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THE 11TH INTERNATIONAL CONGRESS ON TARGETED ANTICANCER THERAPIES PARIS, 4–6 MARCH 2013 (TAT 2013)

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Targeted cancer therapy is one of the most expansive fields of modern oncology. The development of new targeted cancer therapies is one of the main drivers for the further evolution of personalized cancer medicine. The concept of personalized medicine is based upon the notion that cancer development and progression are driven by genomic abnormalities and that these abnormalities are different not only between various types of cancer, but also between individual patients. Such findings have opened the door to the development of targeted cancer therapeutics, directed against tumor-specific molecular abnormalities.

A range of new and promising targeted drugs currently under development for improved cancer therapy were presented during the **11th International Congress on Targeted Anticancer Therapies, Paris, 4–6 March 2013 (TAT 2013)**. TAT 2013 was attended by over 500 participants from 46 countries. More than 60 plenary lectures and 70 posters, presented by leading experts in clinical cancer research and drug development, were devoted to dozens of emerging targeted agents and new drug targets under development for cancer therapy.

TAT 2013 was held under the presidency of Professor Jean-Charles Soria (Institut Gustave Roussy, Villejuif, France). In welcome address, Prof. Soria emphasized the pivotal role of the TAT congress series in identifying the most promising new cancer drugs and guiding them through the critical early phases of clinical development. The focus of TAT congresses is at early-phase clinical studies of innovative cancer therapeutics and translational research. In our digest we will present the most interesting reports that were made at different Congress sessions.

In session ***"New immune checkpoints as drug targets"***, we want to pay attention to the works dealing with the ligands blocking Programmed Death-1 (PD-1), an inhibitory receptor expressed on T-cells following T-cell activation. All PD-1 ligands are the monoclonal antibodies, predominantly with modified FC-region. Different ligands, in spite of their similar biochemical nature, was shown to be significantly various in their therapeutic efficacy and side effects.

In general, as suggested ***F.S. Hodi (USA)***, the recent clinical success in the development of immune checkpoint modulators has provided new therapeutic opportunities for patients with cancer. This new class of oncology drugs utilizes mechanisms of action that are quite distinct from traditional chemotherapy or small molecule targeted agents. As a result, the side effect profiles and toxicity management frequently differ for immune checkpoint modulators than for other classes of oncologic agents. Inflammatory events as a result of treatment have been reported to involve multiple organ systems including skin, gastrointestinal, endocrine, pulmonary, hepatic, ocular, and the nervous system. The time of onset and duration of toxicities may vary significantly between patient populations and agents utilized. As broader clinical experience occurs, the incidence and types of toxicities are being appreciated across a broad scope of cancers. Therefore, the recognition of such adverse events and their management require special attention and follow up. The most significant clinical experience for immune checkpoint modulators includes CTLA-4 blockade, PD-1 blockade, PD-L1 blockade, and CD137 agonist.

A few of differently targeted agents were considered in session ***"Phase 1 studies, completed or in progress"***. Especially, galeterone (TOK-001) — a small molecule oral drug that disrupts androgen receptor (AR) signaling by a novel triple mechanism: it potently and selectively inhibits CYP17 lyase, potentially antagonizes AR and decreases AR protein levels (wild-type and mutant), leading to antitumor activity — was shown to be perspective in treatment of castration-resistant prostate cancer *(**A. Senderowicz, USA**)*.

Mutant p53-targeting small molecules including PRIMA-1 and PRIMA-1Met = APR-246 that restore wild type conformation to mutant p53, induce apoptosis in tumor cells, and inhibit tumor growth in mice. APR-246 was shown to be safe, to have a favorable pharmacokinetic profile, and to be able to induce p53-dependent biological effects in tumor cells *in vivo* ***(K.G. Wiman, Sweden)***.

CetuGEX, a novel glycoengineered and optimized (as to antibody dependent cellular cytotoxicity, 10- to 250-fold improvement of the ADCC-mediated tumor cell killing in all FcγRIIIa receptor allo-types compared to cetuximab was obtained) anti-EGFR IgG1 monoclonal antibody, was tested in 41 patients with a variety of solid tumors, and confirmed objective responses were obtained *(**S. de Dosso et al., Germany**)*.

ATU027 — a liposomal siRNA formulation, targeting protein kinase N3 — demonstrated significant inhibition of invasive growth as well as metastasis formation and growth in preclinical and clinical studies in different kinds of tumors, not requiring any premedication and not inducing any cytokine activation (TNF-α, IL-1β, IFN-γ, IL-6) *(**D. Strumberg et al., Germany**)*.

Then, the hypomethylating drugs were presented (***M. Maio et al., Italy, USA***). But, unfortunately, any approach represented in this session deals with up-regulation of agents as the antigens involved into the "tumor recognition complexes". Nothing was said about expression of the genes immediately involved into the tumor cell proliferation and/or programmed cell death.

Another interesting reported drug with an epigenetic pathway was a histone deacetylase inhibitor Vorinostat. In contrast to the case of a hypomethylating agent, not only intratumoral drug levels and biomarkers response but also clinical effect was shown *(**K. Dragnev et al., USA**)*.

At last, ***E. Deutsch et al. (France)*** reported the phase I trial of the mTOR inhibitor RAD001 (Everolimus) in combination with radiotherapy followed by chemotherapy in unresectable IIIa/b or IV untreated non-small cell lung cancer (NSCLC). The authors concluded that weekly RAD001 application in combination with radiotherapy followed by chemotherapy was reasonably well tolerated in untreated NSCLC.

Some very interesting reports were presented in the ***Session "Whole-genome sequencing in patient selection for targeted therapies".***

Especially, ***E.E. Voest (The Netherlands)*** devoted his lecture to the following question: is the tumor heterogeneity really a problem? The author points a great importance of complex joint studies in the fields of immunohistochemistry and genetic analyses and creation of several initiatives which are now collecting core biopsies of metastases before and after treatment and the generation of these biobanks which allow address the questions about tumor heterogeneity, especially about potential heterogeneity of different metastases in a patient. Linking the clinical data with NGS data from tumors will allow a more refined analysis of the consequences of mutations on signaling pathways and identify approaches to rationally combine drugs. In summary, tumors are by definition heterogeneous and genetically unstable. In addition to the initial genetic drivers of cancer other mutations may evolve over time making, in theory, metastases a more attractive target to be analyzed as target than the primary tumor. Generating biobanks with paired biopsies will greatly facilitate future research in this area. But even this approach "is not a holy grail".

L. Siu (Canada) pointed that it is very important to differentiate the cancer cell subpopulations with different molecular profiles having the following goals: 1) to form biologically and statistically correct groups in clinical trial; 2) relate molecular targets and drugs having to be applied to the certain molecular profile of the patients group.

F. Janku (USA) considered that phase I clinical trials in unselected patient populations have typically produced low response rates of 4 to11%. Therefore, for many decades, phase I clinical trials have been viewed as merely dose-finding studies with, at best, a modest impact on patient outcome. It has become clear that the traditionally low response rate historically seen in early-phase trials can be increased substantially if patient selection has been driven by molecular matching. Several recent early-phase clinical trials using targeted therapy based upon molecular matching demonstrated response rates of 39 to 81%. Novel technologies, including next-generation sequencing, can yield further insight into the underlying molecular pathology of cancers and concordant sensitivity/resistance mechanisms in response to targeted therapy. It is plausible that druggable molecular abnormalities occur in small subset of patients across different histologic types. Therefore, testing one molecular abnormality at the time is neither practical nor sustainable. Novel technologies such as next-generation sequencing are capable to test for myriad of molecular abnormalities in the whole cancer genome. This provides unparalleled opportunity to create umbrella protocols in order to match these molecular abnormalities with appropriately selected targeted therapies. Moving from dose-finding studies to better designed clinical trials based on molecular technologies provides a greater chance of therapeutic benefit and may significantly shorten the drug development timeline. Thus, matching specific molecular aberrations with appropriately selected targeted therapy is considered as crucial topic in the personalized treatment. Next generation sequencing and large scale genotyping is a step towards truly personalized cancer therapy; however, it brings up multiple challenges, which require multidisciplinary cooperation among clinicians, laboratory scientists and bioinformatics. Implementing proof-of-concept studies into early-phase clinical trials can shorten drug development timelines. Since most responders to appropriately selected targeted therapies ultimately develop progression, mechanisms underlying tumor resistance need to be studied.

J.C. Soria et al. (France) promote such non-traditional approach to clinical trials in oncology as so-called WINTHER trials — non-randomized study that will use an innovative approach which introduces the dual biopsy concept: tumor and normal matched tissue (*e.g.* colon cancer and normal colon mucosa). On top of the classical DNA analysis by NGS techniques, WINTHER will open investigations to RNA and miRNAs for those patients who do not have an "actionable" mutation or DNA alteration. WINTHER will assess the "distance" between normal and tumor tissues, and convert it into relevant drug-target gene matches through innovative systems biology and computational tool. The WINTHER project has been awarded by FP7 European grant. This trial will be conducted

simultaneously at MD Anderson Cancer center, Institut Gustave Roussy (France), Vall d'Hebron (Spain), Sheba (Israel) and Segal Cancer Center (Canada); and a total of 200 patients will be enrolled. Biological investigations will be centralized at Foundation Medicine and at Institut Gustave Roussy. The Endpoint is comparison of progression-free- survival (PFS within the trial, with the previous PFS of the last therapeutic line prior entering the trial): a) Arm A (DNA based-decision): PFS2/PFS1 >1.5 in 50% of patients b) Arm B (RNA-based-decision): PFS2/PFS1 >1.5 in 40% of patients.

WINTHER is an innovative personalized medicine trial, developed by the WIN consortium, with an ambitious design aiming at providing a biology-oriented therapy to the vast majority of patients with advanced solid tumors.

As the authors suppose, WINTHER, in contrast to traditional trials, allows the following:

- Includes all patients, with or without actionable genetic aberrations.
- Investigates both DNA and RNA.
- Includes a variety of different technologies: Next Generation Sequencing, Copy Number Variations, gene expression, miRNA, Comparative Genomic Hybridization.
- Based on a dual biopsy of tumor and matched normal tissue of same histology, which enables: evaluating the genetic distance between tumor and normal tissue; discarting variability factors between individuals; limiting the number of irrelevant aberrations and noise; increasing the power to detect a signal.

A special *session* was devoted to the problem of ***"Metabolic drug targets".***

J. Pouyssegur et al. (***France***) suggested that one of the most perspective groups of the metabolic targets is represented by HIF-1-dependent proteins such as membrane-bound carbonic anhydrases (CAIX, CAXII), monocarboxylate transporters (MCT1 and MCT4) as well as their chaperon Basigin/EMMPRIN/CD147. This approach is related to HIF-1 involvement in angiogenesis.

S.E. Critchlow (UK) recommended to remember classic Warburg's approach, and to apply pharmacological inhibition or disruption of lactate metabolism as a promising therapeutic strategy to target a range of human cancers. It is significant this approach has key cross-points with the previous one, such as selective inhibition of lactate transport by MCT1 inhibition.

R.F. Wooster (***USA***) proposed to inhibit fatty acid synthase in cancer cells because this leads to altered mRNA expression of metabolic genes.

Breakages in the mitochondrial electron-transport chain are characteristic for practically all malignancies and are suitable to be the therapeutic targets. ***S. Agresta and K.E. Yen Agios (USA)*** presented a very interesting report in this field. They have synthesized small molecules specifically inhibiting the mutant forms of isocitrate dehydrogenase 1 (IDH1) and 2 (IDH2) and studied its effect on *in vitro* proliferation and differentiation of cultured hemopoietic cells. In spite of seeming availability, the drugs being orientated to one target only, it all the same what namely, are in principle not able to ensure radical effect. The most evident causes of this are the following: 1) heterogeneity of any tumor cell population; 2) compensation (briging) of drug-disrupted signal pathways of the cancer cell by collateral pathways (a common phenomenon in all complex systems). Because of this, it is necessary to elaborate the methods to affect the complex of targets.

In this aspect, we must pay rapt attention to the reports of ***special session "Miscellaneous drugs and targets"***.

P.A. Janne (***USA***) reported a successful trial of Crizotinib — a multi-targeted kinase inhibitor of both ALK kinase and ROS1 — protein product of ALK's partner fusion gene — in non-small cell lung cancer patients.

E.R. Plummer (***UK***) reported the trial of ATR (Ataxia Telangiectasia and Rad 3 related) kinase being involved in the signaling of DNA double strand breaks, which are potent cytotoxic lesions. Inhibition of ATR in preclinical models enhances the cytotoxicity of ionising radiation and a number of commonly used chemotherapeutic agents.

G. Trinchieri (***USA***) reminded of an old but always actual problem of the gut bacteria's role in cancer therapy. Specific alterations of therapy-induced inflammation in antibiotics-fed or germ-free mice impair the response of sub-cutaneous cancers to CpG oligonucleotide-immunotherapy or platinum chemotherapy. In microbiota-depleted mice, decreased cytokine production from tumor-infiltrating monocyte-derived cells following CpG-OGN treatment reduced tumor necrosis whereas deficient chemotherapy-induced production of reactive oxygen species by tumorinfiltrating neutrophils impaired tumor destruction. Thus, optimal response to cancer immunotherapy and chemotherapy and survival requires an intact commensal microbiota.

L. Ellis (***USA***) identified a novel soluble form of the Notch ligand, Jagged-1, that lacked the C-terminal domain. Then there were constructed antibodies to the cleaved site of Jagged-1, with the intent to prevent the induction of the cancer stem cell phenotype in colorectal cancer cells by blocking angiocrine signaling. In addition, the studies identified ADAM-17 as a target of angiocrine signaling. ADAM-17 has also been investigated as a target in other cancers.

S.L. Chan et al. (***Hong Kong***) demonstrated satisfactory results of phase I and II clinical trial of Belinostat — an inhibitor of histone deacetylase.

F. Mouliere et al. (***France***) described their new original method to analyze circulating cell-free DNA (ccfDNA) and its perspectives in the personalized medicine in application to the management care of colorectal cancer patients.

Among reports that were presented at the ***session "Emerging new drugs and targets in hemato-oncology",*** the most interesting one was made by ***H. Keilhack (USA)***, which was devoted to pre-clinical characterization of E7438, a potent, selective EZH2 inhibitor with robust antitumor activity against EZH2 mutated NHL xenografts in mice. The coupled enzymatic activity of wild-type and mutant EZH2 results in hyper-trimethylation of histone H3 lysine 27 (H3K27), which drives lymphomagenesis in heterozygous patients bearing the EZH2 mutations. Through iterative medicinal chemistry, the author's group have developed a selective inhibitor of EZH2 with good pharmacological properties, E7438. E7438 binds to the enzyme in a manner competitive with *S*-adenosyl methionine (SAM) and a Ki for wild-type EZH2 of 2.5 ± 0.5 nM. The compound potently inhibits all known mutants of EZH2 that have been identified in non-Hodgkin lymphoma (NHL) patient samples.

Other lectures of this session dealt with the general therapeutic trends in hemato-oncology.

One another special ***session*** was devoted to the proffered papers on ***"New drugs and targets"***.

I.A. Umelo et al. (Belgium) reported the case of a patient with advanced NSCLC in whom was identified a novel V855A (Valine → L-Alanine) somatic mutation situated in exon 21 of the HER3 tyrosine kinase domain. Remarkably, the mutation maps at a position homologous to the frequently described EGFR tyrosine kinase inhibitor (TKI)-sensitive L858R (Leucine → L-Arginine) activating mutation situated in exon 21 of the EGFR tyrosine kinase domain.

O. Rixe et al. (USA) reported NOV C-ter, a novel VEGF-independent anti-angiogenic agent with promising preclinical anti-tumor efficacy. NOV (nephroblastoma overexpressed) C-Ter (NOV C-Ter) is the carboxy-terminal sequence (170 aa) of NOV/CCN3 (357 aa), the third member of CCN family. NOV/CCN3 is secreted by vascular cells and is involved in angiogenesis through the regulation of various cell functions including proliferation, differentiation, survival, adhesion and migration. *In vitro*, NOV C-Ter inhibits endothelial cell tube formation on matrigel and tumor induced vascular network formation. Interestingly, when tested on HUVEC, NOV C-Ter appears to selectively inhibit SCHN2, apelin and adrenomedullin pathways, with a non-significant inhibitory effect on VEGF. Moreover, MAP Kinase and AKT phosphorylation are both decreased in HUVEC after exposure to NOV C-Ter. Evaluation of NOV C-Ter using the NCI anticancer drug screen panel did not reveal a direct cytotoxic effect on epithelial cancer cell lines.

A.J. Wagner et al. (USA) described SAR299155 — a specific inhibitor of the p53-MDM2 interaction with highly potent *in vitro* and *in vivo* antitumor activities in genetically characterized liposarcoma.

L. Agoni et al. (USA) characterized rigosertib — a more effective radiosensitizer than cisplatin in concurrent chemo-radiation treatment of cervical carcinoma both *in vitro* and *in vivo*.

K. Silence et al. (Belgium) reported pre-clinical studies of ARGX-110 which is a defucosylated, humanized IgG1 monoclonal antibody that selectively targets and neutralizes CD70, a ligand of CD27. Expression of CD70 is normally restricted in activated B- and T- cells, as well as mature dendritic cells. Overexpression has been documented in a variety of solid and hematological tumors, where it is thought to play a role in evasion of immune surveillance.

A special ***session*** was devoted to ***"Drugs targeting the RAS/RAF/MEK pathway"***. The Ras-including pathways are traditionally considered to be one of the most important class of the signaling pathways in cancer cell biology.

As ***J. Luo (USA)*** underlined, the RAF family of kinases mediates mitogenic signaling downstream of Ras proteins. Activating mutations in BRAF occur frequently in melanomas and at lower frequencies in colon and other cancers. The BRAF inhibitor vemurafenib shows strong single agent activity in melanomas, though it paradoxically activates the MAPK pathway in KRAS mutant cells. Thus protein complex formation plays an important role in RAF kinase signaling. By comparing the efficacy of vemurafenib and siRNAs against various RAF kinases in KRAS and BRAF mutant colorectal cancer cells, the author shows that the targeting multiple RAF kinases are necessary to effectively inhibit the proliferation of KRAS mutant cells.

C. Carter et al. (USA) in their clinical studies showed that the selumetinib, as monotherapy, has a response rate of only 5% in advanced KRAS mutated NSCLC. But selumetinib in combination with erlotinib has similar activity in KRAS mutated advanced NSCLC as reported monotherapy erlotinib in advanced NSCLC without a known RAS mutation.

Antibody drug conjugates (ADCs) represent a comparatively new but already becoming a traditional therapeutic approach. This was viewed at ***the session "Immunoconjugates for cancer therapy".***

The general questions of ADCs construction and application where reviewed in the lecture of ***S. Lutzker (USA)***.

J.M. Melief (The Netherlands) showed that in preclinical mouse models TLR ligand-peptide conjugates performed better as therapeutic vaccines than long peptides mixed with the same TLR ligands. In humans, this approach is now in elaboration being applied to the HPV-related pathologies.

The ***session "Preclinical models in drug discovery and development"*** was mainly devoted to so-called Avatar mouse models which are the collections of patient derived xenografts being used to search for the optimal therapeutic schemes as to the certain tumor types and/or as to an individual patient. These models appear to be really the most adequate animal models for these applications but we must not forget that a mouse, even if it has a human tumor xenograft in its organism, in any case is not a human.

R.E. Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology of NAS of Ukraine was presented at the Congress by two reports: *1)* ***V. Chekhun et al.*** *"Green tea polyphenols enhance therapeutic efficacy of anticancer drugs as to drug-resistant experimental tumors"* and *2)* ***S. Zaletok et al.*** *"Anticancer effect of green tea nanoextract is associated with modifications in methylation of genes involved in proliferation and apoptosis".*

As it was shown, the green tea alone nanoextract and nano-composite of green tea with red wine lees have their self-dependent antitumor activity as to different experimental tumors and are able to strengthen antitumor activity of certain synthetic inhibitors of the polyamines metabolism such as difluoromethylornithine (DFMO), methylglyoxsal (bis) guanilhydrazone (MGBG) and other antitumor drugs, especially cisplatin and doxorubicin. Their antitumor activity well corresponds to the modulations of the global DNA methylation in the tumor cells as well as methylation profile of promoter regions of the genes being included in polyamines regulation and also the genes of the structural proteins of NF-kB transcription factor functional activity of which essentially depends on the intracellular polyamines content.

This year for the first time the Congress featured the "Oncology Biotech Event", providing biotech companies in oncology opportunities for networking and partnering with the world's academic leaders in early-phase clinical and translational cancer research.

TAT 2013 was offered by NDDO Education Foundation, in a partnership with the European Society for Medical Oncology (ESMO) and co-sponsored by the U.S. National Cancer Institute (NCI)/Center for Cancer Research (CCR).

The next Congress on Targeted Anticancer Therapies (TAT 2014) to be held in Washington (DC, USA), on March 5–7, 2014, under the chairmanship of Professor Giuseppe Giaccone (Lombardi Cancer Center, Georgetown University, Washington, DC).