Tuesday, 21 October 2008 13:15–14:00

Michel Clavel lecture

1 INVITED

No risk, no fun

J. Verweij[1]. [1]*Erasmus University Medical Center, Rotterdam, The Netherlands*

Drug development in oncology, just like in any other field of medicine, is faced with the challenge to make active new compounds available for standard of care in the shortest possible time frame, with the least possible physical risks for patients, and involving the smallest possible number of patients that enables provision of the most convincing dataset.
"No risk, no fun" was one of the favourite sayings of Dr. Michel Clavel. He meant to say that without taking some calculated risks, one would not likely optimally enjoy the possible fun in life. Extending this view to drug development means that a defensive strategy in trial performance may not yield the optimal speed of development. Some creativity is desirable, obviously without jeopardizing patient safety in any means. Unfortunately the strategy particularly of pharmaceutical industry is defensive in the wrong way, and likewise too aggressive in the wrong way. In this lecture I will try to make the point that there are multiple ways conceivable to help in speeding up and streamlining drug development in oncology. Simple cutting and pasting in protocol writing leads to delays in trial performance. In- and exclusion criteria should be well considered, dose levels in phase I studies never pre-fixed, pharmacokinetic analyses performed real-time. The number of centers in a phase I trial should be limited to 1 or a maximum of 2, since there are data indicating higher number of centers slow down accrual. Exceptions to this are conceivable for rare molecular targets, or disease specific tumors in less frequent indications. Expanded cohorts in a phase I trial cannot replace and adequately sized phase II study. The potentials of the use of biomarkers in early clinical development should not be overestimated.
Early clinical drug development studies should be performed in close partnership between the clinical investigators and pharmaceutical industry, and protocols should be developed jointly.

Tuesday, 21 October 2008 14:00–14:45

Keynote lecture

2 INVITED

IGF-I as an emerging target

D. Yee[1]. [1]*University of Minnesota, Masonic Cancer Center, Minneapolis, USA*

Disruption of endocrine signaling pathways has been one of the most successful "targeted" strategies for the prevention and treatment of cancer. The insulin-like growth factor (IGF) system is an endocrine pathway required for normal growth and development. IGF signaling has also been shown to be important for malignant transformation and maintenance of the malignant phenotype. IGF, and its cognate receptors, influence tumor cell metabolism, proliferation, survival, and metastasis. Thus, disrupting IGF action has emerged as a new therapeutic pathway for cancer. As with any endocrine system, there are multiple ligands and receptors. Insulin, IGF-I, and IGF-II interact with the type I IGF receptor (IGF1R), insulin receptor (InsR), and hybrid receptors composed of subunits of both IGF1R and InsR. To date, preclinical data have shown that ligand and receptor neutralization strategies have activity in model systems. In the clinic, disruption of IGF1R function by monoclonal antibodies has emerged as the leading strategy. Early clinical trials demonstrate that these antibodies have single agent activity and enhance the effects of cytotoxic chemotherapy. These promising results suggest that disruption of IGF action will have a place in cancer treatment. Preclinical data suggest that insulin receptor function, sequencing with cytotoxic chemotherapy, and understanding the signaling events downstream of IGF1R/InsR will enhance the therapeutic efficacy of this approach. Careful attention to several aspects of IGF signaling should be considered in the design of future clinical trials.

Tuesday, 21 October 2008 15:15–17:00

PLENARY SESSION 1

Molecular targets – state of the science A

3 INVITED

RET inhibition: therapeutic implications in thyroid cancer

N. Mitsiades[1], J.A. Fagin[2], D.G. Pfister[3]. [1]*Memorial Sloan-Kettering Cancer Center, Department of Medicine, New York, USA;* [2]*Memorial Sloan-Kettering Cancer Center, Department of Endocrinology, New York, USA;* [3]*Memorial Sloan-Kettering Cancer Center, Head and Neck Medical Oncology, New York, USA*

In patients with aggressive thyroid carcinomas, several kinase pathways play a pathogenetic role, including the Ret/Ras/Raf/MEK/ERK and PI3K/Akt cascades. Ret (REarranged during Transfection) is a cell-surface receptor tyrosine kinase (TK) that is activated by members of the glial-derived neurotrophic factor (GDNF) family. Its intracellular domain contains at least 12 autophosphorylation sites that serve as docking sites for several second mediator proteins, leading to activation of the MAPK and Akt cascades. In medullary thyroid carcinomas (MTCs), gain-of-function missense RET mutations lead to a constitutively active kinase (>95% of familial MTCs, 40%-70% of sporadic MTCs). Many papillary thyroid carcinomas express illegitimate chimeric Ret molecules that originate from the fusion of the Ret TK domain with a variety of heterologous gene partners (collectively known as RET/PTC genes). RET/PTC rearrangements lead to constitutive Ret activation because the Ret TK is brought under the regulation of the promoter of the partner gene, which, contrary to Ret, is constitutively expressed in thyrocytes. Importantly, the PTC proteins tend to homodimerize, bringing together the fused Ret TK domains and thus promoting ligand-independent transphosphorylation. Data from early clinical trials of several oral TK inhibitors that target Ret have demonstrated clinical activity in aggressive thyroid cancers. It must be emphasized that these inhibitors target multiple kinases including VEGF receptors, and therefore it is difficult to attribute their in vivo effects to one particular target – but their Ret inhibitory activity nonetheless appears promising. For example, in phase II studies, sorafenib (Bay 43–9006/Nexavar; targets Raf, VEGFR, PDGFR, Ret), motesanib diphosphate (AMG 706; targets VEGFR, PDGFR, Kit, Ret), and sunitinib (SU11248/Sutent; targets VEGFR, PDGFR, Ret) were all active drugs in patients with advanced differentiated thyroid cancer. Single-agent treatment yielded partial responses in 13%-23% and stable disease in 53%-68% of patients (JCO 2008;26:published ahead of print; NEJM 2008;359:31; Proc ASCO 2008, Abstract 6025). In patients with MTC, vandetanib (ZD6474/Zactima; targets VEGFR, EGFR, Ret) and XL184 (targets VEGFR, Met, Ret) have similarly demonstrated promising activity of clinical interest in prospective studies (Proc ASCO 2007, Abstract 6018; Proc ASCO 2008, Abstracts 3522 and 6024). In conclusion, Ret is an important target for the treatment of an aggressive subset of thyroid cancers. Several TK inhibitors have activity against Ret and offer hope in the near future for personalized targeted treatment for these tumors. However, well designed clinical trials that incorporate tumor genotyping and appropriate pharmacodynamic studies will be necessary to delineate to what extent the anti-tumor effects seen with these new agents reflect Ret inhibition versus the inhibition of other kinase targets.

4 INVITED

C-Met as a target in clinical oncology; rationale and current achievements

F.A.L.M. Eskens[1]. [1]*Erasmus University Medical Center, Medical Oncology, Rotterdam, The Netherlands*

For tumors to grow and metastasize, proteolytic breakdown of the extracellular matrix is an essential step. Activation of C-Met, a transmembrane tyrosine kinase receptor, results in cell dissociation and motility and an invasive malignant phenotype with increased angiogenic activity. Activation of C-Met is induced by the natural ligand Hepatocyte Growth Factor/Scatter Factor (HGF/SF). Tumoral hypoxia is a driving factor for increased HGF production. Increased expression and/or autonomous functioning of C-met (due to somatic or germline MET mutations and/or increased autocrine and paracrine HGF-receptor interaction) is associated with increased tumorigenesis in preclinical models and inverse clinical outcome in many epithelial and mesenchymal tumor types, with special emphasis on medullary thyroid and papillary renal cell carcinoma. The C-Met signal transduction pathway has become another intriguing target

for the development of specific inhibitory therapy for which in essence 3 approaches can be conceived;
– Antisense oligonucleotides or ribozymes that can serve to inhibit RNA transcription and receptor synthesis;
– Specific monoclonal antibodies targeting either receptor or ligand;
– Competitive inhibition at the phosphorylation binding domains of the intracellular site of the receptor once ligand-receptor interaction has occurred;

To date, monoclonal antibodies targeting either HGF/SF and C-Met and small molecule C-Met tyrosine kinase inhibitors have been developed and are currently undergoing clinical phase I and II studies, meanwhile showing preliminary hints of clinical activity in papillary renal cell cancer and gastric cancer. Currently, both C-Met selective and broad spectrum receptor TKI are in the clinic, and bearing in mind the experience and knowledge obtained in the last two decades with the use of this type of targeted or cancer cell specific therapy, it is important to asses whether selective C-Met inhibition or more broad spectrum receptor (tyrosine kinase) inhibitory activity is to be preferred. It is obvious that this will partly depend on the toxicities observed, as well on our ability to demonstrate proof-of-principle pharmacodynamic activity. It will also be crucial to assess whether single agent therapy or combinations with other systemic treament options (cytotoxic chemotherapy, other targeted agents, radiotherapy) will result in optimal antitumor activity, and therefore it can be foreseen that, based upon results obtained in preclinical models, in the near future a plethora of (randomised) phase II and III studies incorporating C-met inhibiting agents will be performed.

5 INVITED

Biological roles of PI 3-kinase isoforms

B. Vanhaesebroeck[1]. [1]*Institute of Cancer, Centre for Cell Signalling, London, United Kingdom*

The PI 3-kinase signalling axis is one of the most frequently mutated signalling pathways in cancer. Interference with this pathway is therefore considered an attractive therapeutic approach in oncology. The exact signalling connections in the PI3K pathway are still being unraveled, and it is presently not clear at what level it is best to interfere, i.e. upstream, downstream or at the level of PI3K itself, or combinations. In addition, mammals have 8 distinct isoforms of PI3K, and global inhibition of all isoforms of PI3K may have substantial toxicity in vivo. Therapeutic intervention at the level of PI3K itself may therefore have to be centered on specific (subsets of) PI3K isoforms. This might be exemplified by haematological malignancies where the often the p110delta isoform of PI3K is predominant. It has been particularly difficult to gain insight into the physiological roles of PI3K isoforms by classical mouse gene targeting/knock-out approaches. We have pioneered the use of so-called 'kinase knockin' mice in which we have created germline inactivating mutations in the ATP-binding site of PI3K isoforms. This strategy more faithfully mimics pharmacological inhibitors than the classical knock-out approaches, and has allowed us to uncover isoform-selective roles of several isoforms of PI3K. These genetic strategies, together with pharmacological approaches using newly developed small molecule inhibitors offer a powerful platform to unravel the roles of PI3K isoforms in the normal organism and in disease. An overview of these efforts will be presented.

6 INVITED

Notch as a potential therapeutic target in cancer

L. Miele[1], P. Rizzo[1], C. Osipo[1], K. Foreman[1], M. Bocchetta[2], D. Tonetti[3]. [1]*Loyola University Chicago Medical Center, Breast Cancer Program, Cardinal Bernardin Cancer Center, Illinois, USA;* [2]*Loyola University Chicago Medical Center, Thoracic Oncology Program, Cardinal Bernardin Cancer Center, Illinois, USA;* [3]*University of Illinois, Chicago, USA*

Background: There is increasing evidence for a key oncogenic role of the Notch signaling pathway in several solid tumors. The best characterized to date is breast cancer, with accumulating data on lung cancer. Notch signaling regulates proliferation, survival and differentiation of cancer cells, as well as communication between tumor and endothelial cells. Additionally, there is considerable evidence that Notch is among the pathways that control the self-renewal of "cancer stem cells". Consequently, a number of Notch inhibitors are being developed. Among these, γ-secretase inhibitors (GSIs), are in early clinical trials. However, Notch signaling is notoriously context- and dose-dependent, and is regulated by a complex network of cross-talk interactions with other pathways, some of which include potential therapeutic targets. Understanding these interactions will make it possible to design rational combination regimens.
Materials and Methods: We used several in vitro and in vivo cancer models, including ERα+ (T47D and MCF-7), ERα-, HER2Neu+ (SKBr3), ERα-, HER2/Neulow (MDA-MB-231) breast cancer cells, A549 lung adenocarcinoma cells and others, as well as clinical specimens.
Results: We discovered that: (1) In ERα+ breast cancer cells, estrogen suppresses Notch signaling by regulating the cellular distribution of Notch-1 and causing membrane accumulation of inactive Notch-1. Either estrogen withdrawal, mimicking the effects of aromatase inhibitors, or SERMS such as tamoxifen, cause re-activation of Notch signaling and increased dependence on Notch for proliferation, survival and invasion. Combinations including a GSI and an anti-estrogen are synergistically effective in vitro and in vivo. Such combinations are now being tested in the clinic; (2) In at least one model of tamoxifen resistance, Notch-4 plays a key role and GSIs are highly effective in vitro and in vivo, reversing tamoxifen resistance; (3) ERα-, PR-, Her2low MDA-MB231 cells are highly sensitive to Notch inhibition in vitro and in vivo; (4) Her2/Neu overexpression inhibits Notch signaling by modulating membrane availability of Notch ligands. Treatment of Her2/Neu overexpressing breast cancer cells with trastuzumab or with a tyrosine kinase inhibitor (TKI) causes re-activation of Notch signaling. Combination regimens including a Her2/Neu targeting agent and a GSI are at least additive in vitro and decrease tumor recurrence in vivo. Trastuzumab resistant cells are highly sensitive to GSIs, which reverse trastuzumab resistance; (5) Mammosphere formation by "breast cancer stem cells" is dramatically inhibited by GSIs; (6) In lung adenocarcinoma (ACL) cells, hypoxia stabilizes Notch-1 via HIF-1α. Hypoxic ACL cells are exquisitely dependent on Notch for survival and highly sensitive to GSIs.
Conclusions: Our data support the therapeutic investigation of Notch inhibitors in combination with: (1) endocrine therapy in ERα-positive breast cancers and in some tamoxifen-resistant breast cancers; (2) Her2/Neu targeted agents in Her2/Neu overexpressing and trastuzumab-resistant breast cancers; (3) anti-angiogenic agents or other hypoxia inducers in ACL. Additional combinations for rational targeting of triple-negative breast cancer cells and "cancer stem cells" are currently being studied.