Fourth World Antibody-Drug Conjugate Summit
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The 4th World Antibody Drug Conjugate (WADC) Summit, organized by Hanson Wade was held on February 29–March 1, 2012 in Frankfurt, Germany, which was also the location for the Antibody Drug Conjugate Summit Europe held in February 2011. During the one year between these meetings, antibody drug conjugates (ADCs) have confirmed their technological maturity and their clinical efficacy in oncology. Brentuximab vedotin (ADCETRIS™) gained approval by the US Food and Drug Administration in August 2011 and trastuzumab emtansine (T-DM1) confirmed impressive clinical efficacy responses in a large cohort of breast cancer patients. During the 4th WADC meeting, antibody-maytansinoid conjugates were showcased by representatives of ImmunoGen (T-DM1, SAR3419), lorvotuzumab mertansine/IMGN801, IMGN529 and IMGN853) and Biotest (BT-062). Data on antibody-auristatin conjugates were presented by scientists and clinicians from Seattle Genetics and Takeda (brentuximab vedotin), Pfizer (ST4-MMAF), Agensys/Astella (AGS-16M8F), Progenics (PSMA-ADC) and Genmab (anti-TF ADCs). Alternative payloads such as calicheamincins and duocarmycin used for preparation of ADCs were discussed by Pfizer and Synthone representatives, respectively. In addition, emerging technologies, including site-directed conjugation (Ambrx), a protein toxin as payload (Viventia), hapten-binding bispecific antibodies (Roche), and use of light activated drugs (Photobiotics), were also presented. Last but not least, progresses in solving Chemistry Manufacturing and Control, and pharmacokinetic issues were addressed by scientists from Genentech, Pfizer, Novartis and Pierre Fabre.

Opening Remarks and Introduction Keynote

Alain Beck (Centre d’Immunologie Pierre Fabre), chairman of the summit, opened the meeting with an introduction to antibody drug-conjugates (ADCs) past, present and future.1 Dr. Beck first discussed the concept, structures, antigen targets and indications that have been chosen so far.2 He then gave an update on ADCs currently in preclinical and clinical trials, including different families of payloads (calicheamycins, auristatins, maytansinoids, duocarmycins, doxorubicin, SN-38 and pyrrolo-benzodiazepines),3,4 and reviewed the features of next-generation ADCs.

ADCs are composed of recombinant chimeric, humanized or human antibodies covalently bound by synthetic linkers to highly cytotoxic drugs. The main objective is to combine the pharmacological potency of small (300 to 1000 Da) cytotoxic drugs with the high specificity of monoclonal antibodies (mAbs) that target tumor-associated antigens (TAAs).5 In most cases, the antibody must be highly selective for a TAA with restricted expression on normal cells that is Internalized in cancer cells. The cytotoxic agent selected as the payload kills target cells after internalization and release inside the targeted cells. The current payloads for ADCs in clinical studies are DNA-damaging drugs such as calicheamincins and duocarmycins, or microtubule-targeting drugs such as auristatins and maytansinoids. Linkers attach the cytotoxic agent to the antibody and are designed to be systemically stable and to release the cytotoxic agent in targeted cancer cells. TAAs are frequently plasma membrane proteins that are overexpressed in diseased tissues or expressed at sufficient levels to facilitate cellular cytotoxicity upon internalization. Ideally, the antigen has restricted expression in normal tissues with low or no expression on vital organs. In addition the tumor antigen must be selectively recognized by a high-affinity antibody. Interestingly, expression of an antigen in some normal tissues does not necessarily preclude the development of an ADC. This is the case when the normal tissue is either non-essential or insensitive to the action of the drug (e.g., non-proliferating cells insensitivity toward antimitotic agents such as maytansinoids or auristatin). Prostate-specific membrane antigen (PSMA) is, for example, expressed on normal prostate and on prostate cancer cells, and has been the focus of several ADC programs.6 Targeting of normal prostate tissue may be of no safety concern because most patients may have had their prostate surgically removed prior to ADC therapy. Trastuzumab emtansine is another good example because it has been administered safely at therapeutically effective doses despite HER2 being expressed on some normal tissues.6 Tumor-targeting ADCs specific to markers of angiogenesis have also recently been described.7 These antigens are expressed on the endothelial extracellular matrix. The long residence time allows the localized drug release that leads to intravascular blood coagulation and to tumor cell death.

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To date, the clinical success of ADCs has been very limited compared with that of naked IgGs. Gemtuzumab ozogamicin (Mylotarg; Pfizer), an anti-CD33 mAb conjugated to calicheamicin, was approved by the US Food and Drug Administration (FDA) in 2000 for the treatment of patients with acute myeloid leukemia (AML). Gemtuzumab ozogamicin is a heterogeneous mixture of 50% conjugates (0 to 8 calicheamicin moieties per IgG molecule, with an average of two or three, randomly linked to solvent-exposed lysyl residues of the antibody) and 50% unconjugated antibody. This first-generation ADC product was voluntarily withdrawn from the US market in 2010. Tremendous efforts in the design and validation of ADCs with higher structural homogeneity have been made in the past decade. A second generation of thioantibody drug conjugates was, for example, recently reported following a first paper published in 2008. Junutula and colleagues identified additional conjugation sites in the light chain (LC), the heavy chain Fd moiety (Fd) and Fc part of trastuzumab. Engineered site-specific thio-trastuzumab variants for coupling to thiol-reactive linkers without perturbing antibody structure and function were produced. Based on structural modeling, three variants (LC-V205C, HCA114C, Fc-S396C) were selected. The stability and superior in vivo efficacy of the LC-V205C conjugate may be higher due to faster maleimide ring hydrolysis, which prevented drug loss through the maleimide exchange from antibody to thiol-reactive constituents in the plasma.

Dr. Beck concluded by emphasizing that ADCs are designed to minimize the systemic toxicity of free drug and to augment the antitumor activity of the mAb targeting vehicle. Current novel research concepts relating to study ADC targets, targeting vehicles, linkers and payloads have transformational potential for ADC development. One of the most promising areas of future ADC research is the identification of novel targets with optimal therapeutic indexes of ADCs.10 Recent improvements in drug-linker conjugations, in particular internalization kinetics and intracellular trafficking properties. Recent improvements in drug-linker conjugations, in particular site-specific conjugation methods, resulted in a significant reduction in the off-target toxicity and potentially increased the therapeutic indexes of ADCs.10

**Maytansinoid-Based ADCs**

**John Lambert** (ImmunoGen, Inc.) gave a brief introduction to ImmunoGen’s ADC platform based upon DM1 and DM4, which are two linkable thiol derivatives of the potent tubulin-acting agent maytansine, and a portfolio of linkers with different chemistries that utilize attachment to antibody via accessible surface amino groups of lysine amino acids. This platform has yielded a strong pipeline of maytansinoid-based ADCs (AMCs), with six such compounds in clinical development at the end of 2011, and a further four AMCs set to enter into clinical trials in 2012. Dr. Lambert then described the key clinical data reported for the three most advanced AMCs.

The leading AMC in clinical development is trastuzumab emtansine (T-DM1), which is composed of Genentech/Roche’s HER2-targeting, humanized IgG1 trastuzumab conjugated with DM1 via an uncleavable thioether link formed using the SMCC crosslinker using ImmunoGen’s platform technology. Roche is conducting an extensive clinical development program, with Phase 3 trials to evaluate T-DM1 as a single agent for treating HER2-positive metastatic breast cancer (mBC) in first-line, second-line and third-line settings, and also trials to explore the use of T-DM1 in combination with other agents and to explore its use in adjuvant treatment of HER2-positive breast cancer.14-17

Dr. Lambert described data, previously presented by Dr. Sara Hurvitz at the European Society for Medical Oncology in Stockholm in November 2011, from a Phase 2 trial evaluating T-DM1 in first-line treatment of mBC that exemplified the activity of T-DM1. In this small trial, 137 patients were randomized to receive either T-DM1 as a single agent (n = 67), or a standard-of-care regimen of trastuzumab plus docetaxel (n = 70). The overall response rate (ORR) of the two arms was similar, with 64.2% of patients achieving an objective response on the T-DM1 arm vs. 58.0% for patients receiving trastuzumab plus docetaxel. Furthermore, the progression-free survival (PFS) in the T-DM1 arm was 14.2 mo vs. 9.2 mo for patients receiving standard-of-care, an improvement in favor of T-DM1 that was statistically significant despite the small size of the trial.

The compelling activity in a first-line setting builds upon the previously reported Phase 2 data where HER2-positive mBC patients (n = 110) who were previously treated with trastuzumab, a taxane, capecitabine, lapatinib and an anthracyclin showed an ORR of 35%, with PFS of 6.9 mo, upon treatment with single-agent T-DM1.16 Besides its promising anti-tumor activity, T-DM1 is well-tolerated at the recommended Phase 2 and Phase 3 dose of 3.6 mg/kg given every 3 weeks.14,15 In the two-arm Phase 2 trial treating patients with mBC in the first-line setting, the rate of adverse events (AEs) ≥ grade 3 for the patients treated with T-DM1 was reported to be about half that of the trastuzumab plus docetaxel arm (46.4% vs. 89.4%).17 Furthermore, the nature of the AEs was different between the two arms of the study. The top two AEs ≥ grade 3 in the trastuzumab plus docetaxel arm were neutropenia (61% of patients) and leucopenia (26%), which had frequencies of only 6% and 0%, respectively, in the T-DM1 arm. The top two AEs ≥ grade 3 in the T-DM1 arm were thrombocytopenia (9%) and increased hepatic transaminase levels (9%); the former defined the dose-limiting toxicity (DLT) for T-DM1 in dose-escalation trials.14 In addition, the incidence of alopecia was 67% in patients treated with the docetaxel-containing regimen vs. only 4% in the T-DM1 arm. The sponsor, Roche, expects to have data to support marketing applications in the US and EU from a two-arm Phase 3 trial (EMILIA) that compares single agent T-DM1 in one arm against second line standard-of-care for treatment of HER2-positive mBC, a combination of lapatinib plus capecitabine. The applications may be submitted in the second half of 2012.

Dr. Lambert also described two maytansinoid-based ADCs that contained cleavable disulfide-containing linkers used to attach the maytansinoids to the antibody molecules. SAR3419, developed by ImmunoGen and licensed to Sanofi, is an ADC that is composed of a humanized monoclonal IgG1 anti-CD19 antibody (huB4) attached to the maytansinoid DM4 through reaction with the cross-linking agent SPDB, which forms a link
containing a highly hindered disulfide bond. SAR3419 displays potent in vitro cytotoxicity toward CD19-positive lymphoma cell lines, and shows good efficacy in several different in vivo models of lymphoma, including Burkitt lymphoma and diffuse large B cell lymphoma (DLBCL) implanted into SCID mice. SAR3419 was initially evaluated in two Phase 1 dose escalation studies that explored alternative schedules of administration, every 3 weeks and weekly, in patients with refractory/relapsed B cell non-Hodgkin lymphoma expressing CD19. The maximum tolerated doses (MTDs) of each schedule were 160 mg/m² (-4.3 mg/kg) every 3 weeks, or 55 mg/m² (-1.5 mg/kg) when given weekly. Preliminary clinical activity is encouraging for its future development, with objective responses seen in both indolent and aggressive lymphomas in both Phase 1 studies, and with activity in both rituximab-refractory and rituximab-responsive patients. For example, the ORR at the MTD (55 mg/m²) of the weekly-dose study was 33% (7/21 patients), with duration from 8 weeks to 55+ weeks. The low incidence of clinically significant hematologic toxicity was noteworthy. The reversible ocular toxicity that defined the DLT on the 3-week schedule appeared to be manageable on a weekly dosing regimen. A modified schedule consisting of four weekly doses of 55 mg/m², followed by four doses given at 2-week intervals, was initiated to evaluate an approach to reduce even further the incidence of this toxicity, based on PK simulations developed from the clinical data (the half-life of SAR3419 was 9 d), and on pharmacodynamic observations. Results from study of this schedule have yet to be reported; however, in the latter half of 2011, the sponsor initiated three Phase 2 trials evaluating SAR3419 as a single agent in DLBCL, in adult acute lymphoblastic leukemia, and in combination with rituximab in DLBCL. Dr. Lambert then described lorvotuzumab mertansine (LM), an ADC composed of a humanized version of the N901 antibody conjugated to the maytansinoid DM1 through reaction with the crosslinker SPP, which forms a link containing a hindered disulfide bond. The antibody targets CD56, which is also known as neuronal cell adhesion molecule (NCAM), CD56 is expressed on a variety of cancers of hematopoietic and neuroendocrine origin, including multiple myeloma (MM) and certain leukemias and lymphomas, small cell lung cancer, ovarian cancer, childhood acute lymphoblastic leukemia, MM, and neuroblastoma. LM has exhibited potent anti-tumor activity in a variety of preclinical xenograft models in these disease indications, and is being studied in both solid and hematopoietic tumors in clinical studies. Two Phase 1 studies in CD56-positive solid tumors established 75 mg/m² (2.0 mg/kg) as the MTD, when administered daily for 3 consecutive days every 3 weeks, and 60 mg/m² (1.6 mg/kg) as the MTD on a schedule of weekly x 4 every 6 weeks. In MM, where 70–80% of patients have disease expressing CD56, a Phase 1 dose-escalation study established 112 mg/m² (3.0 mg/kg) as the MTD when LM was administered weekly for 2 consecutive weeks every 3 weeks. The half-life of LM was only about 1 to 1.5 d at doses ≥ 60 mg/m², which is relatively short for an antibody-based therapy, possibly due to the normal tissue antigen sink of CD56 expressed on NK cells. The most common side effects were grade 1 or grade 2, including headache, fatigue, and neuropathy. DLTs were grade 3 fatigue in two of six patients dosed at 140 mg/m² in the MM trial, one of whom experienced grade 3 acute renal failure. Grade 3 toxicities of myalgia (one patient) and headache and back and shoulder pain (one patient) were seen in two of two patients dosed at 94 mg/m² given daily x 3 every 3 weeks in the solid tumor study. As observed with SAR3419, there were no clinically significant changes in hematologic parameters with no evidence for myelosuppression. Encouraging signals of antitumor activity were reported in these three Phase 1 studies of single-agent LM. In MM, of the 37 patients treated with LM at doses ranging from 40 mg/m² to 140 mg/m² (25 patients treated at ≥ 112 mg/m²), there were two objective partial responses and four objective minimal responses, while 15 patients had stable disease for ≥ 3 mo, for a 41% clinical benefit rate (CBR). In the two studies of CD56-positive solid tumors, the CBR (partial responses plus stable disease for ≥ 75 d) was 25% (17/68 patients) in patients with small cell lung cancer (SCLC) from among the total of 113 patients treated in these two Phase 1 studies. Of 8 patients with Merkel cell carcinoma (MCC) among the 45 evaluable patients in the study evaluating daily x 3 dosing every 3 weeks, there were 2 complete responses and 3 patients with clinically meaningful stable disease (4 to 7+ cycles of treatment). While numbers are small, these are remarkable findings in this rare, aggressive small cell cancer of the skin – the median survival of metastatic MCC is only about seven months. The findings of activity in MCC support the observations of activity in SCLC since these aggressive cancers are similar in both cell morphology and dismal outcome of their clinical course. Based on the promising signals of clinical activity in these difficult-to-treat cancers, the preclinical results reporting improved antitumor activity of LM in combination with chemotherapeutic regimens, and the acceptable tolerability profile of LM, in particular the lack of clinically meaningful myelosuppression, clinical studies of LM in combination with carboplatin and etoposide in SCLC, have been initiated. The combination study with carboplatin/etoposide is planned as a randomized Phase 2 trial in the setting of first-line treatment of SCLC patients, after an initial dose-escalation phase not limited to SCLC patients or first-line treatment, to establish the recommended combination regimen for the Phase 2 portion of the study. The study, which opened to enrollment in mid-2011, is designed to provide a clear development path for LM in combination with chemotherapy in first-line treatment of patients with SCLC. A combination study of LM with lenalidomide and low dose dexamethasone in MM patients is also ongoing; early experience demonstrates encouraging activity for this regimen. Dr. Lambert elucidated learnings from the past decade of clinical development of ADCs having potent tubulin agents as payloads. The “lessons” learned include: (1) cancers that are very sensitive to chemotherapeutic agents (e.g., Hodgkin lymphoma, HER2-positive breast cancer) make good targets for ADCs bearing tubulin-acting agents, while cancers generally insensitive to tubulin agents (e.g., colorectal cancer) may not be good targets for such ADCs; (2) the level of acceptable target expression may depend on the target (e.g., HER2 may need high overexpression
to serve as a good ADC target while an ADC targeting CD19 can be active on cell lines bearing only 30,000 or so receptors, but delivery of a lethal quantity of a tubulin-acting payload into a cancer cell via antibody-mediated uptake of an ADC may be difficult to achieve below ~10,000 receptors per cell; some normal tissue expression can be for patient selection of likely better responders such as those over-expressing HER2; some normal tissue expression can be tolerated (e.g., HER2 has widespread normal tissue expression at “normal” levels, as can be seen by consulting www.proteinatlas.org), but effects may depend upon what normal tissue expresses the target antigen in question; the high expression of CD44v6, an antigen overexpressed on squamous cell carcinoma of head and neck, on normal skin epithelial cells, particularly on those skin cells with a high proliferative index, was not tolerated. Finally, Dr. Lambert discussed considerations in selecting tumor models for preclinical studies, especially that such models should resemble human tumors in terms of antigen expression levels, and in sensitivity to the class of payload being utilized in the ADC.

Rajeeva Singh (ImmunoGen, Inc.) discussed a novel mechanism by which maytansinoid may be released from “uncleavable” thioether-linked antibody-maytansinoid conjugates, such as from the SMCC-DM1 thioether linkage in T-DM1,13 under ex vivo oxidative conditions. The clinical PK of T-DM1 shows that while the conjugate is quite stable in circulation, it nevertheless appears to show a slow rate of maytansinoid loss over time. Such maytansinoid loss may be accounted for by a low rate of cleavage of maytansinoid from the antibody or by a slightly faster rate of clearance from circulation of species having a higher than median load of maytansinoids per antibody vs. those species with less than the median number of maytansinoids per antibody. Very low levels of free DM1 were reported to be present in plasma samples from patients treated with T-DM1, an observation that suggests that the thiosuccinimide bond formed by the reaction of SMCC with DM1 can be cleaved, albeit at a very slow rate. Although reversal of the linkage formed by reaction of maleimido-auristatin compounds with the sulfhydryl group of cysteine residues in antibodies (formed by partial reduction of cystine residues) was reported, studies recently reported by Fishkin et al. show that the thiosuccinimide linkage of SMCC-DM1 in conjugates and in test compounds does not undergo reverse reaction, even in the presence of excess dithiothreitol.

Dr. Singh then mentioned that the thiosuccinimide linkage can undergo partial oxidation followed by cleavage under conditions used in ex vivo processing of plasma samples for analysis (e.g., conditions of pH that mimic the pH increase that occurs rapidly in unbuffered plasma, conditions of oxidation that mimic the oxidative stress during sample extraction and concentration). Dr. Singh described the mechanism for the oxidative cleavage of thiosuccinimide linker proposed by Fishkin, et al. The mechanism was further supported by mimicking oxidation with extraneous addition of hydrogen peroxide. The results show that partial cleavage of the oxidized thiosuccinimide linkage occurs.

The key sulfenic acid intermediate proposed in this mechanism was demonstrated by covalent trapping with dimedone. As suggested by Fishkin et al., oxidative stress during sample preparation prior to chromatographic analysis may account for the reported observation of very low levels of free DM1 seen in the PK studies of T-DM1 in clinical trials. Finally, Dr. Singh noted that oxidized thioether-linked maytansinoid conjugates exhibit high, target-specific cytotoxicity toward cancer cells, which may offer a linker chemistry with an alternative mode of release of active maytansinoid from such conjugates within a cancer cell.

Chantal Zuber (Biotest AG) gave a presentation about BT-062, an ADC comprising a chimeric anti-CD138 IgG4 antibody attached to the maytansinoid DM4 through reaction with SPDB, which forms a highly hindered disulfide linker. CD138 (Syndecan-1) is overexpressed in various solid tumors and hematologic malignancies, and is widely used as a marker to identify cells of MM in bone marrow because it is expressed at about 100-fold higher levels on MM than normal plasma cells. The SPDB-DM4 linker-maytansinoid format was selected for BT-062 based upon superior preclinical activity vs. other linker-maytansinoid formats in a variety of model systems. The aim of the first Phase I clinical study was to determine the MTD and DLTs in MM patients given a single dose every 3 weeks. Thirty-two patients were enrolled in this study, which established an MTD of 160 mg/m2 (~4.3 mg/kg). The DLTs at the maximal administered dose were mucositis, an anticipated risk based on the normal expression of CD138 on epithelial cells. Of 13 evaluable patients treated at the MTD, there was one partial response, one objective minor response of duration at least 1.5 y, and 5 patients with SD for at least 105 d, for an overall CBR of about 50%. However, study findings, including PK measurements, suggested a more frequent dosing regimen may yield greater activity at tolerable doses, thus leading to the initiation of a repeated multi-dose study evaluating weekly dosing × 3 every 4 weeks. So far, BT-062 has been well tolerated up to the 120 mg/m2 (~3.2 mg/kg) dose level (6th dose level), and already the dose intensity is twice that achieved on the once every 3 week schedule (360 mg/m2 (~160 mg/m2 over 3 weeks). No DLT has yet been reported, and about 50% of patients appear to derive clinical benefit (defined as progression-free for ≥ 3 mo). A Phase 1/2a clinical study of the combination of BT-062 with lenalidomide plus dexamethasone is planned, based on preclinical data showing improved activity of the combination vs. single agent BT-062.

Dr. Zuber concluded her presentation by showing preclinical evaluation of BT-062 in solid tumors. CD138 is overexpressed in tumors of breast, lung, pancreas and bladder, among others. Anti-tumor activity was demonstrated against CD138-positive xenograft models of primary human tumors in all four above-mentioned indications. In the breast cancer model derived from a patient with triple-negative breast cancer, weekly dosing at 2 mg/kg completely eradicated the tumor xenograft. The exposure in mice at this dose was comparable to the tolerated dose already achieved in the ongoing clinical trial of a weekly dosing schedule. As a result of these data, the sponsor is evaluating the most suitable opportunities to expand the clinical development of BT-062 into selected solid tumors.
Thomas Chittenden (ImmuGen, Inc.) discussed the discovery and evaluation of new antibody-maytansinoid conjugates, and described two preclinical candidates, IMGN529 and IMGN853, as case studies. ImmuGen’s research strategy has been informed by extensive clinical experience with maytansinoid conjugates that have targeted antigens with widely different biological properties. One insight from this clinical experience is that maytansinoid conjugates using ImmuGen’s technology have achieved doses in humans that approach those used for ‘naked’ antibody therapies (on a mg/kg basis), demonstrating the potential for combining both antibody-mediated and maytansinoid-mediated anti-tumor activities in a single therapeutic candidate.

Dr. Chittenden then described the research to discover IMGN529, a novel antibody-maytansinoid conjugate targeting CD37 for B cell malignancies designed to combine both antibody-mediated and payload-mediated mechanisms of action. The antibody component of IMGN529 was selected based on its potent intrinsic activity against tumor cells, including direct cytotoxicity and pro-apoptotic signaling (in the absence of cross-linking), antibody dependent cellular cytotoxicity (ADCC), and complement mediated cytotoxicity (CDC). The functional anti-CD37 antibody thus selected was conjugated to the maytansinoid DM1 using the uncleavable SMCC linker to create IMGN529. IMGN529 conjugate retained the functional properties of its antibody component, but exhibited enhanced cytotoxic potency against lymphoma cell lines in vitro and greater anti-tumor activity in vivo.

Dr. Chittenden also described the research to discover a second antibody-maytansinoid conjugate, IMGN853, which targets the high affinity folate receptor (FOLR1) that is overexpressed in ovarian and non-small cell lung (NSCL) cancers. High level, uniform FOLR1 expression was confirmed in select histological subtypes of ovarian and NSCL tumor samples using a calibrated (semi-quantitative) immunohistochemistry approach. To identify an optimal antibody for payload delivery for this target, large numbers of anti-FOLR1 antibodies were screened for their ability to deliver maytansinoid using an indirect assay. Direct maytansinoid conjugates of candidate antibodies that emerged from the indirect screen were prepared, and a lead antibody selected based on its superior efficacy as a conjugate against tumor xenograft models. The conjugate design was optimized by evaluating different linker-maytansinoid formats. A conjugate incorporating a novel hydrophilic disulfide (cleavable) linker, sulfo-SPDB, was found to be the most active in vivo, and was designated as development candidate IMGN853. It was highly active in several ovarian cancer xenograft models that express FOLR1 at levels comparable to human tumors. Both IMGN853 and IMGN529 are advancing toward clinical testing; the investigational new drug (IND) application for IMGN529 was reported to be active, and the filing of an IND for IMGN853 is expected in the second quarter of 2012.

**Auristatin-Based ADCs**

Christina Oliva (Takeda R&D Europe) presented the success story of the recently approved ADC ADCETRIS® (brentuximab vedotin). ADCETRIS was developed by Seattle Genetics, which has US and Canadian commercialization rights; the Takeda Group has rights to commercialize ADCETRIS in the rest of the world. ADCETRIS was granted accelerated approval by the FDA in August 2012 for two indications: (1) treatment of patients with Hodgkin lymphoma after failure of autologous stem cell transplant (ASCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not ASCT candidates, and (2) treatment of patients with systemic anaplastic large cell lymphoma (ALCL) after failure of at least one prior multi-agent chemotherapy regimen.

ADCETRIS (also known as SGN-35) consists of the anti-CD30 antibody, cAC10, conjugated to MMAE (monomethyl auristatin E) via a Val-Cit linker. Dr. Oliva described the mechanism of action (MOA) of ADCETRIS, which includes binding to CD30-expressing cells, internalization, release of MMAE via proteolytic cleavage, and subsequent cell killing through binding to microtubule and cell-cycle arrest. The striking efficacy and selectivity of ADCETRIS was exemplified by both in vitro and in vivo studies using CD30+/- cell lines. Dr. Oliva then described the limited current options for treatment of Hodgkin lymphoma (HL) and systemic ALCL for patients who have failed previous treatment(s), emphasizing the unmet medical need. Data from clinical trials with these patients showed remarkable efficacy with relatively mild side effects. In a trial with 102 HL patients, the overall response (partial + complete) rate was 75%, with a median duration of response in patients with a complete response (CR) of 20.5 mo. In a trial with 58 systemic ALCL patients, the overall response rate was 86%, with a median duration of response in patients with a CR of 13.2 mo. Across both trials, treatment with ADCETRIS was associated with generally manageable adverse events, including peripheral sensory neuropathy and fatigue.

Dr. Oliva summarized her presentation by emphasizing the durable, complete remissions achieved in HL and systemic ALCL, coupled with manageable adverse events. She concluded by highlighting ongoing and future clinical trials using ADCETRIS in combination, e.g., with ABVD (doxorubicin plus bleomycin plus vinblastine plus dacarbazine) or AVD (doxorubicin plus vinblastine), for frontline therapy in patients with newly diagnosed advance stage HL. She also emphasized the importance of using ADCs in combination with other therapies because it is rare for monotherapies to work.

Mike Sun (Seattle Genetics) focused on Chemistry, Manufacturing, and Controls (CMC) in his discussion of challenges and considerations in the development and scale-up of ADC processes. Seattle Genetics’ technology consists of proprietary auristatin drugs-linkers (e.g., Val-Cit-monomethylauristatin E or vcMMAE) conjugated to antibodies through thiols exposed following reduction of inter-chain disulfide bonds. The resulting ADCs inherit many of the quality attributes found in the parent antibody (e.g., antigen binding), but also acquire unique quality attributes (e.g., drug load characteristics, cytotoxicity, residual process-related impurities) that need to be analyzed, monitored, and controlled during process development. Dr. Sun presented two case studies that highlighted the effects of
the manufacturing process on some of these unique ADC product quality attributes.

The first case study described the control of drug load characteristics by the reduction reaction. Many process parameters (e.g., time, pH) can potentially affect the reduction reaction and thus the drug load characteristics, but the most critical one is the reductant/antibody ratio. Dr. Sun discussed deliberately varying the reductant/antibody ratio on the drug load characteristics. The effect is a predictable increase in average drug load with increasing amount of reductant/antibody as elucidated by using hydrophobic interaction chromatography (HIC) as an analytical tool. Along with the increase in average drug load, the drug load distribution also shifts from lightly-loaded to more heavily-loaded ADC species. In terms of biological effect, the in vitro cytotoxicity was shown to increase linearly with the average drug load. On the other hand, antigen binding of the ADC was not affected by drug load.

For the second case study, Dr. Sun described the clearance of process-related impurities by the ultrafiltration/diafiltration (UF/DF) step. The process-related impurities consist of free drug-related impurities and other reagents and process aids used throughout the manufacturing process. Dr. Sun showed that low molecular weight, water-soluble impurities are cleared ideally, but that free drug-related impurities are cleared less efficiently. Dr. Sun also presented the impact of various parameters on the clearance on these impurities by UF/DF, including the ultrafiltration membrane type, transmembrane pressure (TMP), and membrane load. The data presented show that membrane type, TMP, and membrane load can all have an effect on the clearance efficiency of free drug-related impurities.

Dr. Sun concluded by showing the effects of scale-up on the control of drug load characteristics and the clearance of process-related impurities by the manufacturing process. The results show that the process can be scaled up robustly, with near identical performance demonstrated up to a 150-fold scale-up.

Puja Sapra (Pfizer) summarized the status of Pfizer’s lead ADC programs CMC-544 and 5T4-ADC and concluded by pointing out challenges and opportunities facing ‘next-generation’ ADCs. The ADC CMC-544 comprises an anti-CD22 antibody conjugated to calicheamicin, the same drug payload as that used for the first approved ADC gemtuzumab ozogamicin (Mylotarg®). The antigen CD22 is expressed in > 90% of B cell malignancies and internalizes, whereas it is not expressed on lymphocyte precursors. The ORR of 80%.

ORR of 84% and patients with relapsed DLBCL showed efficacy in both FL lymphoma (DLBCL). A subsequent Phase 1/2 study of CMC-544 in combination with rituximab showed efficacy in both FL and DLBCL; patients with relapsed FL had an overall response rate (ORR) of 84% and patients with relapsed DLBCL had an ORR of 80%.

The ADC 5T4-ADC targets the oncofetal antigen 5T4, which is expressed in many solid tumors such as colorectal, ovarian, and gastric cancers, but has low expression on normal tissues. Dr. Sapra described the selection of the antibody for the 5T4-ADC program between the two candidates A1 and A3 based on binding affinity, in vitro potency, and in vivo efficacy and toxicity. Greater binding affinity with the A3 antibody correlated with better in vitro cell killing activity; however, both antibody candidates displayed equivalent in vivo efficacy. In the end, the choice was made based on the larger therapeutic window of the A1 ADC afforded by lower toxicity. The payload for the 5T4-ADC is Seattle Genetics’ auristatin drug-linker mcMMAF. 5T4-ADC was found to be efficacious in all 5T4-expressing tumor models studied so far, which included both low and high 5T4-expressing models.

Dr. Sapra concluded her presentation by pointing out the challenges and opportunities she sees in designing better ‘next-generation’ ADCs. In terms of targets, it is increasingly difficult to find ‘clean’ targets and a challenge exists to find antigens that preferentially internalize in tumor cells, but not in normal cells. In terms of the delivery vehicle, there is an opportunity for smaller molecular weight targeting modalities because full-length antibodies suffer from poor tumor penetration. Overall, Dr. Sapra stressed the need for more predictive in vitro assays to predict off-target toxicity instead of relying on expensive toxicity studies.

Bill Olson (Progenics) summarized results of translational studies and presented a clinical update of Progenics’ prostate-specific membrane antigen (PSMA) ADC, which is comprised of an anti-PSMA antibody conjugated with vcMMAE. PSMA is ubiquitously expressed in prostate adenocarcinoma, but with limited expression in normal tissues. In prostate cancer, expression of PSMA is primarily extracellular, whereas expression is cytoplasmic in normal prostate. The ADC displayed picomolar PSMA-dependent cytotoxic potency in vitro. The same impressive efficacy was observed in several in vivo models, including docetaxel-refractory tumor models, with no apparent toxicity.

Dr. Olson next gave an update of a Phase 1 dose-escalation study of the PSMA ADC in progressive, castration-resistant metastatic prostate cancer. The dosing frequency was once every 3 weeks with dose escalation starting from 0.4 mg/kg and going to 2.8 mg/kg so far. PK results were predictable with exposure to the ADC increasing with dose and very little free MMAE (< 10 ng/mL) in circulation. No antibodies against the ADC have been observed in any of the patients. Antitumor activity was evaluated by following changes in the levels of prostate specific antigen (PSA) and circulating tumor cells (CTC). PSA reductions were observed at doses of 1.8 mg/kg and higher, with an up to 96% decrease in the PSA level in one patient. Reduction in CTC (and also bone pain) was observed and correlated with changes in PSA levels. In terms of safety, the PSMA ADC was generally well tolerated with very few adverse events of ≥ grade 3. The MTD has not yet been reached and dose escalation continues.

Dr. Olson concluded by introducing a promising new application for PSMA ADC—targeting of the neovascularature of non-prostatic cancers. Although PSMA is not expressed on non-prostatic solid tumors themselves, it is widely expressed on the neovascularature of such tumors. To explore this new application, Progenics performed a large immunohistochemical (IHC) analysis of solid tumor samples. Results showed staining across a broad range of solid tumors (e.g., lung, ovarian, pancreatic), with 90%
of the samples exhibiting moderate to strong neovascular staining. The ‘universal’ expression of PSMA on tumor neovascularization points to a potential utility of PSMA ADC on a broad range of solid tumors.

Leonard Reyno (Agensys/Astellas) presented translational studies and Phase 1 clinical results of the ADC AGS-16M8F, which is an anti-ENPP3 (ectonucleotide pyrophosphatase/phosphodiesterase 3) antibody conjugated with mcMMAF. ENPP3 is expressed in 90% of renal clear cell carcinoma (RCCC) and 69% of papillary renal cell carcinoma (PRCC), but has restricted normal tissue expression. The ADC displayed antigen-dependent in vitro cytotoxicity and inhibited tumor growth in a number of RCCC xenograft models in vivo. Treatment with the ADC was well-tolerated in monkeys with a no observable adverse effect level (NOAEL) of at least 6 mg/kg based on a weekly dose frequency.

Dr. Reyno then presented results of a Phase 1 study of AGS-16M8F ADC in patients with advanced metastatic renal cell carcinoma, including both RCCC and PRCC. The dosing frequency was once every 3 weeks with dose escalation starting from 0.6 mg/kg and going to 4.8 mg/kg so far. Enrollment and dose escalation are ongoing as the MTD has not yet been reached. In terms of safety, two cases of dose-limiting toxicities were encountered (one each at the 0.6 and 4.8 mg/kg dose levels), but were not thought to be related to the ADC. Overall, results show that the ADC is well-tolerated and consistent with the general observation that mcMMAF ADCs are tolerated at higher doses than vcMMAE ADCs. In terms of PK, the half-life of the ADC was observed to be 5 – 8 d with very low levels of free MAAF in circulation (< 10 ng/mL).

Dr. Reyno concluded his talk by discussing future clinical plans for the AGS-16M8F ADC. Dose expansions will continue in the Phase 1 study. For future studies, inclusion of an ENPP3 expression biomarker might be appropriate for cancers with papillary histology (i.e., PRCC). Like Dr. Oliva (Takeda R&D Europe), Dr. Reyno also believes that ADCs will prove most efficacious in combination therapies and not as single agents.

David Satijn (Genmab) described the development of ADCs against tissue factor (TF) for the treatment of solid tumors. TF is overexpressed in many solid tumors, including pancreatic (> 98% incidence) and colorectal cancers (~60% incidence). Genmab generated a panel of human antibodies against TF using the HuMax technology. These antibodies were evaluated for a number of attributes, including affinity, internalization, and lysosomal trafficking. Based on these attributes, a lead panel of three antibodies was selected to move forward with conjugation to either mcMMAF or vcMMAE to generate TF-ADCs.

These ADCs were tested preclinically using the A431 and HPAF-II cell lines both in vitro and in vivo. In vitro, all six ADCs (three antibodies with each conjugated to either mcMMAF or vcMMAE) showed potent cytotoxic activity against both cell lines. In xenograft models, all six ADCs again showed antitumor activity (at doses of 3 mg/kg) as measured by initial tumor reduction and time to tumor recurrence. However, the ADCs conjugated to vcMMAE were significantly more potent than the mcMMAF ADCs regardless of the antibody to which it is conjugated. Some differences in potency were noted between antibodies, but the magnitude of the differences was relatively small. In terms of safety, no clinical signs of toxicity or weight loss were observed in any of the animal groups. Dr. Satijn concluded by announcing that Genmab is on its way to submitting an IND for TF-ADC in early 2013.

Duocarmycin-Based ADCs

Vincent de Groot (Synthon) presented data on combinations of DNA-damaging duocarmycins and suitable linker technologies as an alternative payload technology. Synthon acquired Syntarga and its ADC technology in June 2011, and has entered into a number of new research collaborations with biopharmaceutical and biotechnology companies. ADCs undergoing evaluation by the company’s collaborators comprise the newest Synthon Linker-Drug (L-D) chemistries linked to collaborator antibodies. Synthon is leveraging its proprietary technologies and expertise to generate and commercialize, alone and with partners, a portfolio of next-generation ADC products.

Dr. de Groot explained that Synthon’s duocarmycins are DNA alkylating agents that bind in the minor groove; these drugs are potent as free drugs and as ADCs in vitro against multi-drug resistant cell lines. The drug is not toxic in vivo as free drug at molar levels much higher than ADC efficacious doses. Thus, even if unintentionally released from stable linker, toxicity may be low. The linkers have demonstrated high stability in human plasma for all DNA alkylator-linked L-Ds, and DNA alkylator-linked L-Ds are more stable than DNA binder-linked L-Ds. The aim for the company is to translate from ‘linker-drug discovery’ to ADC product, to select the best linker-drug and target/mAb combination, and to advance their first ADC to the clinic. In the studies done to date, Synthon’s ADCs have been safe at high dose and highly efficacious at low dose. Dr. de Groot presented results of preclinical development, including drug potencies, ADC and payload stabilities in plasma, cleavage kinetics and in vivo therapeutic window aspects for ADCs directed against HER2.

Novel Site-Specific ADCs

Feng Tiang introduced Ambrx technology for site-specific conjugation of payloads to mAbs. He explained that the ribosomal incorporation of non-native amino acids into polypeptides in living cells provides the opportunity to endow therapeutic proteins with unique pharmacological properties. Ambrx uses an expanded set of amino acids to address the limitations intrinsic to the 20 natural amino acids. The technology combines the power of medicinal chemistry with recombinant biosynthesis. Through the application of Ambrx’s proprietary technology, numerous variants of the naturally occurring wild-type protein can be generated, each variant containing a unique amino acid incorporated into the protein backbone at a selected location. This allows for the rational design of molecules in the event that structural information is available or an empirical approach through substitution at every position and subsequent structure-activity-relationship analysis similar to the approach taken to optimize
small molecules or synthetic peptides. This level of control in the application of selective chemistries to proteins represents a new paradigm in protein engineering.

Ambrx is pursuing a broad array of product candidates based upon proteins, antibodies, antibody fragments and antibody-based bioactive protein and peptide carriers. Dr. Tiang and colleagues tailor them to address specific medical needs of patients. Ambrx has the ambition to advance molecules that meet or exceed a target product profile through the application of internal resources or through collaboration with other biopharmaceutical companies. One of the strategies is to efficiently generate multiple variants of wild-type proteins and antibody-drug conjugates optimized for drug-like properties. The best molecules are then selected for further evaluation as product candidates expected to yield a substantial competitive advantage.

In summary, Ambrx produces homogeneous drug substances for ADC optimization to meet target drug profiles. These novel ADCs are created with an expanded genetic code and are straightforward to synthesize and characterize. In a proof-of-concept study, stable antibody titer over 1 g/L was achieved. The site of conjugation was shown to affect biophysical properties and the plasma stability of cathepsin-cleavable linkers. Based on Ambrx technology, ADCs with PK similar or improved, relative to the naked mAb, have been created.

**DeBouganin Toxin Payloads**

**Jeannick Cizeau** (Viventia) gave a talk on deBouganin, a de-immunized toxin payload, and its applications in oncology. Bouganin toxin is a type 1 ribosome inactivating protein (RIP) that was isolated from the leaves of *Bougainvillea spectabilis*. The toxin shows RNA N-glycosidases activity, and is involved in deadenylation of the 28S RNA, blocking translation, and in apoptotic cell death. Bouganin toxin does not have a B chain like other Type 2 RIPs and has no passive uptake into cells. Potency was investigated in a cell-free assay; an IC50 of 15 pM was observed. The cytotoxicity was comparable to other Type 1 RIPs and equally potent to gelonin. The mechanism of action is based on irreversible damage to the ribosomes, leading to apoptosis. There is currently no known mechanism of resistance and, importantly, a better safety profile compared with other type 1 RIPs is observed (less toxic as a free toxin vs. cell lines, LD50 = 32 mg/kg in mice, 40x safer than saporin).

Dr. Cizeau explained that two strategies can be used to manage the payload immunogenicity. The first one is use of local delivery to bypass the immune system. The approach is effective, but has limited utility in oncology. For systemic delivery, de-immunized toxins are required. Plant toxins are preferred because previous exposure is unlikely (compared with exposure to bacterial toxins). De-immunization by T cell epitope depletion is most effective approach and the removal of B cell epitopes not required. Two linkage options can be used. The first option involves forming a fusion protein by genetically linking the toxin to scFv, Fab or diabodies. These dual drugs are expressed as soluble protein, produced by microbial fermentation in one purification stream. The second option is based on chemical conjugation of full-length IgGs by known chemistry allowing the introduction of multiple payloads.

Dr. Cizeau provided a clinical summary of VB6–845, Viventia’s lead drug. Thirteen end-stage patients with EpCAM-positive cancers (kidney, ovary, breast, stomach, pancreas, non-small cell lung, and colorectal) were included and 2 dose cohorts were used (1 and 2 mg/kg/wk, IV dosing in four week cycles until progression). The drug was well-tolerated. Stable disease was observed in 6 of 8 patients after 4 wks and 1 patient after 12 wks, with evidence of tumor reduction observed in 2 patients. Immune response was observed against Fab moiety. As an improvement, re-engineering to remove T cell epitopes in the Fab was performed, a new version was produced, and it is now ready for a Phase 1 study.

In summary, Dr. Cizeau noted that deBouganin is an original and powerful antibody payload technology. De-immunized bouganin is the only protein payload successfully de-immunized as shown in proof-of-concept human study. The mechanism of action is well-understood. The payload is a highly potent cytotoxic agent against cancer stem cells and not affected by multiple drug resistance mechanisms. The product has a strong safety profile and is only cytotoxic once internalized via a suitable targeting carrier. The fusion protein was produced by a cost effective and versatile manufacturing in a single stage process. Alternatively, deBouganin conjugates can also be manufactured as an isolated protein for chemical conjugation.

**Optimizing Design and Translational Strategy**

**Alison Betts** (Pfizer) discussed PK/PD modeling and the clinical translation currently adopted by Pfizer for ADCs. As an introduction, she explained that ADCs are at the forefront of targeted chemotherapy for the treatment of cancer. It is anticipated that over the next 3–5 y ADC programs will increase by 20–40% because of the tremendous potential shown by recent clinical trials. The results indicate increased therapeutic efficacy and improved safety. One of the challenges in oncology drug development is the selection of the correct dose for clinical studies. Tumor growth inhibition in mice is most often used to assess efficacy in preclinical models, but appropriate quantitative interpretation of these data and translation efforts are largely missing. As such, dose selection for the clinic is usually made empirically from toxicology data with application of a safety factor.

Dr. Betts explained that PK/PD modeling has been identified as a useful technique capable of integrating data generated from diverse test platforms in a mechanistic framework. She pointed out that even though there are some applications of PK/PD modeling to describe the behavior of ADCs, efforts to optimize the modeling and simulation are currently scarce and translation to the clinic has not yet been done. She showed a tumor kill PK/PD model that has been used to successfully translate efficacy of the ADC T-DM1 between mice and patients. This PK/PD modeling approach was used to characterize the efficacy of two of Pfizer’s ADCs in mouse, and to predict the clinically efficacious dose for ADCs. Dose predictions for ADCs are 3.5 mg (0.05 mg/kg) to 161 mg (2.3 mg/kg) Q3 weeks, based on data generated vs.
4 tumor cell lines. This compares favorably with T-DM1, which shows clinical activity at the MTD of 3.6 mg/kg Q3 weeks. Dr. Betts concluded that the quantitative and predictive understanding of the PK/PD relationships described could contribute to the design of improved therapies for anti-cancer drugs.

**ADC Competitive Landscape**

Grazia Piizi (Novartis) discussed the ADC competitive landscape from a large pharmaceutical perspective.

**Digoxigenin-Binding Bispecific Antibodies for Targeted Payload Delivery**

Eike Hoffmann (Roche) discussed bispecific digoxigenin-binding antibodies used for targeted payload delivery, which involves generation and optimization of hapten-binding bispecific antibodies. She described the formation of complexes and the targeted delivery of haptenylated payloads, as well as targeted payload delivery in vitro and in vivo. Bispecific antibodies simultaneously bind two different antigens and can be applied to block two targets on cell surfaces to improve therapeutic efficacy. Recognition of two targets may also increase targeting specificity toward tissues or tumors that express both antigens. Bispecifics that bind tumor-associated antigens and effector cells (e.g., by binding CD3) can also be used in immunootherapy to activate effector cells at tumors. Bispecific antibodies are also applicable for payload delivery. One option to achieve targeted delivery is conjugation of hapten to the payload, and subsequent complexation with hapten-binding bispecific antibodies. Complexation via antibody-antigen interaction avoids chemical modification of antibodies, and thereby reduces risks of inactivating the targeting entity or generating immunogenic sites within the protein. A conjugation step for attachment of hapten to payload is still needed, but this procedure can be performed by standard technologies.

Bispecific antibodies that bind cell-surface targets and digoxigenin (Dig) were generated for targeted payload delivery. The targeting moieties are IgGs that bind the tumor antigens HER2, IGF1R, CD22, or LeY. A Dig-binding single-chain Fv was attached in disulfide-stabilized form to the C termini of CH3 domains of targeting antibodies. Bispecific molecules were expressed in mammalian cells and purified in the same manner as unmodified IgGs. These molecules were shown to be stable without aggregation propensity, and to retain binding specificity and affinity to cell-surface antigens and Dig. Digoxigeninylated payloads were generated that retain full functionality and can be complexed to bispecific antibodies in a defined 2/1 ratio. Payloads included small compounds (Dig-Cy5, Dig-doxorubicin) and proteins (Dig-GFP). Complexed payloads are targeted by the bispecifics to cancer cells. These complexes are stable in serum and can be applied for targeted delivery. Because Dig bispecifics also effectively capture digoxigeninylated compounds under physiological conditions, separate administration of uncharged Dig bispecifics followed by application of Dig payload was shown to be sufficient to achieve antibody-mediated targeting both in vitro and in vivo.

**Light-Activated Antibody Fragment-Drug Conjugates**

Mahendra Deonarain (PhotoBiotics, Imperial College London) presented photo-dynamic therapy (PDT) as a promising and emerging modality for cancer therapy. Dr. Deonarain explained that targeted PDT is a form of ADC with many benefits that combine several advantages. Soluble drug can be used with low drug resistance and low toxicity against non-internalizing targets. New pyropheophorbide a (PPa) derivatives have been synthesized that are soluble in physiological buffer and show reduced aggregation. These drugs are photo-active, make better photodynamic ADCs, show better PKs and are more potent in vivo. They present new opportunities in combined therapy and imaging. OptiLink technology is transferable to third-party agents. The proof-of-concept was obtained with non-optimized scFvs and with commercial drugs such as verteporfin. The main method for conjugating drugs to mAbs has been via the thiol side-chains of cysteine residues (Cys-SH). Though affording stoichiometric control during conjugation, this protocol yields only low drug loading ratios, due mainly to ADCs becoming insoluble at higher drug loadings and loss of binding affinity.

Dr. Deonarain then discussed PhotoBiotics’ interest in the use of much smaller mAb fragments such as scFv to covalently attach anti-cancer drugs. This represents a way for specifically targeting photosensitizers to tumors, thereby improving the success of photodynamic therapy. Antibody fragments have benefits such as more rapid tumor penetration and blood clearance that could result in higher potencies and lower side effects, especially for solid tumors that are difficult to treat. PDT was used to treat localized lesions within the body such as tumors or age-related macular degeneration (AMD). The mechanism of action is based on photosensitizers (PSs) to catalyze lesion destruction via irradiation with visible light. This involves initial administration of a PS that over-accumulates in the lesion and not in the surrounding healthy tissue.

Dr. Deonarain explained that exposure to cold laser light of an appropriate wavelength excites the PS, which then mediates the conversion of molecular oxygen into reactive oxygen species (ROS) such as hydroxyl radicals, superoxide anions or singlet oxygen. ROS irreversibly damage cellular components of lesions such as proteins, lipids and DNA or its blood supply, resulting in cell death. An important feature of photo-catalyzed singlet oxygen production is that it returns the PS to its electronic ground state. As a result, a single PS molecule can efficiently generate many times its own concentration of singlet oxygen, making this an efficient cytotoxic drug.

**Satellite Workshop on Pharmacokinetic Analysis of ADCs**

Kedan Lin (Genentech) led a pre-conference workshop on the preclinical PK analyses of ADCs. The workshop focused on the application of PK analysis and the strategy in establishing PK/PD relationships in ADC optimization and development. Dr. Lin started with an overview of ADCs and the multiple factors contributing to the successful development of an ADC,
e.g., target identification, antibody optimization, linker drug selection, drug:antibody ratio determination. The complexity of ADC PK was discussed in detail. As a hybrid between antibody therapeutics and small molecule cytotoxic drugs, ADCs exhibit unique pharmacological and PK properties, which necessitates the monitoring of the behavior and fate of both components in vivo. In addition, ADCs are heterogeneous mixtures of molecular entities or drug species resulting from its manufacturing process, and from biological or chemical modifications following in vivo administration. These characteristics pose specific challenges for ADC quantitation and characterization, and dictate the need for multiple analytes in characterizing ADC PK. Dr. Lin highlighted several commonly monitored analytes, such as total antibody (conjugated and unconjugated antibody), conjugated antibody, conjugated drug, and unconjugated (free) drug, and emphasized their pharmacokinetic significance in exploring the behavior of ADCs.

Several case studies were presented to elucidate the application in site-specific conjugation and the impact of drug antibody ratio on PK, efficacy and toxicity generated intense interest from the workshop attendees.

In the second part of the workshop, Dr. Lin discussed the emerging topics of ADC disposition, and scientific and regulatory considerations in conducting ADME (absorption, distribution, metabolism and elimination) studies during ADC development. Studies of ADCs in vitro catabolism, in vivo tumor and normal tissue uptake and catabolism in tissues, as well as the relationship of drug antibody ratio on efficacy and toxicity of ADCs, have generated a rich data set. This information, coupled with the appropriate PK/PD modeling could provide mechanistic and quantitative understanding of the mechanism of action of ADCs and provide critical guidance in ADC optimization.

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Note

Summaries were prepared from PDFs of the presentations provided by speakers after the meeting. In the cases when a speaker was not able to share their presentation, detailed summaries are not included, although the speaker’s name, affiliation and topic appear in the report.
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