Scientific Meeting Report

Prof. C. Sessa • ESMO Publishing Working Group

8th International Symposium on Targeted Anticancer Therapies

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The 8th International Symposium on Targeted Anticancer Therapies (TAT 2010) was held in Bethesda, MD, USA, March 4–6, 2010 and was chaired by Dr. Giuseppe Giaccone. This was the second congress in this series held in the United States. After the U.S. National Cancer Institute (NCI) joined the NDDO Education Foundation as a partner in the organization of annual TAT congresses in 2008, the venue of the meeting alternates between Europe and the United States. The European Society for Medical Oncology (ESMO) has been a partner since TAT 2005.

Annual TAT meetings are focused on early-phase clinical studies of new targeted agents for the treatment of cancer. TAT 2010 provided overviews – in keynotes and expert reviews – of drug development by molecular target, and also presentations of recent results of individual early-phase studies with particular targeted agents.

The number of participants was close to 300, a bit less than the usual 400-600, possibly because of the USA location. Participants in TAT congresses are typically professionals working in academia, industry and governmental agencies with a common interest in the development of new cancer therapies.

A fixed element of the annual TAT program is drug development methodology for targeted anticancer agents. There is always a session devoted to methodology and regulatory aspects, which includes a report of Task Force on Methodology for the Development of Innovative Cancer Therapies (MDICT), an international task force of prominent phase 1 and 2 investigators, and observers from industry, governmental or regulatory agencies. The Task Force meets annually just before the start of TAT. The 2010 topic was how to select the winners in preclinical and early clinical studies and how to make go/no go decisions at the preclinical/Phase I interface and the Phase I/II interface.

E. Eisenhauer and A.H. Calvert chaired the discussion, of which the main conclusions are as follows:

Regarding the **preclinical/Phase I interface**: pharmacokinetic (PK) and pharmacodynamic (PD) data are important in the decision to move to clinical studies (in particular: cytotoxic concentrations in serum/plasma in sensitive species, knowledge of metabolisms in at least 2 different species), and data of in vivo antitumor efficacy are needed, even though the limited relevance of the tumor models available is still a matter of concern; recommendations were made that molecularly characterized models should be used and that models relevant for the intended clinical development should be identified and selected.

The PK/PD data of efficacy that were indicated as relevant for this stage of development were knowledge of the threshold level for efficacy, schedule dependency and modalities of interaction with the target. Other relevant pharmacological data were innovative character of the target, the availability of PD biomarkers to

select or to define non-responders, and the possibility of achieving in humans the needed drug levels. For analogs, additional favorable properties could be derived from a comparison with existing compounds in terms of lack of cross resistance, ease of administration and activity in the same model.

Regarding the **Phase I/Phase II interface**, provided that the new drug satisfied the requirements of acceptable toxicity (without irreversible major organ effects) and that the upper range of dosing was established using a toxicity endpoint (with a definition of MTD), criteria for selection were the availability of PD target effect in normal and, above all, in tumor tissues with the definition of the minimum desired outcome to continue the development (corresponding to a certain consistent inhibition of the target at certain levels of the recommended dose). PK data were also relevant as well as the observation of objective responses or disease stabilization. However, it was clearly pointed out that failure to observe responses does not need to result in the discontinuation of the clinical development if PK/PD have met the go-criteria.
Similar criteria were recommended in the case of the drug not being first in class.

Another fixed element of the TAT program is the NDDO Honorary Award Lecture. This year, the Lecture was awarded to Dr. Axel Ullrich of the Max Planck Institute in Martinsried near Munich. His work in the past decades has been of crucial importance for the successful development of two targeted agents for cancer: trastuzumab and sunitinib. He founded the biotech company Sugen, where sunitinib was initially discovered and developed before it was taken over by Pfizer.

The **program of the TAT meeting** included a total of 12 plenary sessions, each one consisting of an educational lecture followed by 3 oral presentations on relevant published and unpublished preclinical and/or clinical results.
The first three plenary sessions were on the insulin-like growth factor receptor (IGFR) inhibitors, cancer stem cell targets and cell signaling targets.

- Take home messages in the insulin-like growth factors system lecture were the development of this pathway in combination with other pathways because of feedback loops of the post-receptor inhibition with increase of IGF-1 ligand, and the possible role of insulin receptor (IR) in the modulation of the IGF biology; IGF could cause hypoglycemia by activation of IR and the availability of the new oral dual small molecule tyrosine kinase (TK) inhibitors (anti IGFR and anti IR) (BMS-754 807, OSI 906, both in the clinic) could be advantageous because of the role played by IR in the development of resistance to IGF-1R inhibition.

- In the session on targets in cancer stem cells (CSC), the hedgehog pathway was revised with a classification of tumors dependent on the pathway because of mutations (Gorling syndrome, basal cell carcinoma, medulloblastoma, rhabdomiosarcoma) or because of ligand overexpression (CML, multiple myeloma, pancreas, ovary).

  A list of the ongoing trials with hedgehog targeting agents (GDC-0449 Genentech/Curis) in combination with a variety of anticancer compounds was provided (with lenalidomide and dexamethasone in multiple myeloma, with dasatinib in CML, with FOLFIRI/FOLFOX + bevacizumab in colorectal, as maintenance in ovarian cancer).

  Notch and Wint signaling pathways were also reviewed; in the latter, the pharmacological features of the selective antagonist of the CBP/ß catenin interaction ICG 001 were presented and the distinct roles of the coactivators CBP and p300 in the Wint / ß catenin signaling cascade were pointed out. CBP/ ß catenin-mediated transcription is critical for stem cell /progenitor cell maintenance and proliferation, and as such is desirable to attenuate the nuclear functions of ß catenin, whereas the switch to p 300/ß catenin-mediated transcription is the critical step to initiate differentiation and to decrease cellular potency.
- Among the promising agents against cell signaling targets, the ones discussed were the PIM inhibitor SGI-1776 (Supergen) (currently in Phase I in patients with hormone/docetaxel refractory prostate cancer), the JAK2 inhibitor AZD 1480 (in clinical evaluation in myelofibrosis) which acts by inhibiting Stat3 signaling, and the dual oral RAF/MEK inhibitor RO5126766 (Roche) under evaluation in a multicenter Phase I study in Europe and for which a dose dependent inhibition of both pERK and pMEK has been shown.
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- Another plenary session of great interest was the one on tumor microenvironment, with a very provocative talk by Lee Ellis on the role of the microenvironment influences on CSC. The potential effect of paracrine factors derived from endothelial cells (EC) in promoting CSC phenotype in colorectal cancer (CRC) was studied; this effect was evident also when CRC cells were co-cultured with conditioned media from EC, a situation which appeared to decrease sensitivity to FU, oxaliplatin and irinotecan.
  - Among drugs targeting TK, those discussed in detail were the small molecule inhibitor of the MET oncogene ARQ197 (ArQule), the JAK 2 inhibitors TG101348 and CEP701, and the JAK1/JAK2 inhibitor INC B018424 (clearly demonstrating major differences in toxicity and activity profile among seemingly

similar JAK2 inhibitors in myeloproliferative neoplasms), the ATP competitive inhibitor of ALK (anaplastic lymphoma kinase) and MET PEF 02341066 (Pfizer). The gene rearrangements with constitutive activation of the ALK kinase domain, initially described in anaplastic large cell lymphoma, occur in 3-5% of unselected NSCLC and in a variety of solid tumors. Due to the very promising data of antitumor activity in animals, PF02341066 was brought into clinical development in a phase I study, in which an expanded cohort at the RD has been carried out in molecularly defined patients (NSCLC with ALK gene rearrangements). In 50 evaluable pretreated NSCLC patients with FISH positive ALK gene rearrangement, an objective response rate of 65% and a disease control rate of 90% were reported. The compound has gone directly into a Phase III program with a randomized study of PF02341066 vs. standard second line chemotherapy in NSCLC patients with known ALK rearrangements.

A comprehensive overview of the most promising miscellaneous targets, held the last day of the meeting, included an oral presentation of the bioavailable HSP90 antagonist (PK 04929113, Pfizer), the FLT3 receptor TK inhibitor AC220 (Ambit), currently under evaluation in relapsed or refractory AML patients, the AKT (MK2206 and GSFK6906693) and Pi3K inhibitors (BMK120, GDC0941, CAL101), the dual Pi3K and mTOR inhibitors (BEZ235, GSK1059615), the humanized anti EGFL7 (MEGFO444A, Genentech). The last compound is of high clinical interest because of novelty of the target (vascular restricted, overexpressed in the extracellular matrix during revascularization, not affected by anti VEGF), possibly relevant in the escape mechanisms to antiangiogenics, currently in development with bevacizumab.
It is difficult to find in a single meeting such a comprehensive review of topics of interest in anticancer drug development.
The very specific focus on translational studies, the structure of the meeting with key lectures and invited papers, the medium size of the audience which allows a direct interaction between speakers and participants, the possibility of presenting results from still ongoing early studies, the attention paid to regulatory problems and study design, the high quality of speakers, make TAT a unique opportunity for people active in translational studies to update knowledge, exchange views and stimulate further investigations.
The next TAT meeting will take place in Paris, March 7–9, 2011 and will be chaired by Dr. Soria.

Visit www.tatcongress.org for details of TAT 2011 and access to all abstracts and most TAT 2010 presentations. For suggestions or questions regarding TAT 2011, please contact Marinus Lobbezoo, Congress Director NDDO Education Foundation, at tat@mccm.nl.

Prof. Cristiana Sessa has reported no conflicts of interest.