

9th International Symposium on Targeted Anticancer Therapies (TAT)

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INTRODUCTION

The 9th International Symposium on Targeted Anticancer Therapies (TAT) provided a forum for in-depth discussion on new cancer-specific molecular targets and emerging targeted agents, in particular the most promising ones in early-phase clinical development. Among the new targets discussed this time were e.g. BRAF, KRAS, DNA damage repair, various metabolic and immunological targets, Hsp90, and the PI3K-Akt-mTOR pathway. In addition, the program addressed possibilities for refining anti-angiogenic therapy and the emerging use of whole genome data in drug discovery and development. Carefully designed, program offered three intensive days of scientific interactions and presentations on innovations to 500 delegates from over 40 countries. Congress participants were roughly equally distributed in term of academic and corporate affiliation. The TAT congress series is organized by the NDDO Education Foundation, in partnerships with the European Society for Medical Oncology (ESMO) and the National Cancer Institute (NCI) of the USA. Original phase I clinical trial research data on a range of molecular targets for cancer therapy and the most promising agents under development, as well a unique scientific discussion on why some recent discoveries were not successful in the clinic, constituted the backbone of the meeting, as reviewed in the following report.

NOVEL HISTONE DEACETYLASE INHIBITORS

Pooled analysis of outcomes in 178 patients with relapsed or refractory peripheral T-cell lymphoma treated with the histone deacetylase inhibitor romidepsin in two open-label trials demonstrated an objective response rate of 31%, with a complete response rate of 15%, and a median duration of response of 12 months. The most common drug-related grade 3 and 4 adverse events were neutropenia and thrombocytopenia. It should be noted that treatment with romidepsin was associated

with mild, clinically irrelevant prolongations of the QTc interval; however one sudden death was recorded in a patient with extensive atherosclerotic disease. Specific pharmacodynamic observations indicated a relationship between response to romidepsin and increase in histone acetylation levels in peripheral blood mononuclear cells [Bates, S. et al., Abst PP02].

NEXT GENERATION:PIGENETIC DNA METHYLTRANSFERASE INHIBITORS

A novel-generation DNA methyltransferase inhibitor, S-110 (SGI-110), biologically more stable than decitabine, proved active in preclinical studies, and initial results of the first in human clinical trial to determine the biologically effective dose and assess its safety and efficacy were reported. To prolong half-life and bioavailability and reduce dose requirements compared to decitabine, S-110 was designed as a dinucleotide resistant to degradation. Improved toxicity was noted in experimental models, resulting in sustained hypomethylation with less frequent administration. In ongoing phase I trials, S-110 has shown responses in patients with intermediate-2 or high-risk myelodysplastic syndrome and acute myeloid leukemia, with myelosuppression being the main toxicity. Prolonged survival has been documented in patients with myelosuppression treated with the agent, with sustained DNA hypomethylation significantly correlating with clinical responses [Issa, J.P. et al., Abst IL35].

PROAPOPTOTIC DRUGS AND TARGETS

Mitochondria are central to tumor cell survival, and inhibitor of apoptosis proteins (IAPs) are rational proapoptotic targets for cancer therapy. IAPs block caspase activation and promote caspase degradation, and blockade of the IAP pathways resulting in cell apoptosis is an active area of research. Second mitochondria-derived activator of caspase (Smac) mimetics triggering apoptosis by counteracting the IAP pathways are a very active area of research, with drugs such as SM-164, HGS-1029, RG-7419, TL-32711, LCL-161 and AT-406 currently in initial studies. Smac mimetics are relevant targets for survival and resistance in all cancer types, acting on pathways downstream from all other targeted therapies, suggesting potential for combination therapy with other targeted and chemotherapeutic agents. A representative compound, TL-32711, proved selective for IAP without an effect on survivin, and exhibited favorable pharmacokinetics and evidence of preclinical activity [Adjei, A. et al., Abst IL36].

TARGETING DNA DAMAGE REPAIR

As in the case of checkpoint kinase (Chk) inhibitors, by preventing repair of DNA damage, poly(ADP ribose)polymerase (PARP) inhibitors may overcome resistance to chemotherapy, offering interesting potential for combination therapy. In addition, some tumors specifically lack certain DNA repair mechanisms, which allows for selectivity in the use of agents acting on DNA repair pathways and possibilities for sensitization using relevant combinations of agents. Besides PARP, many DNA repair-related targets have been identified, and studies have been initiated with specific inhibitors. Among these, PARP inhibitors have been shown to potentiate the activity, but also the toxicity of chemotherapy, whereas the DNA-dependent protein kinase (DNA-PK) inhibitor NU-7441, the ataxia telangiectasia mutated (serine-protein kinase ATM; a kinase involved in DNA repair) inhibitor KU-0055993 and the ataxia telangiectasia and Rad3-related protein (serine/threonine-protein kinase ATR; another kinase involved in DNA repair) inhibitor NU-6027 have been associated with radio- and chemosensitization overcoming resistance. The use of these agents in combination with cytotoxic chemotherapy or radiotherapy, or also in combination with other targeted agents to better block DNA damage responses, showed promise, but pharmacodynamic biomarkers are largely missing [Plummer, E.R., Abst IL11]. Specific inhibitors of PARP, such as MK-4827, have already shown activity against BRCA pathway-deficient and sporadic tumors, including triple-negative breast cancer, as well as other breast, endometrial and ovarian cancers [Annunziata, C.M., Abst IL09; Moreno Garcia, V.M. et al., Abst G01].

Serine-threonine protein kinase Chk inhibitors, such as 7-hydroxystaurosporin, AZD-7762 and other novel agents (PF-477736, SCH-900776, XL-844, LY-2603618), by delaying DNA repair after radio- or chemotherapy damage, have shown activity in a number of initial human trials. Whether the use of specific Chk1 or Chk2 or dual inhibitors may offer advantages remains unclear. Additional issues to be clarified include the use of monotherapy versus combination or sequential therapy, and the impact of p53 mutation or deletion on the usefulness of these agents. Among these agents, 7-hydroxystaurosporin was shown active in preclinical and clinical studies, with pharmacodynamic effects suggesting increased apoptosis by preventing DNA repair, whereas AZD-7762 was noted to potently inhibit Chk1, synergistically increasing the effect of cytotoxic chemotherapy and radiotherapy in refractory solid tumors. Although the drug was discontinued from further development, results so far suggest Chk1 as a reasonable target [Senderowicz, A. et al., Abst IL10]. Favorable preclinical results in terms of biological activity were reported with a first-in-class selective, orally bioavailable Chk1 inhibitor, ARRY-575 [Humphries, M.J. et al., Abst PP05].

THE PI3K-Akt-mTOR PATHWAY AS A TARGET

The phosphatidylinositol 3-kinase (PI3K)-protein kinase Akt-mammalian target of rapamycin (mTOR) pathway has been under investigation as a target for anticancer therapy for some time, and agents have been identified with promising activity. Among a number of drugs acting on PI3K, BEZ-235, which also inhibits the mTOR complex (mTORC1 and mTORC2), has shown broad antiproliferative activity as a proapoptotic and antiangiogenic agent, with favorable safety in a phase I trial in patients with PIK3CA/PTEN-altered tumors. XL-147, BKM-120 and GDC-0941, also PI3K inhibitors, have similarly exhibited evidence of favorable activity in phase I trials, without a clear relationship between responses and mutation status. Acting specifically on the α subunit of the enzyme, BYL-719, GDC0032 and INK-1117 have also been associated with favorable phase I trial results. Other Akt inhibitors, such as MK-2206 and GDC-0068, have also been developed. Although these agents have demonstrated rash as an acceptable toxicity in phase I trials, they have resulted in pharmacodynamic and biological activity against a number of tumors, including metastatic pancreas cancer. However, overall results indicate that targeting a single enzyme may be insufficient for controlling cancer, combination being required for effective control of tumor cell proliferation even in tumors with demonstrated mutations or deletions. Which is the best target, how to select patients and what compensatory pathways may be activated upon inhibition of a single target (indicating the best combination approach) are still the subject of research and for which innovative trial design in accurately selected patients will be required [LoRusso, P., Abst IL32]. A representative ATP-competitive Akt inhibitor, GDC-0068, inhibits tumors driven by Akt signaling, including those with defects in the tumor suppressor gene PTEN, mutations in PIK3CA, and amplification of HER2. The compound is currently undergoing phase I study [Tabernero, J. et al., Abst IL33].

The identification of the Akt-mTOR-p53 pathway and the loss of cellular senescence due to loss of the PTEN pointed towards novel related putative targets to be explored. Relevance of senescence to cause permanent cell cycle arrest is increasingly recognized, and mutations of PTEN are common in cancer, indicating therapeutic potential for direct interaction with PTEN or downstream key mediators, which include phosphorylated Akt, ARF, Mdm2, protein p53 and protein p21. As an example, a specific inhibitor of Mdm2, nutlin-3, and a selective PTEN inhibitor, VO-OHpic, stimulated cell senescence by loss of functional PTEN, whereas by inhibiting mTOR, rapamycin had antisenesence activity. Still at the level of preclinical models, the use of VO-OHpic in tumors carrying wild-type PTEN and of nutlin-3 in PTEN-null tumors was suggested to induce cell senescence without damaging DNA [Alimonti, A., Abst IL34].

HSP 90 INHIBITORS

Heat shock protein (HSP 90) inhibitors interfere with the essential chaperone activity that stabilizes and activates "client" proteins essential for cell signaling and the response to stress. Besides

tanespimycin and alvespimycin, additional new compounds are currently in clinical trials to validate this target for anticancer therapy [Neckers, L. et al., Abst IL12]. Chaperone client proteins such as human epidermal growth factor receptor (EGFR), tyrosine-protein kinase Kit and BCR/ABL are rapidly degraded by HSP 90 inhibitors, resulting in potential anticancer activity for novel agents such as 17-aminogeldanamycin and retaspimycin, which have shown activity against non-small cell lung cancer (NSCLC) cells. Focusing on retaspimycin, phase II clinical trial data in patients with mutated or wild-type EGFR demonstrated similar response rates, but the best responses were noted in tumors expressing wild-type receptor. However, additional analysis revealed that all responses were obtained in patients harboring anaplastic lymphoma kinase (ALK) rearrangement. Detailed research identified fused EML4-ALK as a marker for sensitivity to retaspimycin. These results suggest potential for combination with inhibitors of ALK such as crizotinib. It should be noted, however, that retaspimycin retained activity in cells resistant to ALK inhibitors [Ross, RW., Abst IL13]. Three additional HSP 90 inhibitors, ganetespib [Shapiro, G., Abst IL16] (with in vitro synergistic antitumor activity combined with docetaxel [Proia, A. et al., Abst D02]), AUY-922 [Banerji, U., Abst IL14] and AT-13387 [Shapiro, G., Abst IL15] demonstrated a favorable pharmacokinetic profile and activity against breast, lung, gastric and other solid tumors in various combination regimens, while another agent, NVP-HSP990, proved active in preclinical models, with potential for crossing the blood-brain barrier and also acting against central nervous system tumors [Gao, Z. et al., Abst D01].

B-Raf- AND K-Ras-RELATED ANTICANCER TARGETS

The cyclin-dependent kinase 4 and 6 inhibitor PD-0332991 demonstrated prolonged disease stabilization in patients with solid tumors, including colorectal cancer harboring K-Ras mutations, and proved pharmacodynamically active in a phase II trial in patients with K-Ras-mutated, advanced colorectal cancer, with toxicity limited mostly to neutropenia. However, these preliminary data from ongoing study confirmed the activity previously demonstrated in phase I trial, in which favorable pharmacokinetic and biological activity was also accompanied by neutropenia as dose-limiting toxicity that correlated with therapeutic activity. An interesting additional observation related to PD-0332991 in the phase II trial, which included patients screened for Rb positivity, was the usefulness of [18F]-FLT as a surrogate biomarker of activity in bone marrow and solid tumors [O'Dwyer, P.J. et al., Abst PP01].

With no evidence of resistance so far, B-Raf inhibition with vemurafenib or GSK-2118463 was described as a putative strategy for the treatment of melanoma harboring B-Raf mutations [Flaherty, K.T., Abst IL02], and in fact, evidence of activity in metastatic mutated B-Raf-expressing metastatic melanoma has been demonstrated.

EGFR AND FGFR AS TARGETS

New anti-EGFR treatment modalities are under investigation, including SYM-004, a 1:1 combination of two chimeric immunoglobulin G1 antibodies (992 and 1024 anti-EGFR monoclonal antibodies) targeting non-overlapping epitopes of the extracellular domain III of the receptor, thus promoting internalization of the receptor in cancer cells and blocking ligand-binding receptor activation and downstream signaling. Currently in first in human, phase I clinical trial in patients with refractory solid tumors, including wild-type and mutated K-Ras-harboring metastatic colorectal cancer progressing on anti-EGFR monoclonal antibodies, SYM-004 has already been shown to be active in preclinical studies, and preclinical toxicity data suggested good safety and tolerability (rash, mucositis, diarrhea and hypomagnesaemia). Accrual in dose expansion cohort of 12 mg/kg is ongoing [Dienstmann, R. et al., Abst PP03].].

Fibroblast growth factor (FGF) and its receptor have also been studied as a target for anticancer therapy, with a number of monoclonal anti-FGFR antibodies, such as FP-1039, R3Mab, IMC-A1, PRO-001, 1A6, and FGFR-associated tyrosine kinase inhibitors, such as brivanib, masitinib, dovitinib, BIBF-1120, TSU-68, KI-8751 and PD-173074 (most of which also inhibit the ATP binding site of vascular endothelial growth factor receptor 2 [VEGFR-2]), showing potential for improving tumor control, although at the risk of toxicity given the lack of specificity at doses required for blocking FGF pathways. Among specific drugs, ongoing studies in endometrial cancer with FP-1039 and favorable initial phase I data with brivanib and BIBF-1220 as single agents suggest potential for further investigation, but combinations with chemotherapy and antiangiogenic agents also need to be explored, and ongoing trials are under way with E-3810 combined with pemetrexed in NSCLC and brivanib combined with cetuximab in gastrointestinal tumors [de Braud, F. & Delmonte, A., Abst IL07].

Detailed information was independently presented on E-3810. Preliminary phase I clinical trial results indicated the pharmacokinetic feasibility of E-3810 in patients with advanced solid tumors. At daily oral doses, treatment of patients with relapsed or refractory advanced solid tumors, including notably FGFR-1-amplified breast cancer, demonstrated linear pharmacokinetics, with good tolerability and no dose-limiting toxicity up to 30 mg. Evidence of biological activity was documented, with stable disease as best response, although the study was ongoing at the time of presentation [Soria, J.C. et al., Abst G11].

VEGF AND ANTIANGIOGENIC THERAPIES

The humanized anti-EGFL7 (epidermal growth factor-like protein 7) monoclonal antibody MEGF-0444A in combination with bevacizumab exhibited favorable initial phase I clinical trial results against a range of solid tumors. Mechanistically, blockade of EGFL7 results in impaired interactions between endothelial cells and this extracellular matrix protein, which supports endothelial cell survival, resulting in inhibition of tumor vasculature regrowth during maintained antiangiogenic therapy, thus exerting antivasular and antiangiogenic activity complementing the activity of VEGFR-targeted drugs such as bevacizumab [Peterson, A.C., Abst IL05].

Hypoxia is a hallmark of the tumor microenvironment, and factors such as HIF-1-a and HIF-1-b play a role in regulating metabolism through glycolytic enzymes and oxygen consumption. Developing HIF-1 as an anticancer target is at present challenging because of the lack of pharmacodynamic biomarkers and validation in tumor tissue. Furthermore, theoretical considerations indicate that anti-HIF-1 agents would probably have limited value as monotherapy. Nevertheless, a number of drug candidates have been developed, and in fact, well-established drugs such as topotecan have inhibitory activity against HIF-1-a protein expression in advanced solid tumors, such activity correlating with clinical response. Given the relationship between blood supply and hypoxia, combinations of antiangiogenic drugs with inhibitors of HIF-1-a could better suppress tumor development, which was initially confirmed using EZN-2208, a pegylated prodrug of an HIF-1-a expression inhibitor, combined with bevacizumab. As an alternative to HIF-1-blocking agents, anti-interleukin-11 agents could also synergistically potentiate antiangiogenic drug therapy according to preliminary preclinical observations [Melillo, G., Abst IL06].

IMMUNOLOGICAL TARGETS FOR ANTICANCER THERAPY

Redirect immunology toward tumor cells has been explored as a therapy for cancer, with strategies mostly focused on T cells using mutated proteins, viral antigens, oncogenes, tissue-restricted proteins, oncofetal proteins and idiopathic antigens, and also costimulatory factors. Combining antigens to induce effector cell function with costimulatory pathways and the use of antibodies to stimulate or block receptor signals, resulting in immune destruction of tumor cells, is an intriguing domain, but validation of preclinical paradigms is still largely missing. Immune-mediated drugs may also be combined with chemotherapy and vaccines, the latter especially as a strategy against minimal residual disease. Value of combination of immunomodulatory antibodies with different mechanism of action has also been considered. Preclinical and clinical studies are under way, focused mainly on the use of immunomodulatory approaches combined with standard chemotherapy and the use of vaccines for residual disease, but many issues still need validation, specifically whether the use of concomitant or sequential combination therapies may offer advantages [Melero, I., Abst IL29].

PUTATIVE METABOLIC TARGETS FOR INTERVENTION IN CANCER THERAPY

Dysregulated metabolism is a typical feature of cancer cells, and metabolic targeting to prevent the rapid metabolism and growth of cancer cells and induce anticancer activity is another area of intensive research [Pollak, M., Abst IL17]. Studies with metformin have suggested lower levels of insulin, testosterone and insulin-like growth factor I (IGF-I), resulting in caloric restriction that inhibits the growth of cancer cells [Pierotti, M.A. et al., Abst IL18]. However, more selective targets, such as muscle-type pyruvate kinase (PKM2) and isocitrate dehydrogenase [NADP] cytoplasmic (IDH), enzymes that are dysregulated in cancer cells, may offer significant advantages. Use of bioinformatic tools to identify mutations in metabolic enzymes, isoforms of metabolism-regulating enzymes, and dysregulated metabolic pathways in cancer cells has been key for research into putative metabolic targets. In that respect, two isoforms of IDH have been identified with mutually exclusive mutations in glioma, acute myeloid leukemia and other malignancies. Such mutations were related to prognostic implications, although research still needs to clarify whether mutated IDH is a driver for malignancy. Similarly, biomarkers are required, in which regard 2-hydroxyglutarate increases in cells with mutated IDH suggest potential, yet to be explored, for selecting patients and assessing responses to treatment, or as a disease marker [Schenkein, D.P. et al., Abst IL19].

Cancer cells rely more on de novo palmitate synthesis than normal cells, so targeting fatty acid synthase with small-molecule inhibitors was extensively investigated as a putative anticancer therapy. Palmitate is essential for producing triglycerides and phospholipids, which are indispensable components of cell membranes. The enzyme responsible for producing palmitate, fatty acid synthase, is highly expressed and/or amplified in tumor cells, notably in the case of prostate and breast cancer, in which pathological correlations have been identified. Inhibiting fatty acid synthase with compounds such as GSK-2593300A has been demonstrated to result in antiproliferative and antitumor effects in preclinical animal models of prostate cancer. To facilitate further research for therapeutic feasibility, biomarker studies have suggested the use of malonyl-coenzyme A levels, which increase in tumors after fatty acid synthase inhibition and [11C]-acetate-based positron emission tomography imaging [Nisen, P., Abst IL20].

ANDROGEN RECEPTOR AND NOVEL TARGETS IN PROSTATE CANCER

The androgen receptor remains involved in the malignancy despite castration resistance. Potential for the new antiandrogens, such as MDV-3100, with activity on prostate-specific antigen (PSA) levels in chemotherapy-naïve as well as pretreated castration-resistant prostate cancer, is awaiting until clinical trial confirmation on survival benefit. Recognition of the interplay between c-Met and VEGF

and the relationship between c-Met expression and metastasis indicated a putative role for dual inhibitors, which has been confirmed with cabozantinib, although with an apparent negative effect in increasing PSA levels.

Immunotherapy with sipuleucel-T has shown benefits on overall survival, but confirmation is still pending for new cancer vaccines, such as rV-PSA-TRICOM/rF-PSA-TRICOM. Validation of poxvirus vaccine vectors for efficient infection of antigen-presenting cells without integration into the DNA, and the use of a triad of costimulatory molecules (TRICOM, comprising BF7, LFA-3 and ICAM1) resulted in rV-PSA-TRICOM/rF-PSA-TRICOM, a cancer vaccine that proved active and synergistic with chemo- and radiotherapy in preclinical models. It has also resulted in the overall survival advantage in patients with castration-resistant prostate cancer in two phase II studies, with confirmed relationship between survival and PSA responses. The vaccine will be assessed in phase III trials in combination with granulocyte colony-stimulating factor and chemo- and hormonal therapy. Other vaccines using heat-killed recombinant *Saccharomyces* constructs have also demonstrated preclinical antitumor activity as monotherapy and combination therapy, and are currently in phase I clinical trials. Additional vaccine target candidates have been identified, such as the brachyury protein, expressed in carcinoma cells but not in normal tissue. As brachyury induces migration and invasion and controls metastasis of tumors, further developments are expected in the area of cancer immunotherapy using yeast brachyury or brachyury with TRICOM [Madan, R.A. et al., Abst PP07].

CHANNEL: A NOVEL THERAPEUTIC TARGET

The voltage-gated potassium channel Kv11.1 (HERG) has been identified as a target for anticancer therapy. Differences between the cardiac and tumor HERG channel have allowed for non-torsadogenic blockers to be developed, and agents such as E-4031, a specific blocker, induce apoptosis of cancer cells expressing the receptor without cardiac toxicity. E-4031 was active in potentiating chemotherapy and overcoming resistance in models of B-cell acute lymphocytic leukemia, even against cells resistant to corticosteroids. Another compound, CD-160130, also exhibited tumor-to-myocardium selectivity, resulting in apoptosis of chronic lymphocytic leukemia without cardiotoxicity because of the selectivity for the ERG1 isoform expressed in tumor cells. Aberrant expression of the channel in cancer cells and the resulting interference in tumor cell growth cycle, apoptosis, invasiveness and angiogenesis explain the activity of such blockers, which showed in vitro activity also against colorectal cancer cells. Kv11.1 blockade has also been able to counteract chemoresistance and metastatic spread [Arcangelli, A. et al., Abst PP08].

NOVEL MONOCLONAL ANTIBODY WITH ANTITUMOR

The tumor-specific carbohydrate-induced conformational epitope TA-MUC1 can be recognized by glycol-designed humanized monoclonal antibody PankoMab. Preclinical data have shown antitumor properties of PankoMab through antibody-dependent cellular toxicity (ADCC). Phase I dose escalation study showed linear, dose-proportional pharmacokinetics, with an elimination half-life of approximately 192 hours after 3-hour i.v. infusion in patients with refractory TA-MUC1-positive tumors, with no dose-limiting toxicity up to doses of 700 mg every 3 weeks. Biological activity was documented in this phase I trial in patients with locally advanced or metastatic cancer lacking available standard therapy, although with stable disease as best response during preliminary analyses, as the trial was still ongoing at the time of presentation. Activity is expected in ovarian cancer, NSCLC and breast cancer [Fiedler, W. et al., Abst G03].

AURORA KINASE INHIBITORS

Disappointments with mitosis-specific agents such as Aurora and polo-like kinase inhibitors were related to the small fraction of cells in S-phase susceptible to pharmacological activity, except in model studies with a very fast doubling time. In fact, although preclinical studies with these agents demonstrated activity, mitotic arrest is not sustainable, rendering disease stabilization unattainable with mitotic inhibitors. Mitosis disruption is not a well-validated approach to treat cancer in humans, which, as opposed to in vitro studies, exhibit a much slower tumor cell doubling time, but results in bone marrow toxicity because of the rapid mitotic cycle of progenitor cells. The success obtained with taxanes and vinca alkaloids is probably not related to their interference with mitosis. The role of microbubbles during the interphase, and specifically their relationship with oncogenes and proteins related to DNA repair, secondarily indicates the possibility that combinations of drugs acting on microtubules and therapies targeted to DNA repair mechanisms may prove synergistically effective. Nevertheless, it should be noted that disrupting interphase microtubules also results in cell death, explaining the neurotoxicity of these agents [Fojo, T. et al., Abst IL26].

IGF-IR INHIBITORS

Phase III study with figitumumab combined with chemotherapy in patients with NSCLC demonstrated no benefit but increased toxicity, although trial design (unselected patients because of the lack of validated predictive biomarkers upon which to base patient selection) may have been the cause of such negative results following evidence of activity in phase II trial. The target seems to be still

interesting based on mechanism considerations, although blockade of the IGF-I receptor may result in neuroendocrine compensation with increases in growth hormone, glucose and insulin levels, and may encounter resistance based on irrelevance of the IGF-I receptor in specific tumors, inherent resistance or the existence of compensatory intracrine loops. IGF-I receptor ligand expression, epithelial-to-mesenchymal transition markers and receptor proliferation/gene amplification have been suggested as putative tumor markers that need validation before the use of such drugs in further investigations. However, adequate patient selection and dosing and rational combinations then need to be explored too [Pollak M., Abst IL27].

However, an ongoing phase I study to assess the potential of a combination of figitumumab and pegvisomant in patients with Ewing's sarcoma or other aggressive sarcomas or solid tumors with high levels of IGF-I was presented, based on theoretical efficacy of the anti-IGF-I receptor antibody and the potential for the growth hormone receptor blocker to counteract the resulting metabolic deregulation [Haluska, P.H. et al., Abst G02].

Nevertheless, severe muscle loss was described in patients receiving an anti-IGF-I receptor antibody combined with a signal transduction kinase inhibitor, calling for caution in and further evaluation of the use of these agents [Antoun, S. et al., Abst G05].

PROTEASOME INHIBITION

The proteasome inhibitor carfilzomib has already been demonstrated to be effective and well tolerated in the treatment of multiple myeloma. New studies using a novel technology aimed at determining proteasome subunit inhibition in peripheral blood mononuclear and tumor cells from patients with multiple myeloma or solid tumors indicated potent inhibition of chymotrypsin-like subunits and dose-dependent inhibition of the proteasome subunits LMP2 and MECL1 independently of cotreatment with high-dose steroids or lenalidomide, or the renal status. Prolonged proteasome inhibition was detected in peripheral blood mononuclear cells, which was recovered by the end of a 28-day cycle, but near complete inhibition was noted in bone marrow-derived tumor cells of multiple myeloma patients [Lee, S.J. et al., Abst PP09].

COMBINATION OF ANTIVIRAL AGENT AND CHEMORADIOTHERAPY IN HPV RELATED MALIGNANCIES

Preliminary experience combining the antiviral agent cidofovir with radiochemotherapy against human

papillomavirus-related malignancies, including cervical, anal, and head and neck cancer, indicated virus-dependent radiosensitizing activity for the nucleoside analogue. Treatment with cidofovir resulted in decreased human papillomavirus-related oncoproteins and restoration of tumor suppressor p53 and retinoblastoma-associated protein (pRb) levels, accompanied by a marked decline in the metastatic potential. Cidofovir also induced synergistic cell killing with anti-EGFR agents. Phase I study was initiated in patients with non-metastatic cervical cancer and evidence of HPV infection on tumor biopsy and/or Pap smear, to determine the maximum tolerated dose and confirm the antitumor activity of cidofovir combined with chemoradiotherapy and brachytherapy. Preliminary results indicated no dose-limiting toxicity [Deutsch, E. et al., Abst PP10].

DOSE LIMITING TOXICITY IN PHASE I CANCER CLINICAL TRIALS OF TARGETED AGENTS

Regardless of the drug and target, a key issue for validating new putative therapies for cancer is how to assess dose-limiting toxicity. In that respect, a review of 155 phase I trials evaluating 111 molecularly targeted agents detected broad differences in the definition of maximum tolerated and recommended doses. The study identified severity as the most frequent determinant of dose-limiting toxicity, although with broad variability in the degree of severity required for it to be considered dose-limiting. A definition including severity along with duration and degree of reversibility and the need for delaying doses or reducing dose intensity was also considered in a minority of studies, rendering the definition of dose-limiting toxicity very variable and poorly comparable between trials [Le Tourneau, C. et al., Abst PP04].

Instead of conclusion, a study with innovative design for phase I combination trials will be highlighted. Combining targeted anticancer therapies offers promising potentials to affect drugs efficacy and resistance. However, the concern for increased toxicity is a serious issue. The design, proposed by biostatisticians, offers a way to incorporate data from single agent phase I trials into study drug combinations. On-study dose recommendations are justified by quantitative risk assessment for future patients and clinical evaluation of safety data. Categorization of dose-limiting toxicity rate into intervals allows interpretation of risk to protect patients from over-toxicity. The design is currently implemented in multiple combination development programs [Wandel, S. et al., Abst G13].

RELATED INFORMATION

Abstracts and presentations from the TAT 2011 can be viewed at the Congress website: www.tatcongress.org.

Save the date: The next congress, TAT 2012, will be held in Amsterdam, The Netherlands, March 8-10, 2012.

AFFILIATION AND DISCLOSURE

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