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# Prolonged Pemetrexed Maintenance (42 Cycles over 34 Months) in Metastatic Lung Adenocarcinoma: Durable Disease Control and Progressive Renal Impairment—A Case Report

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## Abstract

Continuation maintenance with pemetrexed after platinum-pemetrexed induction is a standard of care in non-squamous non-small cell lung cancer, but very prolonged exposure and its renal consequences are rarely documented in detail. We report the case of a 55-year-old woman with stage IV lung adenocarcinoma (EGFR wild-type, ALK not rearranged; nodal, bone and brain metastases) and an ECOG performance status of 1. She received six cycles of cisplatin-pemetrexed, followed by 42 cycles of pemetrexed maintenance over approximately 34 months (M6 - M40; M0 = start of chemotherapy), with zoledronic acid from M17; the disease remained stable on every quarterly CT scan. After a nine-month break at her own request, progression occurred at M49. Rechallenge with platinum-pemetrexed (four cycles planned, incomplete because of supply shortages) was followed by approximately 19 months of stability from its start, including approximately 12 months without any treatment after M57, which may reflect indolent tumour behaviour rather than a treatment effect. A second pemetrexed maintenance could not be started because of impaired renal function: only dose-adjusted zoledronic acid was given. Cockcroft-Gault clearance fell from 85 - 130 mL/min during induction to 45 mL/min at M40 and 24 mL/min at M58. No dose of pemetrexed was given with a clearance below 45 mL/min; it was postponed from M54 and then permanently discontinued at M58. The only value available at M71 is 54 mL/min, suggesting partial and uncertain recovery after pemetrexed discontinuation. Cisplatin, carboplatin, zoledronic acid and repeated exposure to contrast media may have contributed to the renal injury, and no kidney biopsy was performed. This single case cannot establish the efficacy of prolonged maintenance or of rechallenge; it illustrates the need for

renal monitoring with a single estimator before each cycle, hydration, review of nephrotoxic medications, and shared decisions with nephrology when clearance approaches 45 mL/min.

## Keywords

Lung Adenocarcinoma, Pemetrexed, Maintenance Chemotherapy, Nephrotoxicity, Zoledronic Acid, Case Report

## 1. Introduction

In non-squamous non-small cell lung cancer, pemetrexed maintenance after platinum-based induction improves progression-free survival [1] [2] and overall survival [1] [3]. The first trial evaluated "switch" maintenance after an induction without pemetrexed [1], whereas PARAMOUNT evaluated continuation maintenance after cisplatin-pemetrexed [2] [3], which corresponds to the situation of our patient. In these trials, the number of maintenance cycles remained limited, and treatment lasting more than two years has been reported only in isolated cases [4] [5]. Pemetrexed is eliminated unchanged by the kidneys, and its summary of product characteristics advises against its use when creatinine clearance is below 45 mL/min [6]. Acute and chronic kidney injury have been described during maintenance: in a prospective cohort, 30% to 49% of patients developed acute kidney disease, sometimes progressing to chronic kidney disease and treatment discontinuation [7]. Prolonged exposure has also been associated with chronic renal dysfunction in a retrospective series of 90 patients [8], and tubular toxicity has been described with maintenance pemetrexed [9].

We report a patient who received 42 cycles of pemetrexed maintenance with stable disease and preserved general condition, whose renal function was documented over more than five years, and who received a platinum-pemetrexed rechallenge after a treatment break. We focus on the renal trajectory recalculated with a single estimator and on the other nephrotoxic exposures, and we discuss what this case adds to previous publications. This case illustrates the balance between durable oncological benefit and renal toxicity in a setting of limited drug availability.

## 2. Case Presentation

**Patient and presentation.** A 55-year-old woman, with no notable medical or surgical history and no history of smoking, presented with lower chest pain evolving over six months, followed by bone pain. The performance status (ECOG) was 1 and no peripheral lymphadenopathy was palpable. Time is expressed in months from the start of first-line chemotherapy (M0).

**Diagnosis.** The diagnosis was made in August 2018 (M-1). The chest CT scan showed obstructive atelectasis of the right upper lobe due to compressive medias-

tinal lymphadenopathy, multiple bilateral pulmonary nodules and sclerotic vertebral lesions. Bronchoscopy found complete stenosis of the right upper lobar bronchus with an endobronchial tumour. The biopsy showed a poorly differentiated non-small cell carcinoma, and immunohistochemistry confirmed an adenocarcinoma. EGFR was wild-type, ALK was not rearranged and PD-L1 status was unknown. The brain-chest-abdomen-pelvis CT scan showed enhancing micronodular metastatic brain lesions (occipital, frontal and parietal), a hypodense nodule in hepatic segment IV, coeliac and porta hepatis lymphadenopathy, and sclerotic bone lesions (T10, L4, L5, S3). The bone scan confirmed lesions at C6, T2 and T9. A brain MRI was not performed. The brain lesions were followed by CT scan, remained stable and received no local treatment; radiotherapy was reserved for the onset of neurological symptoms, none of which was documented. The final diagnosis was stage IV lung adenocarcinoma.

**Treatment.** First-line treatment consisted of six cycles of cisplatin-pemetrexed (from 10 September 2018 to 1 February 2019) with folic acid and vitamin B12 supplementation (cisplatin 75 mg/m$^2$, pemetrexed 500 mg/m$^2$). The sixth cycle was delayed by one week because of grade 1 neutropenia and at the patient's request. Continuation maintenance with pemetrexed was then given every three weeks from M6 (7 March 2019) for a total of 42 cycles over 34 months (last cycle on 13 January 2022, M40) at a dose of 500 mg/m$^2$. Zoledronic acid was added at M17 (3 February 2020) after dental care and a normal dental panoramic radiograph. It was given at most treatment visits for approximately two years, at 3.5 mg when clearance was 50 - 60 mL/min and at 3.3 mg when it was 40 - 49 mL/min, in accordance with the renal dose adjustment in the marketing authorisation, and was postponed on several occasions. At the patient's request, treatment was interrupted from M41 to M49. After progression (M49) and the nephrology opinion (24 November 2022), and after a normal panoramic radiograph, four cycles of platinum-pemetrexed rechallenge (carboplatin AUC 5, pemetrexed 500 mg/m$^2$, zoledronic acid; from 24 November 2022 to 3 February 2023) were planned, with oral hydration. Because of supply shortages, the drugs were not delivered together: carboplatin was unavailable at cycle 1 (pemetrexed and zoledronic acid only), and pemetrexed was unavailable at cycle 2 (carboplatin and zoledronic acid only). Pemetrexed was not given at the 4$^{th}$ cycle because of renal function < 45 mL/min. From 9 March 2023 (M54), a second maintenance with pemetrexed and dose-adjusted zoledronic acid and oral hydration was decided; however, the patient received only dose-adjusted zoledronic acid, pemetrexed having been postponed because of a glomerular filtration rate below 45 mL/min (13 June 2023), and then permanently discontinued on 10 July 2023 (M57 - M58), following a nephrology opinion. After the second progression, and given the nephrotoxicity of platinum and pemetrexed, following multidisciplinary discussion, docetaxel 75 mg/m$^2$ every three weeks was started at M71 with zoledronic acid 3 mg. Nephrology had indicated that no renal dose adjustment was necessary for docetaxel, which could be given with zoledronic acid at 3 mg; docetaxel was given at 75 mg/m$^2$. Pembrolizumab combined with plati-

num-pemetrexed was not used at diagnosis or at progression, because immunotherapy was unavailable owing to a lack of resources.

**Course.** Quarterly CT scans showed stable disease throughout maintenance, including in the brain. Treatment was well tolerated: no fatigue, skin rash, neuropathy or digestive symptoms were recorded during the first maintenance, blood counts were reported as acceptable at each visit (nadir values not available), and no febrile neutropenia or grade ≥ 2 toxicity was recorded. Total serum calcium remained between 8.2 and 10.1 mg/dL (2.05 - 2.52 mmol/L) during the first maintenance; albumin-corrected calcium was approximately 10.9 mg/dL (November 2022). Progression occurred at M49 after the break: the right upper lobe lesion increased from 52 × 30 to 59 × 45 mm with an increased number of pulmonary nodules. After reintroduction of platinum in combination with pemetrexed and zoledronic acid, the disease was stable at M52, M61 and M65. At M69, a second progression showed a spiculated lesion of the left lower lobe (30 × 31 mm), an increased number of bilateral nodules and a minimal bilateral pleural effusion, while the right upper lobe mass was stable (64 × 44 mm, invading the right pulmonary artery and the superior vena cava) and the bone lesions were stable. The patient was ECOG 1 with grade 3 mMRC dyspnoea. She received a single cycle of docetaxel 75 mg/m$^2$ with zoledronic acid 3 mg, and follow-up ended after M71 (last documented visit on 7 August 2024; survival of at least 72 months from diagnosis and 71 months from M0; the patient was subsequently lost to follow-up).

**Renal exposure history.** There was no known kidney disease before treatment. Potentially nephrotoxic exposures were cisplatin (six cycles with hydration, with a cumulative cisplatin dose of 450 mg/m$^2$), carboplatin AUC 5 (delivered at three rechallenge cycles), zoledronic acid (approximately two years in the first phase, then again from November 2022 at doses adjusted to renal function, 3 mg at M71) and contrast-enhanced chest-abdomen-pelvis CT scans repeated approximately every three to four months (more than 15 examinations). No NSAIDs, ACE inhibitors/ARBs, diuretics or other nephrotoxic drugs, and no episode of dehydration, are recorded in the file; oral hydration was regularly reinforced by nephrology.

**Pemetrexed administration according to renal function.** Renal function was checked at the visit preceding each cycle. All Cockcroft-Gault (CG) values recorded during the first maintenance were at least 45 mL/min after rounding, the last one (before cycle 42) being 44.9 mL/min. During the second maintenance period (clearance of approximately 33 - 38 mL/min), pemetrexed was not given: the patient received only zoledronic acid with dose adjustment; the values of 24 - 28 mL/min at M57 therefore led to permanent discontinuation and do not correspond to administered cycles. The documented rationale for resuming treatment, after the nephrology opinion of 24 November 2022 (stable renal function, small well-differentiated kidneys without obstruction, negative 24-hour proteinuria), was progression after the break in a patient with prolonged disease control and few alternatives, with reinforced oral hydration and close renal monitoring.

**Table 1.** Timeline of treatment and course (M0 = start of first-line chemotherapy).

| Period | Treatment | Serum creatinine and clearance | Clinical and imaging events |
|---|---|---|---|
| M-1 to M0 (Aug.-Sept. 2018) | Diagnosis (stage IV) | — | Adenocarcinoma, EGFR wild-type; nodal, bone and brain metastases; ECOG 1 |
| M0 to M5 (Sept. 2018-Feb. 2019) | Cisplatin 75 mg/m² - pemetrexed 500 mg/m² × 6, folic acid and vitamin B12 | Recorded clearance: 93 → 130 → 108 → 85 - 89 mL/min | Stable disease (30 × 31 vs 30 × 35 mm); grade 1 neutropenia (cycle 6 delayed by one week) |
| M6 to M40 (Mar. 2019-Jan. 2022) | Pemetrexed 500 mg/m² × 42; zoledronic acid from M17 with dose adjustment according to creatinine clearance | Serum creatinine 0.70 - 1.40 mg/dL (62 - 124 µmol/L); CG 86 (M17) → 49 - 91 (M24 - M33) → 45 (M40) | Stable disease on every CT scan (every 3 - 4 months); ECOG 1; no grade ≥ 2 toxicity recorded; total serum calcium 8.2 - 10.1 mg/dL |
| M41 to M49 (Feb.-Oct. 2022) | Treatment break (patient's request); last zoledronic acid on 15 Feb. 2022 | Serum creatinine 1.20 mg/dL (106 µmol/L); CG 52 (M41) | Stable CT scan in Feb. 2022; progression at M49 (52 × 30 → 59 × 45 mm; more pulmonary nodules) |
| M50 to M53 (Nov. 2022-Feb. 2023) | Rechallenge, 4 cycles planned: carboplatin AUC 5, pemetrexed, zoledronic acid, oral hydration (carboplatin unavailable at cycle 1, pemetrexed at cycle 2) | Serum creatinine 1.29 - 1.50 mg/dL (115 - 133 µmol/L); CG 45 - 48 → 40 | Grade 1 vomiting; stable disease at M52; nephrology opinion (small kidneys, no obstruction, no proteinuria) |
| M54 to M56 (Mar.-May 2023) | Second maintenance with pemetrexed and zoledronic acid decided; only dose-adjusted zoledronic acid was given, pemetrexed being postponed | Serum creatinine 1.40 - 1.60 mg/dL (124 - 141 µmol/L); CG 37 → 33 | Nephrology opinion requested |
| M57 to M69 (Jun. 2023-Jun. 2024) | Pemetrexed postponed on 13 June and discontinued on 10 July 2023 (M57 - M58); surveillance, nephrology follow-up | Serum creatinine 1.91 → 2.20 mg/dL (169 → 195 µmol/L); CG 28 → 24 | Ultrasound: small hyperechoic kidneys; stable disease at M61 and M65; transient consolidations suggestive of infection at M65 |
| M69 | Second progression | — | Left lower lobe lesion 30 × 31 mm, more pulmonary nodules, minimal pleural effusion; right upper lobe mass stable |
| M70 to M71 (Jul.-Aug. 2024) | Docetaxel 75 mg/m² + zoledronic acid 3 mg | Serum creatinine 1.14 mg/dL (101 µmol/L); CG 54 (46 with the last documented weight) | Asymptomatic hypocalcaemia (7.1 mg/dL) corrected; ECOG 1 |

ECOG: performance status; CG: Cockcroft-Gault (mL/min); serum creatinine 1 mg/dL = 88.4 µmol/L (1 mg/L = 8.84 µmol/L).

**Renal function.** Clearance was recalculated with the Cockcroft-Gault equation [10] from serum creatinine, age and weight (Table A1, Figure 1). During induction, the recorded clearance was 93 mL/min at cycle 3, 130 at cycle 4, 108 at cycle 5 and 85 - 89 at cycle 6 (serum creatinine and estimator not transcribed). CG clearance was 86 mL/min at M17 (serum creatinine 0.75 mg/dL, 66 µmol/L). It then fluctuated between 49 and 91 mL/min from M23.5 to M33, with two isolated low values (50 mL/min at M23.5 and 49 mL/min at M29.5, serum creatinine 1.3 mg/dL, each followed by higher values), was 53 - 58 mL/min at M35 - M39, and

fell to 48 then 44.9 mL/min at M40 (serum creatinine 1.40 mg/dL, 124 µmol/L). There was no recovery during the nine-month break: 52 mL/min at M41 (one value) and 45 - 48 mL/min at M50 - M52. Clearance was 40 mL/min at M53, 37 - 38 mL/min at M54 - M55 and 33 mL/min at M56, then 28 mL/min on 13 June 2023 (serum creatinine 1.91 mg/dL, 169 µmol/L) and 24 mL/min on 10 July 2023 (serum creatinine 2.20 mg/dL, 195 µmol/L; M57 - M58). The November 2022 ultrasound showed small kidneys with preserved differentiation, and the June 2023 ultrasound showed small hyperechoic kidneys without obstruction; 24-hour proteinuria was negative in November 2022 and urea was 0.56 g/L in July 2023. Pemetrexed was discontinued. At M71, serum creatinine was 1.14 mg/dL (101 µmol/L). Clearance was recorded as 54 mL/min, which corresponds to CG with a weight of 65 kg; with the last documented weight (about 56 kg), CG is 46 mL/min. Asymptomatic hypocalcaemia (7.1 mg/dL, 1.77 mmol/L) was corrected with calcium and vitamin D. The clearance values in this article are CG values in mL/min, unless otherwise stated. The timeline is summarised in Table 1, the renal data in Supplementary Table A1 and the renal course in Figure 1.

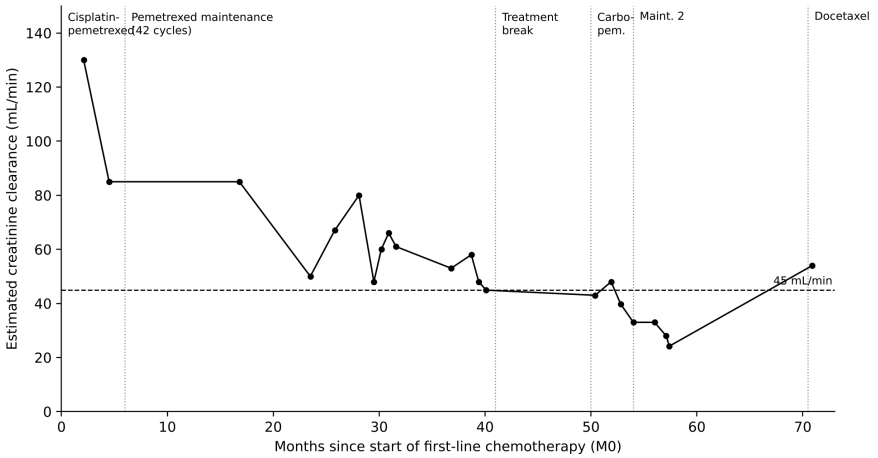



Figure 1. Creatinine clearance (Cockcroft-Gault, mL/min) over time according to treatment phase. The dashed line marks the 45 mL/min threshold. Weights used: see Supplementary Table A1.

## 3. Discussion

**Main findings.** Our patient received 42 consecutive cycles of maintenance with stable disease for approximately 34 months and preserved general condition, beyond the median duration reported in the pivotal trials [1]-[3]. Including induction, she received continuous pemetrexed-based treatment for 40 months (M0 - M40), which explains why the title mentions 42 cycles over 34 months of maintenance. Documented overall survival exceeds 70 months from the start of chemotherapy (approximately 72 months from diagnosis) for a de novo metastatic disease, with bone and brain involvement. The benefit was disease control rather than an objective response, and no biomarker explains it. The disease also remained stable for approximately nine months during the first break and for ap-

proximately 12 months without any anticancer treatment (M57 - M69), which suggests indolent tumour behaviour that may have contributed to the prolonged control; the duration of control therefore cannot be attributed to pemetrexed alone. Adding an anti-PD-1 to platinum-pemetrexed is now a first-line standard irrespective of PD-L1 expression [11]; it was not used here because of its unavailability, owing to a lack of resources.

**Rechallenge.** After nine months without treatment, platinum-pemetrexed rechallenge was followed by disease control of approximately 19 months from the start of the rechallenge (M50.5 to M69), including approximately 16 months after the last administration of pemetrexed. Because of supply shortages, the planned doublet was fully delivered at only one cycle out of four, and the second maintenance could not be started because of impaired renal function. The observed control therefore cannot be attributed to the rechallenge, and indolent behaviour is an alternative explanation. It is compatible with persistent chemosensitivity, without demonstrating it, and a single retrospective case cannot establish a rechallenge strategy, which has been examined in larger retrospective series [12].

**Comparison with previous publications.** Prolonged pemetrexed maintenance has already been reported. Zhao *et al.* described a 52-year-old woman with stage IV adenocarcinoma who received 46 maintenance cycles after six cycles of cisplatin-pemetrexed, with a progression-free survival of 46 months [4]; Furugen *et al.* reported prolonged disease control with a complete response after pemetrexed maintenance [5]; and pemetrexed rechallenge was evaluated in 31 patients by Zhuo *et al.* [12]. Renal toxicity of pemetrexed, including biopsy data, has been described in several case reports [13]-[15]. The closest precedent to our case is a patient who received 51 maintenance doses at a reduced dose and extended interval, with a creatinine clearance between 25 and 55 mL/min [16]. Our case differs from these reports by 1) more than five years of documented follow-up with serial renal estimates covering approximately 51 doses of pemetrexed, 2) the combination in the same patient of prolonged maintenance, zoledronic acid and a platinum rechallenge after a break, with clearance not recovering during the nine-month break and declining again on re-exposure, and 3) a context of limited access to immunotherapy and repeated supply shortages. Its contribution is therefore mainly descriptive and educational: it documents the renal cost of very prolonged pemetrexed exposure rather than a new efficacy signal.

**Nephrotoxicity.** The renal deterioration of this patient is consistent with published data. In a prospective cohort of patients on pemetrexed maintenance, acute kidney disease occurred in 30% of the main cohort and 49% of an independent cohort, leading to chronic kidney disease and treatment discontinuation in a substantial proportion of them [7]. A retrospective series of 90 patients concluded that prolonged exposure can induce chronic renal dysfunction and stressed the importance of avoiding dehydration and nephrotoxic combinations [8]. In a retrospective cohort of 134 patients, cisplatin induction (OR 8.76), more than 15 maintenance cycles (OR 3.84) and an undrained third-space fluid collection (OR

4.19) were reported as independent risk factors [17]; the number of cycles and concomitant use of NSAIDs, ACE inhibitors/ARBs or diuretics were also identified as risk factors in a recent series [18], and changes in renal function during PARAMOUNT maintenance were analysed separately [19]. Our patient combined cisplatin induction, prolonged maintenance and zoledronic acid, carboplatin and repeated exposure to contrast media. The recalculated trajectory does not allow the contribution of each factor to be separated. Zoledronic acid carries its own renal risk stated in the marketing authorisation, and additive tubular effects with cisplatin and pemetrexed are plausible but cannot be isolated here. Clearance was 85 - 89 mL/min between M4.5 and M17; the two isolated low values at M23.5 and M29.5 (approximately 50 mL/min) were followed by higher values, and progressive deterioration occurred from approximately M35, during combined exposure to pemetrexed and zoledronic acid. Clearance did not recover during the nine-month break (52 mL/min at M41, 45 - 48 mL/min at M50 - M52), which suggests chronic injury established before the rechallenge, and it continued to fall between M53 and M58, while only zoledronic acid was being given. Dehydration cannot be excluded although no episode is recorded. Small hyperechoic kidneys, without obstruction or proteinuria, suggest chronic tubulo-interstitial injury, in keeping with the tubular toxicity described with pemetrexed [9], but without a kidney biopsy the attribution to pemetrexed remains presumptive.

**Practical lessons.** 1) Estimate clearance before each cycle with the same formula, Cockcroft-Gault with the current weight. 2) Reassess the benefit-risk balance when clearance approaches 45 mL/min. 3) Ensure hydration and avoid other nephrotoxic drugs. 4) Adjust zoledronic acid to renal function and monitor serum calcium and dental health. 5) Record the pemetrexed dose administered, the rationale when treatment is given below 45 mL/min, blood counts and concomitant nephrotoxic drugs.

**Context, strengths and limitations.** Supply shortages delayed or modified several cycles which reflects the constraints of oncology practice in our setting. The strengths are the long follow-up, the regular imaging and the documented involvement of nephrology. The limitations are the retrospective single case, incomplete biomarkers, the absence of formal RECIST measurements, clearance recalculated with weights not recorded in the file, the absence of a kidney biopsy, incomplete documentation of blood count nadirs, and several concomitant nephrotoxic exposures.

## 4. Conclusion

This single case shows prolonged disease stability over 42 cycles (34 months) of pemetrexed maintenance in a patient with stage IV EGFR wild-type, ALK-negative lung adenocarcinoma, accompanied by progressive deterioration of renal function whose cause is probably multifactorial (pemetrexed, platinum, zoledronic acid, contrast media) and cannot be attributed to pemetrexed alone. It does not allow the efficacy of prolonged maintenance or of rechallenge to be established, and part of

the disease control may reflect indolent tumour behaviour. Renal function appears to have recovered only partially and uncertainly after discontinuation. Administration of pemetrexed below the 45 mL/min threshold must remain exceptional and documented; the case underlines the importance of regular monitoring of Cockcroft-Gault clearance before each cycle, hydration, review of other nephrotoxic drugs, and shared decisions with nephrology.

## Ethics and Consent Statement

The patient was lost to follow-up after August 2024 and could not be reached despite several telephone call attempts. It was therefore not possible to obtain her written consent for publication. All data were anonymised and do not allow the patient to be identified.

## Author Contributions

M.A.: Writing original draft, writing review and editing. M.B.A.: Writing review and editing. L.A., K.O., Z.B., S.A. and N.M.: Supervision and guidance. All authors read and approved the final manuscript.

## Conflicts of Interest

The authors declare no conflict of interest regarding the publication of this article.

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## Appendix

**Table A1.** Serum creatinine, estimated clearance and treatment at each recorded visit (source: clinical file). Cockcroft-Gault (CG) in mL/min, MDRD (IDMS) in mL/min/1,73 m$^2$. Weight is not recorded in the file: the weights shown were reconstructed from the clearances documented by the team and must be replaced by measured weights. The "Pemetrexed" and "Zoledronic acid" columns indicate actual administration during the visit as described in the text.

| Date | M | Serum creatinine mg/dL (µmol/L) | Weight (kg) | CG | Recorded clearance | Pemetrexed | Zoledronic acid | Remarks |
|---|---|---|---|---|---|---|---|---|
| 23/10/2018 | 1.4 | — | — | — | 93 | Yes (cis-pem) | Not started | Cisplatin-pemetrexed, cycle 3 |
| 14/11/2018 | 2.1 | — | — | — | 130 | Yes (cis-pem) | Not started | Cycle 4 |
| 04/01/2019 | 3.8 | — | — | — | 108 | Yes (cis-pem) | Not started | Cycle 5 |
| 25/01/2019 | 4.5 | — | — | — | 85 | Postponed | Not started | Cycle 6 postponed |
| 01/02/2019 | 4.7 | — | — | — | 89 | Yes (cis-pem) | Not started | Cycle 6 |
| 03/02/2020 | 16.8 | 0.75 (66) | 65 | 86 | 85 | Yes | 1st injection, 4 mg | Maintenance, cycle 14 |
| 24/08/2020 | 23.5 | 1.30 (115) | 65 | 50 | 50 | Yes | 3.5 mg | Maint. cycle 22; |
| 14/09/2020 | 24.1 | 0.70 (62) | 65 | 91 | — | Yes | Yes, 4 mg | Maint. cycle 23 |
| 05/10/2020 | 24.8 | 0.95 (84) | 65 | 67 | 67 | Yes | Yes, 4 mg | Maint. cycle 24 |
| 16/11/2020 | 26.2 | 0.74 (65) | 65 | 86 | 87 | Yes | Yes, 4 mg | Maint. cycle 26 |
| 14/01/2021 | 28.2 | 0.94 (83) | 65 | 68 | 80 | Yes | Yes, 4 mg | Maint. cycle 28; the recorded value of 80 is inconsistent with the serum creatinine (CG 68) |
| 25/02/2021 | 29.5 | 1.30 (115) | 65 | 49 | 48 | Yes | 3.3 mg | Maint. cycle 30; isolated value (file: "13 vs 7") |
| 18/03/2021 | 30.2 | 1.00 (88) | 65 | 64 | 60 | Yes | Yes, 4 mg | Maint. cycle 31 |
| 09/04/2021 | 30.9 | 0.94 (83) | 65 | 68 | 66 | Yes | Yes, 4 mg | Maint. cycle 31/32 |
| 30/04/2021 | 31.6 | 1.04 (92) | 65 | 61 | 61 | Yes | Yes, 4 mg | Maint. cycle 32 |
| 11/06/2021 | 33.0 | 0.96 (85) | 65 | 66 | — | Yes | Postponed | Maint. cycle 34 |
| 16/08/2021 | 35.2 | 1.20 (106) | 65 | 53 | 53 | Yes | 3.5 mg | Maint. cycle 36 |
| 09/11/2021 | 38.0 | 1.09 (96) | 65 | 58 | 58 | Yes | 3.5 mg | Maint. cycle 39 |
| 01/12/2021 | 38.7 | 1.09 (96) | 65 | 58 | 58 | Yes | 3.5 mg | Maint. cycle 40 |
| 22/12/2021 | 39.4 | 1.31 (116) | 65 | 48 | 48 | Yes | 3.3 mg | Maint. cycle 41 |
| 13/01/2022 | 40.1 | 1.40 (124) | 65 | 45 | 44.9 | Yes (last cycle, no. 42) | Postponed | Maint. cycle 42 (last) |
| 15/02/2022 | 41.2 | 1.20 (106) | 65 | 52 | — | No (break) | Yes (last injection; dose not recorded) | Treatment break (patient's request) |
| 08/11/2022 | 49.9 | 1.97 (174) | 65 | 32 | — | No (break) | — | Break; external laboratory (previous values 1.4 and 1.2 mg/dL) |
| 24/11/2022 | 50.5 | 1,35 (119) | 65 | 45 | — | Yes | Yes (adjusted dose) | Rechallenge, cycle 1; carboplatin out of stock |
| 15/12/2022 | 51.2 | 1.30 (115) | 65 | 48 | 48 | No (out of stock) | Yes (adjusted dose) | Rechallenge, cycle 2; pemetrexed out of stock |

**Continued**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 05/01/2023 | 51.8 | 1.30 (115) | 65 | 48 | 48 | Yes | Yes (adjusted dose) | Rechallenge, cycle 3 (carboplatin + pemetrexed + dose-adjusted zoledronic acid) |
| 03/02/2023 | 52.8 | 1.40 (124) | 58 | 40 | 39.8 | No | Yes (adjusted dose) | Rechallenge, cycle 4 without pemetrexed |
| 09/03/2023 | 53.9 | 1.49 (132) | 57 | 37 | — | No | Yes (adjusted dose) | Second maintenance decided; oral hydration, pemetrexed not received because of impaired renal function. |
| 30/03/2023 | 54.6 | 1.45 (128) | 56 | 37 | — | No | Yes (adjusted dose) | Zoledronic acid alone with oral hydration |
| 20/04/2023 | 55.3 | 1.40 (124) | 56 | 38 | — | No | Yes (adjusted dose) | Zoledronic acid with oral hydration |
| 11/05/2023 | 56.0 | 1.60 (141) | 55 | 33 | 33 | No | Yes (adjusted dose) | Nephrology opinion requested |
| 13/06/2023 | 57.1 | 1.91 (169) | 56 | 28 | 28 | No (postponed) | — | Pemetrexed postponed; nephrology opinion |
| 10/07/2023 | 58.0 | 2.20 (195) | 56 | 24 | 24.22 | No (permanently discontinued) | — | Pemetrexed permanently discontinued; ultrasound (23/06/2023): small hyperechoic kidneys |
| 07/08/2024 | 70.9 | 1.14 (101) | 56 | 46 | 54 | No (docetaxel) | 3 mg (nephrology opinion) | Docetaxel 75 mg/m$^2$; recorded clearance of 54 mL/min (weight 65 kg); asymptomatic hypocalcaemia corrected |

Induction values were recorded without serum creatinine and are shown as recorded.