Cancer Chemother Pharmacol (2012) 69:1063–1069
DOI 10.1007/s00280-011-1806-6

ORIGINAL ARTICLE

Preclinical pharmacokinetics of MEHD7945A, a novel EGFR/HER3 dual-action antibody, and prediction of its human pharmacokinetics and efficacious clinical dose

Amrita V. Kamath · Dan Lu · Priyanka Gupta · Denise Jin · Hong Xiang · Anne Wong · Cecilia Leddy · Lisa Crocker · Gabriele Schaefer · Mark X. Sliwkowski · Lisa A. Damico-Beyer

Received: 21 September 2011 / Accepted: 15 November 2011 / Published online: 28 December 2011

Abstract
Purpose MEHD7945A is a novel dual-action monoclonal antibody in which each of the two antigen-binding fragments is capable of binding to EGFR and HER3 with high affinity. It is being evaluated as a potential therapy for human cancer. The purpose of these studies was to characterize the pharmacokinetics (PK) of MEHD7945A in mouse and monkey and predict its human PK and efficacious dose.
Methods PK of MEHD7945A was determined in SCID beige mice and cynomolgus monkeys after administration of single intravenous doses. Human PK profiles were projected from monkey PK profiles using a species-invariant time method, and human population PK parameters were estimated using a nonlinear, two-compartment model comprising specific (target-mediated) and nonspecific clearance pathways. The antitumor efficacy in mice bearing human tumor xenografts was used in conjunction with human PK projections to estimate human efficacious doses.
Results The total clearance of MEHD7945A decreased with increase in dose in both mouse and monkey. The nonspecific clearance in monkey was estimated to be 14 mL/day/kg. The predicted nonspecific clearance range in humans was 6–10 mL/day/kg. Doses of 8–12 mg/kg administered every 2 weeks in humans were predicted to achieve exposure of 300 day μg/mL per week to match the efficacious exposure observed in xenograft models.
Conclusions The PK of MEHD7945A was nonlinear in mouse and monkey in the dose range tested. The nonspecific clearance in monkey was approximately twofold higher than typical humanized IgG1 antibodies. The projected human efficacious dose and dose regimen appear to be achievable in patients.

Keywords EGFR · HER3 · Pharmacokinetics · Dual-action antibody

A. V. Kamath (✉) · D. Lu · P. Gupta · D. Jin · H. Xiang · L. A. Damico-Beyer
Department of Pharmacokinetics and Pharmacodynamics, Genentech, Inc., South San Francisco, CA 94080, USA
e-mail: kamath.amrita@gene.com

A. Wong
Department of Biochemical and Cellular Pharmacology, Genentech, Inc., South San Francisco, CA 94080, USA

C. Leddy
Department of BioAnalytical Research and Development, Genentech, Inc., South San Francisco, CA 94080, USA

L. Crocker
Department of Translational Oncology, Genentech, Inc., South San Francisco, CA 94080, USA

G. Schaefer · M. X. Sliwkowski
Department of Research Oncology, Genentech, Inc., South San Francisco, CA 94080, USA

Introduction

EGFR and HER3 are members of the epidermal growth factor receptor (ErbB/HER) family of Type I transmembrane tyrosine kinase receptors that also includes HER2 and HER4. The receptors in this family are mediators of cell growth and differentiation, and deregulation of EGFR and HER3 signaling plays an important role in tumorigenesis [1, 2]. EGFR is a clinically validated target in non-small cell lung cancer, squamous cell carcinoma of the head and neck, colorectal cancer, and pancreatic cancer, and several anticancer therapeutics are available against this target such as erlotinib, gefitinib, cetuximab, and panitumumab [3]. Unlike EGFR, HER3 lacks intrinsic kinase activity and only

undergoes tyrosine phosphorylation when dimerized with another receptor [2]. When dimerized with EGFR or HER2, HER3 is a potent signaling partner via the PI3K/AKT pathway, and the HER3-PI3 kinase node is emerging as a potential target for anticancer therapy [4–6]. Because of the observed extensive crosstalk among these receptors, blocking the signaling of more than one of the receptors may be more efficacious and potentially overcome resistance to currently available EGFR therapies [7].

To target both EGFR and HER3 receptors, a novel antibody engineering strategy that produces a dual-action antibody in a conventional immunoglobulin G1 (IgG1) format was utilized where each of the two antigen-binding fragments (Fabs) is capable of binding to two different antigens with high affinity [8]. MEHD7945A, the HER3/EGFR dual-action antibody, is a phage-derived, human, monoclonal IgG1 antibody that binds to HER3 and EGFR with high affinity [9]. MEHD7945A was shown to inhibit EGFR- and HER3-mediated signaling in vitro and in vivo and had the potential to elicit antibody-dependent cell-mediated cytotoxicity [9]. MEHD7945A was more broadly efficacious in multiple tumor models compared to monospecific anti-HER antibodies, showing that combined inhibition of EGFR and HER3 with a single antibody is beneficial [9]. MEHD7945A is being investigated as a potential therapy against solid epithelial tumors in cancer patients.

MEHD7945A binds to both EGFR and HER3 in monkey and human with comparable affinity between species, but affinity for HER3 is higher than for EGFR. However, in the mouse, it binds to EGFR but not HER3 [9]. In this report, we have characterized the pharmacokinetics (PK) of MEHD7945A in mouse and monkey and predicted its human PK. In addition, antitumor activity data from xenograft models were combined with human PK estimates to project the efficacious dose in the clinic.

Materials and methods

Antibodies

MEHD7945A was generated at Genentech, Inc. and was provided in a clear liquid form for the in vivo monkey PK and mouse efficacy studies. Histidine buffer 8 (20 mM his-acetate, 0.02% polysorbate 20, 240 mM sucrose, pH 5.5) was used as the vehicle control and as the diluent for MEHD7945A. For the mouse PK study, MEHD7945A was provided in phosphate-buffered saline (PBS).

Pharmacokinetic study in SCID beige mice

The PK study in SCID beige mice was approved by the Institutional Animal Care and Use Committee at Genentech, Inc. Female SCID beige mice received a single intravenous (IV) dose of 1, 10, or 50 mg/kg of MEHD7945A via the tail vein ($n = 12$/group). Blood samples were collected via retro-orbital bleeds performed on alternating eyes, and the terminal blood sample was collected via cardiac stick from each animal in each dosing group at the following time points with three mice per time point: 15 min, 1, 4, 8, and 24 h; and 2, 4, 8, 10, 14, 21, and 28 days, and processed to collect serum. Composite serum concentration–time profiles were constructed for pharmacokinetic analysis.

Pharmacokinetic study in cynomolgus monkeys

The PK study in cynomolgus monkeys was approved by the Institutional Animal Care and Use Committee and conducted at Covance Laboratories, Inc. (Madison, WI). Three female cynomolgus monkeys were assigned to each of three treatment groups and given a single IV bolus dose of 1, 10, or 30 mg/kg of MEHD7945A each. Blood samples ($\sim$1 mL) for PK and anti-therapeutic antibody (ATA) analysis were collected from each animal via the femoral vein and processed to collect serum. PK samples were collected on day 0 (predose, 0.167, 1, 2, 4, 8, and 12 h postdose), and 1, 2, 3, 5, 7, 10, 14, 21, 28, 35, and 42 days, while ATA samples were collected predose (7 days prior to dosing and on day 0) and 14, 21, 28, 35, and 42 days.

Bioanalysis of serum samples from pharmacokinetic studies

Serum samples from SCID beige mice and cynomolgus monkeys were analyzed for MEHD7945A concentrations using a quantitative enzyme-linked immunosorbent assay (ELISA). For the mouse serum samples, the ELISA utilized a soluble human HER3-IgG capture agent and a goat anti-human IgG F(ab)′2-horseradish-peroxidase (HRP) detection agent. For the monkey serum samples, the ELISA utilized an immobilized HER3 Fc ECD as the capture agent and HRP-conjugated 10C4 antibody (10C4.1-mouse anti-Genentech recombinant human monoclonal antibody framework) as the detection agent. A minimum serum sample dilution of 1:100 was used on all samples, and the minimum quantifiable concentrations were 31.3 and 80 ng/mL for the mouse and monkey samples, respectively.

Anti-therapeutic antibody (ATA) assay

Serum samples from cynomolgus monkeys were analyzed for ATA levels using a homogenous bridging biotin–digoxigenin (DIG) ELISA. In this format, samples were incubated together with biotin-conjugated MEHD7945A and DIG-conjugated MEHD7945A. Bridged complexes

were captured on streptavidin-coated microtiter plates (Thermo Scientific, Rockford, IL) and then detected by the addition of HRP-labeled anti-DIG antibody (Jackson ImmunoResearch, West Grove, PA). Samples with a mean signal (measured in absorbance units, AU) equal to or greater than the cut point were considered positive. The cut point was obtained by multiplying the mean AU of the negative control by the assay cut point multiplication factor which was determined using a panel of 37 individual drug-naïve cynomolgus monkey sera (Bioreclamation, Inc., Westbury, NY).

Antitumor efficacy studies in mice

The efficacy studies in mice were approved by the Institutional Animal Care and Use Committee at Genentech, Inc. Female C.B-17 SCID mice (8–10 week old) were inoculated with 5 million NCI-H292 (a non-small cell lung cancer), or 5 million FaDu (a head and neck squamous cell carcinoma) cells, suspended in Hanks' balanced salt solution (HBSS). When tumors reached a mean volume of 170–215 mm^3, mice with similarly sized tumors were randomized into treatment cohorts ($n = 8$ or 9 mice/group) and animals received a single intraperitoneal (IP) dose of vehicle (control group) or MEHD7945A (treatment groups). The doses of MEHD7945A used were 6.25, 12.5, 25, and 50 mg/kg in the NCI-H292 study, and 3.125, 6.25, 12.5, and 25 mg/kg in the FaDu study. Tumors were measured twice each week for the duration of the study using UltraCal-IV calipers, and tumor volume was calculated using the following formula: Tumor volume (mm^3) = (length × $width^2$) × 0.5. The results were shown as mean tumor volume ± standard error of the mean (SEM) for the time that at least half the animals in the group remained on study. Time to tumor doubling (TTD) was calculated and is defined as the time in days for a tumor to double in volume from the day of randomization.

Pharmacokinetic data analysis

Serum concentration–time profiles were used to estimate the following PK parameters in mouse and monkey using non-compartmental analysis (WinNonlin, version 5.2.1; Pharsight Corporation, Mountain View, CA): total drug exposure defined as area under the serum concentration–time curve extrapolated to infinity (AUC_{inf}), total clearance (CL_{tot}), volume of distribution at steady state (V_{ss}), and observed maximum serum concentration (C_{max}). A naïve pooled approach was used in mouse to provide one estimate for each dose group, while in monkey, each animal was analyzed separately, and results for each dose group were summarized as mean ± standard deviation (SD).

In addition, the monkey serum concentration–time data were fit to a nonlinear, two-compartment model comprising specific (target-mediated) and nonspecific CL pathways [10] as shown in Fig. 1, using population PK analysis (NONMEM, version VI, ICON Development Solutions, Ellicott City, MD) to obtain the following PK parameters: clearance from the central compartment (CL) that is the nonspecific clearance pathway, distributional CL (CL_d), volumes of distribution of the central compartment (V_1) and the peripheral compartment (V_2), and parameters of the specific clearance pathway which are maximum target-mediated elimination rate under conditions of target saturation (V_{max}), and the concentration for reaching 50% V_{max} (K_m). The results were summarized as one estimate for each parameter and the % standard error of the estimate (% SEE).

Prediction of human PK and clinical target dose range

The monkey serum concentration–time profiles were transformed to human concentration–time profiles using a species-invariant time method as described previously [11, 12]. A scaling exponent of either 0.75 or 0.90 was used to estimate human CL, and a scaling exponent of 1 was used to estimate the volume of the central compartment (V_1) [12, 13]. The estimated human serum concentration–time data obtained from this method were used to predict population PK parameter estimates for humans using the PK model shown in Fig. 1. The estimated human PK parameters were then used to estimate the clinical dose and dose regimen to achieve the target efficacious exposure observed in the antitumor efficacy studies in mice using population simulations by NONMEM. The interindividual variability on V_{max}, CL, and V_1 was assumed to be 30% based on what is generally observed in humans for monoclonal antibodies [12, 14].

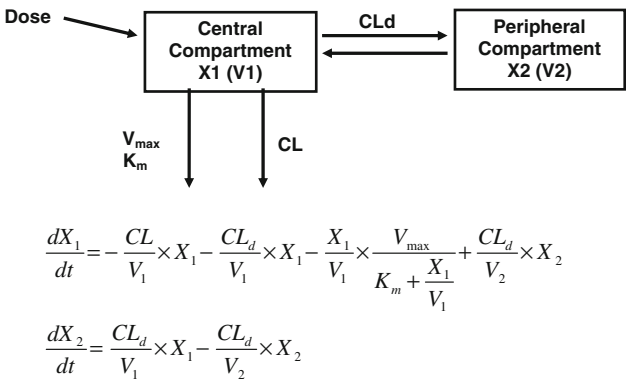

Fig. 1 Two-compartment nonlinear PK model

Results

Pharmacokinetics in SCID beige mice

The PK profiles of MEHD7945A following a single IV bolus dose in SCID beige mice at doses of 1, 10, and 50 mg/kg are shown in Fig. 2, and PK parameters are summarized in Table 1. As the dose increased from 1 to 50 mg/kg, C_{max} increased dose proportionally, while AUC_{inf} increased in a greater than dose-proportional manner. The total clearance (CL_{tot}) decreased with the increased doses, going from 20.8 mL/day/kg at the 1 mg/kg dose to 7.15 mL/day/kg at the 50 mg/kg dose. The V_{ss} ranged from 114 to 160 mL/kg at the doses tested indicating some extravascular distribution. These data suggest that the PK of MEHD7945A is nonlinear in a dose range of 1–50 mg/kg in female SCID beige mice.

Pharmacokinetics in cynomolgus monkeys

The PK profiles of MEHD7945A following a single IV bolus dose in cynomolgus monkeys at doses of 1, 10, and 30 mg/kg are shown in Fig. 3, and PK parameters after non-compartmental analysis are summarized in Table 1. After a single IV bolus dose of MEHD7945A, Cmax increased dose proportionally, from 1 to 30 mg/kg, and AUCinf increased more than dose proportionally, from 1 to 30 mg/kg. MEHD7945A CLtot decreased as dose increased from 1 to 30 mg/kg, going from 45.7 at 1 mg/kg to 14.1 ml/day/kg at 30 mg/kg. V_{ss} ranged from approximately 44.5 to 59.6 mL/kg at the doses tested. ATAs were detected in nine of the nine animals (100%) given MEHD7945A. The potential effect of ATAs on PK parameter estimates could not be assessed, as all animals tested ATA positive. These data suggest that in female cynomolgus monkeys following dose administration of MEHD7945A at 1, 10, or 30 mg/kg, the pharmacokinetics are nonlinear in a dose range from 1 to 30 mg/kg.

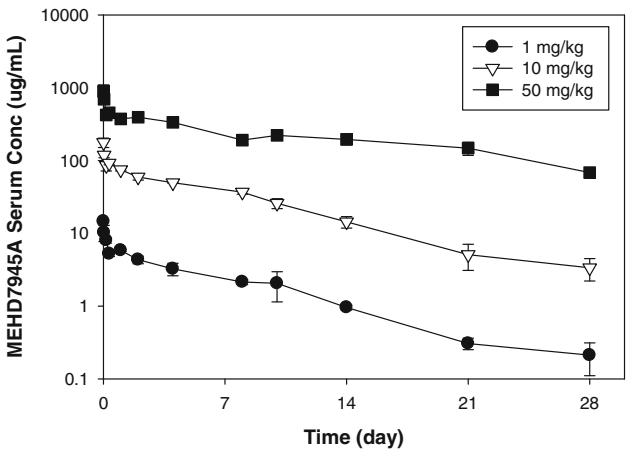

Fig. 2 MEHD7945A average serum concentration–time profiles in SCID beige mice after IV administration

The monkey concentration–time profiles were described well by a nonlinear, two-compartment model comprising specific (target-mediated) and nonspecific CL pathways, and the estimated PK parameters are shown in Table 2. Using this model, the estimated nonspecific CL was 14.2 mL/day/kg, which is approximately twofold higher than the clearance of a typical human IgG1 in monkeys [12]. Estimated values for the V_{max} and K_m for the specific CL pathway were 243 μg/day/kg and 1.61 μg/mL, respectively.

Antitumor efficacy in xenograft models

MEHD7945A was evaluated for antitumor activity in NCI-H292 human non-small lung cancer and FaDu human head and neck cancer xenograft models at 4 dose levels. The NCI-H292 model was selected because of its previously characterized sensitivity to anti-EGFR targeted agents, and the FaDu model was selected because it showed sensitivity toward HER3 targeting agents and also demonstrated enhanced antitumor effects resulting from dual inhibition of EGFR- and HER3-mediated signaling [9]. As shown in Figs. 4 and 5, after a single IP dose of MEHD7945A, substantial antitumor activity was seen in both the NCI-H292 and the FaDu models. In the NCI-H292 model, tumor response was sustained for approximately 14, 21, 30, and 35 days in the 6.25, 12.5, 25, and 50 mg/kg groups, respectively. A relationship between TTD and dose of MEHD7945A was also observed. Compared with the TTD of 3 days in the vehicle group, doses of 6.25, 12.5, 25, or 50 mg/kg MEHD7945A resulted in an increased TTD of 27.5, 34, 36, and 43 days, respectively. In the FaDu model, tumor response was sustained for approximately 10, 28, 42, and 55 days in the 3.125, 6.25, 12.5, and 25 mg/kg groups, respectively. A correlation between dose level and TTD was also observed. While TTD for the vehicle group was 4 days, administration of 3.125, 6.25, and 12.5 mg/kg MEHD7945A increased the TTD to 15, 39, and 51.5 days, respectively. In addition, administration of 25 mg/kg MEHD7945A resulted in an even greater inhibitory activity, as the TTD of that group was not reached by the end of the study (Day 66).

Prediction of human pharmacokinetics

The cynomolgus monkey was selected to scale pharmacokinetics to humans because it is generally considered the most relevant species for predicting the human PK of antibodies [12]. For MEHD7945A, it was also the only species which showed binding to both targets (EGFR and HER3) unlike in the mouse where MEHD7945A only

Table 1 MEHD7945A pharmacokinetic parameters in SCID beige mice and cynomolgus monkeys by non-compartmental analysis

	SCID beige mice			Cynomolgus monkeys		
Dose (mg/kg)	1	10	50	1	10	30
C_{max} (μg/mL)	14.6	177	897	23 ± 3.9	249 ± 15	823 ± 50
AUC_{inf} (day μg/mL)	48.2	707	7,000	22 ± 1.7	489 ± 23	2,140 ± 232
CL_{tot} (mL/day/kg)	20.8	14.1	7.15	46 ± 3.7	20 ± 1.0	14 ± 1.6
V_{ss} (mL/kg)	160	114	116	44 ± 5.3	60 ± 4.8	57 ± 4.5

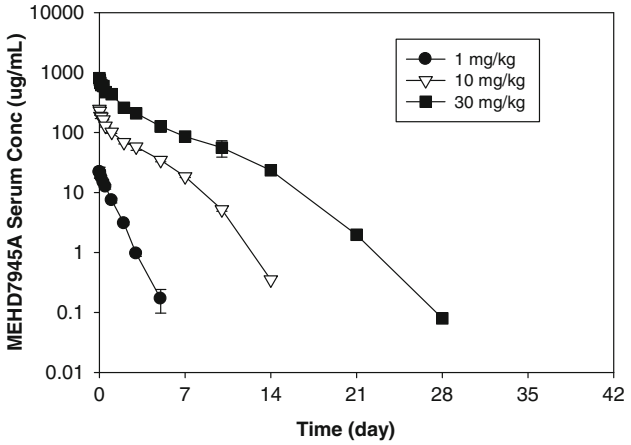

Fig. 3 MEHD7945A average serum concentration–time profiles in cynomolgus monkeys after IV administration

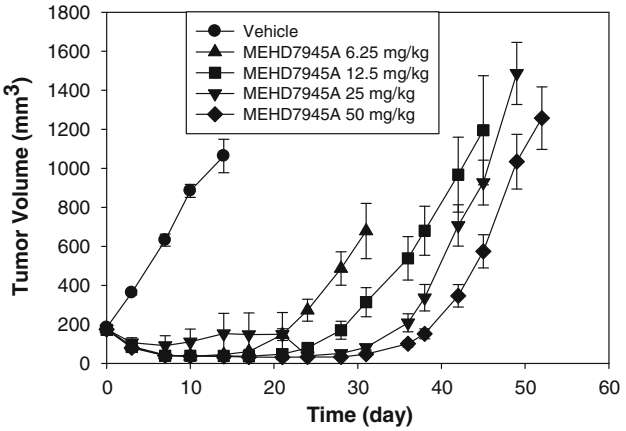

Fig. 4 Antitumor efficacy of MEHD7945A in NCI-H292 non-small cell lung cancer xenograft model after a single IP dose

Table 2 MEHD7945A pharmacokinetic parameters in cynomolgus monkeys using a nonlinear two-compartment model and population PK analysis

Parameter	Estimate	% SEE[a]
CL (mL/day/kg)	14.2	6.45
V_1 (mL/kg)	43.7	3.62
V_{max} (μg/day/kg)	243	8.64
K_m (μg/mL)	1.61	18.0
CL_d (mL/day/kg)	23.0	9.87
V_2 (mL/kg)	34.7	4.32

[a] % standard error of estimate

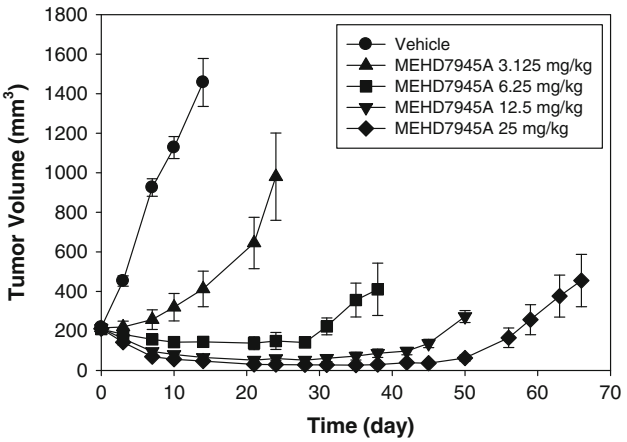

Fig. 5 Antitumor efficacy of MEHD7945A in FaDu head and neck cancer xenograft model after a single IP dose

bound to EGFR but not HER3. Pharmacokinetics from the single IV dose PK study in cynomolgus monkeys were used to estimate human pharmacokinetics using a species-invariant time method [11]. The estimated human serum concentration–time profiles obtained by this method were described well by a nonlinear, two-compartment model comprising target-mediated and nonspecific CL pathways, and the estimated population PK parameters are shown in Table 3. The estimated nonspecific CL range was 6.37–10.3 mL/day/kg, which is approximately twofold higher than typical human IgG1. Estimated values for the V_{max} and K_m of the specific CL pathway were 107–175 μg/day/kg and 1.61 μg/mL, respectively.

Projection of clinical target dose range

Efficacy data obtained from xenograft models was used to estimate MEHD7945A exposure required to achieve tumor growth inhibition. The antitumor activity of MEHD7945A

Table 3 MEHD7945A predicted human PK parameters using a nonlinear two-compartment model and population PK analysis

Parameter	Slow clearance (CL exponent = 0.75)		Fast clearance (CL exponent = 0.9)	
	Estimate	% SEE[a]	Estimate	% SEE[a]
CL (mL/day/kg)	6.37	6.28	10.3	2.99
V_1 (mL/kg)	43.6	3.60	43.7	2.38
V_{max} (μg/day/kg)	107	6.64	175	2.16
K_m (μg/mL)	1.61	9.81	1.61	1.88
CL_d (mL/day/kg)	10.3	9.67	16.7	4.83
V_2 (mL/kg)	34.1	4.49	34.4	1.76

[a] % standard error of estimate

was evaluated in the NCI-H292 (a non-small cell lung cancer) and FaDu (a head and neck squamous cell carcinoma) xenograft models in a dose range of 6.25–50 or 3.125–25 mg/kg, respectively, given as a single IP dose. The lowest dose to maintain tumor stasis for at least 3 weeks after a single dose was chosen as the target efficacious dose. A dose of 12.5 mg/kg was found to maintain tumor stasis for 21 days in the NCI-H292 xenograft model, while in the FaDu xenograft model, a dose of 6.25 mg/kg was able to maintain tumor stasis for 28 days. The weekly exposure estimated for these doses using PK parameters from the single-dose mouse PK study assuming 100% bioavailability was 294 and 107 day μg/mL for NCI-H292 and FaDu, respectively. The similarity of serum concentrations on Day 7 postdose obtained from the observation in the FaDu efficacy study and from the simulation using PK parameters from the mouse PK study supported the assumption of 100% bioavailability of MEHD7915A in mice (data not shown). Based on these results, exposure of 300 day μg/mL per week at steady state was chosen as a conservative target for efficacy. The estimated human PK parameters were then used to estimate the clinical dose and dose regimen to achieve the target efficacious exposure. Doses in humans to be administered every week (Q1W), every 2 weeks (Q2W), every 3 weeks (Q3W), or every 4 weeks (Q4W) were predicted to match the efficacious exposure in xenograft models and are listed in Table 4.

Table 4 Estimated MEHD7945A dose range to achieve target exposure in >90% of patients

Dose regimen	Target AUC at steady state (day μg/mL)	Estimated target dose range in humans based on predicted slow and fast CL (mg/kg)
Q1W	300	4–6
Q2W	600	8–12
Q3W	900	11–17
Q4W	1,200	14–22

Doses of 8–12 mg/kg administered once every 2 weeks (Q2W) in humans are predicted to achieve exposure of 300 day μg/mL per week to match efficacious exposure observed in xenograft models.

Discussion

MEHD7945A is a novel dual-action antibody that targets both EGFR and HER3 and has been shown to have superior activity compared to monospecific HER antibodies in nonclinical studies [9]. We are very interested in developing MEHD7945A as an anticancer therapeutic due to its potential to treat EGFR/HER3-driven disease as well as delay HER3-dependent drug resistance which may result in better clinical outcomes [9, 15]. To gain a better understanding of the therapeutic potential of MEHD7945A, we assessed its pharmacokinetics in mouse and monkey, antitumor activity in xenograft models and predicted its human PK and efficacious dose range in the clinic.

In both mouse and monkey, the PK of MEHD7945A was nonlinear in the dose range tested and the total clearance decreased with increase in dose likely due to saturation of the target. As MEHD7945A binds to only EGFR in mouse but binds to both EGFR and HER3 in monkey and human with comparable affinity, only the monkey PK was used to predict human PK. In monkeys, the nonspecific clearance of MEHD7945A was 14.2 mL/day/kg and was approximately twofold greater than what is typically observed for a human IgG1 [12]. Since monkey PK was used for human PK predictions, the predicted nonspecific CL in humans of 6.37–10.3 mL/day/kg was also twofold higher than for a typical human IgG1. However, since all monkeys in the study were ATA positive, it was difficult to assess the impact of ATA on the clearance. The ATA response was likely directed against the human framework of MEHD7945A; however, the epitope characterization was not performed in this study. Since MEHD7945A is a human IgG1, we anticipate that the incidence of ATAs will be low in humans. Because of the uncertainty in the PK projection given the nonlinear nature of the CL of MEHD7945A and the potential impact of ATA on the cynomolgus monkey PK data used to predict the human CL, it is important to verify these predictions in Phase I. The observed human PK information from Phase I will be used to support the dose selection for subsequent clinical trials.

MEHD7945A showed strong single-agent antitumor activity in a wide range of xenograft models that are dependent on the activity of EGFR, HER3, or both receptors for tumor growth [9]. Two representative models were selected to estimate efficacious doses in humans, NCI-H292 (non-small cell lung cancer) and FaDu (head

and neck squamous cell carcinoma). MEHD7945A showed impressive antitumor activity in both models after a single IP dose even at the lowest dose tested. The antitumor activity is likely mediated through the blockade of EGFR in the NCI-H292 model and through the combined inhibition of HER3 and EGFR in the FaDu model. Combining the efficacious exposure from the xenograft models and the predicted human PK estimates, clinical doses for various regimens in patients were predicted. For the Q2W and Q3W dosing regimens commonly used in these patients, doses of 8–12 mg/kg given Q2W or 11–17 mg/kg given Q3W are predicted to match the efficacious exposure observed in xenograft models.

In summary, the PK of MEHD7945A was nonlinear in mouse and monkey. The nonspecific CL in monkey was approximately twofold higher than typical humanized IgG1 antibodies. The human PK was predicted from monkey data and will be verified in a Phase 1 study. The projected human efficacious doses and dose regimens appear to be achievable in patients.

Acknowledgments We thank the In Vivo Studies Group at Genentech for conducting the mouse PK study and Celso Wang for coordinating the monkey PK study with Covance Laboratories.

References

1. Arteaga C (2003) Targeting HER1/EGFR: a molecular approach to cancer therapy. Semin Oncol 30(3 Suppl 7):3–14
2. Hynes NE, MacDonald G (2009) ErbB receptors and signaling pathways in cancer. Curr Opin Cell Biol 21:177–184
3. Ciardiello F, Tortora G (2008) EGFR antagonists in cancer treatment. N Engl J Med 358:1160–1174
4. Soltoff SP, Carraway KL, Prigent SA, Gullick WG, Cantley LC (1994) ErbB3 is involved in activation of phosphatidylinositol 3-kinase by epidermal growth factor. Mol Cellular Biol 14:3550–3558
5. Schoeberl B, Pace EA, Fitzgerald JB, Harms BD, Xu L, Nie L, Linggi B et al (2009) Therapeutically targeting ErbB3: a key node in ligand-induced activation of the ErbB receptor-PI3K axis. Sci signal 2:ra31
6. Hsieh AC, Moasser MM (2007) Targeting HER proteins in cancer therapy and the role of the non-target HER3. Br J Cancer 97:453–457
7. Sergina NV, Moasser MM (2007) The HER family and cancer: emerging molecular mechanisms and therapeutic targets. Trends Mol Med 13:527–534
8. Bostrom J, Yu SF, Kan D et al (2009) Variants of the antibody herceptin that interact with HER2 and VEGF at the antigen-binding site. Science 323:1610–1614
9. Schaefer G, Haber L, Crocker LM, Shia S, Shao L et al (2011) A two-in-one antibody against HER3 and EGFR has superior inhibitory activity compared to monospecific antibodies. Cancer Cell 20(4):472–486
10. Mould DR, Green B (2010) Pharmacokinetics and pharmacodynamics of monoclonal antibodies. Biodrugs 24(1):23–39
11. Dedrick RL (1973) Animal scale-up. J Pharmacokinet Biopharm 1:435–461
12. Deng R, Iyer S, Theil FP, Mortensen D, Fielder P, Prabhu S (2011) Projecting human pharmacokinetics of therapeutic antibodies from nonclinical data. mAbs 3(1):61–66
13. Mahmood I (2004) Interspecies scaling of protein drugs: prediction of clearance from animals to humans. J Pharm Sci 93:177–185
14. Dirks NL, Meibohm B (2010) Population pharmacokinetics of therapeutic monoclonal antibodies. Clin Pharmacokinet 49: 633–659
15. Schoeberl B, Faber AC, Li D, Liang MC et al (2010) An ErbB3 antibody, MM-121, is active in cancers with ligand-dependent activation. Cancer Res 70:2485–2494