

Curriculum Vitae Professor Dr. Peter Langguth

Affiliation/Position	Institute of Pharmaceutical and Biomedical Sciences Head Department of Pharmaceutical Technology and Biopharmaceutics, Johannes Gutenberg University Mainz Staudingerweg 5 D-55128 Mainz, Germany Phone: ++49-1575-238 3389 Fax: ++49-6131-392 50 21 e-mail: langguth@uni-mainz.de
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Personal information

Date of birth	24. July 1959
Marital status	married, 1 child

Professional appointments

2015 – 2023	Qualified Person Good Manufacturing Practice, Central-Apotheke Steinbach
2013 – ongoing	Director Quality and Qualified Person Good Manufacturing Practice BioNTech RNA Pharmaceuticals, Mainz
Apr 2005 – Mar 2008	Elected Dean of the Faculties of Chemistry, Pharmacy and Earth Sciences, Johannes Gutenberg University Mainz
Jul - Aug 2004	Visiting Research Scientist at the Center for Drug Evaluation and Research (CDER), US Food and Drug Administration, Rockville
Apr 2003 – Mar 2005	Elected Associate Dean of the Faculties of Chemistry and Pharmacy, Johannes Gutenberg University Mainz
Oct 1998 – ongoing	Chairman and Full Professor (C-4) Department of Pharmaceutical Technology and Biopharmaceutics, Johannes Gutenberg University Mainz
Apr 1996 – Oct 1998	Group head ASTRA HÄSSLE AB, responsible for projects related to oral drug absorption and delivery, intestinal drug absorption and pharmacokinetics of new compounds
Apr 1992 – Aug 1992	Visiting Research Scientist at the College of Pharmacy, University of Michigan, Ann Arbor (USA) in the group of Prof. Dr. Gordon L. Amidon
Apr 1989 – Mar 1996	Senior Assistant School of Pharmacy, Dept. Pharmaceutical Technology, Swiss Federal Institute of Technology (ETH) Zurich, Switzerland

Sep 1988 – Apr 1989	Scientific Assistant Department of Pharmaceutical Technology, University of Frankfurt/Main, Germany
Aug 1986 – Aug 1988	Post-doctoral research fellow (supported by German Academic Exchange Service) at the College of Pharmacy, University of Florida, Gainesville, under the direction of Professor Dr. E.R. Garrett. Investigations on oral absorption and pharmacokinetics of morphine and influence of naltrexone coadministration on PK and PD
Sep 1985 – Jul 1986	Research studies on development of transdermal systems and transdermal absorption studies at STADA AG, Dortelweil, Germany
Apr 1984 – Sep 1984	Research studies at ALZA Corporation, Palo Alto, CA, as visiting graduate student; introduction into Form Fill Seal Transdermal and OROS® technologies

Education/Training/Degrees

May 1995	Habilitation and Venia legendi for Pharmaceutical Technology und Biopharmaceutics at the Swiss Federal Institute of Technology, ETH in Zürich
Mar 1994	Recognition as specialized pharmacist for “Pharmaceutical Technology” by the Chamber of Pharmacists of the State of Hessen
May 1983 – Dec 1985	Ph.D. studies at the Pharmacological Institute for Natural Sciences at J.W. Goethe University in Frankfurt/M. under the direction of Professor Dr. Dr. E. Mutschler.; Ph.D. in Pharmacology in Dec. 1985
Dec 1983	Approbation (Board Examination) as Pharmacist
Nov 1982 – Nov 1983	Pharmacy practice, Ursula Apotheke, Niederreifenberg
Apr 1979 – Nov 1982	Undergraduate studies in Pharmacy, Johann Wolfgang Goethe-University in Frankfurt/Main, Germany

Foreign languages

English, (good skills oral & written)
French, Swedish (basic skills)

Membership in professional associations

International Association for Pharmaceutical Technology (APV)
Head of the APV Focus Group on Biopharmaceutics and Pharmacokinetics
(1997 - 2013)
German Pharmaceutical Society (DPhG)
Head of the DPhG Focus Group on Pharmaceutical Technology and
Biopharmaceutics (2001 -)
Drug Delivery Foundation, Ann Arbor Michigan, Member Board of Directors
Federal Institute for Drugs and Medical Devices, Bonn (BfArM) Member
Expert Committee on Standard Registrations
European Federation of Pharmaceutical Sciences (EUFEPS)
American Association of Pharmaceutical Scientists (AAPS)

Membership in Editorial Boards und Functions as Editor

Pharmaceutical Research, Kluwer Academic Publishers (2001 - 2006)
Molecular Pharmaceutics, American Chemical Society (2004/06)
Biopharmaceutics and Drug Disposition, John Wiley & Sons (2005 -)
European Pharmacopoeia, Editor Scientific Commentaries to the EP
responsible for comments on excipients, pharmaceutical technology and
processes (2002 -) Wissenschaftliche Verlagsgesellschaft Stuttgart

Additional qualifications

- Head of manufacturing Clinical trial batches University Mainz since 2001
- Qualified person §15 German Drug Law since 2005
- Project head Genetic engineering University of Mainz

Awards

A) Members of the Working Group

- Pfizer Drug Discovery Symposium, 12. – 13. Sept. 2002 in Sandwich / England for the contribution:
A. Koggel, H. Spahn-Langguth, P. Langguth:
Intestinal absorption of quaternary ammonium compounds –
Involvement of P-glycoprotein in the limited oral bioavailability
- Boehringer Ingelheim Award to Dr. Stefan Grube for the dissertation
“Excipient and food drug interactions with special emphasis on
trospium chloride”, University of Mainz (2008)
- German Pharmaceutical Society Annual Meeting 28. Sept. – 1. Oct.

2009, Lesmüller poster award for the contribution:

O. Pfeifer-Lehmann, M. Kappl, P. Langguth, H. Häusler, P. Graß:
Investigation on the adhesion force in interactive powder mixtures
for inhalation using atomic force microscopy

- Association of Engineers (VDI) award 2009/10 to Claudius Weiler for his dissertation “Generation of dispersible powders for inhalation by spray-drying”
- German Pharmaceutical Society 2010 Symposium on Frontiers in Medicinal Chemistry, Münster 14.-17.3.2010 for the contribution: “Nano-Release of therapeutic drug-carriers – Liberation study from liposomes” by Eva Wurster, Thomas Nawroth and Peter Langguth
- Boehringer Ingelheim Award to Dr. Philipp Buch for the dissertation “Solubility and permeability as in vitro predictors for in vivo performance of fenofibrate IR solid dosage forms”. University of Mainz (2012)
- German Pharmaceutical Society Annual Meeting 2014, Leesmüller poster award for the contribution; S. Kindgen, H. Wachtel, P. Langguth: “Hydrodynamics in the PhEur/USP disintegration tester”
- DPhG Jahreskongress 2023, DPhG-FFQM Prize for the Promotion of Drug Quality 2023 to Sophie Luise Meiser and Jonas Pielenhofer from the working group of Prof. Dr. Peter Langguth, Institute for Biopharmacy and Pharmaceutical Technology at Johannes Gutenberg University, Mainz. Both submitted work in the area of „Quality-by-Design (QbD), Nanotechnology / Clinical Pharmacy“, which was carried out by an interdisciplinary research group.
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B) Personal awards to P. Langguth

- International Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology in Nürnberg, Germany:
APV Research Award 2004 for Outstanding Research Achievements in Pharmaceutical Sciences
- Phoenix Scientific Award 2007 for Outstanding Achievements in Pharmaceutical Technology
- Fellowship of the American Association of Pharmaceutical Scientists AAPS (2010)
- Silver Medal from the International Association of Pharmaceutical Technology APV (2010)
- United States Food and Drug Administration (2021) Award and Contract 75F40121C00020 “Disintegration and dissolution of IR solid dosage forms and influence of food induced viscosity on its kinetics, tools and methodologies for bioequivalence and substitutability evaluation”

Heading collaborative research groups

SAMT – Schwerpunkt für Arzneistofftransport und Targeting (Solute and Particle Transport) University of Mainz 2008-2012

OrBiTo – Oral Biopharmaceutic Tools. Innovative Medicines Initiative Joint Undertaking (<http://www.imi.europa.eu>) under grant agreement n° 115369 (2012-2018). Co-Lead of Work package 3: In vivo tools

Research interests

Biopharmaceutics of drug formulations with inherent delivery problems, macromolecules (e.g., RNA therapeutics, protein therapeutics, low soluble drugs, high first-pass-extraction drugs, natural compounds) including modulators of immune response

Drug formulation and drug product quality

Membrane transport of xenobiotics related to bioavailability and effect

In vitro-/ in vivo correlations

Drug targeting (gastrointestinal tract, selected organs)

Pulmonary delivery systems

Food-drug interactions

Adjunct Faculty Positions

Professor Langguth holds an Adjunct Faculty Position at the Department of Chemistry and Applied Biosciences of the Swiss Federal Institute of Technology (ETH) Zürich, Switzerland (<http://www.vvz.ethz.ch/Vorlesungsverzeichnis/dozentPre.do?semkez=2014S&dozide=10003140&ansicht=2&lang=de>). He is heading the module “Advanced Biopharmacy” in the Pharmaceutical Sciences MSc program since 2008. This teaching engagement takes place annually for approximately 40 working hours per year.

Publications

343 original papers in international journals (Web of Science), 13 issued patents; > 50 review articles; >300 congress contributions (oral & posters) H-Index: 48 (Web of Science). Total number of citations: 96616 (access date December 14, 2023). A list of publications is available at: <http://www.ncbi.nlm.nih.gov/pubmed/?term=langguth+p> or <https://webofscience.com/wos/woscc/citation-report/9240858d-8812—46cf-9078-7bc53dc95932-24d811ae>

10 selected publications from last 5 years:

The first 6 publications describe our work in the area of formulation and translation of mRNA vaccines as cancer therapeutics. Publications 6-10 deal with formulation development and oral biopharmaceutics and in vivo predictive dissolution.

Kranz, L. M., Diken, M., Haas, H., Kreiter, S., Loquai, C., Reuter, K. C., Meng, M., Fritz, D., Vascotto, F., Hefesha, H., Grunwitz, C., Vormehr, M., Husemann, Y., Selmi, A., Kuhn, A. N., Buck, J., Derhovanessian, E., Rae, R., Attig, S., Diekmann, J., ... Sahin, U. (2016). Systemic RNA delivery to dendritic cells exploits antiviral defence for cancer immunotherapy. *Nature*, 534(7607), 396–401. <https://doi.org/10.1038/nature18300>

Grabbe, S., Haas, H., Diken, M., Kranz, L. M., Langguth, P., & Sahin, U. (2016). Translating nanoparticulate-personalized cancer vaccines into clinical applications: case study with RNA-lipoplexes for the treatment of melanoma. *Nanomedicine (London, England)*, 11(20), 2723–2734. <https://doi.org/10.2217/nmm-2016-0275>

Uebbing, L., Ziller, A., Siewert, C., Schroer, M. A., Blanchet, C. E., Svergun, D. I., Ramishetti, S., Peer, D., Sahin, U., Haas, H., & Langguth, P. (2020). Investigation of pH-Responsiveness inside Lipid Nanoparticles for Parenteral mRNA Application Using Small-Angle X-ray Scattering. *Langmuir : the ACS journal of surfaces and colloids*, 36(44), 13331–13341. <https://doi.org/10.1021/acs.langmuir.0c02446>

Siewert, C. D., Haas, H., Cornet, V., Nogueira, S. S., Nawroth, T., Uebbing, L., Ziller, A., Al-Gousous, J., Radulescu, A., Schroer, M. A., Blanchet, C. E., Svergun, D. I., Radsak, M. P., Sahin, U., & Langguth, P. (2020). Hybrid Biopolymer and Lipid Nanoparticles with Improved Transfection Efficacy for mRNA. *Cells*, 9(9), 2034. <https://doi.org/10.3390/cells9092034>

Siewert, C., Haas, H., Nawroth, T., Ziller, A., Nogueira, S. S., Schroer, M. A., Blanchet, C. E., Svergun, D. I., Radulescu, A., Bates, F., Huesemann, Y., Radsak, M. P., Sahin, U., & Langguth, P. (2019). Investigation of charge ratio variation in mRNA - DEAE-dextran polyplex delivery systems. *Biomaterials*, 192, 612–620. <https://doi.org/10.1016/j.biomaterials.2018.10.020>

Ziller, A., Nogueira, S. S., Hühn, E., Funari, S. S., Brezesinski, G., Hartmann, H., Sahin, U., Haas, H., & Langguth, P. (2018). Incorporation of mRNA in Lamellar Lipid Matrices for Parenteral Administration. *Molecular pharmaceutics*, 15(2), 642–651. <https://doi.org/10.1021/acs.molpharmaceut.7b01022>

Zane, P., Gieschen, H., Kersten, E., Mathias, N., Ollier, C., Johansson, P., Van den Bergh, A., Van Hemelryck, S., Reichel, A., Rotgeri, A., Schäfer, K., Müllertz, A., & Langguth, P. (2019). In vivo models and decision trees for formulation development in early drug development: A review of current practices and recommendations for biopharmaceutical development. *European journal of pharmaceutics and biopharmaceutics* 142, 222–231. <https://doi.org/10.1016/j.ejpb.2019.06.010>

Zaheer, K., & Langguth, P. (2019). Designing robust immediate release tablet formulations avoiding food effects for BCS class 3 drugs. *European journal of pharmaceutics and biopharmaceutics* 139, 177–185. <https://doi.org/10.1016/j.ejpb.2019.03.015>

Al-Gousous, J., Tsume, Y., Fu, M., Salem, I. I., & Langguth, P. (2017). Unpredictable Performance of pH-Dependent Coatings Accentuates the Need for Improved Predictive in Vitro Test Systems. *Molecular pharmaceutics*, 14(12), 4209–4219. <https://doi.org/10.1021/acs.molpharmaceut.6b00877>

Al-Gousous, J., Amidon, G. L., & Langguth, P. (2016). Toward Biopredictive Dissolution for Enteric Coated Dosage Forms. *Molecular pharmaceutics*, 13(6), 1927–1936. <https://doi.org/10.1021/acs.molpharmaceut.6b00077>

Expert opinion
with respect to the opposition proceedings against
patent EP 3 288 980 B1

in the matter of
Pajaro Limited ./ Bristol-Meyers Squibb Company

Client:
Bird&Bird LLP

Technical expert:
Univ.-Prof. Dr. phil. nat. Peter Langguth

Institute of Pharmaceutical and Biomedical Sciences
Johannes Gutenberg-University
Staudingerweg 5
55099 Mainz

Mainz, 21 December 2023

Prof. Dr. P. Langguth
December 21, 2023

I. Introduction

Claim 1 of EP 3 288 980 B1 reads as follows:

A composition comprising nivolumab for use in treating a melanoma in a patient:

- (i) wherein the patient is identified as having a PD-L1 positive melanoma tumor by measuring a PD-L1 expression on the melanoma tumor; and
- (ii) wherein the patient is to be administered a flat dose of 480 mg of nivolumab as monotherapy once every four weeks, wherein the patient is not administered a combination of nivolumab and ipilimumab.

Dr. Andreas Obermeier from Bird & Bird LLP who is representing Pajaro Limited in opposition proceedings against Patent EP 3 288 980 B1 of Bristol-Meyers Squibb Company informed me that during the opposition proceedings another opponent submitted an expert declaration by Prof. Leonard (currently cited as D65a) that discusses claim 1.

Dr. Obermeier asked me to provide an expert opinion on what was known in this technology at the filing date of the opposed patent. I was told that the expert opinion will be used in the present opposition proceedings.

The following documents have been provided to me:

No.	Citation
D2 und D59a	WO 246 und NCT 109
D3	Tsai et al. 2014
D5	Weber et al. 2015
D6	Scott 2015
D7	BMS Press release 2016
D8	Brahmer et al. 2015
D10	Topalian et al. 2012
D12a	NCT 867
D14a	Larkin et al. 2015
D16	Bai et al. 2012
D19	Opdivo FDA label 2015
D41	Barbee et al. 2015
D53	EMA Opdivo 2015
D54a	FDA Review Opdivo 2015
D55	Brahmer et al. 2010
D61	Toutain et al. 2004
D63	NCT 918
D65a	Expert opinion of Prof. Leonard

I have read all above-identified documents.

II. About my background

My name is Peter Langguth and I am currently a professor at the Institute of Pharmaceutical and Biomedical Sciences, Johannes Gutenberg-University. My professional background is shown in the accompanying document entitled Annex E1.

III. Summary

After reading all above-identified documents, the following conclusions can be made based on my knowledge and experience until 27 April 2016 (which is the date what I was asked to consider):

- The flat dosage regimen of 480 mg nivolumab Q4W for treating cancer (e.g., NSCLC) had already been implemented in clinical phase III studies published prior to the filing date of the opposed patent (see D12a). Based on the implementation in clinical phase III studies, the flat dose of 480 mg Q4W must be considered safe and effective (see below).
- As such, the only unknown was whether one would have used 480 mg Q4W nivolumab dose to also treat an additional type of cancer, melanoma which had been disclosed previously to be treatable with the same dosage regimens, including both body-weight based and flat dosages, as NSCLC (see D5 (3mg /kg Q2W for melanoma), D8 (3mg /kg Q2W for NSCLC), D10 (0.3 to 10 mg /kg for melanoma and NSCLC), D59a (80 or 240 mg Q2W for melanoma and NSCLC) and D63 (240 mg Q2W for melanoma and NSCLC)).
- Based on my knowledge and the above-identified documents, one would have been motivated to use the dosage regimen of 480 mg Q4W nivolumab for treating melanoma on at least three independent grounds 1) this dose was already being used in phase III clinical trials for NSCLC (a cancer known to be treatable with nivolumab at the same dosage regimens as melanoma), 2) this 480 mg Q4W dosage regimen is a preferred and therapeutically equivalent alternative to the 240 mg Q2W dosage regimen that had already been used for melanoma and NSCLC and 3) many advantages were known at the time to be associated with use of a flat dose and providing treatment less frequently (see D16).

IV. In-depth analysis

1) **I agree with the expert opinion of Prof. Leonard (D65a)**

I have studied the expert opinion of Prof. Leonard and confirm in particular his conclusions on the key publications that he cited and on which he based his opinion (e.g., D54a, FDA Clinical Pharmacology and Biopharmaceutics Review; D55, Brahmer et. al., 2010).

The opinion expressed by Prof. Leonard touches the following questions: (1) Which dosing parameters of antibody treatment would the skilled person modify and within what limits? (2) Would the skilled person be motivated to change a body weight adjusted dose to a flat dose based on the knowledge available on and before 27 April 2016? (3) How would the skilled reader interpret the data regarding receptor occupancy and half-life and how would he/she apply these findings when trying to modify a treatment schedule for an antibody, in particular, nivolumab? His answers are comprehensible and correct from the point of view of an expert.

2) **I would like to emphasize the following considerations**

Based on common general knowledge and the published information one would have found the dosage regimen of 480 mg Q4W as suitable or even optimal dosage regimen for treating melanoma patients and would have been motivated to use it:

- The flat dosage regimen of 480 mg Q4W nivolumab for treating cancer (e.g., NSCLC) had already been implemented in clinical phase III studies published prior to the filing date of the opposed patent (see D12a).
- Melanoma and NSCLC had been disclosed to be treatable by using the same body weight-based or flat dosage regimens of nivolumab (see D5 (3mg /kg Q2W for melanoma), D8 (3mg /kg Q2W for NSCLC), D10 (0.3 to 10 mg /kg for melanoma and NSCLC), D59a (80 or 240 mg Q2W for melanoma and NSCLC) and D63 (240 mg Q2W for melanoma and NSCLC). In particular, a body weight-based dose of 3 mg/kg Q2W of nivolumab was known to be safe and effective (see D3 and D10) and was the only weight-based dose used in several clinical phase III studies (see D5, D7, D8 and D14a). It was the only approved dose for treating melanoma (see D53 and D54a).
- Use of flat dosages over body-weight-based dosages as well as dosages at a less frequent time interval were known at the time to be advantageous (see D16; explained in detail below). Moreover, conversion of the body weight-based dose of 3 mg/kg Q2W nivolumab to a flat dose of 240 mg Q2W (e.g., for melanoma and NSCLC) or 480 mg Q4W (for NSCLC) had already been performed in the prior art (see D12a, D59a and D63). This 480 mg Q4W dosage regimen is a preferred and therapeutically equivalent alternative to the 240 mg Q2W dosage regimen that had already been used for melanoma and NSCLC.

Therefore, the only unknown at the filing date of the opposed patent was whether one would have used the known safe and effective 480 mg Q4W nivolumab dose to treat an additional type of cancer, melanoma or to modify the known 3 mg/kg Q2W and 240 mg Q2W dosage regimen for melanoma to be less often and use the preferred and therapeutically equivalent alternative 480 mg Q4W dosage regime.

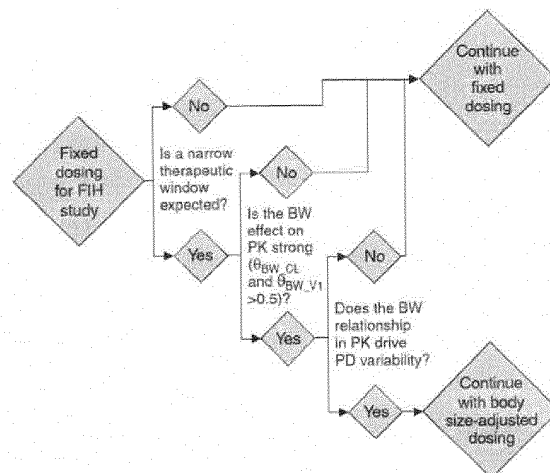
For me the answer to this question is yes since it was a straight-forward approach to administer 480 mg Q4W to treat melanoma:

a) At the time one had already changed from a weight-based dose of 3 mg/kg Q2W nivolumab to a flat 240 mg Q2W dose for treating melanoma. Therefore, one not only had the motivation to use a flat dose instead of a weight-based dose, but in fact did so (see D59a, D63).

In addition to the studies demonstrating this motivation, reference D16 (Bai et al 2012) cited by Prof. Leonhard confirms this. This reference is of particular relevance to explain the advantage of switching from a body weight adjusted dose to a flat dose. It discusses many other potential covariates besides body weight that allegedly are of relevance, and which allegedly explain why pharmacokinetics is rarely proportional to body size in case of antibody treatments. Nevertheless, the authors of D16 concluded that (page 119, abstract, "Conclusions"):

The pharmacokinetic variability introduced by either dosing regimen is moderate relative to the variability generally observed in pharmacodynamics, efficacy and safety. Therefore, mAb dosing can be flexible. Given many practical advantages, fixed dosing is recommended to be the first option in first-in-human studies with mAbs.

They visualized their conclusion in Figure 6:



Consequently, as long as the therapeutic window is wide, the fixed dosing is preferred.

Furthermore, both, EMA and FDA reviews (D53 and D54a) mention only body weight as a relevant covariate affecting clearance and volume of distribution of nivolumab.

Turning to nivolumab a body weight-based dose of 3 mg/kg Q2W of nivolumab was known to be safe and effective (see D3 and D10) and was the dose used in several clinical phase III studies (see D5, D7, D8 and D14a).

It was known that potential benefits of flat dosing are simplified administration of a drug across a wide range of tumor types, providing greater convenience to healthcare providers by helping to facilitate dosing calculations and drug preparation, improving patient compliance, and possibly helping to reduce healthcare costs (see e.g., D16). Furthermore, the fixed dosing is recommended to be the first option in first-in-human studies with mAbs (see D16, abstract).

Nivolumab was known to be a drug with a wide therapeutic window (see e.g., D55).

Furthermore, evidence of clinical activity was reported from receptor occupancy even at very low doses of 0.3 mg/kg and at nivolumab serum concentration as low as 0.04 µg/mL, resulting in occupation of more than 70% of PD-1 receptors on T cells. Given typical serum half-lives of nivolumab of 12 days for doses up to 3 mg/kg and 20 days for the 10 mg/kg dose (reference D55) an analysis of exposure-response relationship of safety and efficacy in reference D54a resulted in a trough concentration range of 7 to 28 µg/mL which is well above the serum concentration needed for sufficient response, based on the relationship between receptor occupancy and dose/serum concentrations. It is therefore concluded by Prof. Leonard that *"the response rate is largely independent of the dose or plasma exposure (no dose or exposure-efficacy relationship). Consequently, in terms of efficacy, the dose can be chosen very flexibly within the range of 0.1 to 10 mg/kg."* Based on review of the FDA Review Document (D54a in "Summary statistics for pharmacokinetic parameters of nivolumab") this statement of the independence of the response rate from dose or plasma exposure within a broad dosage range was also extended to the safety of nivolumab (occurrence of adverse events) in the dose range of 0.1 to 10 mg/kg Q2W and *"indicating that the dose can be chosen very flexibly within the range of 0.1 to 10 mg/kg."*

Thus, it was straightforward to convert the well-established body weight-based dose of 3 mg/kg Q2W of nivolumab into a flat dose of 240 mg Q2W. This conversion (based on 80 kg per patient) had already been done previously and was implemented in clinical studies published prior to the filing date of the opposed patent (see D2, D12a and D59a).

This conversion factor based on 80 kg was known in the art. According to EMA (D53) and FDA (D54a) the mean body weight of patients treated was approx. 80 kg (see D53, page 42; D54a, page 17). This conversion factor was also used in clinical studies published prior to the filing date (see D2, D12 and D59a). Another source in favor of a mean weight of 80 kg was based on the BW distribution in patients across tumor types in nivolumab clinical studies (D13). While said publication was published after 27 April 2016, it shows that the conversion factor did not change even after analyzing all bodyweights of all clinical studies.

Furthermore, in their evaluation of Opdivo (2015) the EMA (D53) and FDA (D54a) had analyzed a range of body weight of 34 – 162 kg (mean body weight 81 kg) for the nivolumab exposures with CDA209037. Thus, a flat dose of 240 mg given to the 2 extreme different body weight patients equals $240\text{mg}/162\text{kg} = 1,481\text{ mg/kg}$ and $240\text{mg}/34\text{kg} = 7,059\text{ mg/kg}$.

Given the results of the study by Brahmer et al (2010) (D55) in which cohorts of 6 patients received doses of nivolumab at 0.3, 1, 3 or 10 mg/kg it was concluded by Prof. Leonard that based on the analysis of D55 all doses were generally well tolerated, and a maximum tolerated dose (MTD) was not reached in this study (D55). Thus, a flat dose of 240 mg was known to be well within the accepted safety range established by the study of Brahmer et al. (D55) for the range of body weights of 34 to 164 kg.

Thus, the well-established body weight-based dose of 3 mg/kg Q2W which was used in several clinical phase III trials can and importantly was converted into a flat dose of 240 mg Q2W (which is safe and effective even for patients having a body weight being far away from the mean body weight of 80 kg) prior to the filing date of the patent being opposed. Therefore, the motivation of conversion of the body-weight-based dose of 3 mg/kg Q2W to a flat dose of 240 mg Q2W (e.g., for melanoma and NSCLC) or 480 mg Q4W (for NSCLC) had already been performed in the prior art (see D12a, D59a and D63) and advantages with such had already been demonstrated.

b) In the present treatment regimen a flat dose of 480 mg Q4W is a preferred and therapeutically equivalent alternative to the 240 mg Q2W

A dose of 480 mg every 4 weeks was expected to be advantageous mainly due to patient comfort, convenience and compliance (less frequent appointments) and cost effectiveness (cost of transportation; cost of doctor visits). Further, a 480 mg dose of nivolumab had already been used for treating cancer, NSCLC, at the time of the filing of the opposed patent.

Thus, I would have considered it advantageous to use a flat dose of 480 mg Q4W instead of a flat dose of 240 mg Q2W in case the flat dose of 480 mg Q4W is considered safe and effective. And this was the case: this alternative dosage regimen of 480 mg Q4W had already been implemented in clinical phase III studies for treating NSCLC patients published prior to the filing date of the opposed patent (see D12a). Based on the implementation in clinical phase III studies the flat dose of 480 mg Q4W must be considered safe and effective.

Furthermore, a flat dose of 480 mg Q4W was expected to be an equivalent alternative to the dose of 240 mg Q2W. Said expectation is scientifically based on the flat dose response curve of nivolumab, the long elimination half-life of nivolumab (26.7 days), the wide therapeutic window of nivolumab (0.1 to 10 mg/kg) and this dose was already being used in phase III clinical trials for NSCLC (a cancer known to be treatable with the same dosage regimens as melanoma) (see D12a).

Thus, the flat dose of 480 mg Q4W is safe and effective, and I agree with the conclusion of Prof. Leonard that a flat dose of 480 mg Q4W is an equivalent alternative to the 240 mg Q2W since the dose response curve of nivolumab is flat, the half-life of nivolumab is long and its therapeutic window is wide.

Consequently, one would have considered the dosage regimens of 240 mg Q2W and 480 mg Q4W as being safe and effective.

c) One would have been motivated to use the dose of 480 mg Q4W used for other cancer types, e.g., NSCLC in a phase III trial for melanoma

The 480 mg Q4W dose used for clinical phase III trials in NSCLC patients was also expected to be safely and efficiently used in clinical trials for melanoma patients due to the same mode of action of the PD1 inhibitor in the different type of cancer and previous teachings of melanoma and NSCLC being treatable with the same dosage regimens (e.g., body-weight based (3 mg/kg Q2W) or flat (240 mg Q2W); see D14, D59a, D63).

In a large, phase 1b, dose-escalation study CA209003 (see D10), nivolumab was adequately tolerated up to 10 mg/kg every two weeks across tumor types, including melanoma, NSCLC, and RCC, with no maximum tolerated dose identified. Nivolumab 3 mg/kg and 240 mg Q2W was used in clinical phase III studies for melanoma and NSCLC (D5, D7, D8 and D14a). Therefore, one would have been motivated to consider other flat doses used for NSCLC as well as other cancer types known to have similar or same dosage regimens in the treatment of melanoma. A dosage of 480 mg every 4 weeks was used in clinical phase III study ID CA209-384 entitled "A Dose Frequency Optimization, Phase IIIB/IV 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 4 Months of Nivolumab at 3 mg/kg or 240 mg Every 2 Weeks" (D12a).

Furthermore, the increase in duration from two weeks to four weeks is advantageous for numerous reasons including providing greater convenience to healthcare providers by helping to facilitate dosing calculations and drug preparation, improving patient compliance and comfort and possibly helping to

reduce healthcare costs (see e.g., D16). Furthermore, the flat dosing is recommended to be the first option in first-in-human studies with mAbs (see D16).

Thus, one would have been motivated to use the 480 mg every 4 weeks to treat melanoma as it was known to be safe and effective and it would be advantageous over the 240 mg every 2 weeks to reduce the frequency of administration significantly thereby decreasing patient pain while increasing patient convenience and compliance (less frequent appointments/administration), greater convenience to healthcare providers by helping to facilitate dosing calculations and drug preparation, and possibly helping to reduce healthcare costs (see e.g., D16).

Consequently, based on my knowledge one would have been motivated to administer the dosage regimen of 480 mg Q4W to treat melanoma as they had already done for NSCLC and to modify the known 3 mg/kg Q2W and 240 mg Q2W dosage regimen for melanoma to be less often and use the preferred and therapeutically equivalent alternative 480 mg Q4W dosage regime.

Mainz, 21 December 2023



Univ.-Prof. Dr. phil. nat. Peter Langguth