Friday, 19 November 2010 11:00–13:05

PLENARY SESSION 8

Angiogenesis and tumour microenvironment

460 INVITED

Antiangiogenic drug alterations of the tumor microenvironment which can impact chemotherapy efficacy

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Among the most interesting findings of antiangiogenic drugs assessed in phase III trials is the necessity for bevacizumab (the anti-VEGF antibody) to be combined with chemotherapy in order for it to achieve a clinical benefit in most approved indications, and in contrast, the failure of VEGF receptor tyrosine kinase inhibitors (TKIs) such as sunitinib or sorafenib to improve chemotherapy efficacy. As a result, there is much interest in uncovering the mechanisms by which an antibody drug such as bevacizumab can enhance chemotherapy efficacy and why TKIs fail to do so. Results will be summarized implicating one potential mechanism for antibodies: inhibiting the mobilization and tumor colonization of a variety of circulating bone marrow-derived cell (BMDC) populations, including endothelial progenitor cells (CEPs) induced by chemotherapy. Thus certain chemotherapy drugs or other agents such as vascular disrupting agents (VDAs) using maximum tolerated doses can induce a rapid host response comprised of multiple elevated cytokines and chemokines, including G-CSF and SDF-1. This in turn promotes the mobilization of CEPs. However, other types of BMDCs appear to be involved as well, the nature of which is under study. They may include various monocytic/macrophage populations in addition to Gr1+CD11d+ myeloid derived suppressor cells. The BMDC VDA or chemotherapy-induced mobilization and tumor colonization response can be blocked by co-treatment with an antiangiogenic antibody targeting the VEGF pathway, and thus increase the VDA/chemotherapy efficacy. However, some limited data we have obtained indicate that antiangiogenic TKIs may not possess this inhibitory effect.
The nature of the growth factors contributing to the BMDC response are being evaluated. In the case of VDAs, the major growth factor implicated is G-CSF, whereas in the case of paclitaxel, it is SDF-1. Thus the results suggest a way in which targeting SDF-1 may improve chemotherapy efficacy while the G-CSF results may have implications for the use and effects of recombinant G-CSF growth factor support to accelerate recovery from myelosuppression.
Finally, we have also found that antiangiogenic TKIs such as sunitinib and sorafenib can also induce a host multi-cytokine response and as such, this may blunt their ability to enhance the efficacy of chemotherapy. This host response may also contribute to other important outcomes including drug resistance and alterations in tumor aggressiveness over time.

461 INVITED

Third generation anti-angiogenic strategies: novel players, novel principles

P. Carmeliet. *Belgium*

Abstract not received

462 INVITED

Micro-environmental influences on cancer stem cells

L. Ellis[1], J. Lu[1], S. Samuel[1], F. Fan[1], L. Xia[1], X. Ye[1], E. Sceusi[1], F. Tozzi[1], Y. Zhou[1]. [1]*University of Texas MD Anderson Cancer Center, Unit 173, Houston Texas, USA*

Cancer stem cells (CSC), can arise either from normal stem cells or due to the influence of the tumor micro-environment. Although the vasculature of tumors delivers oxygen and nutrients to the growing tumor, it has also been hypothesized that endothelial cells contribute to the growth of tumor cells in a paracrine fashion. Gilbertson and colleagues have shown that glioma cancer stem cells reside in the perivascular niche (Caner Cell 2007). We studied the potential role of endothelial cell (EC) derived paracrine factors on promoting the CSC phenotype in human colorectal cancer (CRC) cells. Co-culturing of CRC cells with ECs markedly increased the ALDH-positive population and the sphere forming ability in CRC cells. In addition, CRC cells also displayed increased CD133 and CD44 protein levels. Furthermore, this effect could be mimicked simply by co-culturing CRC cells with conditioned media obtained from ECs. Similarly, treatment of CRC cells with conditioned medium from ECs significantly increased the ALDH-positive population, sphere forming ability, and the expression of CD133 and CD44. Conditioned medium from ECs, concomitantly decreased spontaneous apoptosis in CRC cells as demonstrated by a decrease in Annexin V-positive population, down-regulation of cleaved PARP and Caspase 3, and up-regulation of Bcl2. CRC cells exposed to EC conditioned medium also displayed decreased sensitivity to 5-FU, oxaliplatin and irinotecan. Subsequent studies have been repeated in pancreatic cancer. The search for soluble factors that mediate this observation are ongoing.

463 INVITED

Immunotherapy in 2010 – still alive?

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For too long, the immunotherapy of solid tumours has been considered as a promising treatment modality without being firmly established as a standard treatment option. Objective remissions were consistently reported, however with a great variety of approaches and only in a minority of patients in whom this could not be predicted. On the other hand, in some (randomized) trials with vaccine therapy the results suggested a detrimental effect. However, data on the efficacy of T-cell directed therapy are accumulating, and these are being supported by a positive correlation with specific immune parameters. Robust phase III data on T-cell directed immunotherapy are scarce, which is largely due to the lack of financial support by pharmaceutical industries. Immunotherapy directed to the regulatory T cell response is another area that showed great promise in small (pre) clinical studies, and this line of reserach was strongly boosted by the positive results of a phase III trial in melanoma with ipilimumab, an anti-CTLA4 antibody. Further benefit may be expected to combine this with tumor antigen-specific immunotherapy. Lastly, data are accumulating that certain cytotoxic drugs may have immunostimulatory effects, which provides a rationale to combine chemotherapy and immunotherapy. Taken together, immunotherapy is more alive than ever, but will only outgrow its status of promising treatment when convincing results from well-designed trials are available.

464 INVITED

Molecular imaging of therapy response

W. Weber. *Germany*

Abstract not received

Friday, 19 November 2010

Poster Sessions

Angiogenesis, metastasis and inhibitors

465 POSTER DISCUSSION

A Phase 1 dose escalating study of ACE-041, a novel inhibitor of ALK-1 mediated angiogenesis, in patients with advanced solid tumors

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Background: Activin receptor-like kinase-1 (ALK-1) is a type I receptor predominantly expressed on activated vascular endothelial cells that mediates signaling by members of the TGF-β superfamily of proteins. ACE-041, a soluble receptor fusion protein consisting of the ligand-binding extracellular domain of ALK-1 linked to a IgG1-Fc region, binds with high affinity to BMP9 and BMP10 but not TGFβ1, 2 or 3, VEGF or bFGF. ACE-041 is able to inhibit both VEGF and bFGF stimulated angiogenesis indicating that ALK-1 is downstream of VEGF and bFGF signaling. In a variety of murine tumors, ACE-041 has demonstrated the ability to decrease both tumor vascularity and growth.

Methods: The primary objective of this phase 1 study is to evaluate the safety and tolerability of ACE-041. Secondary objectives include identifying MTD, PK, preliminary activity on PD markers and antitumor activity by RECIST, PET-CT and DCE-MRI. Cohorts of 3−6 patients are being enrolled at escalating dose levels. ACE-041 is administered SC every 3 weeks for a total of 4 doses or until disease progression. Patients with confirmed stable or responding disease may continue treatment for up to 12 months.
Results: 19 patients (11M, 8F) have been enrolled. Five dose levels (0.1 to 1.6 mg/kg) have been completed; the sixth cohort (3.2 mg/kg) is ongoing. The t1/2 is approximately 10−15 days and the Tmax is 4−7 days. ACE-041 is well tolerated with no DLTs reported thus far. Common to this population, preliminary AEs included nausea, fatigue, anorexia, headache, fever and vomiting, which were generally of low grade toxicity. Stable disease was observed in 3 patients having previously progressed on chemo- and/or anti-VEGF therapy lasting at least 6 cycles; one aggressive carcinoid patient (6 cycles before progressing) and 2 patients still on treatment (NSCLC and head and neck) after 7 cycles. Additionally, in a heavily pre-treated NSCLC patient with an adrenal metastasis enrolled at the 1.6 mg/kg dose level, a positive major response on 18-FDG-PET was observed with a significant decrease in metabolic activity 2 weeks following the first dose.
Conclusions: ACE-041 is a first-in-class inhibitor of angiogenesis targeting ALK-1. Treatment thus far has been well tolerated and preliminary evidence of antitumor activity has now been observed in this first-in-human study. The study is ongoing and final results will be presented at the meeting.

466 POSTER DISCUSSION

PI3K inhibition is necessary and sufficient to induce an anti-angiogenic response in vivo based on suppression of tumor vascular structure

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Background: Vascular endothelial growth factor (VEGF) is a validated target for tumor angiogenesis and the PI3K pathway acts as a central mediator of VEGF driven endothelial cell survival and vascular permeability. While it has been demonstrated that a dual PI3K/mTOR inhibitor can suppress eNOS-induced vascular permeability and vasodilatation resulting in a reduction in the dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) parameter K^{trans}, the effects on vascular structure has not been elucidated [1]. Therefore, our aims were to further ascertain the role of PI3K pathway signaling on vascular structure and physiology by utilizing small molecule inhibitors that target PI3K (GDC-0941 and GNE-490), mTOR (rapamycin) or both (GDC-0980).
Methods: An array of in vivo imaging techniques were employed to evaluate the vascular response in human HM7 colorectal cancer xenografts: ex-vivo micro-computed tomography angiography (μCT-angio), DCE-MRI, vessel size imaging (VSI) by MRI and dynamic contrast-enhanced ultrasound (DCE-U/S) perfusion imaging.
Results: GDC-0980 strongly suppressed both tumor physiological and structural vascular parameters. The DCE-MRI parameter, K^{trans}, was reduced by 24% relative to the control group. DCE-U/S imaging showed that GDC-0980 reduced blood flow within the enhancement region by 8% and reduced the enhancement fraction (Ef) by 55%. GDC-0980 reduced μCT-angio vascular density (VD) by 57% relative to control. In-vivo VSI demonstrated a significant reduction in blood volume, the vessel density related parameter Q and increased vessel size; all changes consistent with a loss of small vessels. DCE-MRI and DCE-US demonstrate that GDC-0980 can suppress permeability and perfusion while uCT-angio, VSI and DCE-U/S Ef data indicates a strong effect on vascular structure. In addition, GDC-0941 also caused a significant decrease in VD while rapamycin did not. Interestingly, GNE-490, a pan-PI3K inhibitor that has similar pharmacokinetic parameters to GDC-0980, produced similar uCT-angio VD results as GDC-0980, suggesting that mTOR inhibition is not required for maintenance of vascular structural effects.
Conclusion: Inhibition of PI3K alone is necessary and sufficient to generate the dramatic physiological and structural changes in tumor vasculature that is characteristic of an anti-angiogenic response in vivo.

References

[1] Schnell et al., Cancer Res. 2008, p. 6598–6607.

467 POSTER

Updated efficacy and safety results for a randomized phase 2 trial of a tumor vascular disrupting agent fosbretabulin tromethamine (CA4P) with carboplatin (C), paclitaxel (P) and bevacizumab (B) in stage IIIB/IV non-squamous non-small cell lung cancer (NSCLC): The FALCON trial

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Background: CA4P is a reversible tubulin-binding tumor vascular disrupting agent (VDA) that has previously shown clinical activity in combination with chemotherapy and antiangiogenic therapy. Enrollment of a phase 2 study evaluating CA4P in combination with C (Carboplatin) + P (Paclitaxel) + B (Bevacizumab) in advanced non-squamous NSCLC was recently completed.
Methods: In an open-label, randomized controlled study for patients with untreated, histologically-confirmed, stage IIIb or IV, non-squamous, NSCLC 60 patients were randomized to receive up to 6 cycles of C + P + B with (CA4P arm) or without CA4P (control arm). After 6 cycles of therapy, patients without progression continued to receive their randomized treatment B or B + CA4P until progression. The primary endpoint is progression-free survival (PFS). Secondary endpoints include response rate and overall survival.
Results: As of June, 2010, the target enrollment of 60 patients was completed. Of these, 53 patients (safety population) received treatment (26 in CA4P arm and 27 in control arm) by the most recent data analysis (May 6, 2010). 30 patients enrolled at least 12 months prior to the data analysis, and these patients composed the efficacy population. For this group, PFS was 6.9 months in the CA4P arm vs. 6.2 months in the control arm with a HR and 95%CI of 0.70 (0.27, 1.82). Partial responses were seen in 60% of patients for the CA4P arm vs. 40% for the control arm. Safety profiles in both treatment arms were comparable. Hypertension, mostly grade 1 and 2, and neutropenia were more frequent in the CA4P arm. Toxicities were manageable and did not result in differences in dose intensity between the two treatment arms. There were three reversible cardiac ischemia events in the CA4P arm, none of which required hospitalization. Updated safety and efficacy data will be presented.
Conclusions: The addition of CA4P to standard doses of C + P + B continues to be well tolerated with trends towards improved outcomes in the CA4P arm.

468 POSTER

Anti-tumoral and anti-metastatic activity of a tetravalent bispecific antibody (TAvi6) targeting VEGF and Angiopoietin-2

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Background: VEGF blockade has been validated clinically as a treatment for human cancers. Angiopoietin-2 (Ang-2) expression has been shown to function as a key regulator of blood vessel remodeling and tumor angiogenesis. In tumors Ang-2 is up-regulated and a bad prognostic factor. Recent data demonstrated that Ang-2 inhibition mediates antitumoral effects. We have generated TAvi6, a novel bispecific antibody targeting VEGF-A and Ang-2 and tested its anti-tumor efficacy. TAvi6 is a tetravalent IgG-like bispecific antibody based on bevacizumab and targets Ang-2 with 2 disulfide-stabilized scFvs (LC06) fused to the C-terminus of the heavy chain.
Material and Methods: TAvi 6 was profiled in biochemical and cellular (angiogenesis) assays. Antitumoral efficacy was assessed in established s.c. Colo205, s.c. Calu-3 and orthotopic i.m.f.p. KPL-4 xenografts in SCID beige mice. Mice were treated with bevacizumab or <Ang-2> antibody LC06 (10 mg/kg), the respective combination (each 10 mg/kg) and TAvi6 (13.3 mg/kg). In addition, TAvi6 was evaluated in tumors progressing after 1st-line treatment with Avastin, for inhibition of metastasis to the lung quantified by Alu-PCR and for inhibition of angiogenesis in the cornea micropocket assay. Tumors were explanted for histological analysis.
Results: In biochemical assays (affinity, Tie2-Ang-2 interaction) and cellular assays (Tie2 phosphorylation, HUVEC proliferation, tube formation) TAvi6 shows properties identical to the parental antibodies bevacizumab and LC06. In the orthotopic KPL-4–003 xenograft tumor growth inhibition was 79% for bevacizumab; 39% for LC06; 90% for the combination and 91% for TAvi6. In the s.c. Colo205–009 xenograft TGI was 66% for