherlands, which has been shown to be of increasing importance in the era of targeted therapy. Indeed, the tumour is not a homogeneous entity and is very dynamic because its growth is clonal rather than linear. Tumour heterogeneity is present both within a tumour and also between the primary tumour and metastases. Therefore, knowledge of the alteration of only one gene may not be sufficient for a targeted drug therapy. This has necessitated the development of technologies that allow the sequencing of the whole genome. Next generation sequencing and large scale genotyping are steps towards truly personalised cancer therapy; however, it brings up multiple challenges, which require multidisciplinary cooperation among clinicians, laboratory scientists and bioinformatics. In order to study the urgent problem of tumour heterogeneity, new preclinical models are needed. Dr. Filip Janku, MD Anderson Cancer Center,

Houston TX, USA discussed next generation in early phase clinical trials; using this technology, it was possible to identify which of ERBB2 gene amplifications is one of the mechanisms of acquired resistance to anti-EGFR treatments, such as cetuximab and panitumumab, in colorectal cancer. Based on these results, a phase II clinical study was initiated in patients with metastatic colorectal cancer who are resistant to anti-EGFR and carry this amplification.

Emerging technologies such as multiplexed somatic mutation genotyping and massive parallel genomic sequencing have become increasingly feasible at point-of-care locations to classify cancers into molecular subsets. Because these molecular subsets may differ substantially between each other in terms of sensitivity or resistance to systemic agents, there is consensus that clinical trials should be more stratified for, or be performed only, in patients with such molecularly defined subsets. This approach, however, poses challenges for clinical trial design because smaller numbers of patients would be eligible for these trials, while the number of novel anticancer drugs warranting further clinical exploration is rapidly increasing. Based on these ideas, the Winther trial was designed to select rational therapeutics based on the analysis of tumour and matched normal tissue biopsies in subjects with advanced malignancies. Prof. Jean-Charles Soria, Institut Gustav Roussy, Villejuif, France presented the design of this international study, which began patient enrolment in spring 2013.

PRECLINICAL MODELS IN DRUG DISCOVERY AND DEVELOPMENT

Preclinical models in drug discovery and development were discussed in plenary session 11, which started off with a presentation by Prof. Gail Eckhardt, University of Colorado, Aurora, CO, USA on the challenges to using patient derived tumour xenograft (PDTX) models in drug development. While PDTX models reflect the tumour heterogeneity and are genetically similar to the primary tumour, they are unable to recapitulate the immune response and the predominant murine tumour microenvironment after several passages. The use of this preclinical model may be useful to screen the antitumour activity of drugs but, more likely, it may identify possible predictive markers of sensitivity or resistance to drugs.

COLLABORATIVE PHASE I TRIALS BETWEEN SMALL BIOTECH AND ACADEMIA

For the first time, the TAT Congress featured the "Oncology Biotech Event" that provided opportunities to biotech companies working in oncology for networking and partnering with the world's academic leaders in early-phase clinical and translational cancer research. This year's Congress gave particular attention to the role of biotech companies, which nowadays are the originators of the new cancer drugs and technologies being developed for phase I clinical studies. In particular, during the last Plenary session (session 12), it was illustrated how timely networking and partnering between

biotech and academy may pay off. In this way, companies will have the opportunity to liaise with the global phase I community well before their new technologies are ready for clinical trials. Only in this way will we achieve the best matches between the needs of biotech in clinical research on the one hand, and clinical investigators' expertise and interests on the other hand.

CONCLUSION

This Congress is unique; it is the only conference where all the latest information on the development of potential anticancer drugs is discussed. The structure of the conference also allows the various participants to meet and exchange ideas and to create new collaborations between different research groups.

AFFILIATION AND DISCLOSURE

The report is provided by Dr. Teresa Troiani, Medical Oncology Department, Second University of Naples, Naples, Italy. Dr. Troiani is a member of the ESMO Translational Research Working Group.

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