The Oncologist®

New Drug Development and Clinical Pharmacology

Fixed Dosing of Monoclonal Antibodies in Oncology

Jeroen J.M.A. Hendrikx,[a] John B.A.G. Haanen,[b] Emile E. Voest,[c] Jan H.M. Schellens,[d,e] Alwin D.R. Huitema,[a,f] Jos H. Beijnen[a,e]

[a]Department of Pharmacy & Pharmacology, The Netherlands Cancer Institute and MC Slotervaart, Amsterdam, The Netherlands; Departments of [b]Medical Oncology and Immunology, [c]Molecular Oncology, and [d]Clinical Pharmacology, The Netherlands Cancer Institute, Amsterdam, The Netherlands; [e]Department of Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands; [f]Department of Clinical Pharmacy, University Medical Center Utrecht, Utrecht, The Netherlands

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Monoclonal antibodies • Cancer • Fixed dosing

Abstract

Most monoclonal antibodies in oncology are administered in body–size-based dosing schedules. This is believed to correct for variability in both drug distribution and elimination between patients. However, monoclonal antibodies typically distribute to the blood plasma and extracellular fluids only, which increase less than proportionally with the increase in body weight. Elimination takes place via proteolytic catabolism, a nonspecific immunoglobulin G elimination pathway, and intracellular degradation after binding to the target. The latter is the primary route of elimination and is related to target expression levels rather than body size. Taken together, the minor effects of body size on distribution and elimination of monoclonal antibodies and their usually wide therapeutic window do not support body–size-based dosing. We evaluated effects of body weight on volume of distribution and clearance of monoclonal antibodies in oncology and show that a fixed dose for most of these drugs is justified based on pharmacokinetics. A survey of the savings after fixed dosing of monoclonal antibodies at our hospital showed that fixed dosing can reduce costs of health care, especially when pooling of preparations is not possible (which is often the case in smaller hospitals). In conclusion, based on pharmacokinetic parameters of monoclonal antibodies, there is a rationale for fixed dosing of these drugs in oncology. Therefore, we believe that fixed dosing is justified and can improve efficiency of the compounding. Moreover, drug spillage can be reduced and medication errors may become less likely. ***The Oncologist*** 2017;22:1212–1221

Implications for Practice: The currently available knowledge of elimination of monoclonal antibodies combined with the publicly available data from clinical trials and extensive population pharmacokinetic (PopPK) modeling justifies fixed dosing. Interpatient variation in exposure is comparable after body weight and fixed dosing and most monoclonal antibodies show relatively flat dose-response relationships. For monoclonal antibodies, this results in wide therapeutic windows and no reduced clinical efficacy after fixed dosing. Therefore, we believe that fixed dosing at a well-selected dose can increase medication safety and help in reduction of costs of health care without the loss of efficacy or safety margins.

Introduction

Today, in the field of oncology, most drugs are administered in a body–size-based dosing schedule instead of a fixed dose for all patients. For most cytotoxic small molecule anticancer agents, body surface area (BSA) (in m^2) is used for dosing. The origin of BSA-based dosing is related to the narrow therapeutic window of these antineoplastic agents [1]. By comparing the maximum tolerated dose (MTD) in humans to the MTD in different animal species used in preclinical experiments, it was observed that MTDs were comparable when expressed in milligram per m^2 [[2], [3]]. This allowed a safer setting of the starting dose and dose escalation of new agents in phase I studies [1]. The acceptance of dosing in mg/m^2 was further fueled by the general belief that pharmacokinetic parameters like clearance can be scaled between individuals according to BSA [1, 4]. Dosing in milligram per m^2 is, therefore, considered to correct for variability in drug distribution and elimination observed after fixed dosing. However, BSA-based dosing is still under debate since there is a lack of clinical trial data that BSA-based dosing indeed reduces interindividual variation in drug exposure [5]. A large meta-analysis by McLeay et al. [6] showed that BSA, lean

Correspondence: Jeroen J.M.A. Hendrikx, Ph.D., Plesmanlaan 121, PO Box 90203, 1006 BE Amsterdam, The Netherlands. Telephone: 0031-205-127-948; e-mail: J.Hendrikx@nki.nl Received April 14, 2017; accepted for publication June 29, 2017; published Online First on July 28, 2017. http://dx.doi.org/10.1634/theoncologist.2017-0167

body weight, and total body weight all were equally successful for prediction of total drug clearance.

Like cytotoxic anticancer agents, monoclonal antibodies in oncology were initially administered in body–size-based dosing schedules. Rituximab (Food and Drug Administration [FDA]-approved in 1998), the first monoclonal antibody approved in oncology, was developed at a milligram per m^2 dosing schedule [7]. Single doses up to 500 mg/m^2 and 4 weekly doses of 375 mg/m^2 were evaluated in the clinical studies [8–10]. For trastuzumab (FDA-approved in 1998), at first, antitumor activity was evaluated at a fixed dose of 100 mg (with a 250 mg loading dose) [11, 12]. However, based on unpublished phase I trials and without publicly available explanation, further dose escalation was executed at a milligram per kilogram dosing schedule [13]. By now, almost all approved monoclonal antibodies in oncology are dosed at a milligram per kilogram-based schedule as originally developed for trastuzumab (Table 1).

We believe that body weight dosing of monoclonal antibodies is also open for debate and that fixed dosing is justified and has several advantages. Fixed dosing can improve efficiency of the compounding. Moreover, drug spillage can be reduced and medication errors may become less likely [14, 15]. Here, we discuss the rationale for fixed dosing of monoclonal antibodies in oncology and propose fixed dosing schemes for all currently approved antibodies in oncology.

Distribution and Elimination of Monoclonal Antibodies

As reviewed previously by our group, pharmacokinetics of monoclonal antibodies are complex and differ substantially from those of small molecule drugs [16]. In oncology, monoclonal antibodies are of the immunoglobulin G (IgG) subtype and primarily administered intravenously [17]. Only rituximab, trastuzumab, and catumaxomab are licensed for nonintravenous, parenteral administration [18–21]. After administration, the distribution of monoclonal antibodies is limited by their size and hydrophilicity. Typically, monoclonal antibodies distribute only in the blood plasma and extracellular fluids, resulting in low distribution volumes (usually 2–12 L) [16, 22].

Clearance of monoclonal antibodies differs distinctively from small molecule drugs. Where small molecule drugs undergo renal and/or hepatic clearance, monoclonal antibodies are too large to be cleared from the body by means of these elimination routes [16, 22]. Antibodies are primarily metabolized by two main mechanisms (Fig. 1; Table 2) [16, 22]. A nonspecific IgG elimination pathway is responsible for a linear clearance rate of monoclonal antibodies via proteolytic catabolism. Proteolytic catabolism takes place in cells after endocytosis of the antibody, with the main contribution of cells that are in rapid equilibrium with blood plasma (e.g., skin, muscle, liver, and gut tissue) [23]. In this process, the antibody is engulfed by the cell membrane and catabolized by lysosomes inside the cell. In the absence of the neonatal Fc receptor (FcRn, or Brambell receptor) this would lead to rapid clearance of monoclonal antibodies. However, this receptor is expressed in vascular endothelium, immune cells (e.g., macrophages and dendritic cells), intestinal epithelium, and hepatocytes and binds to monoclonal antibodies [23]. After binding, the FcRn receptor mediates monoclonal antibody transport to the extracellular matrix, thus preventing intracellular breakdown by catabolism. At therapeutic levels of monoclonal antibodies, the FcRn mechanism is not likely to be saturated and homeostasis between intracellular breakdown and FcRn mediated rescue is maintained [24]. This results in slow linear clearance of monoclonal antibodies via proteolytic catabolism. A second, more rapid elimination route for many monoclonal antibodies is target binding [25]. This is followed by internalization of the monoclonal antibody-target complex and intracellular degradation. Since this route is highly affected by both affinity of the antibody for its respective target, and target expression, it is usually saturable. The combination of both elimination pathways leads to linear clearance of the monoclonal antibody at plasma concentrations that exceed the minimum target inhibitory concentration due to saturation of the intracellular degradation (which is the case at therapeutic plasma concentrations of monoclonal antibodies). Once the plasma concentration of the antibody drops below the minimum target inhibitory concentration, intracellular catabolic degradation is not saturated anymore and elimination of monoclonal antibodies is mostly dominated by this target mediated clearance route [16, 22].

Effect of Body Weight on Elimination and Distribution of Monoclonal Antibodies

For monoclonal antibodies, the distribution volume is limited to the volume of the blood plasma and extracellular fluids [16, 22]. As a result, body composition is of less importance than for small molecule drugs, for which volume of distribution is also determined by adipose, connective, and muscular tissue [26, 27]. Although blood volume is increased in obese patients and decreased in underweight patients compared to normal weight patients, the change in blood volume is less than proportional with the change in body weight [28, 29]. As a result, total blood volume is better correlated to lean body weight than to body weight [29]. Moreover, estimation of total blood volume by lean body weight also corrects for differences in body composition (e.g., muscle/fat ratio) between male and female patients. For example, estimated on lean body weight, the blood volume of a male patient (height 1.8 m) with a body weight of 140 kg will be 1.5-fold higher than for a 70-kg patient. On the other hand, blood volume of a 50-kg patient will be 1.2-fold lower, while body weight is 1.4-fold lower. Thus, a linear dosing schedule (e.g., mg/kg) will result in higher plasma levels in obese patients and lower levels in underweight patients (Table 3).

Elimination of small molecule drugs might be changed in obese patients as a result of altered renal and hepatic blood flow and differences in phase I and II metabolism [27]. Clearance of monoclonal antibodies, on the other hand, is not likely to be affected since it is not dependent on renal or hepatic blood flow [29]. As described above, monoclonal antibodies are subject to two elimination routes: (a) proteolytic catabolism and (b) intracellular degradation after binding to the target. For monoclonal antibodies targeting soluble targets (e.g., bevacizumab and ramucirumab), target internalization and degradation play no role and clearance is limited to proteolytic catabolism [22]. In contrast, for monoclonal antibodies targeting antigens at cell surfaces, intracellular degradation may play a major role. Obviously, binding to the target at the cell surface is not related to body weight, but mainly to tumor load, target expression levels in tumors versus endogenous expression, and affinity of

Table 1. Monoclonal antibodies approved for treatment of cancer and a proposal for fixed dosing

Generic name	Approved dose	Therapeutic window[a]	Volume of distribution at steady state (L)	Body weight effect on volume of distribution[b]	Clearance (L/day)	Body weight effect on clearance[b]	Proposed fixed dose	Corresponding body size based dose after fixed dosing	References
Bevacizumab	5 mg/kg; 2 weekly 10 mg/kg; 2 weekly 15 mg/kg; 3 weekly	5–15 mg/kg	2.66	0.411	0.207	0.368	40–140 kg: 600 mg, 2 weekly	4.2–15 mg/kg	[33, 36, 37]
Catumaxomab	Day 0: 10 ug Day 3: 20 ug Day 7: 50 ug Day 10: 150 ug	*Intraperitoneal administration with limited absorption into the systemic circulation.*					*Approved fixed dose*		[19, 20]
Cetuximab	250 mg/m^2 weekly (400 mg/m^2 loading dose)	250–400 mg/m^2	5.22	0.42 (effect of BSA was evaluated)	0.497	None	1.3–2.2 m^2: 500 mg, weekly (with 800 mg loading dose)	227–384 mg/m^2 (364–615 mg/m^2 loading dose)	[34, 35, 38]
Ipilimumab	3 mg/kg; 3 weekly	3–10 mg/kg	4.15	0.708	0.360	0.642	40–60 kg: 150 mg, 3 weekly 60–100 kg: 250 mg, 3 weekly 100–140 kg: 350 mg, 3 weekly	2.5–3.8 mg/kg 2.5–4.2 mg/kg 2.5–3.5 mg/kg	[57–59]
Nivolumab	3 mg/kg; 2 weekly	1–10 mg/kg	8.0	0.580	0.228	0.707	40–140 kg: 240 mg, 2 weekly	1.7–6 mg/kg	[44, 60]
Obinutuzumab	1,000 mg per cycle (cycle 2–6)	1,000–2,000 mg	2.76	0.383	0.083	0.231	*Approved fixed dose*		[61–63]
Ofatumumab	1,000 mg; 4 weekly (untreated CLL) 2,000 mg; weekly (refractory CLL)	1,000–2,000 mg	3.26	0.076	0.369	0.229	*Approved fixed dose*		[64–66]
Panitumumab	6 mg/kg; 2 weekly	2.5–9 mg/kg	3.66	0.526	0.269	0.411	40–80 kg: 300 mg, 2 weekly 80–140 kg: 500 mg, 2 weekly	3.75–7.5 mg/kg 3.5–6.25mg/kg	[67–69]
Pembrolizumab	2 mg/kg; 3 weekly	1–10 mg/kg	8.1	0.489	0.23	0.595	40–140 kg: 150 mg, 3 weekly	1.1–3.8 mg/kg	[49, 70, 71]
Pertuzumab	420 mg; 3 weekly (840 mg loading dose)	420–1,050 mg	3.07	0.747	0.239	0.516–0.589	*Approved fixed dose*		[72–75]
Ramucirumab	8 mg/kg; 2 weekly	8–10 mg/kg	5.5	Not reported	0.336	Not reported	*Insufficient data*		[56, 76]
Rituximab	375 mg/m^2; interval is variable	375–2,250 mg	2.98	0.73	0.257	1.02	1.3–2.2 m^2: 800 mg per administration	364–615 mg/m^2	[39, 40, 77]
Trastuzumab	2 mg/kg/week (with an additional 2 mg/kg as loading dose)	1–>8 mg/kg	2.95	0.556	0.225	1.07	40–140 kg: 450 mg, 3 weekly	3.2–11.3 mg/kg	[13, 41–43, 78]

Fixed dose is proposed if the effect of body weight on the volume of distribution and clearance is minimal (<0.5). If the effect of body weight is strong (>0.5) or unknown and a wide therapeutic window is reported, a fixed dosing approach might be considered for practical reasons.

[a]The therapeutic window is based on a minimum effective dose at the interval of the approved dose and a maximum tolerated (or tested) dose after single administration.

[b]The effect is presented as the exponent used in population pharmacokinetics models in formula 1 to correct for the effect of body weight, whereas 0 is used for no effect and 1 is used for a linear effect.

Abbreviations: BSA, body surface area; EMA, European Medicines Agency; CLL, chronic lymphocytic leukemia.

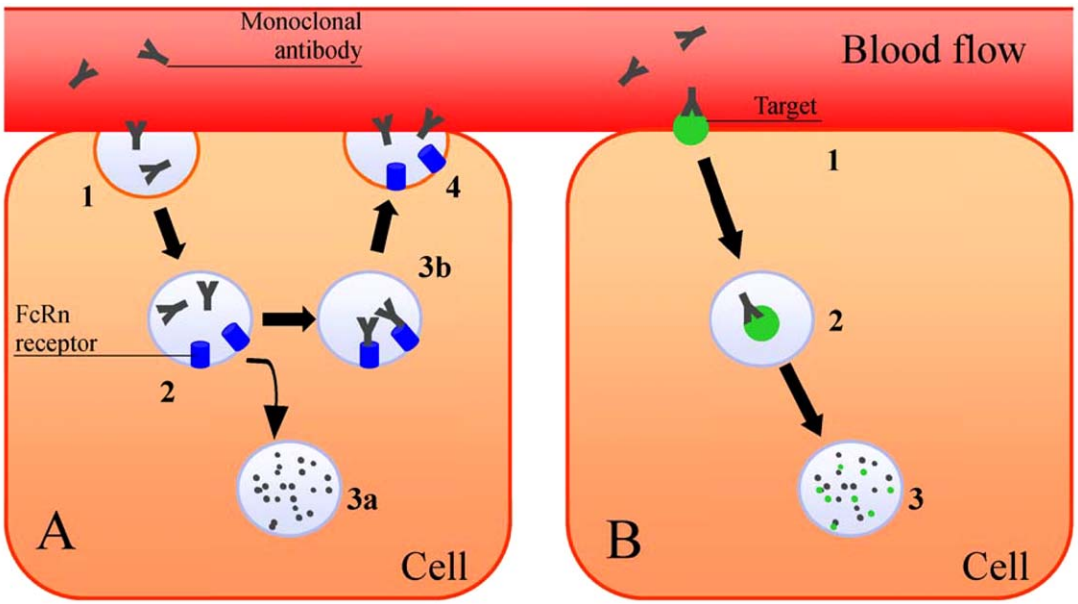

Figure 1. Metabolism of monoclonal antibodies. Antibodies are metabolized via proteolytic catabolism **(A)** and intracellular degradation after binding to the target **(B)**. Proteolytic catabolism takes place in cells after endocytosis of the antibody. In this process, the antibody is engulfed by the cell membrane **(A1)** and catabolized by lysosomes **(A2)** inside the cell. In the absence of the neonatal Fc receptor (FcRn, or Brambell receptor), this would lead to rapid clearance of monoclonal antibodies **(A3a)**. However, this receptor is expressed in vascular endothelium, immune cells (e.g., macrophages and dendritic cells), intestinal epithelium, and hepatocytes and binds to monoclonal antibodies **(A3b)**. After binding, the FcRn receptor mediates monoclonal antibody transport to the extracellular matrix, thus preventing intracellular breakdown by catabolism **(A4)**. A second, more rapid elimination route for many monoclonal antibodies is target binding **(B1)**. This is followed by internalization of the monoclonal antibody-target complex **(B2)** and intracellular degradation **(B3)**. Characteristics of both elimination routes are presented in Table 2.

Table 2. Characteristics of elimination pathways of monoclonal antibody

Characteristic	Proteolic catabolism (Figure 1, panel A)	Target binding (Figure 1, panel B)
Clearance	Slow, dose related	Fast, target related
Location	Skin, muscle, liver, and gut tissue	Tissue (over)expressing the target (e.g., tumor tissue)
Metabolism rate	Linear in therapeutic range	Saturated in therapeutic range

the monoclonal antibody. Therefore, intracellular degradation of monoclonal antibodies targeting antigens at the cell surface is not likely to be body weight dependent. Proteolytic catabolism of monoclonal antibodies targeting soluble targets or targets at the cell surface takes place in the endosomal space, which is estimated to be 0.5% of the total tissue volume [23]. Since total tissue volume is changed in underweight and obese patients, endosomal space—and, thus, the rate of proteolytic catabolism—is likely to be changed too. However, the clinical impact of this change is limited since the absolute rate of proteolytic catabolism is low due to the FcRn receptor.

Obviously, binding to the target at the cell surface is not related to body weight, but mainly to tumor load, target expression levels in tumors versus endogenous expression, and affinity of the monoclonal antibody. Therefore, intracellular degradation of monoclonal antibodies targeting antigens at the cell surface is not likely to be body weight dependent.

Body Weight Versus Fixed Dosing of Monoclonal Antibodies

Although the volume of distribution of monoclonal antibodies is changed in underweight and obese patients compared to normal weight patients, the change in volume of distribution is less than the change in body weight (Table 3). As a result, underweight patients will receive a relatively low dose compared to normal weight patients and obese patients will receive a relatively high dose when based on body weight. Interestingly, for fixed dosing, the opposite is true; since absolute volume of distribution is lower in underweight patients, a relatively higher dose will be administered, whereas obese patients will receive a relatively lower dose. This raises the question of whether fixed dosing is worse, equal, or better in terms of interpatient variability than body–size-based dosing for the general population. Obviously, for a normal weight patient both dosing schedules are equal since the fixed dose is usually based on a normal weight patient. Wang et al. [30] investigated the effect of fixed dosing versus body–weight-based dosing using an in silico model. This model used a median body weight of 75.7 kg (range

Table 3. Theoretical blood concentrations of monoclonal antibodies after intravenous bolus administration based on blood volume and body weight

BW (kg)	LBW (kg)	BV (L)	Rel. BW	Rel. LBW	Rel. BV	C_0 after administration of 1 mg/kg (μg/mL)	C_0 after administration of 70 mg (μg/mL)
Male (height 1.80 m, 1 mg/kg)							
50	49.2	5.01	0.71	0.86	0.87	10.0	14.0
70	57.4	5.79	1.00	1.00	1.00	12.1	12.1
140	85.8	8.49	2.00	1.50	1.47	16.5	8.2
Female (height 1.65 m, 1 mg/kg)							
50	42.3	4.4	0.71	0.89	0.90	11.5	16.0
70	47.4	4.8	1.00	1.00	1.00	14.5	14.5
140	65.0	6.5	2.00	1.37	1.35	21.5	10.7

In this table, theoretical blood concentrations of monoclonal antibodies are presented for obese and underweight males and females compared to normal weight patients. In this theoretical example, a monoclonal antibody dose of 1 mg/kg (body weight-based dosing) or 70 mg (fixed dosing) is chosen. The total blood volume is estimated based on lean body weight. Theoretical blood concentrations are calculated and, based on the assumption that directly after the bolus injection of monoclonal antibodies, the administered dose is only distributed over the total blood volume. Lean body weight (LBW) for the male is calculated using the equation LBW = 0.407 × body weight (BW) + 26.7 × height - 19.2 and for the female using the equation LBW = 0.252 × BW + 47.3 × height 48.3. Blood volume (BV) is calculated using the equation BV = 0.095 × LBW + 0.34. Equations are derived from Boer [29]. Theoretical blood concentration directly after intravenous bolus administration is calculated by dividing the administered dose by the calculated BV. Relative to a 70 kg patient (Rel.) BW, Rel. LBW, and Rel. BV are calculated by dividing the specified parameter by the value of that parameter for a 70 kg patient.

Abbreviations: BV, blood volume; BW, body weight; C_0, theoretical blood concentration directly after intravenous bolus administration; LBW, lean body weight; Rel., relative to a 70 kg patient.

38.8–187.2 kg) to estimate the area under the plasma concentration-time curve (AUC) after fixed and body–weight-based dosing of monoclonal antibodies. In population pharmacokinetic calculations, the volume of distribution and clearance are typically corrected for individual body weight by multiplying the parameter by the following:

$$\left(\frac{BW}{BW_m}\right)^{exp} \quad (1)$$

In this formula, BW represents the individual weight and BW_m represents the typical body weight of a normal weight patient. An exponent (*exp*) is used for the effect of body weight, whereas 0 is used for no effect and 1 is used for a linear effect. The exponent is estimated by the population pharmacokinetic model to describe the pharmacokinetic data derived from clinical trials. Wang et al. [30] showed that in the case where an exponent of <0.32 is used in formula 1 to correct for the body weight effect on clearance, fixed dose administration results in less than $\pm 20\%$ difference in AUC between patients with extreme body weight compared to normal body weight. On the other hand, an exponent of >0.68 results in a less than $\pm 20\%$ difference in AUC when body weight-dosing is used. Both dosing approaches showed a maximum of $\pm 100\%$ difference in AUC. Bai et al. [31] confirmed these results and showed that fixed dosing results in reduced interpatient variability in AUC compared to body weight-dosing when an exponent of <0.5 was used in in silico pharmacokinetic models to normalize body weight effect on clearance. Fixed dosing also reduced interpatient variability in maximal plasma concentrations in case an exponent of <0.5 was used to normalize body weight effect on volume of distribution. In conclusion, these data show that, for monoclonal antibodies with modest effects (an exponent of <0.5 used in PopPK models in formula 1) of body weight on the volume of distribution and clearance, fixed dosing can result in reduced interpatient variability compared to body weight dosing.

Justification of Fixed Dosing of Monoclonal Antibodies in Oncology

For monoclonal antibodies, effects of body weight on the volume of distribution and clearance are usually described in the scientific discussion that is part of the public assessment reports of the European Medicines Agency (EMA). However, this is often based on limited data from phase I and II studies and sparingly described. More information can be gained from publications describing, for example, modeling of pharmacokinetic data in the population (PopPK model). In Table 1, we summarized the effects of body weight on the volume of distribution and clearance of monoclonal antibodies in oncology and proposed a fixed dose for most of these drugs based on pharmacokinetics. Of the 16 monoclonal antibodies in oncology, 4 are already approved as fixed dose therapy (catumaxomab, obinutuzumab, ofatumumab, and pertuzumab). Recently, the FDA modified the dosage regimen for nivolumab [32]. The originally approved recommended dosage regimens of 3 mg/kg was modified to 240 mg for all patients. The approval was based on population pharmacokinetics analyses and dose/exposure-response analyses, and the FDA concluded that exposure was comparable in both regimens and that dose/exposure response relationships appear to be relatively flat.

As described above, when minimal effects (exponent of <0.5 used in PopPK models in formula 1) of body weight are observed on the volume of distribution and clearance, fixed dosing results in decreased interpatient variability compared to body weight dosing and is thus advised. Therefore, we advise fixed dosing for cetuximab and bevacizumab because minimal effects of body weight on the volume of distribution and clearance are observed [33–38], and thus, a fixed dose strategy is likely to perform better in terms of reduction of

inter-patient variability than the currently registered body weight-based dosing.

When strong effects of body weight are observed (an exponent of >0.68 in formula 1), body weight-based dosing results in lower interpatient variability than fixed dosing [30]. However, for monoclonal antibodies with a wide therapeutic range, fixed dosing can still be considered for practical reasons since a maximum of $\pm 100\%$ difference in AUC is to be expected compared to a mean AUC of the registered body-weight dosing [30]. This is true for most monoclonal antibodies in oncology and justifies fixed dosing in this respect. Proposed fixed dosing schemes for each drug are summarized in Table 1 and will be discussed here.

Monoclonal antibodies targeting CD20 like obinutuzumab and ofatumumab are already approved at a fixed dose. Although rituximab is approved at a fixed dose in rheumathology, this monoclonal antibody is dosed based on BSA in oncology. Effects of body weight on clearance and effects on the volume of distribution seem to be substantial (exponent 1.02, 95% confidence interval [CI]: 0.54–1.64; exponent 0.73, 95% CI: 0.45–1.05, respectively) [39]. Despite the substantial effects of body weight on the pharmacokinetic parameters, Wang et al. [30] showed that distribution of AUCs and maximal plasma concentrations of individuals (40–140 kg) were similar between BSA-based and fixed dosing. Moreover, recently subcutaneous administration of rituximab in oncology is approved at a fixed dose after studies showing similar exposure and variability after intravenous administration of 500 mg/m^2 or subcutaneous administration of 1,600 mg [40]. The differences in administration routes and total doses make comparison between fixed and BSA-based dosing incomplete, but it supports fixed dosing. Taken into account the therapeutic window, the experience with fixed dosing in rheumatology and the fixed dosing after subcutaneous administration in oncology, fixed dose of intravenously administered rituximab for oncological indications seems reasonable. Based on similar exposure after fixed and BSA-based dosing, a fixed dose based on single vial content seems justified.

Like for rituximab, the HER2 binding antibody trastuzumab has recently been approved for subcutaneous administration in a fixed dose. For intravenous administration, the effects of body weight on the volume of distribution were limited (exponent 0.556; 95% CI: 0.211–0.824), but the effects on clearance appeared substantial (exponent 1.07; 95% CI: 0.889–1.25) [41, 42]. Interestingly, a more recent PopPK model based on a larger dataset showed that the most important covariate for clearance was the number of metastatic sites and not body weight. However, both covariates were considered not clinically relevant in comparison with the large interpatient variability of clearance, and the effects of body weight on clearance were not even taken into account in the final model [41]. At first, antitumor activity of trastuzumab was evaluated at a fixed dose of 100 mg; however, further dose escalation was tested at a milligram per kilogram dosing schedule [11–13]. According to the EMA report, PK parameters were roughly similar from phase I to III, although direct comparisons were difficult due to the change in dosing strategy from fixed to body-weight adjusted doses [43]. More recently, Wang et al. [30] showed that the distribution of AUCs and maximal plasma concentrations of individuals (40–140 kg) were similar between body weight-based and fixed dosing. Taking together, fixed dosing of trastuzumab is advised.

For the PD-1 binding antibody nivolumab, the effects of body weight are substantial (exponent for volume of distribution: 0.580; exponent for clearance: 0.707), but the therapeutic window is wide. Doses of 1–10 mg/kg are equally effective [44], underlying the appropriateness of fixed dosing of nivolumab. This is also reflected in the recent modification of the approved recommended dose by the FDA to a fixed dose of 240 mg for every patient and the multiple ongoing clinical trials with a fixed dose [32, 45–47]. Furthermore, a recently published PopPK model showed a flat dose-response relationship and a similar benefit-risk profile for fixed dosing and body weight-based dosing [48]. Volume of distribution of the other approved PD-1 binding antibody pembrolizumab is minimally affected by body weight, and the effects of body weight on clearance were limited. The wide therapeutic window supports fixed dosing, especially since simulated dose-response data indicate that 1 mg/kg is sufficient for clinical efficacy [49]. A recent evaluation of dosing strategies of pembrolizumab is published by Freshwater et al. [50]. Their PopPK model shows that exposure after body weight-based dosing and fixed dosing (2 mg/kg and 200 mg) is similarly distributed over the population. Moreover, minimal plasma exposure after fixed dosing is within the range of previously reported plasma exposure with near maximal efficacy [50]. The appropriateness is also reflected in the multiple ongoing clinical trials with a fixed dose [51, 52].

For the CTLA-4 binding antibody ipilimumab, the effects of body weight are based on data from two phase II studies, with a total of 420 patients. The effect of body weight on clearance in the model is substantial (exponent: 0.642), although the 95% CI is wide (95% CI: 0.423–0.819). Thereby, for ipilimumab, a dose-response relation and a dose-toxicity relation are observed [53, 54]. The response in patients treated with 10 mg/kg was better than patients treated with 0.1 or 3 mg/kg [53]. Overall survival was 15.7 (95% CI: 11.6–17.8) and 11.5 (95% CI: 9.9–13.3) months for the 10 and 3 mg/kg group, respectively [54]. However, more dose-limiting toxicities were observed at higher dose levels. A dose of 10 mg/kg was associated with higher rates of treatment-related grade 3–5 adverse effects (34.3% vs. 18.5% for the 3 mg/kg group) and grade 3–5 immune-mediated adverse reactions (33.5% vs.17.4% for the 3 mg/kg group) [54]. Moreover, the higher dose led more often to treatment discontinuation (26.1% vs. 16.0%). Overall, 10 mg/kg seems tolerable after multiple doses and provides slightly increased survival compared to 3 mg/kg, but dose-limiting toxicities and treatment discontinuation is observed among a quarter of all patients. Response rates do not justify treatment at 0.1 mg/kg, which might be due to plasma concentrations being below a minimal effective concentration for sufficient target inhibition [53–55]. Based on the therapeutic window, fixed dosing is applicable, when multiple fixed doses are used for different weight ranges. As described in Table 1, for ipilimumab, three body weight cohorts can be made, with a fixed dose (based on commercially available vials) for each cohort. For example, all patients between 60 and 100 kg will receive 250 mg, resulting in individual doses of 2.5–4.2 mg/kg (registered dose 3 mg/kg).

Table 4. Overview of savings after fixed dosing of monoclonal antibodies at our hospital

Generic name	Fixed dosing scheme used	Period	Number of preparations of infusion	Median body weight used for dose calculation of preparations (range)	Vial content	Number of vials saved by fixed dosing compared to body weight-based dosing	Costs saved (€)[b]
Ipilimumab	Administered dose rounded to vial content	August 2014–November 2015	315	81.5 kg (55.0–126.0 kg)	50 mg	357	1,608,285
	250 mg (60–100 kg) Administered dose rounded to vial content (<60 kg, >100 kg)	November 2015–November 2016	65	76.9 kg (50.1–150.0 kg)	50 mg	10	45,050
Nivolumab	240 mg (60–100 kg) Administered dose rounded to vial content (<60 kg, >100 kg)	August 2015–November 2016	1,592	81.0 kg (44.1–137.7 kg)	40 mg 100 mg	1,709 484 more vials used by fixed dosing[a]	301,596
Pembrolizumab	Administered dose rounded to vial content	October 2015–November 2016	984	80.3 kg (51.7–130.4 kg)	50 mg	499	972,052
Ipilimumab + nivolumab	Ipilimumab 150 mg + nivolumab 40 mg (50–67 kg) Ipilimumab 200 mg + nivolumab 80 mg (67–83 kg) Ipilimumab 250 mg + nivolumab 100 mg (83–100 kg) Ipilimumab 300 mg + nivolumab 120 mg (100–120 kg)	July 2015–November 2016	36	79.9 kg (54.3–93.0 kg)	Ipilimumab: 50 mg Nivolumab: 40 mg 100 mg	20 2 more vials used by fixed dosing[a] 4	94,935
							Total: 3,021,918

Data represent the number of preparations of infusion made for the monoclonal antibodies ipilimumab, nivolumab, and pembrolizumab at the Pharmacy Department of the Antoni van Leeuwenhoek, a comprehensive cancer center, up to November 2016. For each preparation of infusion, we calculated the number of vials used based on our fixed dose regimen and the theoretical number of vials needed based on the registered dose. For example, a fixed dose of 240 mg nivolumab for a patient with a body weight of 90 kg was prepared using one vial of 40 mg and two vials of 100 mg. Based on the registered dose, two vials of 40 mg and two vials of 100 mg would have been used. In this example, usage of one vial of 40 mg was saved by our fixed dosing strategy.

[a]For nivolumab, fixed dosing can lead to a shift of usage of 40 mg vials to 100 mg vials or vice versa. For example, a fixed dose of 240 mg nivolumab for a patient with a body weight of 60 kg was prepared using one vial of 40 mg and two vials of 100 mg. Based on the registered dose, two vials of 40 mg and one vials of 100 mg would have been used. In this example, one vial of 40 mg was saved; however, one vial of 100 mg more was used. At population level, the cost reduction by saving vials exceeds the costs of the extra vials used. We corrected the calculated costs saved for the extra vials used.

[b]Costs saved are calculated by multiplying the number of vials saved by the price of a vial. For nivolumab, costs of extra vials used are extracted from the savings. Prices of the vials are based on list prices in The Netherlands.

The effects of body weight on pharmacokinetics of the epidermal growth factor receptor (EGFR) binding antibody panitumumab are described in a PopPK model based on data of 14 clinical studies. The effects of body weight on clearance were minimal (exponent <0.5), and the effects on the volume of distribution were limited (exponent 0.526, 95% CI: 0.415–0.632). As a result, individual variation in exposure will be limited (around $+/-$ 20%) at fixed dosing [30]. Given the therapeutic window and the limited effects of body weight on individual variation in exposure, fixed dosing of panitumumab can be employed.

For the vascular endothelial growth factor 2 (VEGF2) binding monoclonal antibody ramucirumab, no PopPK model has been reported, although a PopPK model has been described in the EMA report [56]. Unfortunately, details about the model have not been shared. However, body weight (range 30–139 kg) was tested as a covariate in the described model and not included in the final model since it did not reduce interpatient variability. Pharmacokinetic data from phase I studies show a nonlinear profile from 2–8 mg/kg and a linear profile from 8–13 mg/kg. Based on the absence of detailed PopPK data and the absence of efficacy data of doses lower than 8 mg/kg, data on the feasibility of fixed dosing of ramucirumab are lacking. Therefore, although fixed dosing seems feasible, it cannot yet be advised.

Cost Reduction by Fixed Dosing of Monoclonal Antibodies in Oncology

Monoclonal antibodies are expensive drugs and have a high impact on the health care budget. Therefore, reduction in spillage will result in decreased costs of these drugs. Fixed dosing can help in reducing spillage since (a) the complete content of a vial can be used for preparation and (b) prepared infusions can be used for other patients when treatment is canceled at the last moment. However, costs can be further reduced by fixed dosing since patients with a body weight above average are relatively overdosed at a body weight-based schedule (see section Effect of Body Weight on Elimination and Distribution of Monoclonal Antibodies and Table 3). At our hospital, a comprehensive cancer center, we already implemented a fixed dose for immunotherapeutic monoclonal antibodies (ipilimumab, nivolumab, and pembrolizumab) for standard care. We analyzed the number of preparations of infusion made for these monoclonal antibodies at the Pharmacy Department up to November 2016 (Table 4). For each preparation of infusion, we compared the number of vials used in our fixed dose regimen and the theoretical number of vials needed based on the registered dose. For example, a fixed dose of 240 mg nivolumab for a patient with a body weight of 90 kg was prepared using one vial of 40 mg and two vials of 100 mg. Based on the registered dose, two vials of 40 mg and two vials of 100 mg would have been used. In this example, usage of one vial of 40 mg was saved by our fixed dosing strategy. With the fixed dosing strategy for these three immunotherapeutic monoclonal antibodies, we saved over €3 million at population level. This shows that fixed dosing can reduce costs of health care, especially when pooling of preparations is not possible (which is often the case in smaller hospitals).

Interpatient variation in exposure is comparable after body weight, and fixed dosing and most monoclonal antibodies show relatively flat dose-response relationships. For monoclonal antibodies, this results in wide therapeutic windows and no reduced clinical efficacy after fixed dosing.

Future Perspective

At the moment, the rationale for fixed dosing of monoclonal antibodies is gaining recognition, and fixed dosing of recently developed monoclonal antibodies is often under the attention of the manufacturer [45, 46, 48, 50–52]. However, for earlier developed monoclonal antibodies, fixed dosing has not extensively been investigated. Still, for almost all monoclonal antibodies used in oncology, a strong rationale for fixed dosing exists based on pharmacokinetic and pharmacodynamics data. Therefore, we think that evidence for efficacy and safety of a fixed dose will not be coming—and needed—from extensive clinical comparability studies. We believe that nonclinical studies will become most important. This concept has already been proven by the case of nivolumab, for which the FDA approved fixed dosing based on population pharmacokinetics analyses and dose/exposure-response analyses [32]. Therefore, we think that in the future, further rationale for fixed dosing is proven by PopPK analyses rather than clinical randomized studies.

Conclusion

Based on pharmacokinetic parameters of monoclonal antibodies, there is a rationale for fixed dosing of these drugs in oncology. The currently available knowledge of elimination of monoclonal antibodies combined with the publicly available data from clinical trials and extensive PopPK modeling justifies fixed dosing. Interpatient variation in exposure is comparable after body weight, and fixed dosing and most monoclonal antibodies show relatively flat dose-response relationships. For monoclonal antibodies, this results in wide therapeutic windows and no reduced clinical efficacy after fixed dosing. Therefore, we believe that fixed dosing at a well-selected dose can increase medication safety and help in reduction of costs of health care without the loss of efficacy or safety margins.

Author Contributions

Conception/design: Jeroen J. M. A. Hendrikx, Jan H. M. Schellens, John B. A. G. Haanen, Emile E. Voest, Alwin D. R. Huitema, Jos H. Beijnen
Collection and/or assembly of data: Jeroen J. M. A. Hendrikx, Alwin D. R. Huitema, Jos H. Beijnen
Data analysis and interpretation: Jeroen J. M. A. Hendrikx, Jan H. M. Schellens, John B. A. G. Haanen, Emile E. Voest, Alwin D. R. Huitema Jos H. Beijnen
Manuscript writing: Jeroen J. M. A. Hendrikx, Jan Schellens, John B. A. G. Haanen, Emile E. Voest, Alwin D. R. Huitema, Jos H. Beijnen
Final approval of manuscript: Jeroen J. M. A. Hendrikx, Jan H.M. Schellens, John B. A. G. Haanen, Emile E. Voest, Alwin D. R. Huitema, Jos H. Beijnen

Disclosures

The authors indicated no financial relationships.

References

1. Sawyer M, MJ Ratain. Body surface area as a determinant of pharmacokinetics and drug dosing. Invest New Drugs 2001;19:171–177.

2. Freireich EJ, Gehan EA, Rall DP et al. Quantitative comparison of toxicity of anticancer agents in mouse, rat, hamster, dog, monkey, and man. Cancer Chemother Rep 1966;50:219–244.

3. Pinkel D. The use of body surface area as a criterion of drug dosage in cancer chemotherapy. Cancer Res 1958;18:853–856.

4. Crawford JD, Terry ME, Rourke GM. Simplification of drug dosage calculation by application of the surface area principle. Pediatrics 1950;5:783–790.

5. Mathijssen RH, de Jong FA, Loos WJ et al. Flat-fixed dosing versus body surface area based dosing of anticancer drugs in adults: Does it make a difference? ***The Oncologist*** 2007;12:913–923.

6. McLeay SC, Morrish GA, Kirkpatrick CM et al. The relationship between drug clearance and body size: Systematic review and meta-analysis of the literature published from 2000 to 2007. Clin Pharmacokinet 2012;51:319–330.

7. Grillo-Lòpez AJ, White CA, Varns C et al. Overview of the clinical development of rituximab: First monoclonal antibody approved for the treatment of lymphoma. Semin Oncol 1999;26:66–73.

8. Maloney DG, Liles TM, Czerwinski DK et al. Phase i clinical trial using escalating single-dose infusion of chimeric anti-CD20 monoclonal antibody (IDEC-C2B8) in patients with recurrent b-cell lymphoma. Blood 1994;84:2457–2466.

9. Maloney DG, Grillo-Lòpez AJ, Bodkin DJ et al. IDEC-C2B8: Results of a phase I multiple-dose trial in patients with relapsed non-hodgkin's lymphoma. J Clin Oncol 1997;15:3266–3274.

10. Maloney DG, Grillo-Lòpez AJ, White CA et al. IDEC-C2B8 (rituximab) anti-CD20 monoclonal antibody therapy in patients with relapsed low-grade non-hodgkin's lymphoma. Blood 1997;90:2188–2195.

11. Baselga J, Tripathy D, Mendelsohn J et al. Phase II study of weekly intravenous recombinant humanized anti-p185HER2 monoclonal antibody in patients with HER2/neu-overexpressing metastatic breast cancer. J Clin Oncol 1996;14:737–744.

12. Pegram MD, Lipton A, Hayes DF et al. Phase II study of receptor-enhanced chemosensitivity using recombinant humanized anti-p185HER2/neu monoclonal antibody plus cisplatin in patients with HER2/neu-overexpressing metastatic breast cancer refractory to chemotherapy treatment. J Clin Oncol 1998; 16:2659–2671.

13. Tokuda Y, Watanabe T, Omuro Y et al. Dose escalation and pharmacokinetic study of a humanized anti-HER2 monoclonal antibody in patients with HER2/neu-overexpressing metastatic breast cancer. Br J Cancer 1999;81:1419–1425.

14. Pouliquen AL, Escalup L, Jourdan N et al. Dose standardisation of anticancer drugs. Int J Clin Pharm 2011;33:221–228.

15. Chatelut E, White-Koning ML, Mathijssen RH et al. Dose banding as an alternative to body surface area-based dosing of chemotherapeutic agents. Br J Cancer 2012;107:1100–1106.

16. Keizer RJ, Huitema AD, Schellens JH et al. Clinical pharmacokinetics of therapeutic monoclonal antibodies. Clin Pharmacokinet 2010;49:493–507.

17. Scott AM, Allison JP, Wolchok JD. Monoclonal antibodies in cancer therapy. Cancer Immun 2012; 12:14.

18. Hamizi S, Freyer G, Bakrin N et al. Subcutaneous trastuzumab: Development of a new formulation for treatment of HER2-positive early breast cancer. Onco Targets Ther 2013;6:89–94.

19. European medicines agency (ema): Removab - epar product information. Available at http://www.ema.europa.eu. Accessed March 15, 2016.

20. European medicines agency (ema): Removab - epar scientific discussion. Available at http://www.ema.europa.eu. Accessed March 15, 2016.

21. Shpilberg O, Jackisch C. Subcutaneous administration of rituximab (MabThera) and trastuzumab (Herceptin) using hyaluronidase. Br J Cancer 2013; 109:1556–1561.

22. Mould DR, Green B. Pharmacokinetics and pharmacodynamics of monoclonal antibodies: Concepts and lessons for drug development. BioDrugs 2010;24:23–39.

23. Garg A, Balthasar JP. Physiologically-based pharmacokinetic (PBPK) model to predict IgG tissue kinetics in wild-type and FcRn-knockout mice. J Pharmacokinet Pharmacodyn 2007;34:687–709.

24. Bleeker WK, Teeling JL, Hack CE. Accelerated autoantibody clearance by intravenous immunoglobulin therapy: Studies in experimental models to determine the magnitude and time course of the effect. Blood 2001;98:3136–3142.

25. Lammerts van Bueren JJ, Bleeker WK, Bøgh HO et al. Effect of target dynamics on pharmacokinetics of a novel therapeutic antibody against the epidermal growth factor receptor: Implications for the mechanisms of action. Cancer Res 2006;66:7630–7638.

26. Bearden DT, Rodvold KA. Dosage adjustments for antibacterials in obese patients: Applying clinical pharmacokinetics. Clin Pharmacokinet 2000;38:415–426.

27. Hanley MJ, Abernethy DR, Greenblatt DJ. Effect of obesity on the pharmacokinetics of drugs in humans. Clin Pharmacokinet 2010;49:71–87.

28. Lemmens HJ, Bernstein DP, Brodsky JB. Estimating blood volume in obese and morbidly obese patients. Obes Surg 2006;16:773–776.

29. Boer P. Estimated lean body mass as an index for normalization of body fluid volumes in humans. Am J Physiol 1984;247:F632–F636.

30. Wang DD, Zhang S, Zhao H et al. Fixed dosing versus body size-based dosing of monoclonal antibodies in adult clinical trials. J Clin Pharmacol 2009; 49:1012–1024.

31. Bai S, Jorga K, Xin Y et al. A guide to rational dosing of monoclonal antibodies. Clin Pharmacokinet 2012;51:119–135.

32. Modification of the Dosage Regimen for Nivolumab. Available at http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm520871.htm. Accessed March 15, 2016.

33. Lu JF, Bruno R, Eppler S et al. Clinical pharmacokinetics of bevacizumab in patients with solid tumors. Cancer Chemother Pharmacol 2008;62: 779–786.

34. Azzopardi N, Lecomte T, Ternant D et al. Cetuximab pharmacokinetics influences progression-free survival of metastatic colorectal cancer patients. Clin Cancer Res 2011;17:6329–6337.

35. European medicines agency (EMA): Erbitux - epar scientific discussion. Available at http://www.ema.europa.eu. Accessed March 15, 2016.

36. European medicines agency (EMA): Avastin - epar scientific discussion. Available at http://www.ema.europa.eu. Accessed March 15, 2016.

37. European medicines agency (EMA): Avastin - epar product information. Available at http://www.ema.europa.eu. Accessed March 15, 2016.

38. European medicines agency (EMA): Erbitux - epar product information. Available at http://www.ema.europa.eu. Accessed March 15, 2016.

39. Ng CM, Bruno R, Combs D et al. Population pharmacokinetics of rituximab (anti-CD20 monoclonal antibody) in rheumatoid arthritis patients during a phase ii clinical trial. J Clin Pharmacol 2005;45: 792–801.

40. European medicines agency (EMA): Mabthera - epar scientific discussion. Available at http://www.ema.europa.eu. Accessed March 15, 2016.

41. Bruno R, Washington CB, Lu JF et al. Population pharmacokinetics of trastuzumab in patients with HER2+ metastatic breast cancer. Cancer Chemother Pharmacol 2005;56:361–369.

42. Cosson VF, Ng VW, Lehle M et al. Population pharmacokinetics and exposure-response analyses of trastuzumab in patients with advanced gastric or gastroesophageal junction cancer. Cancer Chemother Pharmacol 2014;73:737–747.

43. European medicines agency (EMA): Herceptin - epar scientific discussion. Available at http://www.ema.europa.eu. Accessed March 15, 2016.

44. European medicines agency (EMA): Opdivo - epar scientific discussion. Available at http://www.ema.europa.eu. Accessed March 15, 2016.

45. NCT02713867. A dose frequency optimization, trial of nivolumab 240 mg every 2 weeks vs nivolumab 480 mg every 4 weeks in subjects with advanced or metastatic non-small cell lung cancer who received up to 12 months of nivolumab at 3 mg/kg or 240 mg every 2 weeks (checkmate 384). Available at https://clinicaltrials.gov/ct2/show/record/NCT02713867?term=NCT02713867&rank=1. Accessed March 15, 2016.

46. NCT02046733. Small cell lung carcinoma trial with nivolumab and ipilimumab in limited disease. Available at https://clinicaltrials.gov/ct2/show/NCT02046733?term=NCT02046733&rank=1. Accessed March 15, 2016.

47. NCT02754726. Combination therapy for patients with untreated metastatic pancreatic ductal adenocarcinoma. Available at https://clinicaltrials.gov/ct2/show/NCT02754726?term=NCT02754726&rank=1. Accessed March 15, 2016.

48. Zhao X, Suryawanshi S, Hruska M et al. Assessment of nivolumab benefit-risk profile of a 240-mg flat dose relative to a 3-mg/kg dosing regimen in patients with advanced tumors. Ann Oncol 2017 [Epub ahead of print].

49. European medicines agency (EMA): Keytruda - epar scientific discussion. Available at http://www.ema.europa.eu. Accessed March 15, 2016.

50. Freshwater T, Kondic A, Ahamadi M et al. Evaluation of dosing strategy for pembrolizumab for oncology indications. J Immunother Cancer 2017;5:43.

51. NCT02129556. Anti-pd-1 monoclonal antibody in advanced, trastuzumab-resistant, her2-positive breast cancer (panacea). Available at https://clinicaltrials.gov/ct2/show/NCT02129556?term=NCT02129556&rank=1. Accessed March 15, 2016.

52. NCT02636725. Axitinib and pembrolizumab in subjects with advanced alveolar soft part sarcoma and other soft tissue sarcomas. Available at https://clinicaltrials.gov/ct2/show/NCT02636725?term=pembrolizumab+flat+dose&rank=3. Accessed March 15, 2016.

53. Wolchok JD, Neyns B, Linette G et al. Ipilimumab monotherapy in patients with pretreated advanced melanoma: A randomised, double-blind, multicentre, phase 2, dose-ranging study. Lancet Oncol 2010;11:155–164.

54. Ascierto PA, M Del Vecchio, Robert C et al. Overall survival (os) and safety results from a phase 3 trial of ipilimumab (ipi) at 3 mg/kg vs 10 mg/kg in patients with metastatic melanoma (mel). Ann Oncol 2016;27:1106O.

55. Weber JS, O'Day S, Urba W et al. Phase I/II study of ipilimumab for patients with metastatic melanoma. J Clin Oncol 2008;26:5950–5956.

56. European medicines agency (EMA): Cyramza - epar scientific discussion. 2015. Available at http://www.ema.europa.eu. Accessed March 15, 2016.

57. Feng Y, Masson E, Dai D et al. Model-based clinical pharmacology profiling of ipilimumab in patients with advanced melanoma. Br J Clin Pharmacol 2014; 78:106–117.

58. European medicines agency (EMA): Yervoy - epar product information. Available at http://www.ema.europa.eu. Accessed March 15, 2016.

59. European medicines agency (EMA): Yervoy - epar scientific discussion. Available at http://www.ema.europa.eu. Accessed March 15, 2016.

60. European medicines agency (EMA): Opdivo - epar product information. Available at http://www.ema.europa.eu. Accessed March 15, 2016.

61. Gibiansky E, Gibiansky L, Carlile DJ et al. Population pharmacokinetics of obinutuzumab (ga101) in chronic lymphocytic leukemia (cll) and non-hodgkin's lymphoma and exposure-response in cll. CPT Pharmacometrics Syst Pharmacol 2014;3:e144.

62. European medicines agency (EMA): Gazyvaro - epar scientific discussion. Available at http://www.ema.europa.eu. Accessed March 15, 2016.

63. European medicines agency (EMA): Gazyvaro - epar product information. Available at http://www.ema.europa.eu. Accessed March 15, 2016.

64. Struemper H, Sale M, Patel BR et al. Population pharmacokinetics of ofatumumab in patients with chronic lymphocytic leukemia, follicular lymphoma, and rheumatoid arthritis. J Clin Pharmacol 2014;54: 818–827.

65. European medicines agency (EMA): Arzerra - epar scientific discussion. Available at http://www.ema.europa.eu. Accessed March 15, 2016.

66. European medicines agency (EMA): Arzerra - epar product information. Available at http://www.ema.europa.eu. Accessed March 15, 2016.

67. Ma P, Yang BB, Wang YM et al. Population pharmacokinetic analysis of panitumumab in patients with advanced solid tumors. J Clin Pharmacol 2009; 49:1142–1156.

68. European medicines agency (EMA): Vectibix - epar scientific discussion. Available at http://www.ema.europa.eu. Accessed March 15, 2016.

69. European medicines agency (EMA): Vectibix - epar product information. Available at http://www.ema.europa.eu. Accessed March 15, 2016.

70. European medicines agency (EMA): Keytruda - epar product information. Available at http://www.ema.europa.eu. Accessed March 15, 2016.

71. Ahamadi M, Freshwater T, Prohn M et al. Model-based characterization of the pharmacokinetics of pembrolizumab: A humanized anti-PD-1 monoclonal antibody in advanced solid tumors. CPT Pharmacometrics Syst Pharmacol 2017;6:49–57.

72. Ng CM, Lum BL, Gimenez V et al. Rationale for fixed dosing of pertuzumab in cancer patients based on population pharmacokinetic analysis. Pharm Res 2006;23:1275–1284.

73. Garg A, Quartino A, Li J et al. Population pharmacokinetic and covariate analysis of pertuzumab, a HER2-targeted monoclonal antibody, and evaluation of a fixed, non-weight-based dose in patients with a variety of solid tumors. Cancer Chemother Pharmacol 2014;74:819–829.

74. European medicines agency (EMA): Perjeta - epar scientific discussion. Available at http://www.ema.europa.eu. Accessed March 15, 2016.

75. European medicines agency (EMA): Perjeta - epar product information. Available at http://www.ema.europa.eu. Accessed March 15, 2016.

76. European medicines agency (EMA): Cyramza - epar product information. Available at http://www.ema.europa.eu. Accessed March 15, 2016.

77. European medicines agency (EMA): Mabthera - epar product information. Available at http://www.ema.europa.eu. Accessed March 15, 2016.

78. European medicines agency (EMA): Herceptin - epar product information. Available at http://www.ema.europa.eu. Accessed March 15, 2016.