Friday 1 October 08:00–09:45

PLENARY SESSION 8

Optimising targets for angiogeneic inhibition

458 INVITED

What has 30 years of angiogenesis research and drug development taught us about cancer treatment?

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The term angiogenesis, referring to the growth of new bloods, was first described in 1787 by a British Surgeon, John Hunter. Two centuries later, it was recognized to play an important role in embryonic development and physiological processes such as placenta formation. In 1971 a Boston surgeon, Judah Folkman hypothesized that tumor growth was dependent upon angiogenesis and that tumor angiogenesis could be a target for cancer therapy. He speculated that targeting genetically stable endothelial cells could inhibit tumor growth without the development of drug resistance which occurs in the genetically unstable tumor cells. Shortly after, Folkman and colleagues discovered that cartilage contains factors that inhibit tumor angiogenesis. In the 1980s, numerous endogenous angiogenic factors and anti-angiogenic factors were discovered and characterized; the most significant factor for the tumor field being vascular endothelial factor (VEGF) first discovered by Harold Dvorak in 1983 as a vascular permeability factor and later by Napoleon Ferrara in 1989 as a critical angiogenic factor in embryonic development and tumor growth. In the 1990s several different molecules with anti-angiogenic properties went into clinical trials in cancer patients. These first trials did not meet the high expectations generated by the experimental data in animal models. Moreover, animal data (Robert Kerbel, 2001) showed that tumors can become resistant to anti-angiogenic therapy. Potential mechanisms of resistance include secretion of alternative angiogenic factors by the genetically unstable tumor cells or selection of tumor cells that either can survive hypoxic conditions or co-opt existing blood vessels in surrounding tissues. This indicated that combination therapies with agents targeting tumor cells or alternative anti-angiogenic pathways may be more effective than single agent therapy, particularly in advanced disease. This has been supported by animal studies and has led to clinical trails of anti-angiogenic compounds in combination with conventional chemotherapy as well as the design of small molecule kinase inhibitors that target multiple signaling pathways in vascular cells as well as in tumor cells. In 2003, the first large scale clinical trial showing a prolonged survival in patients with cancer after treatment with a very selective anti-angiogenic drug (Avastin, an inhibitory antibody against VEGF) in combination with a standard chemotherapy regimen was reported along with promising data from phase I trials with small molecule inhibitors targeting VEGF signaling pathways. This has validated the concept of anti-angiogenic therapy for cancer and generated enormous interest in the area. Attractions of this approach include an improved safety profile compared to conventional cytotoxic therapies, the application to a broad range of tumor types, the potential for combinations with most other therapeutic approaches including the newer and safer molecular targeted anti-tumor therapies and the potential for use in the adjuvant as well as advanced disease setting. Challenges for the future include determining the patient populations most likely to respond to anti-VEGF or other anti-angiogenic therapies, the best molecular markers for patient stratification, the stage of disease most responsive to therapy, the best surrogate markers for predicting patient response and the safest and most effective combination therapies. It is an exciting new era in cancer therapy.

459 INVITED

Targeting VEGF with Avastin

N. Ferrera. *USA*

Abstract not received.

460 INVITED

Clinical development of AVE 8062 and ZD6126

P. LoRusso. *USA*

Abstract not received.

461 INVITED

Tyrosine kinase inhibitors that target more than the VEGF-R: SU 11248 and ZD6474

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Targeting the VEGF pathway has historically been considered the most direct method of inhibiting tumor angiogenesis. The recent approval of bevacizumab has benchmarked this approach in the clinic for colorectal cancer, whereas data with this antibody also appears promising in renal cell cancer and non-small cell lung cancer. Among the VEGF-R directed small molecule tyrosine kinase inhibitors, most are only relatively specific for the VEGF-R, and at least two of these, SU11248 and ZD6474, are capable of inhibiting a spectrum of other growth factor receptors that are thought to be relevant in the treatment of cancer. ZD6474 is an anilinoquinazoline with in vitro inhibitory activity against both the VEGFR2 and EGFR. Although there is a 10-fold difference in sensitivity to ZD6474 between the two receptors (IC50 of 40 and 500 nM, respectively), these concentrations are clearly achievable in the plasma of cancer patients at tolerable doses. Interestingly, toxicities of ZD6474 in phase I were partly mechanism-based and included mild hypertension, diarrhea, and skin rash. Objective responses were observed in patients with non-small cell lung cancer. SU11248, an indolinone, demonstrates sub-micromolar inhibitory activity against the VEGFR2, c-KIT, Flt-3, PDGFR-beta and FGFR, in decreasing order of potency. In phase I studies of SU11248, tumor regressions were observed in patients with renal cell cancer, neuroendocrine tumors, and imatinib-refractory GIST. Several observations can be made regarding these less specific inhibitors. The preclinical studies generally demonstrate tumor regression in addition to inhibition of tumor growth, and efficacy is also observed in larger, well-established tumors. In the clinic, the spectrum of toxicities is a bit more complex than more specific tyrosine kinase inhibitors, whereas tumor regressions are more common. As with all biologically-targeted compounds, the challenge will be to improve patient selection, which may be more difficult with agents that modulate more than one aberrant signaling pathway.

Friday 1 October 10:15–12:00

PLENARY SESSION 9

Apoptosis pathway targeting agents

462 INVITED

Targeting apoptosis in cancer with APO2L/TRAIL

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Apo2L/TRAIL is a recently discovered member of the tumor necrosis factor (TNF) gene superfamily that triggers apoptosis through engagement of two specific death receptors: DR4 and DR5. Upon engaging DR4 and/or DR5, Apo2L/TRAIL assembles a death-inducing signaling complex (DISC) that activates the apoptosis-initiating proteases caspase-8 and caspase-10 through the adaptor molecule Fas-associated death domain (FADD). As a soluble, zinc-coordinated trimer, Apo2L/TRAIL selectively induces apoptosis in many types of tumor cells but not in most normal cells, suggesting that it may be useful for cancer treatment. Unlike most conventional cancer therapeutic agents, Apo2L/TRAIL activates the apoptotic caspase cascade independently of the p53 tumor suppressor gene. In several cancer xenograft models, based upon established tumor cell lines or patient-derived tumors, Apo2L/TRAIL has demonstrated single agent anti-tumor efficacy as well as synergy with various types of chemotherapy. Thus, Apo2L/TRAIL might be effective not only for the second-line treatment of tumors that have acquired resistance to conventional therapy, but also for augmenting the efficacy of current first-line treatment in several types of cancer.

463 INVITED

Translation targeting TRAIL receptors to the clinic

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Apoptosis is a biochemical process of serial activation of upstream initiator cysteine aspartyl specific proteases (Caspases) that recruit downstream effector caspases, mediate proteolysis and ultimately result in cell death.[1] Effector (or *executioner*) caspases induce selective cleavage