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MEETING REPORT

HIGHLIGHTS FROM THE 9TH INTERNATIONAL SYMPOSIUM ON TARGETED ANTICANCER THERAPIES (MARCH 7-9, 2011 – PARIS, FRANCE)

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SUMMARY

With a focus on innovative agents with cancer-specific molecular targets arising as promising drug candidates in early-phase clinical trials, the 9th International Symposium on Targeted Anticancer Therapies offered 3 intensive days of highly scientific presentations and discussions to a varied international audience including internationally renowned experts and investigators. Original phase I clinical trial research and overall discussions on a range of molecular targets for cancer therapy and the most promising agents under development constituted the backbone of the meeting, as reviewed in the following report. Targeted anticancer therapies have become a mantra in oncology, despite the fact that many issues related to predictive biomarkers and patient selection have limited the interpretation of clinical trials and have even challenged the demonstration of efficacy. A review of methodological and regulatory issues in the development of targeted agents, and specifically on how to identify patients likely to benefit from a targeted agent based on phase II trial results, largely emphasized the need for predictive and diagnostic biomarkers and the distinction between the two. Cancer is a very heterogeneous condition in which many cellular pathways may be dysregulated, and trials need to adequately validate biomarkers for patient selection, for which tissue analyses are mandatory, as is randomized validation of prognostic and predictive biomarkers. Questions such as when to start phase II trials for drugs without validated biomarkers (only if compelling mechanism of action and significant activity demonstrated in phase I trials) or how important a biomarker may be regarding the tumor's biological pathways, as in many cases it may not be possible to identify such pathways, deserve consideration. An additional issue is the design of multi-agent, multi-arm trials to identify new, as yet unknown biomarkers and to validate biomarkers suggested based on preclinical studies. This may have clear implications in demonstrating the efficacy of a novel drug in phase III trials (Calvert, A.H., Abst IL25).

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DRUGS ACTING ON DNA TRANSCRIPTION

Two main approaches to gene silencing, DNA methyltransferase and histone deacetylase inhibition, have been studied. Pooled analysis of outcomes in 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, indicating single-agent activity with acceptable tolerability. However, it should be noted that treatment with romidepsin was associated with mild, clinically irrelevant prolongation of the QTc interval, indicating the need for care in patients at increased risk for sudden death, who should probably not be treated with the agent. 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).

A novel-generation DNA methyltransferase inhibitor, S-110 (SGI-110), biologically more stable than decitabine, proved active in preclinical studies, and was reported to be under initial human clinical trial investigation to determine the biologically effective dose and assess its safety and efficacy. 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 and chronic myeloid leukemia, but only anecdotal responses in solid tumors, at the cost of myelosuppression as 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 chemotherapeutic agents. A representative compound, TL-32711, proved selective for IAP without an effect on survivin, and exhibited favorable pharmacokinetics in preclinical studies; evidence of preclinical activity was demonstrated (Adjei, A. et al., Abst IL36).

TARGETING DNA DAMAGE REPAIR

As in the case of checkpoint kinase 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, shows 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).

Potential as a treatment for solid tumors was also discussed with serine/threonine-protein kinase Chk inhibitors such as 7-hydroxystaurosporine, AZD-7762 and other novel agents (PF-477736, SCH-900776, XL-844, LY-2603618), which, 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 to be determined. 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 to be 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, resulting in activity against refractory solid tumors. Although the drug was discontinued from further development, successes so far suggest Chk1 inhibition as a reasonable therapeutic option (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 a subunit of the enzyme, BYL-719, GDC-0032 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 for which innovative trial design in accurately selected patients will be required (LoRusso, P., Abst IL32). A representative ATP-competitive Akt inhibitor, GDC-0068, exerted in vitro and in vivo activity in preclinical studies, demonstrated activity on biomarker outcomes and is currently undergoing phase I studies (Tabernero, J. et al., Abst IL33).

The identification of the Akt–mTOR–protein p53 pathway and the loss of cellular senescence due to loss of phosphatase and tensin homolog (PTEN) pointed towards novel related putative targets to be explored. Senescence to cause permanent cell cycle arrest is a target in anticancer therapy, 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 antisenescence activity. Pending validation even in 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

Other novel targets actively studied for anticancer therapy include heat shock protein HSP 90 inhibitors, which 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 also 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, which, in preclinical studies, already showed potential for further reducing tumor volume. It should be noted, however, that retaspimycin retained activity in cells resistant to ALK inhibitors (Ross, R.W., 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 were very preliminary data from ongoing studies that confirmed the activity previously demonstrated in phase I trials, 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 was the usefulness of [^{18}F]-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-2118436 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. Potential to be demonstrated has been suggested with combinations of B-Raf and Met kinase inhibitors, which may improve survival in squamous cell carcinoma (Eggermont, A.M.M., Abst IL30).

EGFR AND FGFR AS TARGETS

EGFR has been a target for anticancer therapy and selective drugs are already available. However, new treatment modalities are under investigation, including SYM-004, a 1:1 combination of two chimeric immunoglobulin G_1 antibodies (992 and 1024) targeting nonoverlapping 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 phase I clinical trials 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 up to doses of 12 mg/kg (Dienstmann, R. et al., Abst PP03).

With context-dependent activity but because of tumor-specific genetic alterations, fibroblast growth factor (FGF) and its receptor have also been studied as targets 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 (intedanib), TSU-68 (orantinib), 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 (rabeprazole) 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 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

Looking for strategies to complement antiangiogenic therapy with VEGFR-targeted agents, the anti-neuropilin-1 monoclonal antibody MNRP-1685A proved pharmacodynamically active and synergistic with bevacizumab, but its association with proteinuria precluded further development as a drug candidate. As an alternative, 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 antivascular and antiangiogenic activity complementing the activity of VEGFR-targeted drugs such as bevacizumab (Peterson, A.C., Abst IL05).

In addition, the identification of hypoxia-inducible factor 1 (HIF-1) as a putative target for antitumor therapy suggested potential usefulness in combination with antiangiogenic factors, possibly overcoming resistance to the latter and thus achieving better responses. Hypoxia is a hallmark of the tumor microenvironment, and factors such as HIF-1α and HIF-1β 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-1α 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-1α could better suppress tumor development, which was initially confirmed using EZN-2208, a pegylated prodrug of an HIF-1α 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). Detailed preclinical profiling of an additional HIF-1α inhibitor, imidazoacridinone, also indicated potential as antiangiogenic therapy, with activity against VEGF protein expression even in normoxic conditions (Skwarska, A. et al., Abst D06).

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, and combination of immunomodulatory antibodies with different mechanisms of action has also been suggested to be of therapeutic value. 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).

In the context of immunotherapies for cancer, the fact that bio- and chemotherapy has not been able to demonstrate a benefit on overall survival in patients with metastatic melanoma, but has resulted in significant toxicity, has prompted the research into immunological targets, including, notably, the use of the anti-cytotoxic T-lymphocyte protein 4 (CTLA-4) monoclonal antibody ipilimumab or vaccines. Without an effect in activating but effectively maintaining immune reactions, ipilimumab and tremelimumab have been shown to be active against melanoma at the cost of immune-related adverse events (rash, colitis, vitiligo, pituitary swelling) directly related to clinical benefit, absolute lymphocyte count and the expression of the antigen NY-ESO as putative predictors of response (lymphocyte counts have been related to response to treatment and overall survival). As opposed to chemotherapy, ipilimumab induced gains in overall survival in phase II trials, but its role as adjuvant or first-line therapy still remains to be delineated (Eggermont, A.M.M., Abst IL30).

The role of epithelial cell adhesion molecule (Ep-CAM) in epithelial tumors has been recognized, as has that of CD3 –a component of the T-cell receptor complex– in binding to macrophages and natural killer cells, resulting in activation of immunity and leading to antitumor responses. This resulted in the development of catumaxomab, a trifunctional bispecific antibody against human Ep-CAM and human CD3 that offered clinical benefit to be further explored in patients with malignant ascites, with a predictable and manageable safety and tolerability profile (Schmidt-Rimpler, C. et al., Abst G07).

Supplementary immunological targets that have been explored include monoclonal antibodies that activate or block immune system receptors, promoting immunogenicity against tumor antigens. These approaches have been studied particularly in the context of polychemotherapy for lymphocytic leukemia in children and testicular cancer in adults (Melero, I., Abst IL-29). It should be added in this context that cotreatment with cyclophosphamide synergistically prevented metastases in animal models (Khranovska, M. et al., Abst E05).

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, although the risks of stem cell toxicity are currently poorly understood (Pollak, M., Abst IL17). Studies with metformin have suggested anticancer chemopreventive activity by lowering insulin, testosterone and insulin-like growth factor I (IGF-I) levels, 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 dehydro-

genase (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 identified typically 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).

In that regard, and because cancer cells rely more on de novo palmitate synthesis than normal cells, 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, and 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 [^{11}C]-acetate-based positron emission tomography imaging (Nisen, P., Abst IL20).

ANDROGEN RECEPTOR AND NOVEL TARGETS IN PROSTATE CANCER

Exploring new drugs and targets for intervention in castration-resistant prostate cancer, cabazitaxel (a microtubule-stabilizing taxane), sipuleucel-T (an autologous dendritic cell vaccine) and abiraterone (a cytochrome P450 CYP17 inhibitor that suppresses androgen synthesis), and especially MDV-3100 (an androgen receptor blocker), demonstrated putative activity in preclinical and clinical trials, while denosumab proved superior to zoledronate in preventing skeletal-related events in case of bone metastases. Castration-resistant prostate cancer is a challenging setting for developing new drugs, the objective of which should be to prolong survival, an outcome lacking surrogate endpoints, and also to prevent skeletal-related events. Prolongation of survival has been attained with drugs such as cabazitaxel, but not satraplatin (which prolonged progression-free but not overall survival). The androgen receptor remains involved in the malignancy despite castration resistance, but potential for the new antiandrogens, such as MDV-3100, with activity on prostate-specific antigen (PSA) levels in chemotherapy-naive, as well as pretreated castration-resistant, prostate cancer, should still wait until clinical trial confirmation of a benefit on survival, although benefits on skeletal-related events have already been established with denosumab. In addition, recognition of the interplay between c-Met and VEGF in the disease 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. As an alternative, immunotherapy with sipuleucel-T has also offered benefits on overall survival, but confirmation is still pending for new cancer vaccines, such as rV-PSA-TRICOM/rF-PSA-TRICOM. However, integrating all these new agents into the treatment paradigm for prostate cancer is still pending clarification and review (Stenrberg, C.N., Abst IL21; de Bono, J.S., Abst IL22; Massard, C., Abst IL23). In the preclinical arena, activity was reported with novel alternatives such as the *R*-bicalutamide derivatives ISIR-9 and ISIR-11, which in contraposition to *R*-bicalutamide exhibited not only cytostatic, but also cytocidal activity (Tesei, A. et al., Abst D10).

As mentioned, cancer vaccines have also been a subject of research in the context of prostate cancer. Validation of poxvirus vaccine vectors for efficient infection of antigen-presenting cells without integration into the DNA, and the use of a *tri*ad of *co*stimulatory *m*olecules (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 and resulted in significant overall survival advantages in patients with castration-resistant prostate cancer in two phase II studies. A relationship between survival and PSA responses confirmed the benefits of the vaccine, which 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, and additional vaccine target candidates have been identified, such as the 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).

ADDITIONAL PUTATIVE NEW TARGETS FOR ANTICANCER THERAPY

The voltage-gated potassium channel K_v11.1 (HERG) has also 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 has been 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 blockers, such as the compounds mentioned, which showed in vitro activity against leukemia and also colorectal cancer cells. K_v11.1 blockade has also been able to counteract chemoresistance and metastatic spread (Arcangelli, A. et al., Abst PP08).

Looking for new targets, the identification of APIM (AlkB homologue 2 PCNA-interacting motif) as a common motif in proteins that inter-

act with proliferating cell nuclear antigen (PCNA) led to the development of ATX-101, an APIM-comprising peptide that potentiates the action of chemotherapeutic drugs by inhibiting the interaction between PCNA and key proteins participating in DNA repair and cell cycle control. Activity was demonstrated in animal models of multiple myeloma and prostate cancer (Alevizopoulos, K. & Otterlei, M., Abst H09).

Among these agents, the anti-carbohydrate-induced conformational epitope TA-MUC1 antibody PankoMab 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 the 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).

On the contrary, 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 method 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. In that regard, the success obtained with taxanes and vinca alkaloids is probably not related to their interference with mitosis, but to the role of microtubules during the interphase, and specifically their relationship with oncogenes and proteins related to DNA repair, which 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).

In a similar way and despite promising preclinical and early clinical evidence, negative results were obtained with insulin-like growth factor I receptor (IGF-I receptor) blockers that were explained by poor activity, inherent resistance, low-quality studies (regarding the use of adequate biomarkers and/or arbitrary selection of combinations) or metabolic toxicity. Although IGF-I receptor expression is increased in tumor cells and the target has been validated in preclinical models using anti-receptor antibodies, anti-ligand antibodies, tyrosine kinase inhibitors or other drug strategies, the only drug modality to reach clinical trials, anti-receptor antibodies, resulted in encouraging phase II but negative phase III clinical trial results. In fact, studies with figitumumab combined with chemotherapy in patients with NSCLC demonstrated no benefit but increased toxicity, although poor 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 trials and preclinical studies. The target still seems interesting based on mechanistic 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 can be further investigated, and then adequate patient selection and dosing and rational combinations need to be explored (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 announced, 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 as cancer therapy (Antoun, S. et al., Abst G05).

MISCELLANEOUS INFORMATION ON ANTICANCER THERAPIES

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 MECl-1 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).

Improvements in response predictors were discussed in the context of NSCLC. For example, responses of NSCLC to erlotinib and patient survival were effectively prevented by profiling kinase activity (Ruijtenbeek, R. et al., Abst F03). In addition, higher expression of estrogen receptor-β in female compared to male patients with the disease suggested antiestrogen therapy for the target population (Bogush, T.A. et al., Abst F04).

An additional study related with colorectal cancer identified phosphorylated ribosomal protein S6 kinase beta-1 (S6K1) as a marker of resistance to the MEK inhibitor selumetinib (Martinez-Lacaci, I. et al., Abst B08), whereas independent studies in colon, breast and head and neck tumor cells identified the eukaryotic translation initiation factor 3 subunit F (eIF3f) as a predictor of sensitivity to EGFR-targeted agents such as trastuzumab, cetuximab and erlotinib (Zindy, P. et al., Abst B09).

Preliminary experience combining the antiviral agent cidofovir with radiochemotherapy against human papillomavirus-related malig-

nancies, 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 studies were initiated in patients with non-metastatic cervical cancer to determine the maximum tolerated dose and confirm the antitumor activity of cidofovir combined with radiotherapy, brachytherapy and chemotherapy. Preliminary results indicated no dose-limiting toxicity (Deutsch, E. et al., Abst PP10).

Additional drugs in early development that showed promising activity and proved feasible regarding pharmacokinetics and safety in initial phase I trials during this year's meeting included the camptothecin analogue namitecan (Sessa, C. et al., Abst PP06), while potential in the preclinical arena was described with the histone deacetylase inhibitor OCID-4681-S-01 (Nidhyanandan, S. et al., Abst D03), the polyamine-vectorized spermine-conjugated topoisomerase II inhibitor F-14512 (Brel, V. et al., Abst D05), the proteasome-inhibiting, PPARγ-activating glycyrrhetinic acid derivatives, including *N*-[2-[3-[3,5-bis-(trifluoromethyl)phenyl]ureido]ethyl]glycyrrhetin amide (Lallemand, B. et al., Abst C04; Lallemand, B. et al., Abst C05), the ruthenium-based antimitotic and antiangiogenic agent NAMI-A (Bergamo, A. et al., Abst D08), the monovalent anti-Met antibody DN-30 (Comoglio, P.M. et al., Abst D13), aaptamine isolated from the marine Vietnamese sponge *Aaptos* spp. and its 9-demethyloxy and iso derivatives 9-demethyloxyaaptamine and isoaaptamine (Dyshlovoy, S. et al., Abst D11), the calcium-dependent potassium channel-blocking fungal phytotoxin ophiobolin A (Bury, M. et al., Abst D18), the natural VEGFR-1-blocking triterpenoids lantadene A and B (Sharma, D.R. et al., Abst D07), and a series of original gold-based dithiocarbamates (Fregona, D., Abst D19). In addition, the prostacyclin-releasing pyridine salt 1,4-dimethylpyridinium proved to be potentially useful for preventing lung metastases in breast cancer models, and in combination with cyclophosphamide significantly reduced primary tumor volume as well (Blazejcyk, A. et al., Abst D16). Lactoferricin derivatives targeting negatively charged membrane lipid phosphatidylserine residues specifically exposed in cancer cells resulting in melanoma cell killing were also described (Riedl, S. et al., Abst D12), while anti-melanoma activity was reported with narciclasine, an apoptosis inducer isolated from *Narcissus* spp. (Van Goietsenoven, G. et al., Abst D17).

ADDITIONAL ISSUES

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, but 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).

DISCLOSURES

The author states no conflicts of interest.