

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMGEN INC.,
Petitioner,

v.

BRISTOL-MYERS SQUIBB COMPANY
Patent Owner.

Case No. IPR2025-00602
Patent No. 10,174,113

DECLARATION OF DR. DHAVAL K. SHAH, PH.D.

Amgen Exhibit 1029 Amgen v. BMS

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I. INTRODUCTION

1. I, Dhaval K. Shah, Ph.D., have been retained by counsel to render certain opinions as an expert witness, for the above-referenced inter partes review (“IPR”) proceeding regarding U.S. Patent No. 10,174,113 (“the ’113 patent”).

This declaration sets forth the opinions I have formed in this IPR and provides the bases and reasons for those opinions.

2. This declaration is based on information currently available to me. I declare that I have personal knowledge of the facts set forth in this declaration and, if called to testify as a witness, could and would do so competently.

3. I am being compensated at my usual consulting rate, plus actual expenses, for my work on this matter. My compensation is in no way dependent upon my opinions or testimony or the outcome of this proceeding.

II. QUALIFICATIONS

4. I am an expert in clinical pharmacology and pharmacokinetic/pharmacodynamic (PK/PD) modeling and simulation. I am a Professor of Pharmaceutical Sciences in the School of Pharmacy and Pharmaceutical Sciences of the University at Buffalo, State University of New York.

5. I obtained a Bachelor of Pharmacy degree from the K.B. Institute of Pharmaceutical Education and Research in Gujarat, India, in 2002, and a Master of

Science degree in Pharmaceutics from the Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research in Punjab, India, in 2003.

6. In 2010, I completed my Doctor of Philosophy degree in Pharmaceutical Sciences at the School of Pharmacy and Pharmaceutical Sciences of the University at Buffalo, State University of New York. The title of my thesis was *Pharmacokinetic Strategy to Improve the Safety and Efficacy of Intraperitoneal Chemotherapy*.

7. From 2010-2013, I was a Senior Scientist and, later, a Principal Scientist at Pfizer, focusing on translational research and pharmacokinetic/pharmacodynamic (PK/PD) modeling and simulation.

8. In September 2013, I joined the faculty of the School of Pharmacy and Pharmaceutical Sciences of the University at Buffalo, State University of New York as an Assistant Professor (2013-2018), and subsequently have been promoted to Associate Professor (2018-2024) and Professor (2024-present).

9. The focus of my research has been discovery and development of novel antibody-based therapeutics with the help of PK/PD modeling and simulation principles.

10. Over the course of my career, I have published over 105 scientific articles and a number of book chapters in various highly regarded scientific

journals on topics including pharmacokinetic/pharmacodynamic modeling, drug development, and clinical pharmacology.

11. I have received a number of awards and other recognition for my work. For example, in 2009, I received the American Association of Pharmaceutical Scientists (AAPS) Outstanding Manuscript in Modeling and Simulation Award for my article entitled “Use of an anti-vascular endothelial growth factor antibody in a pharmacokinetic strategy to increase the efficacy of intraperitoneal chemotherapy.” *J Pharmacol Exp Ther.* 2009 May; 329(2):580-91. In 2014, I received a second AAPS Outstanding Manuscript in Modeling and Simulation Award for an article entitled “Bench to bedside translation of antibody drug conjugates using a multiscale mechanistic PK/PD model: a case study with brentuximab-vedotin.” *J Pharmacokinet. Pharmacodyn.* 2012 Dec;39(6): 643-659.

12. I have also presented or served as a panelist at numerous meetings, symposiums, and conferences on topics including PK/PD modeling and drug development.

13. I have been a member of the editorial advisory boards of the *British Journal of Clinical Pharmacology*, the *Journal of Pharmacokinetics and Pharmacodynamics*, and the *American Association of Pharmaceutical Scientists (AAPS) Journal* Theme issue titled “Systems Pharmacokinetics Models for Antibody-Drug Conjugates.”

14. I have received numerous grants and other funding to support my research as a principal investigator, co-principal investigator, or co-investigator, including grants from the National Institute of Cancer, the National Institute of Allergy and Infectious Diseases, the National Institute of General Medical Sciences the Center for Protein Therapeutics, University at Buffalo, AstraZeneca, and EVQLV and Manhattan Biosolutions (UB-CAT), Oncolinx, Childhood Eye Cancer Trust, and Roche Pharmaceuticals.

15. I have taught a range of courses in the area of drug development and PK/PD principles, including Basic Pharmaceutical Principles in Drug Development, Introduction to Pharmacokinetics and Biopharmaceutics-II, Pharmaceutical Chemistry: The Chemical Basis of Drug Action, and the Department of Pharmaceutical Sciences' Pharmaceutics Seminar. I have also offered lectures on specific topics in courses such as Drug Delivery: Principles and Applications, Pharmaceutical Analysis, Protein Pharmaceuticals, and Advanced Pharmacokinetics, Advanced Pharmacodynamics, and Drug Metabolism and Disposition.

16. An additional account of my work experience, qualifications, and publications is included in my curriculum vitae, which is labeled as EX1030.

III. MATERIALS REVIEWED AND CONSIDERED

17. My findings, as explained below, are based on my years of education, research, experience, and background in the field of tumor immunology and immunotherapy, as well as my investigation and study of relevant materials for this declaration. When developing the opinions set forth in this declaration, I applied the principles and techniques of PK modeling that are generally accepted and used in the field of immunotherapy development. In forming my opinions, I have studied and considered the materials identified in Appendix A.

18. In this declaration, citations are to the original page number (to the extent one exists) or otherwise to the page number added by the exhibit label.

IV. SUMMARY OF OPINIONS

19. The objective of this analysis was to develop a mathematical model that can characterize the clinical pharmacokinetics (PK) of anti-PD1 antibody nivolumab in cancer patients and subsequently use the model to predict the PK of the antibody under different dosing regimens.

20. I have been informed that relevant dates for this analysis are April 28, 2015, which is the earliest claimed priority date of the '113 patent, and April 28, 2014, which is the date one year before. All of my analysis was performed using techniques and data that were available and known to POSAs at least as of April

28, 2014, and would have continued to be known and available as of April 28, 2015.

21. I have been informed and understand that a flat dose of 240 mg nivolumab administered once every two weeks was disclosed as a treatment for melanoma at least as of October 23, 2013. Specifically, I understand that Version 1 of the NCT01968109 clinical trial protocol with the Brief Title “Safety Study of Anti-LAG-3 With and Without Anti-PD-1 in the Treatment of Solid Tumors” and a “Last Update Posted” date of October 23, 2013 (EX1007), discloses “BMS-936558” (a.k.a. nivolumab) “240 mg solution intravenously” “every 2 weeks” for “incurable melanoma.”

22. I was asked to consider whether pharmacokinetic analysis using data and methodologies available by April 28, 2014 would support a conclusion that an injection of a dose of 480 mg of nivolumab every four weeks (or “480 mg Q4W”) would have been expected to have a comparable effect to the known dose of 240 mg of nivolumab every two weeks (or “240 mg Q2W”).

23. After studying this question as detailed below (*see* Section VI), I conclude that a dose of 480 mg of nivolumab every 4 weeks would have been expected to have a comparable effect to the known dose of 240 mg of nivolumab every 2 weeks. This conclusion is supported by at least two results of my study.

24. First, modeling the concentration of nivolumab in the bloodstream for both the 240 mg Q2W and 480 mg Q4W doses shows that both exceed an exposure threshold (defined below in Section VI.D) after reaching steady state,¹ as reflected in Figure 1. This observation suggests that the 480 mg Q4W regimen, like the 240 mg Q2W regimen, exceeded the threshold after reaching steady state.

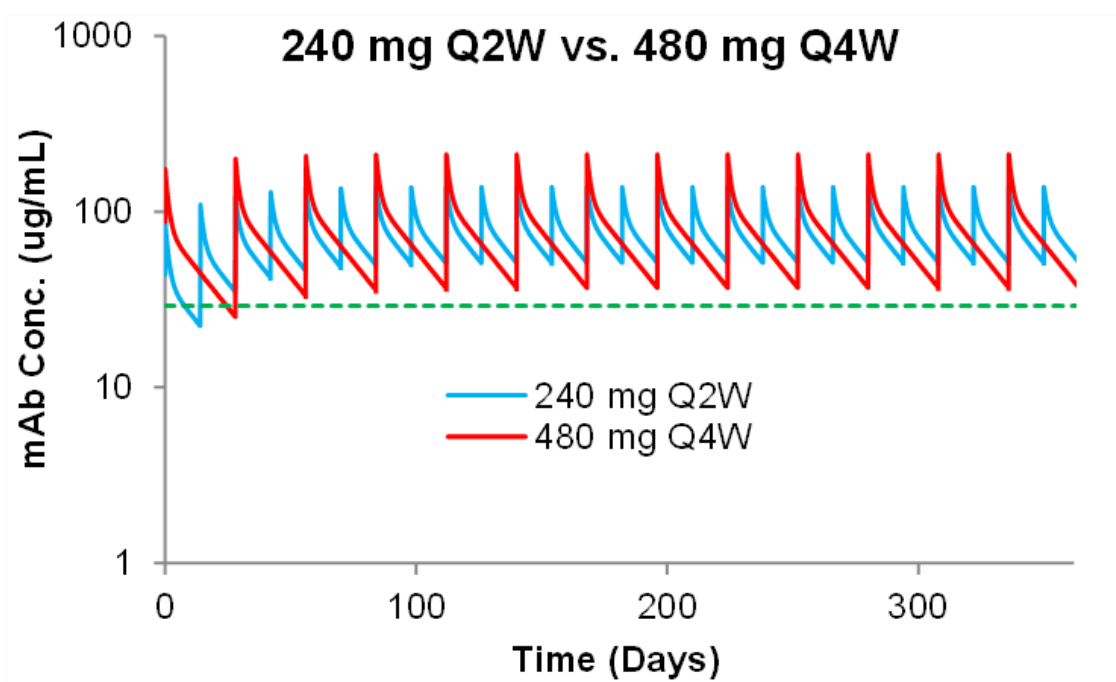


Figure 1: Model simulated PK of nivolumab following intravenous administration of 240 mg dose every 2 weeks and 480 mg dose every 4 weeks. Dotted line represents the exposure threshold (log Y-axis).

¹ Steady state refers to a dynamic equilibrium established in which the amount of drug administered is in equilibrium with the amount eliminated. As shown in Figure 1, there is an initial period during which concentration builds up, after which the steady state is observed.

25. Second, I compared the area under the concentration vs. time curve (AUC) for 4 weeks at the steady-state (AUC_{SS}^{4wk}) for both the dosing regimens (i.e., 240 mg Q2W and 480 mg Q4W) and found that both the regimens yielded almost identical AUC values. The AUC_{SS}^{4wk} for 240 mg Q2W dosing regimen was 2069 $\mu\text{g/mL}\cdot\text{day}$ and AUC_{SS}^{4wk} for 480 mg Q4W dosing regimen was 2069 $\mu\text{g/mL}\cdot\text{day}$. This observation suggests that both the regimens are identical in terms of the exposure of nivolumab they achieve in the systemic circulation.

26. Each of these results independently provides a basis to reasonably expect that the 480 mg Q4W regimen would have exerted the same effect for a patient as the 240 mg Q2W.

27. My methodology and results are set forth in detail below in Section VI. First, I provide a brief introduction to some key principles of pharmacokinetics and the pharmacokinetics of nivolumab in Section V.

V. PHARMACOKINETICS OF NIVOLUMAB

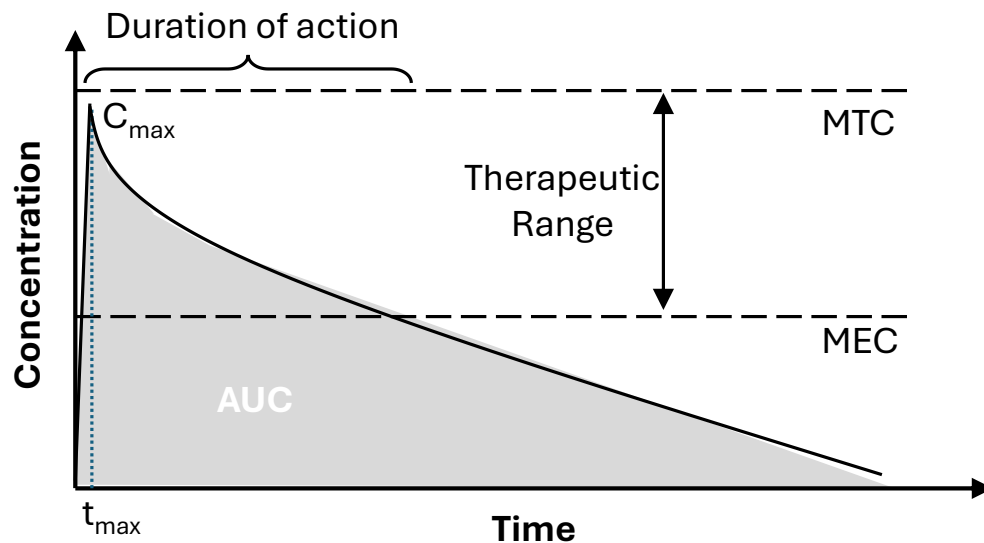
A. Introduction to Pharmacokinetics

28. Pharmacokinetics is the term that describes the absorption, distribution, metabolism, and excretion of drugs, including antibodies such as nivolumab.

29. Drugs, including antibodies such as nivolumab, must be present at their intended target tissue in a sufficient concentration or quantity in order to

produce the intended clinical benefit. The concentration of the drug in blood plasma is frequently used as a proxy for the concentration of the drug at its intended target because the two are typically in dynamic equilibrium and measuring the concentration of a drug in plasma is more readily measured.

30. Clinical pharmacologists describe the “minimum effective concentration,” abbreviated as “MEC,” as the minimum concentration of the drug in plasma for the drug to have its intended clinical effect.



31. After a drug is administered, its concentration in plasma will first rise to “ $C_{\max}$,” which refers to the maximum concentration of the drug after administration. The term “ $t_{\max}$ ” refers to the time it takes for the concentration to reach $C_{\max}$. After reaching $C_{\max}$, the concentration will begin to decrease as the drug is metabolized or eliminated from the body. The term “ $t_{1/2}$ ” (not shown above), which is known as the drug’s half-life, refers to the time it takes for the

drug's concentration to reduce by half. The longer the $t_{1/2}$, the more slowly the drug is metabolized or eliminated from the body. "AUC" refers to the "area under the curve," which is the concentration of the drug integrated over time and is akin to the total overall exposure to the drug.

32. The occurrence and severity of adverse events (side effects) can also be proportional to the concentration of the drug in plasma. The "minimum toxic concentration," abbreviated "MTC" describes the concentration at which a drug produces unwanted side effects.

33. Dosing regimens aim to keep the concentration of a drug above the MEC so it produces the intended clinical benefit but below the MTC so it does not cause numerous or severe side effects. The range of concentrations above the MEC but below the MTC known as the "therapeutic range" or "therapeutic window."

34. For drugs with narrow therapeutic windows, special care must be taken to not exceed the MTC, but to keep the concentration of the drug above the MEC. There is more flexibility in designing dosing regimens for drugs with wide therapeutic windows. Drugs with wide therapeutic windows can be administered using higher doses less frequently which results in greater convenience and compliance. Drugs with higher $t_{1/2}$ values can also be administered less frequently than drugs with shorter $t_{1/2}$ values because the concentration of drugs with higher

$t_{1/2}$ values is maintained above the MEC for longer than drugs with shorter $t_{1/2}$ values.

B. Nivolumab's Known PK Characteristics

35. Nivolumab was known to have a wide therapeutic window at least by April 28, 2014. For example, a 2010 paper by Brahmer discloses a “phase I study [that] sought to determine the safety and tolerability of anti-PD-1 blockade in patients.” EX1009 at p. 3167. Brahmer discloses “[t]hirty-nine patients with advanced metastatic melanoma ... received a single intravenous infusion of anti-PD-1 (MDX-1106) in dose-escalating six-patient cohorts at 0.3, 1, 3, or 10 mg/kg....” *Id.* Brahmer discloses “MDX-1106” is also known as “BMS-936558/ONO-4538” (i.e. nivolumab). *Id.* at p. 3168.

36. Brahmer discloses “MDX-1106 was well-tolerated: no DLTs were observed after one dose.” *Id.* at p. 3169. “DLT” means “[d]ose-limiting toxicity,” which is akin to the MTC I described above. *Id.* at p. 3168. Brahmer also discloses additional PK data that I have used for my analysis, as described below in Section VI.

37. Topalian, a 2012 paper similarly disclosed nivolumab's wide therapeutic window. Topalian discloses administering “1.0, 3.0, or 10.0 mg per kilogram of body weight” of nivolumab. EX1011 at p. 2444. Topalian discloses that “[a] maximum tolerated dose was not defined at the doses tested in this study.”

Id. at p. 2446. And only “[f]ifteen of 296 patients (5%) discontinued treatment owing to treatment-related adverse events.” *Id.* Topalian also discloses that “[a]ntitumor activity was observed at all doses tested.” *Id.* “In patients with melanoma, 26 objective responses were observed at doses ranging from 0.1 to 10.0 mg per kilogram, with response rates ranging from 19 to 41% per dose level” and “[a]t a dose of 3.0 mg per kilogram, objective responses were noted in 7 of 17 patients (41%).” *Id.* at p. 2449.

38. Nivolumab was known to have a linear relationship between the dose administered and the resulting $C_{\max}$ and AUC, by April 28, 2014. For example, Brahmer, published July 1, 2010, discloses “maximum concentration ($C_{\max}$) and AUC directly related to dose” for nivolumab. EX1009 at p. 3171. Topalian, published June 28, 2012, similarly disclosed that the “pharmacokinetics of the antibody were linear, with a dose-proportional increase in the peak concentration and area under the curve.” EX1011 at p. 2449.

39. Nivolumab’s concentration in the blood plasma was also known, prior to April 28, 2014, to be long-lasting, with a half-life of between 12 and 20 days. For example, Brahmer, published July 1, 2010, discloses “[s]tandard pharmacokinetic measurements of MDX-1106 serum concentrations yielded an approximate serum half-life ($t_{1/2}$) of 12 days (0.3-, 1-, or 3-mg/kg dose) to 20 days (10 mg/kg).” EX1009 at p. 3171.

VI. DETAILED DISCUSSION OF ANALYSIS

A. Development of PK Model

40. In order to develop the PK model, I used clinical PK of nivolumab reported by Brahmer in 2010 (EX1009). Brahmer reports the PK of nivolumab after single intravenous infusion at multiple dose levels (i.e., 0.3, 1, 3, and 10 mg/kg). EX1009 at p. 3173. I selected the PK data reported at the highest dose level (i.e., 10 mg/kg) for the model development because Topalian has reported that the PK of nivolumab is linear and dose-proportional. See EX1011 at p. 2449.

41. In order to model the data, I digitized the PK data from the publication using Grab It! Software, which is a Microsoft Excel based application that digitizes graphs or charts to obtain the original data.² Figure 2 below shows the original PK data from Brahmer (left panel; see EX1009 at p. 3173, Fig. 4) and the digitized data (right panel), demonstrating similarity between the reported and digitized PK profiles.

² Grab It! Software was available by April 28, 2014. I note that the webpage associated with the program shows that it was first released June 19, 2003. See Appendix B, CNET, “Grab It XP for Windows,” https://download.cnet.com/grab-it-xp/3000-2053_4-41084.html.

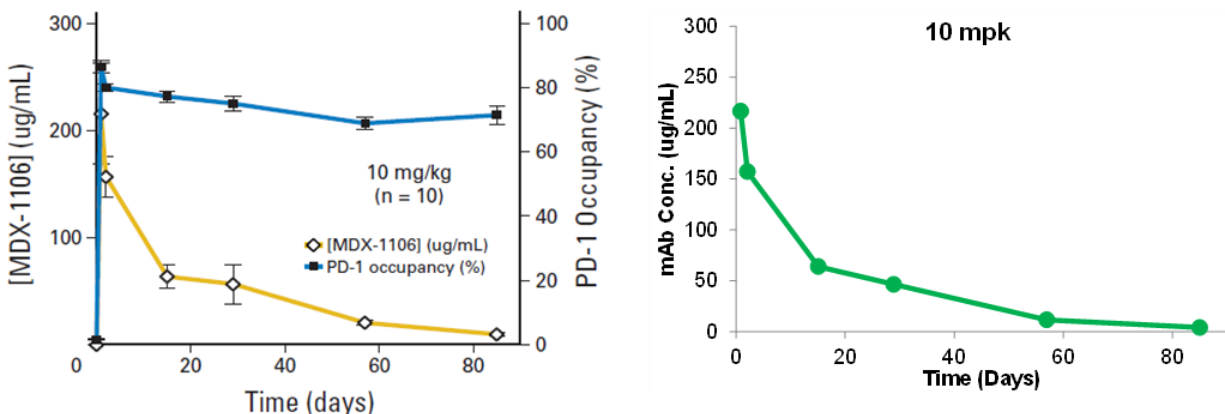


Figure 2: Serum concentrations of nivolumab in cancer patients after intravenous administration of 10 mg/kg dose. The left panel shows PK data reported by Brahmer and right panel shows digitized PK data.

42. I plotted the digitized PK of nivolumab on log Y-axis to assess the nature of its disposition (Figure 3, left panel). I also compared the PK of nivolumab with the clinical PK of four other FDA approved antibodies (Figure 3, right panel) to assess uniqueness of its PK profile.

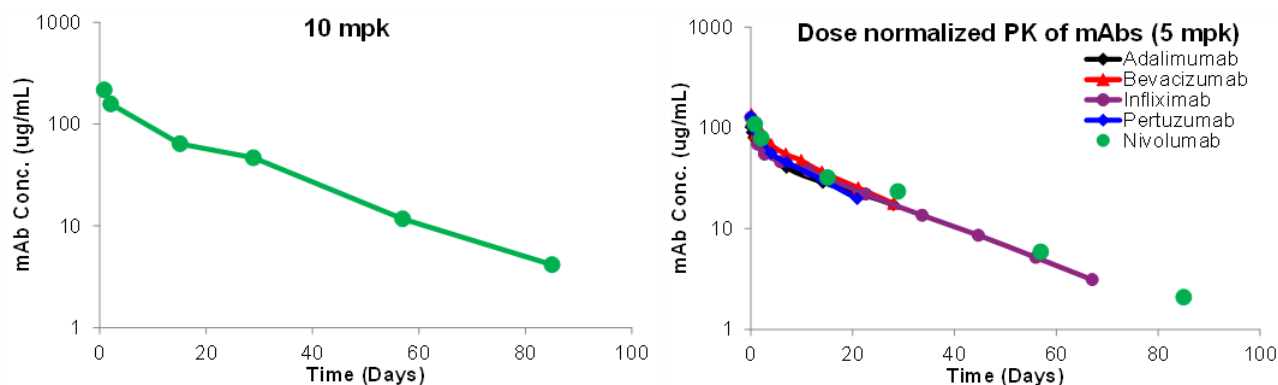


Figure 3: (Left Panel) Clinical PK of nivolumab obtained after intravenous administration of 10 mg/kg dose, plotted on log Y-axis. (Right panel) Clinical PK of nivolumab superimposed over the PK of select FDA approved antibodies following normalization of PK profiles at 5 m/kg dose.

43. As shown in Figure 3, nivolumab displayed a bi-exponential PK profile, which was very similar to the PK of several other FDA approved antibodies. This observation suggests that nivolumab follows the same distribution and elimination pathway as other antibodies, and demonstrates PK behavior that is typical for an antibody.

B. Description of 2-Compartment PK Model

44. In order to develop the PK model for nivolumab, I used a compartmental modeling approach, which is the most widely used approach to capture the systemic PK of antibodies. More specifically, I used a 2-compartment PK model, as this model is physiologically more accurate, was supported by the bi-exponential PK profile of nivolumab in the clinic (Figure 3), and has been commonly used for characterizing the PK of antibodies in the clinic by April 28, 2014. See EX1041 (Dirks); EX1042 (Lobo). For example, Dirks was published in October 2010 and Lobo was published November 2004.

45. Figure 4 below shows a diagram of a 2-compartment PK model, which describes the distribution and elimination of antibody in the human body through two distinct compartments: a central compartment (with volume V_1) and a peripheral compartment (with volume V_2). In this model, the drug is assumed to move between these two compartments, with elimination occurring from the central compartment.

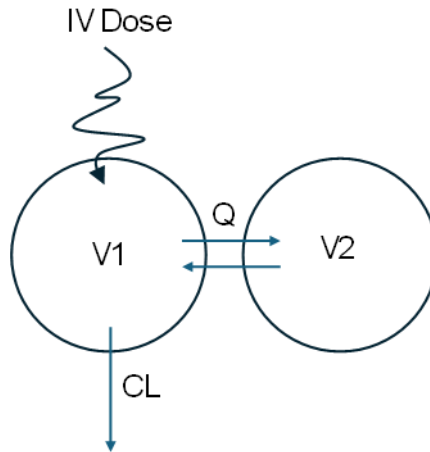


Figure 4: Diagram of a 2-compartment PK model.

46. The 2-compartment PK model is parameterized using 4 parameters. Parameter V_1 is the volume of the central compartment, where the drug is initially distributed, and typically represent blood volume. V_1 is usually expressed in the units of liters (L). Parameter V_2 represents the volume of a second, less accessible, peripheral compartment, where the drug can distribute more slowly. V_2 is usually expressed in the units of liters (L). Drug exchange is assumed to occur between the central and peripheral compartments using the parameter Q , which is known as inter-compartmental distribution clearance, and essentially represent the rate at which the drug is exchanged between the central and peripheral compartments. Q is usually expressed in the units of liters per day (L/day). Parameter CL is also known as clearance, and represent the rate at which the drug is eliminated from the body. CL is expressed in the units of liters per day (L/day). Intravenously administered drug is assumed to be dosed directly within

the central compartment, allowed to distribute to the peripheral compartment, and assumed to eliminate from the body via the clearance process from the central compartment. Below are the differential equations that are used to characterize the PK of antibody via the 2-compartment PK model.

47. Equation 1 for characterizing antibody concentration in the central compartment (C_1) is provided below. The initial condition for this equation is the dose of the antibody divided by volume V_1 .

$$\frac{dC_1}{dt} = -\frac{CL}{V_1}C_1 - \frac{Q}{V_1}(C_1 - C_2) \quad (\text{Eq. 1})$$

48. Equation 2 for characterizing antibody concentration in the peripheral compartment (C_2) is provided below. The initial condition for this equation is zero.

$$\frac{dC_2}{dt} = \frac{Q}{V_2}(C_1 - C_2) \quad (\text{Eq. 2})$$

C. Application of Model

49. I fitted the 2-compartment PK model to the nivolumab PK data obtained following intravenous administration of 10 mg/kg dose, as described in Section VI.A and shown in Figure 2, using the software ADAPT (BMSR

Biomedical Simulations Resource, University of Southern California).³ In order to estimate the parameters per typical patient, the body weight of the typical patient was assumed to be 80 kg, consistent with the average body weight reported in a study of melanoma patients. See EX1035 (Feng) at p. 108 (describing an average body weight of 80.11 kg).

50. Figure 4 shows the quality of model fitting, where the PK profile simulated using the fitted model parameters is superimposed over the observed data. As shown in Figure 4, the 2-compartment PK model is able to capture the clinical PK of nivolumab very well. This observation provides confidence in the model's ability to predict the clinical PK of nivolumab under different dosing regimens.

³ ADAPT is a computation modeling platform for PK/PD modeling that was available by April 28, 2014. Indeed, it has been available since the 1980s. See Appendix C, University of Southern California, "BMSR Biomedical Simulations Resource," <https://bmsr.usc.edu/software/adapt/>.

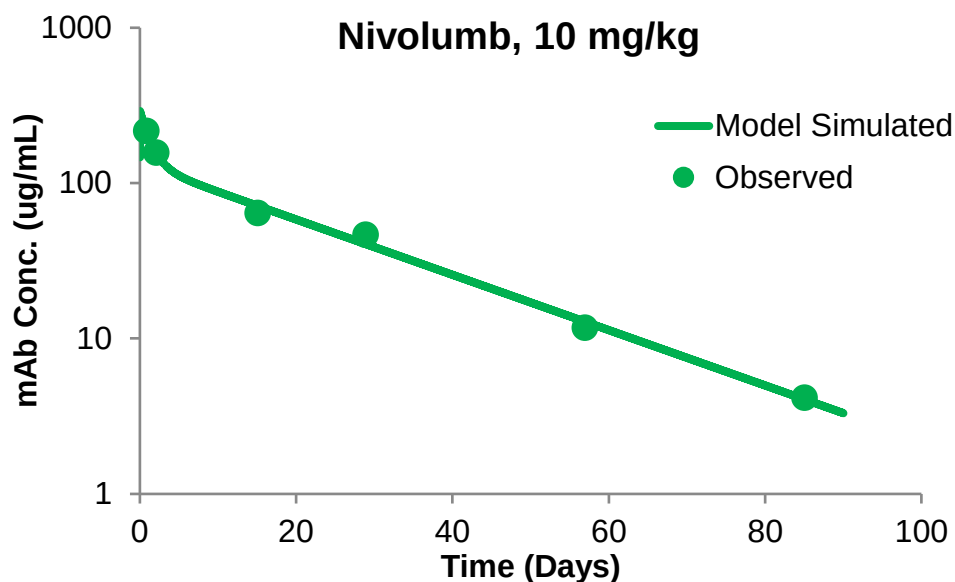


Figure 5: Model simulated and observed PK of nivolumab superimposed over each other.

51. The estimated values of parameters CL, V1, V2, and Q were 0.232 L/day, 2.723 L, 2.594 L, and 0.917 L/day, respectively. These parameter values are very similar to the values reported in the literature for the respective parameters in other antibodies. *See, e.g., EX1041 (Dirks).*

D. Determination of Exposure Threshold

52. To determine whether the PK of the 480 mg Q4W regimen would be comparable to the PK of the 240 mg Q2W regimen, I determined an effective concentration threshold. To determine the threshold concentration for nivolumab, I analyzed target occupancy data reported by Brahmer and Topalian and reproduced below in Figure 6. *See EX1009 at p. 3173, Fig. 4; EX1011 at p. 2452, Fig. 1 Panel A.* It was observed that even after single dose of nivolumab, the target

occupancy persists for an extended period of time. For example, Brahmer's occupancy over time data shows that, after an initial reduction, occupancy remained substantially the same throughout the remainder of the 60- or 80-day study period. See Figure 6 (bottom); EX1009 at p. 3173. Furthermore, even at lower doses (e.g., 0.1 mg/kg) high target occupancy was achieved. See Figure 6. Further, the data indicate that maximum target occupancy at doses higher than 1 mg/kg dose was very similar (~80%). Since initial occupancy achieved by the antibody was observed to persist even in the presence of declining antibody concentrations, I set the maximum concentration of antibody (i.e., $C_{\max}$) achieved after 1 mg/kg dose as the exposure threshold.

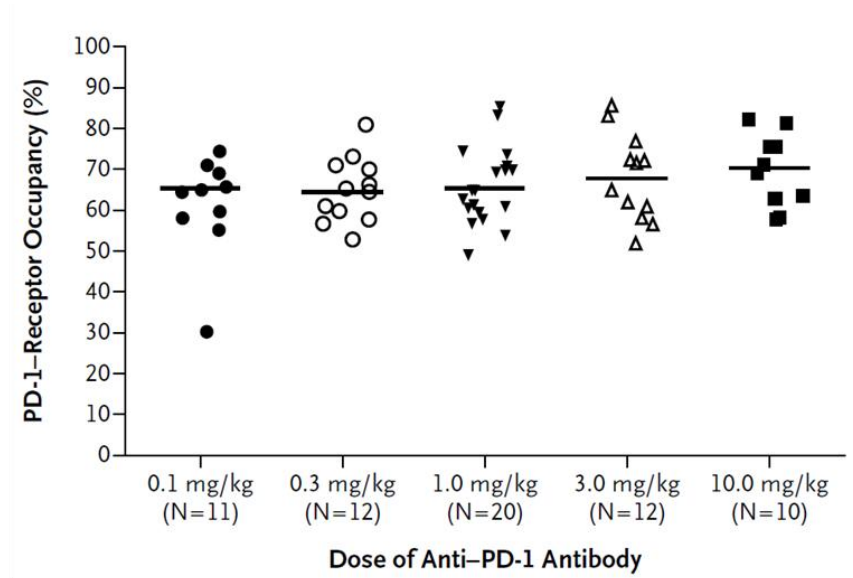
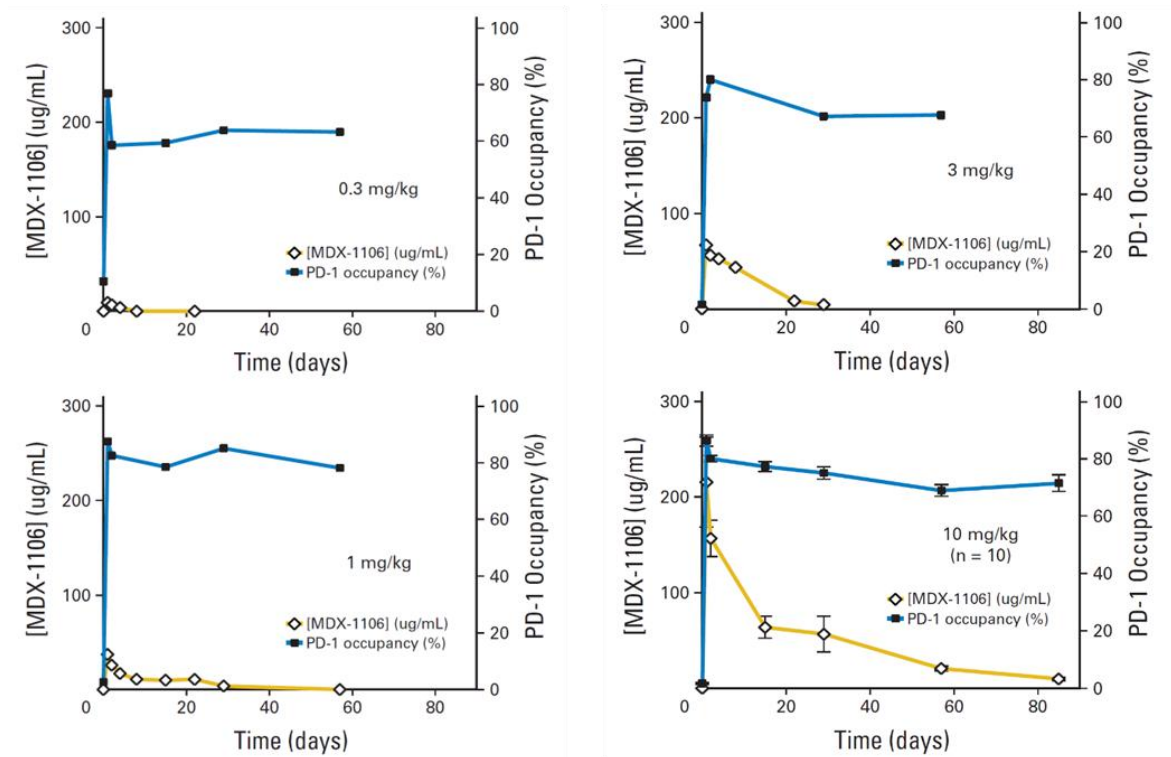


Figure 6: PD-1–receptor occupancy on circulating T cells of cancer patients following administration of nivolumab at different dose levels disclosed in Topalian (EX1011 at p. 2452, Fig. 1 Panel A) (top) and Brahmer (EX1009 at p. 3173, Fig. 4) (bottom).

53. Figure 7 shows the PK of nivolumab after 1 mg/kg intravenous dose, simulated using the 2-compartment PK model. It was found that 29 $\mu\text{g/mL}$ was the C_{max} for this dose. Thus, I determined an exposure threshold concentration for nivolumab of 29 $\mu\text{g/mL}$.

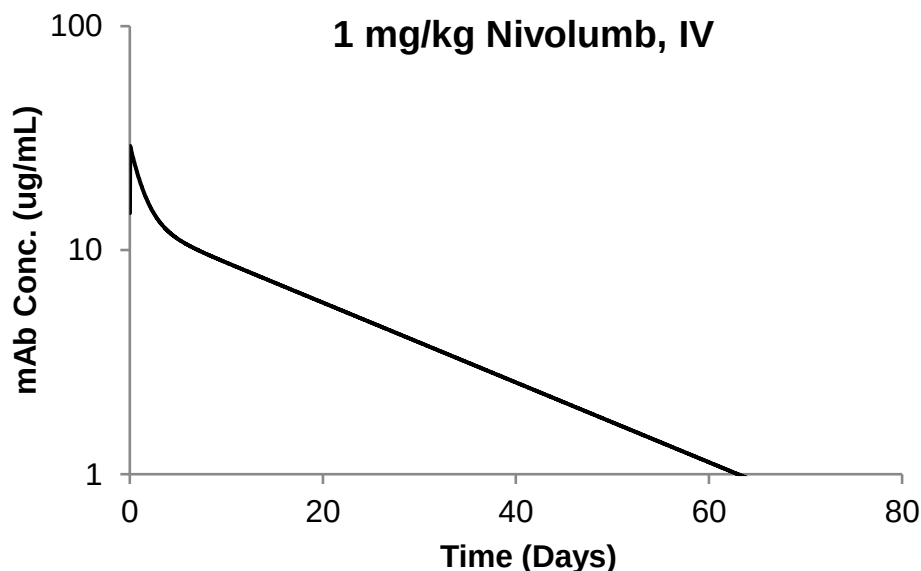


Figure 7: Model simulated PK of nivolumab following 1 mg/kg intravenous dose.

E. Modeling of 240 mg Q2W PK

54. Since 240 mg of nivolumab administered to a cancer patient every 2 weeks (Q2W) was reported at least by October 23, 2013 (EX1007), I first simulated the PK of nivolumab at this dosing regimen to confirm the validity of the threshold concentration identified using 1 mg/kg dose. These results are shown in Figure 8. I also inserted a green dashed line in Figure 8 showing the exposure threshold concentration discussed above in Section VI.D. As shown in Figure 8, administration of nivolumab at 240 mg dose every 2 weeks maintains trough

concentrations (*i.e.*, the lowest concentration levels) above the threshold levels at steady state. In addition, the $C_{\max}$ concentration achieved after the first dose is also higher than the threshold concentration. As such, this analysis supports 29 $\mu\text{g/mL}$ as a threshold above which nivolumab concentrations need to be maintained at the steady state to match or exceed the threshold. The simulations in Figure 8 also further supports a theoretical basis for the 240 mg Q2W dosing regimen of nivolumab in melanoma patients.

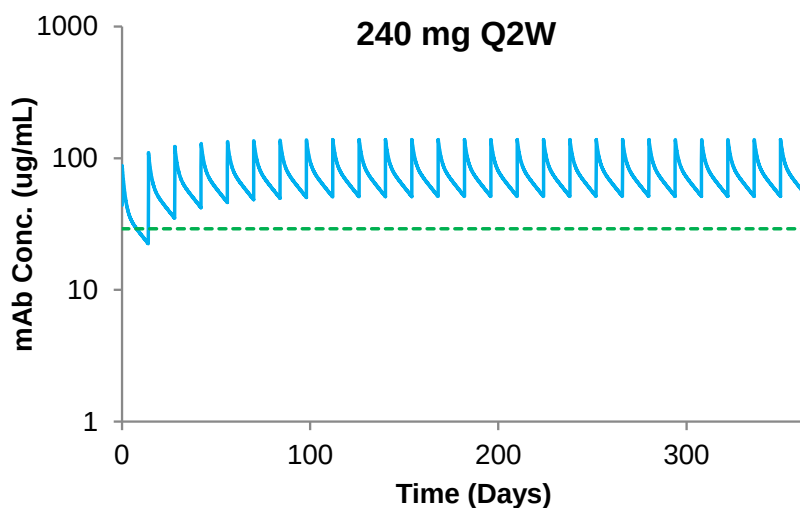


Figure 8: Model simulated PK of nivolumab following the administration of 240 mg intravenous dose given every 2 weeks. The dotted line represents the exposure threshold.

F. Modeling of 480 mg Q4W PK

55. In order to a priori assess the alternative dosing regimen, where nivolumab is administered intravenously at 480 mg dose every four weeks (480 mg Q4W), I used the 2-compartment model to simulate the PK of nivolumab at this dosing regimen. Figure 1 (provided above and also repeated below) shows the

simulated PK of nivolumab following intravenous administration of 240 mg dose every 2 weeks and 480 mg dose every 4 weeks. As shown in Figure 1, model simulations show that this dosing regimen maintained the concentrations of nivolumab above the threshold of 29 $\mu\text{g/mL}$ at the steady state. In addition, model simulations suggest that the concentrations of nivolumab after the first dose will always be higher for the 480 mg Q4W regimen than the concentrations achieved following the first dose (and before the second dose) of 240 mg Q2W dosing regimen. As such, model simulations support the selection of 480 mg Q4W as an alternative dosing regimen for nivolumab with similar PK as compared to 240 mg Q2W.

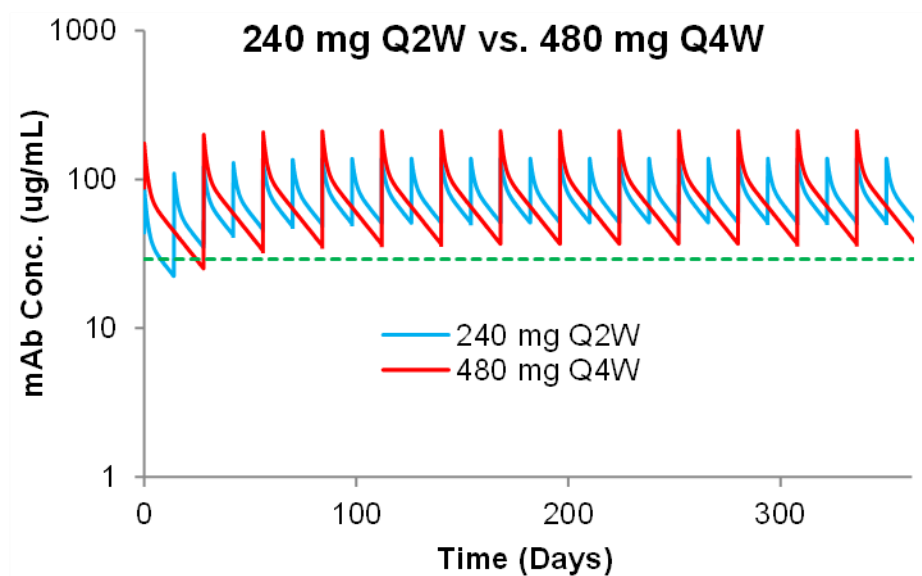


Figure 1: Model simulated PK of nivolumab following intravenous administration of 240 mg dose every 2 weeks and 480 mg dose every 4 weeks. Dotted line represents the exposure threshold (log Y-axis).

56. Figure 9 shows the same data as Figure 1 graphed with a linear Y-axis:

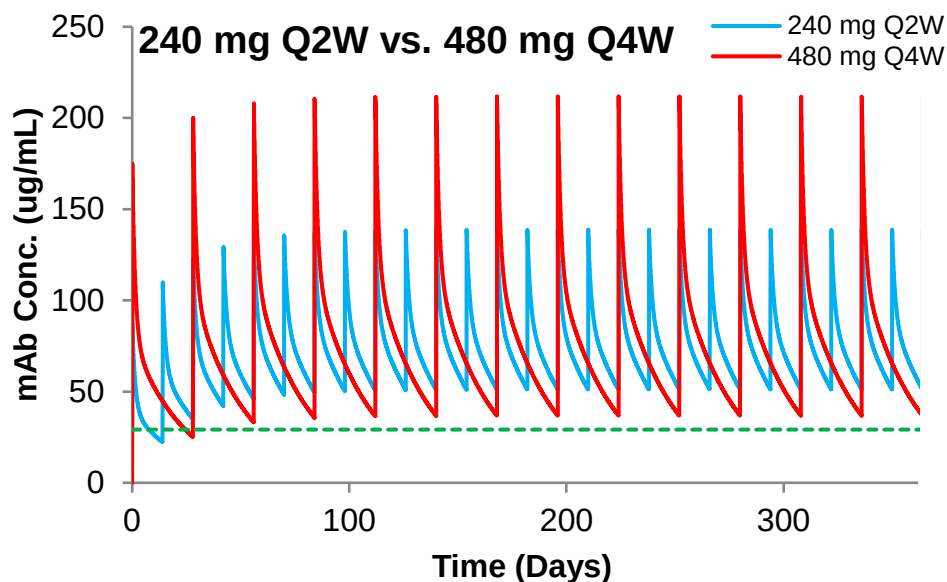


Figure 9: Model simulated PK of nivolumab following intravenous administration of 240 mg dose every 2 weeks and 480 mg dose every 4 weeks. Dotted line represents the exposure threshold (linear Y-axis).

G. Determination of Area Under the Curve at Steady State

57. Finally, I calculated the area under the concentration vs. time curve (AUC) for 4 weeks at the steady-state (AUC_{SS}^{4wk}) for both dosing regimens (i.e., 240 mg Q2W and 480 mg Q4W). Both regimens yielded almost identical AUC values. The AUC_{SS}^{4wk} for 240 mg Q2W dosing regimen was 2069 $\mu\text{g/mL}\cdot\text{day}$ and AUC_{SS}^{4wk} for 480 mg Q4W dosing regimen was 2069 $\mu\text{g/mL}\cdot\text{day}$. This observation suggests that both the regimens are comparable in terms of the exposure of nivolumab they achieve in the systemic circulation.

H. Safety Considerations

58. Comparing the 480 mg dose to the maximum tolerated dose information available from Brahmer and Topalian shows that it was known, before April 28, 2014, that the 480 mg dose would not have exceeded a maximum tolerated dose for an average weight, or even significantly lighter than average weight patient. As discussed above, Brahmer did not observe dose limiting toxicity up to 10 mg/kg. EX1009 at pp. 3167-68. Similarly, Topalian tested a 10 mg/kg dose and found that “[a] maximum tolerated dose was not defined at the doses tested in this study.” EX1011 at p. 2446. The 480 mg dose corresponds to 6 mg/kg for an 80 kg patient, well under the 10 mg/kg level.

VII. CONCLUSION

59. Based upon my pharmacokinetic analysis as described above, I conclude that an injection of a dose of 480 mg of nivolumab every four weeks would have comparable PK as compared to the PK of a dose of 240 mg of nivolumab every two weeks.

* * *

I declare that all statements made herein of my own knowledge are true, that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and

the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

I declare under penalty of perjury that the foregoing is true and correct.

A handwritten signature in black ink, appearing to read "Dhaval K. Shah".

Dhaval K. Shah, Ph.D.

Dated: 2/26/2025

Appendix A

Appendix A: Materials Considered

EX1001	U.S. Patent No. 10,174,113 (“’113 Patent”)
EX1007	NCT01968109 Version 1, Brief Title: “Safety Study of Anti-LAG-3 With and Without Anti-PD-1 in the Treatment of Solid Tumors” (Last Update Posted to clinicaltrials.gov: October 23, 2013) (“NCT-109”)
EX1009	Brahmer et al., Phase I Study of Single-Agent Anti-Programmed Death-1 (MDX-1106) in Refractory Solid Tumors: Safety, Clinical Activity, Pharmacodynamics, and Immunologic Correlates. J. Clin. Oncology. 2010 Jul 1; 28(19):3167–3175. (“Brahmer”)
EX1011	Topalian et al., “Safety, Activity, and Immune Correlates of Anti-PD-1 Antibody in Cancer,” N Engl J Med. 2012 Jun 28; 366(26):2443-54. doi: 10.1056/NEJMoa1200690. Epub 2012 Jun 2. (“Topalian”)
EX1035	Feng et al., Model-based Clinical Pharmacology Profiling of Ipilimumab in Patients with Advanced Melanoma. Br J Clin Pharmacol. 2014 Jul; 78(1):106-17. (“Feng”)
EX1041	Dirks et al., Population Pharmacokinetics of Therapeutic Monoclonal Antibodies. Clin. Pharmacokinet. 2010 Oct; 49(10):633-59. (“Dirks”)
EX1042	Lobo et al., Antibody Pharmacokinetics and Pharmacodynamics, J Pharm Sci. 2004 Nov; 93(11):2645-68. (“Lobo”)

Appendix B



2024 Global Threat Report

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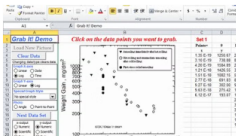
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By DataTrend Software

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Appendix C



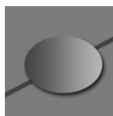
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ADAPT

ADAPT is a computational modeling platform developed for pharmacokinetic and pharmacodynamic applications. It is intended for basic and clinical research scientists and is designed to facilitate the discovery, exploration and application of the underlying pharmacokinetic and pharmacodynamic properties of drugs. ADAPT has been developed under the direction of David Z. D'Argenio in collaboration with Alan Schumitzky and Xiaoning Wang.



Since 1985, ADAPT has been developed and supported by the Biomedical Simulations Resource (BMSR) in the Department of Biomedical Engineering at the University of Southern California, under support from the National Institute for Biomedical Imaging and Bioengineering (P41-EB001978) and the National Center for Research Resources (P41-RR01861) of the National Institutes of Health. It is distributed by the BMSR at no charge to the user, under the terms of a Release Agreement. We ask that all users of ADAPT provide us with a completed Release Agreement so that we can maintain a database of ADAPT users.

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System Requirements

- Operating System
 - Windows 11/10/8/7
- Other Software REQUIRED
 - Intel oneAPI Base Toolkit + HPC Toolkit
 - Microsoft Visual Studio

Features in ADAPT 5

Individual Analysis

- Estimation module (ID) includes weighted least squares, maximum likelihood (ML), generalized least squares (GLS), maximum a posterior Bayesian estimation (MAP)
- Simulation module (SIM) includes capabilities for single and multisubject simulations
- Sample schedule design module (SAMPLE) provides the ability to calculate D- and C-optimal designs

Population Analysis

- Parametric population PK/PD modeling using maximum likelihood estimation via the EM algorithm with sampling (MLEM), as introduced by Schumitzky (1995) and by Walker (1996), with extensions and enhancements by Bauer & Guzy (2004).
- Iterated two-stage (ITS) analysis as proposed by Prevost (1977) and Steimer, Mallet and colleagues (1984).
- Convenient standard two-stage (STS) and naive pooled data (NPD) modeling, each with WLS, ML, and MAP estimators.

Other ADAPT Software

[S-ADAPT](#)

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