Toxicity of pemetrexed during renal impairment explained-Implications for safe treatment

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Toxicity of pemetrexed during renal impairment explained—Implications for safe treatment


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Abstract
Pemetrexed is an important component of first line treatment in patients with non-squamous non-small cell lung cancer. However, a limitation is the contraindication in patients with renal impairment due to hematological toxicity. Currently, it is unknown how to safely dose pemetrexed in these patients. The aim of our study was to elucidate the relationship between pemetrexed exposure and toxicity to support the development of a safe dosing regimen in patients with renal impairment. A population pharmacokinetic/pharmacodynamic analysis was performed based on phase II study results in three patients with renal dysfunction, supplemented with data from 106 patients in early clinical studies. Findings were externally validated with data from different pemetrexed dosing regimens. Alternative dosing regimens were evaluated using the developed model. We found that pemetrexed toxicity was driven by the time above a toxicity threshold concentration. The threshold for vitamin-supplemented patients was 0.110 mg/mL (95% CI: 0.092-0.146 mg/mL). It was observed that in patients with renal impairment (estimated glomerular filtration rate [eGFR]: <45 mL/min) the approved dose of 500 mg/m² would yield a high probability of toxicity.

Abbreviations: ANC, absolute neutrophil count; AUC, area under the concentration-time curve; BSA, body surface area; CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CrCl, creatinine clearance; CTCAE, Common Terminology Criteria for adverse events; eGFR, estimated glomerular filtration rate; Emax, maximum inhibitory effect; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; PD, pharmacodynamic; PK, pharmacokinetics; Q3W, once every 3 weeks.
of severe neutropenia in the range of 51.0% to 92.6%. A pemetrexed dose of 20 mg for patients (eGFR: 20 mL/min) is shown to be neutropenic-equivalent to the approved dose in patients with adequate renal function (eGFR: 90 mL/min), but would result in an approximately 13-fold lower area under the concentration-time curve. The pemetrexed exposure-toxicity relationship is explained by a toxicity threshold and substantially different from previously thought. Without prophylaxis for toxicity, it is unlikely that a therapeutic dose can be safely administered to patients with renal impairment.

**KEYWORDS**

estimated glomerular filtration rate, neutropenia, non-small cell lung cancer, pemetrexed, prophylactic strategies

**What’s new?**
The folate analog pemetrexed, while effective against non-squamous non-small cell lung cancer (NSCLC), carries a high risk of toxicity for NSCLC patients with impaired renal function. Identifying safe, effective doses for this patient subset is of critical importance. In this study, a high frequency of neutropenia was observed in pemetrexed-treated NSCLC patients with renal impairment, despite dose individualization based on renal function. Analyses indicate that pemetrexed toxicity is driven by time above a toxicity threshold concentration. The findings question the possibility of achieving therapeutic efficacy at safe doses for pemetrexed in renally impaired NSCLC patients without toxicity prophylaxis.

1 **INTRODUCTION**
Pemetrexed is a folate analogue and a cornerstone in the treatment of non-squamous non-small cell lung cancer (NSCLC), mesothelioma and thymoma.\(^1\)\(^-\)\(^3\) Despite renal function being the main determinant of systemic exposure of pemetrexed, the approved dose is based on body surface area (BSA; 500 mg/m\(^2\) every 21 days). Although pemetrexed treatment is generally well tolerated in patients with adequate renal function, the principle toxicity related to its exposure is myelosuppression, which predominantly presents as neutropenia.\(^4\)\(^,\)\(^5\) Since the introduction of vitamin B11 and B12 supplementation during the treatment of pemetrexed, the incidence of severe hematological toxicities decreased, although neutropenia remains frequently observed during treatment.\(^6\) In an early phase I study, BSA-based dosing (150 mg/m\(^2\) Q3W) in a non-vitamin supplemented patient with renal impairment led to severe toxicities, including grade 4 neutropenia and, subsequently, pemetrexed toxicity-related death.\(^7\) Consequently, a creatinine clearance (CrCl) <45 mL/min became a contraindication in the pemetrexed label. Since lung cancer and mesothelioma are often diagnosed in elderly patients and age is correlated with a decline in renal function, a considerable proportion of patients is likely withheld effective treatment with pemetrexed.\(^8\)\(^,\)\(^9\)

The quest to optimize pemetrexed treatment continued and Latz et al suggested a linear relationship between pemetrexed plasma concentration and inhibition of the proliferation rate of neutrophils at the approved 500 mg/m\(^2\) dose level.\(^10\) It was postulated that a dose adjusted to renal function to target a predefined pharmacokinetic (PK)-based cumulative area under the concentration-time curve (AUC) of 164 mg·h/L would prevent toxicity while maintaining efficacy.\(^11\) Additionally, their results indicated that the efficacy and toxicity of pemetrexed are considered to be linearly related to its systemic exposure.\(^5\)\(^,\)\(^10\) Therefore, we recently studied this hypothesis in patients with renal impairment aimed at attaining a similar AUC as in patients with adequate renal function in a phase II study. However, our study was halted prematurely as patients unexpectedly developed severe myelotoxicity, despite a presumably nontoxic systemic exposure. This indicated that the exposure-toxicity relationship in patients with impaired renal function was different from previously suggested. To allow safe dosing of pemetrexed in patients with impaired renal function, it is pivotal to unravel this relationship. The aim of our study was to elucidate the relationship between pemetrexed exposure and toxicity to support the development of a safe dosing regimen in patients with renal impairment.

2 **METHODS**

2.1 **Data**

For the primary analysis of the pemetrexed exposure-neutropenia relationship, a dataset was composed from two sources. Pemetrexed PK and absolute neutrophil count (ANC) pharmacodynamic (PD) data of a phase I dose-finding study (ClinicalTrials.gov NCT00003706) were kindly provided by Eli Lilly.\(^7\)\(^,\)\(^12\) In our study, patients with varying renal functions were dose-escalated from a starting dose of pemetrexed of 150 to 500 mg/m\(^2\) every 21 days depending on their...
renal function to a maximum of 600 mg/m². Individual data on age, gender, ethnicity, body weight, vitamin B11 and B12 supplementation, serum creatinine and ANCs were available, as well as pemetrexed-dosing related information such as dose, infusion rates, sampling times and plasma concentrations. These data were extended with the results of our single-arm phase II pharmacokinetic and safety study (NCT03656549). In our study, patients with a creatinine clearance <45 mL/min were dosed based on creatinine clearance to attain a similar cumulative AUC as in patients with adequate renal function (164 mg·h/L ± 25%). ANC values <2.0 × 10⁹/L were collected just before administration of pemetrexed at each 21-day cycle and at day 14. The estimated glomerular filtration rate (eGFR) based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and the Cockcroft-Gault equation were calculated for the individual patients. None of the patients in the dataset received other anticancer drugs, like cisplatin or carboplatin. A detailed description of the methods and results of this phase II study is included as supplementary data.

For the external validation of the hypothesized relationship, data of patients treated with pemetrexed at the maximum tolerated dose (MTD) in the early phase I studies by McDonald et al and Rinaldi et al were used. The demographic and pharmacokinetic data of the study by McDonald et al were provided by Eli Lilly, including age, gender, body weight and serum creatinine, as well as pemetrexed dose, infusion rates, sampling times and plasma concentrations. For the studies by Rinaldi et al, the methods are described in the supplementary material.

2.2 | Pharmacokinetic-pharmacodynamic analysis

The population PK/PD analysis of pemetrexed was performed by means of nonlinear mixed effects modeling. The pharmacokinetics were described using a previously developed model, based on the available pemetrexed pharmacokinetic data of the same dataset in patients with varying renal function. A well-established semimechanistic model describing the interplay between circulating neutrophils and plasma concentrations of pemetrexed served as the basis for the analysis. For the analysis the drug effect of pemetrexed on the proliferation of the neutrophils was modeled either as a linear relationship between drug concentration and neutrophil proliferation rate or as a time above threshold relationship. The development and evaluation of this analysis is described in detail in the supplementary material.

2.3 | External validation

To externally evaluate our final model, we performed clinical trial simulations. We compared the predicted frequencies of neutropenia for various dosing regimens. Monte Carlo simulations (n = 1000 trials) were performed of the trials with the established MTD in the early phase I studies for the following dosing regimens: 4 mg/m²/day for five consecutive days every 3 weeks, 40 mg/m²/week for four consecutive weeks, every 6 weeks and 600 mg/m² over 3 weeks, that were performed without prophylactic vitamin supplementation. The ANCs were simulated on day 8 and day 15, as reported for these dosing regimens. Neutropenia was graded according to the National Cancer Institute Common Terminology Criteria (CTCAE) version 4.03 (with a lower limit of normal ANC of 2.0 × 10⁹/L). The relative frequency of model-predicted neutropenia per patient was calculated over the total of these 1000 trial simulations. The distribution of the predicted number of neutropenic patients per trial associated to this relative frequency was visualized for both relationships and compared to the actual observed frequencies for each dosing regimen. Further details of this external validation are described in the supplementary material.

2.4 | Evaluation of the relationship between renal function and development of neutropenia

We assessed the probability for the development of ≥ grade 3 neutropenia after pemetrexed administration in the approved dose across different renal function groups. For this purpose, patients with varying renal functions (eGFR of 5, 10, 15, 20, 25, 30, 35, 40, 45, 60, 75 and 90 mL/min) were simulated (n = 1000) after receiving a single 500 mg/m² pemetrexed dose for each eGFR. The probability to develop a ≥ grade 3 neutropenia was calculated for patients with and without vitamin supplementation. The details of the simulations are described in the supplementary material.

In addition, we assessed the typical ANC curves for vitamin-supplemented patients. Typical patients with adequate renal function (eGFR: 90 mL/min) and decreased renal function (eGFR: 20 mL/min) after a pemetrexed dose of 500 mg/m² were simulated. Next, we calculated the pemetrexed dose to be administered to a patient with an impaired renal function (eGFR: 20 mL/min) to harbor a similar neutropenic response as a patient dosed with 500 mg/m² pemetrexed with an eGFR of 90 mL/min. The corresponding AUC for this dose was calculated.

3 | RESULTS

3.1 | Data

In addition to the three patients from our own phase II study, data of 106 patients were obtained. The final dataset thus consisted of 109 patients with known demographic characteristics, vitamin supplementation status and pemetrexed-dose related information. The baseline characteristics of the population are summarized in Table 1. A total of 566 pemetrexed plasma concentrations and 1513 ANCs at different time points were available for analysis. A wide range in eGFR (calculated using the CKD-EPI equation) of 8.4-154.9 mL/min was observed. Overall, eight patients had a renal function for which pemetrexed is currently contraindicated. In addition, about
TABLE 1  Baseline characteristics of the population used for the PK/PD modeling

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>109</td>
</tr>
<tr>
<td>Gender, male</td>
<td>75 (68.8%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>62</td>
</tr>
<tr>
<td>Range</td>
<td>25-80</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>74.4</td>
</tr>
<tr>
<td>Range</td>
<td>47.5-127.2</td>
</tr>
<tr>
<td>BSA (mg/m²)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>1.90</td>
</tr>
<tr>
<td>Range</td>
<td>1.44-2.60</td>
</tr>
<tr>
<td>eGFR (calculated with CKD-EPI; mL/min)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>97.2</td>
</tr>
<tr>
<td>Range</td>
<td>8.4-154.9</td>
</tr>
<tr>
<td>Received vitamin supplementation</td>
<td>78 (71.6%)</td>
</tr>
<tr>
<td>Pemetrexed dose (mg/m²)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>500</td>
</tr>
<tr>
<td>Range</td>
<td>129.5-613.4</td>
</tr>
</tbody>
</table>

Abbreviations: BSA, body surface area; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; PK/PD, pharmacokinetics/pharmacodynamic.

three-quarters of the patients received vitamin B11 and B12 supplementation.

3.2  Pharmacokinetic-pharmacodynamic analysis

The model of Latz et al describing a linear exposure-toxicity relationship was used as a starting point of our analysis. As an alternative model we hypothesized a relationship in which the development of neutropenia after pemetrexed administration is driven by the time above a threshold concentration of pemetrexed. This threshold model was based on the analogy between pemetrexed and methotrexate that also exhibits threshold-driven toxicity. This hypothesis was also driven by the fact that early clinical studies suggested the presence of a threshold-driven toxicity, revealing an MTD for a daily pemetrexed dose of 4 mg/m²/day and 40 mg/m²/week, the linear exposure-toxicity relationship under-predicted frequencies of any grade of neutropenia to occur, with a maximum of two out of six patients. In contrast, the threshold relationship predicts higher frequencies in these dosing regimens, which is in line in what has been observed in the clinical studies. The predicted frequencies per grade of neutropenia can be found in the supplemental materials (Figures S5-S7). Thus, a linear relationship between neutrophil proliferation and plasma concentrations as previously suggested by Latz et al seemed incapable of predicting neutropenia in patients with prolonged exposure to low plasma concentrations of pemetrexed, as is the case in patients with daily dosing or patients with renal impairment.

3.3  External validation

The predictive performance of both the linear and threshold-driven neutropenia relationship for the outcomes of the phase I studies in pemetrexed is depicted in Figure 1. The observed frequency of any grade of neutropenia as found in the phase I pemetrexed studies is marked by a dashed vertical gray line in the panels. For the 600 mg/m² every 21 days both relationships predicted similar frequencies of neutropenic events. However, for low dose pemetrexed (4 mg/m²/day and 40 mg/m²/week), the linear exposure-toxicity relationship under-predicted frequencies of any grade of neutropenia to occur, with a maximum of two out of six patients. In contrast, the threshold relationship predicts higher frequencies in these dosing regimens, which is in line in what has been observed in the clinical studies. The predicted frequencies per grade of neutropenia can be found in the supplemental materials (Figures S5-S7). Thus, a linear relationship between neutrophil proliferation and plasma concentrations as previously suggested by Latz et al seemed incapable of predicting neutropenia in patients with prolonged exposure to low plasma concentrations of pemetrexed, as is the case in patients with daily dosing or patients with renal impairment.

3.4  Evaluation of the relationship between renal function and development of neutropenia

Figure 2 illustrates the probability to develop ≥ grade 3 neutropenia after a single BSA-based pemetrexed dose of 500 mg/m² in patients with varying renal function. In patients with adequate renal function (eGFR: 45-90 mL/min) the probabilities range from 18.7% to 45.9% in the vitamin-supplemented group and between 34.3% and 69.9% in the nonsupplemented group. As observed, in vitamin-supplemented patients with impaired renal function, it is predicted that more than half of the patients develop ≥ grade 3 neutropenia, probabilities range from 51.0% for an eGFR of 40 mL/min to 92.6% in patients with an eGFR of 5 mL/min.

In Figure 3A-C, the predicted neutropenic responses after pemetrexed treatment in a typical vitamin-supplemented patient are depicted for a threshold-driven relationship. For patients with an adequate renal function (eGFR: 90 mL/min), the approved dose of pemetrexed will result in a predicted ANC nadir of 2.2 × 10⁹/L (see Figure 3A). Moreover, in a typical patient with a decreased renal function (eGFR: 20 mL/min) the approved dose will result in grade 4 neutropenia (Figure 3B). Figure 3C illustrates the typical ANC values predicted based upon the threshold relationship for a patient with eGFR 90 mL/min dosed with 1000 mg (corresponding to 500 mg/m²) pemetrexed and a patient with eGFR 20 mL/min dosed with 20 mg of pemetrexed. Note that the curves overlap and therefore, a dose of 0.017-0.047). Vitamin supplementation increased the threshold concentration to 0.110 mg/L (95% CI: 0.092-0.146 mg/L). A detailed description of both models can be found in the supplemental material.
FIGURE 1  Model-predicted frequencies of ≥ grade 1 of neutropenia observed in the simulations of the phase I studies according to the linear exposure-toxicity relationship (left panel) or the threshold relationship (right panel). A, after pemetrexed 4 mg/m²/day for 5 consecutive days every 21 days. B, after pemetrexed 40 mg/m²/week for 4 consecutive weeks every 6 weeks. C, after pemetrexed 600 mg/m² every 21 days. The y-axis represents the relative frequency of trials in which the predicted frequency of neutropenia was found. The dashed line represents the actual observed frequency.

FIGURE 2  Probability to develop ≥ grade 3 neutropenia in patients with varying renal functions dosed with 500 mg/m² pemetrexed, with vitamin supplementation (black line) or without vitamin supplementation (gray line).
of 20 mg in a patient with impaired renal function is likely as safe as the approved dose in patient with adequate renal function. The calculated pemetrexed AUC of this 20 mg dose with an eGFR of 20 mL/min was 12.7 mg/C1h/L. This indicates that the dose has to be reduced almost a 50-fold for a neutropenia-equivalent dose, resulting in an approximately 13-fold lower AUC in patients with renal impairment compared to patients with adequate renal function.

4 | DISCUSSION

We performed an in-depth analysis of the exposure-toxicity relation of pemetrexed based on pharmacokinetic and ANC data collected from early clinical studies and from our failed renal impairment study. We showed that a threshold-driven toxicity predicts the development of neutropenia and that the previously suggested linear exposure-toxicity relationship is an inappropriate predictor for pemetrexed toxicity in case of long-term exposure to low pemetrexed plasma concentrations, for example, in daily dosing or in case of renal impairment. The clinical implication of our findings is that the therapeutic efficacy of a safe dose in patients with impaired renal function can be questioned.

Initially, in an early phase I study, a reduced BSA-based pemetrexed dosing in a vitamin unsupplemented patient with renal impairment led to a systemic exposure of 360 mg·h/L and fatal toxicities. This is an exposure twice as high as in patients with adequate renal function dosed with the approved dose of pemetrexed. Underlines that dosing in patients with renal impairment is not as straightforward as initially thought.

Other early phase I studies of pemetrexed already showed that prolonged yet low exposure to pemetrexed resulted in severe neutropenia. To elaborate, the MTDs in the daily and weekly dose schedule in nonvitamin-supplemented patients with adequate renal function were 4 and 40 mg/m² respectively and, thus, markedly lower than the MTD of 600 mg/m² found for pemetrexed in a 21-day cycle. The external validation showed that both the linear and the threshold-driven exposure-toxicity relationship are capable to predict neutropenia in the standard 3-weekly dosing schedule. However, only the threshold relationship can accurately predict the development of neutropenic responses in patients with impaired renal function, while a linear exposure-toxicity relationship is not able to capture these responses accurately in this patient group. For methotrexate, another antifolate, structurally similar to pemetrexed, a toxicity threshold was previously identified in patients receiving high-dose treatment, further supporting the plausibility that pemetrexed-induced neutropenia is also dependent on such a threshold-driven relationship. This finding may explain recent findings by Kwok and colleagues, who found that presence of third space fluid during treatment with pemetrexed is a significant risk factor for this toxicity. Presence of third space fluid may result in an increase of a peripheral compartment volume.
resulting in a prolonged terminal elimination half-life and, thus, a risk factor for development of toxicity.

The typical pemetrexed threshold concentration identified in our study was 0.030 mg/L for vitamin-unsupplemented patients and 0.110 mg/L for vitamin-supplemented patients. In antiproliferative assays in CCRF-CEM cell lines, Taylor et al and Shih et al showed 0.007 and 0.011 mg/L pemetrexed respectively to be the concentration in which half of the maximum inhibitory effect occurred.24,25 When corrected for the approximately 81% plasma protein binding of pemetrexed26 this would translate to values of 0.036 mg/L and 0.057 mg/L respectively, which is in the same order of magnitude as found in our study.

Vogelzang et al showed that 26.3% of patients supplemented with vitamin B11 and B12 during pemetrexed treatment developed grade 3/4 neutropenia vs 37.5% in the unsupplemented group of patients with adequate renal function.6 This is in line with the results of our model-based predicted frequency for a typical patient with adequate renal function (Figure 2). Moreover, we show that vitamin-supplementation increases the threshold concentration. This is also suggested by an early study in mice showing that lethality as a consequence of toxicity occurs at lower concentrations in the folate-deficient species.27 Although nowadays vitamin supplementation is standard of care during treatment, does not alter the efficacy of pemetrexed6 and reduces the occurrence of severe side effects, there remains a high incidence of neutropenia during pemetrexed treatment, especially in the renally impaired patients,4 underlining the unmet need of a safe and effective dosing regimen for this patient group.

A limitation of our study is that, although based on a large database, only data from a limited number of patients with renal impairment were available. Nonetheless, the external validation confirmed its predictive capability across different dosing regimens and renal functions and this is the largest study thus far with an integrated analysis of the data from two prospective renal impairment studies with pemetrexed. Another limitation may be that none of the patients in our analysis concomitantly used other anticancer drugs, like carboplatin or cisplatin. Although this enabled an unclouded assessment of the neutropenic effects of pemetrexed, it should be noted that pemetrexed is often combined with these drugs. As these platinum-based anticancer agents may also cause myelotoxicity it is likely that the probability of toxicity in combination with these drugs is even higher.28

Since we now know that potentially subtherapeutic pemetrexed doses in patients with renal impairment can still result in severe neutropenia, we strongly recommend against administration of pemetrexed in this patient group. A pemetrexed dose leading to an equivalent neutropenic response in patients with renal dysfunction is considerably lower and leads to a substantial (13-fold) lower AUC than after a pemetrexed dose of 500 mg/m² for a patient with adequate renal function. Whether the AUC of a pemetrexed dose is the determinant for antitumor efficacy, is currently unknown. The early phase I studies showed that administration of 600 mg/m² Q3W superior efficacy of pemetrexed, but similar neutropenic response compared to the 4 mg/m²/day for five consecutive days Q3W and the 40 mg/m²/week for four consecutive weeks every 6 weeks dosing regimen.16-18 This suggests that exposure-response and exposure-toxicity relationships for pemetrexed have different pharmacokinetic drivers. Moreover, for the structural analogue methotrexate a relationship between AUC and efficacy in the treatment of primary central nervous system lymphoma has been observed, while toxicity is explained by a time-above-threshold concentration.29,30 We currently assume that AUC is a better predictor for efficacy than the time-above-threshold concentration, and we hypothesize that the efficacy of treatment with pemetrexed at a substantial lower exposure than found for the approved dose might be compromised. For methotrexate, administration of folinic acid 24-36 hours after start is used to “rescue” nonmalignant cells.31 Folinic acid, not to be confused with folic acid (vitamin B11), has been shown to be capable to completely reverse pemetrexed-induced cytotoxicity in human tumor cell lines.27 Moreover, folinic acid has been shown to be able to revert the clinical signs of toxicity and hematological alterations induced by a potentially lethal pemetrexed dose in dogs.32 Currently, in the drug label of pemetrexed, use of high dose folinic acid rescue for management of pemetrexed overdose is proposed.33 It may be argued that standard folinic acid rescue (eg, 30 mg three time daily routinely started 24 hours after administration of pemetrexed, with sufficient wash-out before administration of the next pemetrexed dose) may have the potential to allow safe dosing of pemetrexed in renally impaired patients. Other prophylactic strategies worth studying include the use of prophyactic granulocyte colony-stimulating factor (G-CSF), which is already used as standard of care to reduce the severity of chemotherapy-induced neutropenia34,35 or glucarpidase, an enzyme that can inactivate methotrexate and, based on in vitro experiments, shows similar activity for pemetrexed.36,37 The efficacy and safety of all these strategies should be evaluated in a prospective study to enable pemetrexed treatment at a therapeutic dose in patients with impaired renal function.

In summary, we show that pemetrexed-induced neutropenia is likely driven by the time above a threshold pemetrexed concentration and this has caused previous studies of pemetrexed in patients with impaired renal function to fail. To enable therapeutic dosing of pemetrexed in patients with impaired renal function without toxicity, further investigations on prophylactic treatments are essential.

CONFLICT OF INTEREST
René J. Boosman, Thomas P. C. Dorlo, Nikki de Rouw, Jacobus A. Burgers, Michel M. van den Heuvel, Bonne Biesma, Sander Groes, Alwin D. R. Huitema and Rob ter Heine declare that they have no competing interests. Anne-Marie C. Dingemans reports financial support from advisory boards Sanofi, Amgen, Bayer, Eli-Lilly and Roche and as lecturer from Jansen, Pfizer and AstraZeneca. Lizza E. L. Hendriks reports the following conflicts outside the submitted work: research funding from Roche, Boehringer-Ingelheim, AstraZeneca and Takeda (all to the institution); advisory boards for Boehringer-Ingelheim, BMS, Eli-Lilly, Roche, Pfizer, Takeda, MSD and Amgen (all institutional, except once for Roche); travel and...
conference reimbursements from Roche; funded mentorship sessions with key opinion leaders from AstraZeneca, fees for webinars/medtalks from AstraZeneca and funded interview sessions from Roche (to the institution); local principal investigator in clinical trials from AstraZeneca, Novartis, BMS, MSD, Merck, GSK, Takeda, Blueprint, Roche, Janssen Pharmaceuticals and Miroti. Joachim G. J. V. Aerts reports personal fees and nonfinancial support from MSD, personal fees from BMS, Boehringer-Ingelheim, Amphera, Eli-Lilly, Takeda, Bayer, Roche and AstraZeneca, outside the submitted work; in addition, Prof. Aerts has a patent allogenic tumor cell lysate licensed to Amphera, a patent combination immunotherapy in cancer pending, and a patent biomarker for immunotherapy pending. Ron H. J. Mathijssen reports grants from notherapy in cancer pending, and a patent biomarker for immuno-therapy pending. René J. Boosman reports grants from Astellas, Bayer, Boehringer-Ingelheim, Cristal Therapeutics, Pamgene, Pfizer, Novartis, Servier and Roche, personal fees from Novartis and Servier and a patent from Pamgene, outside the submitted work.

**ETHICS STATEMENT**

Our study has been performed in accordance with the Declaration of Helsinki and has been approved by the Central Committee on Research Involving Human Subjects of Amhem-Nijmegen, the Netherlands (reference number: 2018-4442). ClinicalTrials.gov identifier: NCT03656549; first submitted: September 4, 2018. https://clinicaltrials.gov/ct2/show/NCT03656549. Before inclusion in our study informed consent to participate was obtained from the participants.

**DATA AVAILABILITY STATEMENT**

All data generated or analyzed during this study are included in this published article and its supplementary information files. Further information is available from the corresponding author upon request.

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**REFERENCES**


SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of this article.