Friday, 24 October 2008 14:00–15:45

PLENARY SESSION 10

Challenges in the development of antibodies and antibody conjugates

464 INVITED

Antibodies/antibody conjugates in development

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No abstract received

465 INVITED

Challenges in the development of antibody drug conjugates

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Background: The effectiveness of conventional cytotoxic chemotherapeutic drugs is often limited by their acute and chronic toxicity to normal tissues. One potential mechanism for broadening the therapeutic window of cytotoxic agents is by chemical linkage to monoclonal antibodies directed against tumor antigens, which alters their biodistribution and pharmacokinetic properties. Such antibody drug conjugates (ADCs) function as pro-drugs with the cytotoxic agent remaining largely inert until released at sites of antibody binding. Although promising conceptually, the clinical development of ADCs has until recently been hindered by low cytotoxic drug potency, linker instability and/or insufficient or non-tumor-specific antigen expression. Many of these issues are being addressed in ADCs now under clinical development by multiple companies including Genentech. At Genentech the most clinically advanced ADC is trastuzumab-DM1 (T-DM1) which is in Phase II testing in patients with HER2+ metastatic breast cancer (MBC). This ADC utilizes the highly potent anti-microtubule maytansine derivative DM1, which has picomolar IC50 cell killing activity in vitro as a free drug, conjugated to the anti-HER2 monoclonal antibody trastuzumab via exposed lysine residues (average 3.5 DM1 molecules/Ab). The maleimidomethyl cyclohexanecarboxylate linker (MCC) has been designed to minimize the extracellular release (and hence toxicity) of free DM1 which also improves the PK of the ADC and minimizes competition for target binding by the deconjugated antibody. In Phase I testing, T-DM1 has demonstrated promising antitumor activity when administered intravenously on either a q3-week or weekly schedule to patients with HER2+ MBC. On the q3-week schedule the dose-limiting toxicity was thrombocytopenia that was atypical from conventional chemotherapy in being rapidly reversible and non-cumulative in nature suggesting an alternative mechanism for megakaryocyte toxicity. Early and preliminary results from the first 30 efficacy evaluable patients enrolled in the on-going Phase II study of T-DM1 in trastuzumab- and chemotherapy-pretreated HER2+ MBC has demonstrated an investigator assessed confirmed response rate of 30% with predominantly mild toxicity supporting the concept of ADCs having an improved therapeutic index compared to conventional cytotoxic chemotherapy. A further improvement in ADC technology being developed by Genentech is engineering antibodies to contain a specific number of non-cross linked cysteine residues accessible for thio-ether conjugation. These “ThioMabs” yield a more homogenous ADC drug substance with fewer high-order drug-bearing antibody species which disproportionally contribute to toxicity in preclinical experiments. A Phase I study of a ThioMab ADC conjugated to a highly potent auristatin anti-microtubule drug has recently been initiated.
Conclusions: Well-designed ADCs have the potential to be both more effective and safer than conventional cytotoxic chemotherapy in patients whose tumors express the target antigen. Further studies will be needed to determine how best to utilize ADCs in cancer treatment including determining the optimal dose and schedule, the level of tumor antigen expression required for anti-tumor activity and how best to combine these drugs with other therapies.

466 INVITED

Challenges in targeting proteases as anti-cancer therapy

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The generation of antibodies with necessary potency and specificity for the human target and cross reactivity for use in preclinical studies remains a challenge. Antibody phage display, coupled with automated selections and screening, provides a fast and efficient approach for the discovery of therapeutic lead candidates. In vitro selection designs are readily developed that facilitate the identification of leads that have high potency and react with both the human target and the orthologous target in preclinical species. Such approaches have allowed us to generate cancer antibody drug candidates with more predictable preclinical development strategies. Our potent and highly selective MMP-14 inhibitor antibody, DX-2400, will be used to illustrate this approach. DX-2400 has pharmacologically validated the key role of MMP-14 in cancer progression in vivo in a wide variety of tumor models and offers a new potential approach for cancer treatment.

467 INVITED

The targeted oncology platform at ImClone Systems: novel receptor blocking antibody therapeutics and approaches

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Based on the notable clinical results achieved to date with the IgG1 monoclonal antibody (MAb) cetuximab in the treatment of head and neck, colorectal, nonsmall cell lung, and other cancers, ImClone Systems is developing a portfolio pipeline of fully human MAbs against high value targets with relevance in both oncologic and nononcologic indications. Antibody engineering and development efforts are focused on MAbs that target proliferative receptors on malignant cells, supportive stroma, and vasculature to achieve maximal blockade of ligand activation and anticancer activity. The IgG1 construct, which has the potential to increase efficacy through antibody-dependent cell-mediated cytotoxicity (ADCC) and other immune effector mechanisms, is a mainstay of ImClone’s platform, and highly specific MAbs that induce maximal immune effector activity, whenever relevant, are being engineered and developed. Fully human IgG1 MAbs in development include those targeting growth factor receptors that confer proliferative advantages to malignant cells (e.g., IMC-11F8 targeting the epidermal growth factor receptor; IMC-A12 targeting the insulin-like growth factor receptor, IMC-RON8 targeting the c-MET receptor tyrosine kinase family member RON; IMC-EB10 targeting FLT3 that promotes the survival and proliferation of several types of leukemia; IMC-3G3 targeting the platelet-derived growth factor receptor [PDGFR]-alpha [PDGFRα]/PDGF axis that is responsible for paracrine and autocrine proliferative interactions between tumor cells, stroma, and vasculature; and IMC-2C5 that targets PDGFRβ, which is upregulated in most solid cancers). ImClone is also developing fully human IgG1 MAbs which block ligands from activating vascular receptors that are critical for malignant angiogenesis (e.g., IMC-18F1 targeting vascular growth factor receptor [VEGFR] 1 [VEGFR1] that is expressed by vascular endothelial and cancer cells alike; IMC-1121B targeting VEGFR2; IMC-3C3 targeting VEGFR3 that plays critical roles in both angiogenesis and lymphangiogenesis; and IMC-3A4 targeting the endothelial cell-specific adhesion molecule VE cadherin, which is crucial for the proper assembly of vascular structures during angiogenesis and maintenance of vascular integrity. In an effort to achieve maximal therapeutic indices, ImClone is also developing IgG1 fully human MAbs against targets whose expression is restricted to specific types of cancer cells and have the potential to induce cytotoxicity by immune effector mechanisms. This approach is exemplified by IMC-20D7S, which targets gp75, a carboxylic oxidase that is involved in melanin synthesis and expressed exclusively by melanocytes and melanoma cells; IMC-20D7S induces cytotoxicity, in part, by immune effector mechanisms, most notably ADCC. Five pipeline MAbs (IMC-11F8, -1121B, -A12, -3G3, -18F1) are currently in clinical development, with a sixth (IMC-EB10) entering phase 1 evaluations in late 2008. In addition to the aforementioned targets and MAbs, ImClone is currently evaluating a variety of other unique cancer targets for therapeutic development, as well as novel platforms to optimize combinations of therapeutics, antibody expression processes, and antibody engineering approaches, particularly bispecific antibodies and antibody alternatives. These targets, antibody therapeutics, and novel approaches will be discussed.