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Published in:

Current Problems in Cancer: Case Reports

DOI:

[10.1016/j.cpcr.2024.100280](https://doi.org/10.1016/j.cpcr.2024.100280)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version

Publisher's PDF, also known as Version of record

Publication date:

2024

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

van de Wal, D., Roets, E., Bleckman, R. F., Nützinger, J., Heeres, B. C., Kerst, J. M., Mohammadi, M., Reyners, A. K. L., Desar, I. M. E., Oosten, A. W., Steeghs, N., & van der Graaf, W. T. A. (2024). Treatment dilemmas in patients with gastrointestinal stromal tumors (GIST) who experienced imatinib-induced pneumonitis: A case series. *Current Problems in Cancer: Case Reports*, 13, Article 100280. <https://doi.org/10.1016/j.cpcr.2024.100280>

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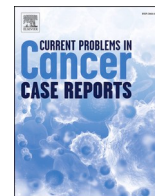
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Current Problems in Cancer: Case Reports

journal homepage: www.elsevier.com/locate/cpccr

Treatment dilemmas in patients with gastrointestinal stromal tumors (GIST) who experienced imatinib-induced pneumonitis: A case series

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ARTICLE INFO

Keywords:

Imatinib

Adverse event

GIST

Pneumonitis

Interstitial lung disease

Case series

ABSTRACT

Introduction: Imatinib has led to a phenomenal progress in the treatment of GIST. A rare and lesser-known side effect of imatinib is pneumonitis, an uncommon multicausal interstitial lung disease.

Methods: Patients registered within the Dutch GIST Registry (DGR) were reviewed. For the patients identified with an imatinib-induced pneumonitis we reported the time on imatinib to develop pneumonitis, how the pneumonitis was diagnosed, graded and managed, and how the GIST treatment was managed.

Cases: Of the 1934 patients registered in the DGR, 1161 patients received imatinib at some point, of which nine patients (0.8 %) were identified with an imatinib-induced pneumonitis. At time of the pneumonitis, patients received a daily imatinib dose of 200–400 mg for a mean duration of 486 days. One patient was able to continue imatinib in a lower dose, in the other eight patients imatinib was interrupted, and six of these patients started prednisolone treatment. After management of the imatinib-induced pneumonitis, four patients stopped imatinib permanently, two patients were rechallenged with imatinib, and two patients started treatment with second-line sunitinib.

Conclusion: Imatinib-induced pneumonitis is a rare side effect, which may affect GIST management considerably. After the management of imatinib-induced pneumonitis, clinicians are left with difficult treatment dilemmas.

Introduction

Gastrointestinal stromal tumor (GIST) is a rare cancer with an incidence of approximately 8 per million person-years in the Netherlands (van der Graaf et al., 2018). The introduction of tyrosine kinase inhibitors (TKIs), specifically imatinib, has led to a phenomenal progress in the treatment of advanced and metastatic GISTs. Now, imatinib is also prescribed as an adjuvant treatment for 3 years in patients with high-risk disease, and is considered as Neo-adjuvant treatment for large tumors or in cases where significant resection associated morbidity is anticipated (Casali et al., 2022).

A lesser-known side effects of imatinib is pneumonitis, an uncommon multicausal interstitial lung disease (ILD), characterized by lung inflammation (Common Terminology Criteria for Adverse Events (CTCAE) v5.0 2024). Interstitial pneumonitis in imatinib treated patients has been described in literature, mostly in case reports about patients with chronic myeloid leukemia, but also in patients with GIST (Izumiyama et al., 2009; Grimison et al., 2005; Rosado et al., 2003; Bergeron et al., 2002; Go et al., 2013; Ma et al., 2003; Lee et al., 2015; Seki et al., 2007). In a Japanese case series with 27 cases of imatinib-induced ILD, four of which occurred in GIST patients, it was reported that patients respond well to corticosteroid treatment and that

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<https://doi.org/10.1016/j.cpcr.2024.100280>

Received 18 December 2023; Accepted 29 January 2024

Available online 30 January 2024

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pre-existing pulmonary disease might be a risk factor (Ohnishi et al., 2006). Additionally, smoking, male sex and older age were identified as risk factors for the development of TKI related pneumonitis (Lee et al., 2015; Choi et al., 2018; Uchida et al., 2022; He and Zhou, 2019). It is unclear if imatinib can be safely reintroduced after successful management of imatinib-induced ILD. Therefore, clinicians are often faced with a treatment dilemma; whether to stop imatinib permanently or rechallenge imatinib, and if so, in which dose and with concurrent corticosteroids, or switch to a next line TKI. With this case series, we provide an overview of the cases and management of imatinib-induced pneumonitis in Dutch GIST patients.

Methods

Patients registered within the Dutch GIST Registry (DGR) with dyspnea, pneumonia, or pneumonitis were reviewed. The DGR is a prospectively maintained database, including patients (≥ 18 years) with GIST, treated in one of the five GIST expert centers in the Netherlands (Leiden University Medical Center, Erasmus Medical Center [Rotterdam], University Medical Center Groningen, Radboud University Medical Center [Nijmegen], and the Netherlands Cancer Institute [Amsterdam]) since January 2009. The DGR was approved by the local independent ethics committee (IRBd20-212).

Of the 1934 GIST patients registered in the DGR in July 2023, 1161 patients received imatinib therapy at some point in time. Of these imatinib treated patients, 137 (11.8 %) patients experienced dyspnea, pneumonia, or pneumonitis as an adverse event. Since we were interested in imatinib induced pneumonitis specifically, we reviewed these cases and identified nine patients (0.8 %). All data, including patient (age, gender, co-morbidities), tumor (location, status at diagnosis (i.e., localized, locally advanced or metastatic disease)), treatment (type of treatment, daily dose, dosing schedule, duration of treatment, adverse events on treatment), and follow-up data were obtained from the DGR. For the pneumonitis we report how it was diagnosed (i.e., with CT chest and/or bronchoalveolar lavage (BAL)), which grade it concerned according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 (Common Terminology Criteria for Adverse Events (CTCAE) v5.0, 2024), and if for the management of the pneumonitis imatinib was stopped and/or prednisolone was started, with a prednisolone dose above 40 mg per day considered as a high dose. The cases are presented in accordance with the CARE reporting checklist.

Cases

In total, we identified nine patients with imatinib-induced pneumonitis. As an illustration, we describe the case of a 53-year old female

in more depth. She was diagnosed with a metastatic GIST and started treatment with imatinib 400 mg once daily. After a week, she developed nausea, vomiting and fever. The imatinib was interrupted briefly, her side effects resolved and the imatinib was resumed at a lower dose of 200 mg, not only because of the side effects but also because of a confirmed CYP3A4*22 mutation, which was found in the context of a pharmacogenetic-pharmacokinetic study (van Eerden et al., 2023). In that study, patients with this mutation received a lower dose of imatinib, with the hypothesis that a similar exposure would be achieved as in patients without a CYP3A4*22 mutation on the standard imatinib dose of 400 mg. However, this patient achieved low trough levels of imatinib (503 $\mu\text{g/L}$) and the dose was increased step-by-step to 400 mg again. After 3 days on imatinib 400 mg, 69 days after the first dose of imatinib, she experienced shortness-of-breath, fatigue and a dry cough. A PET-CT scan to evaluate the response of imatinib on the GIST subsequently showed extensive diffuse inflammatory opacities in both lungs (Fig. 1 left image). Other causes for these inflammatory opacities, such as a COVID-19 infection, were ruled out by a PCR and banal cultures, and the symptoms and PET-CT image were classified as imatinib-induced interstitial pneumonitis. Although the GIST responded well to imatinib and showed no signs of activity on the PET-CT, imatinib had to be interrupted due to the pneumonitis and prednisolone 40 mg once daily was started. Her pneumonitis related symptoms resolved quickly. After 4 weeks of prednisolone treatment the CT chest improved (Fig. 1 right image), after which the prednisolone was gradually tapered off. At a dose of prednisolone 20 mg, and 41 days without TKI treatment, second-line sunitinib was introduced with no signs of a relapse pneumonitis.

In Table 1A, the demographic, GIST and imatinib treatment characteristics of the nine patients at diagnosis of the imatinib-induced pneumonitis are presented. Six of the nine patients experienced fever, dyspnea, (dry) cough, and fatigue. In all cases, as is presented in Table 1B, the diagnosis pneumonitis was based on CT chest imaging that revealed signs of interstitial lung disease with inflammatory or ground glass opacities in both lungs. In two patients an additional BAL was performed, in one patient during the second episode of pneumonitis, which showed inflammation with significant lymphocytosis. In a third patient, a BAL was planned, but could not be performed because of low oxygenation levels. At time of development of the pneumonitis, patients received an imatinib dose of 200–400 mg once daily with a mean imatinib trough level of 1388 $\mu\text{g/L}$ (range 526–2382 $\mu\text{g/L}$). Imatinib trough levels were available in only five patients. Of the five patients where trough levels of imatinib were available, one patient had a high trough level (2382 $\mu\text{g/L}$), three patients had trough levels within a normal range (1000–1700 $\mu\text{g/L}$), and one patient had a low trough level (526 $\mu\text{g/L}$). The mean duration on imatinib until patients developed

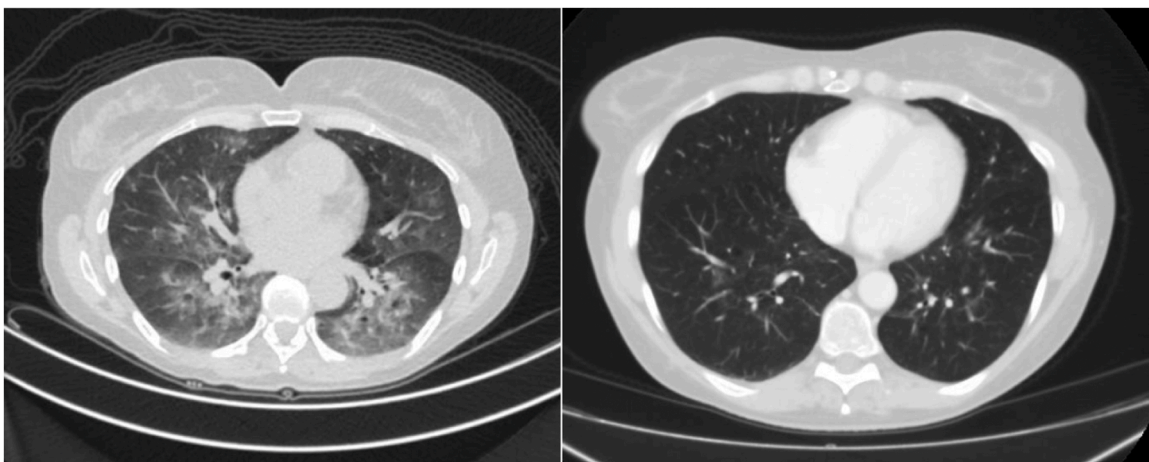


Fig. 1. CT images of a patient at diagnosis of the pneumonitis (left image) and after 4 weeks of treatment with high dose prednisolone (right image).

Table 1A
Overview of the demographic, GIST and imatinib treatment characteristics at diagnosis of the imatinib-induced pneumonitis.

	Sex	Age at pneumonitis	Relevant comorbidities and medical history	Smoking	GIST site	Treatment setting	Treatment type and dose GIST	Trough level imatinib	Duration on imatinib	Concomitant AEs at moment of pneumonitis diagnosis
1	F	53	–	Quit 1 year ago	Small intestine	Palliative	Imatinib 400 mg QD* *Decreased to 200 mg because of fever and vomiting and later step-by-step increased to 400 mg again because of low imatinib trough levels	526 µg/L	69 days	Dyspnea gr 1 Dry cough gr 1 Fatigue gr 1
2	M	87	Hypertension	Unknown	Gastric	Neo-adjuvant	Imatinib 400 mg QD	–	45 days	Fever gr 2 Urinary/pulmonary infection gr 3
3	M	80	Hypertension Diabetes mellitus type 2 Polymyalgia rheumatic Rectal carcinoma Fracture of C4 vertebra	Quit 30 years ago	Small intestine	Palliative	Imatinib 200 mg QD* *Dose reduction from 400 mg to 200 mg after 19 days of treatment due to oedema	1378 µg/L	28 days	Dyspnea gr 3 Infection gr 3 due to liver cysts Fatigue gr 1 Oedema gr 2
4	M	81	Prostate cancer Radiation cystitis Atrium fibrillation Heart failure	Unknown	Unknown	Palliative	Imatinib 300 mg QD* *Dose reduction from 400 mg to 300 mg after 23 days of treatment due to skin toxicity	–	1557 days	Watery eyes gr 1
5	F	76	Hypercholesterolemia TIA	Unknown	Small intestine	Palliative	Imatinib 400 mg QD	2382 µg/L	358 days	Myalgia gr 1 Periorbital oedema gr 1 Nausea gr 1
6	F	59	Diabetes mellitus type 2 Hypertension Atrium fibrillation	Quit 36 years ago	Small intestine	Palliative	Imatinib 300 mg QD* *Decreased to 100 mg because of skin toxicity and later step-by-step increased to 300 mg	–	103 days	Dyspnea gr 1
7	M	64	Hypertension Hypercholesterolemia Mitral valve insufficiency Coronary artery bypass grafting TIA	Quit 1 year ago	Gastric	Palliative	Imatinib 400 mg QD	1631 µg/L	1941 days	–
8	M	78	TIA Bladder cancer	Quit 30 years ago	Gastric	Neo-adjuvant	Imatinib 300 mg QD* *Dose reduction from 400 mg to 300 mg after 91 days of treatment due to skin toxicity	1021 µg/L	153 days	Fatigue gr 1 Skin toxicity gr 2 Myalgia gr 2 Dyspnea gr 2
9	M	61	Multiple HNP	Active	Gastric	Neo-adjuvant	Imatinib 400 mg QD	–	120 days	Skin toxicity gr 2 Infection gr 2

Abbreviations: TIA = transient ischemic attack; HNP = herniated nucleus pulposus; QD = once daily; AEs = adverse events.

pneumonitis was 486 days (range 28–1941 days). There seemed to be no association between pneumonitis and either the dose, duration and trough level of imatinib.

Due to the pneumonitis, imatinib was interrupted in 8 out of 9 (88.9 %) patients. One patient, diagnosed with a grade 1 pneumonitis, continued imatinib in a lower dose without starting any treatment for the pneumonitis. Six patients, all diagnosed with a grade 2 or 3 pneumonitis, started treatment with prednisolone, which was a high dose in 4 of the 6 patients. After their symptoms resolved, the high dose prednisolone was gradually tapered off, except in one patient, and patients were able to stop prednisolone after 5 to 17 weeks of treatment. In the other two patients interrupting imatinib was sufficient and no additional treatment was needed for the pneumonitis.

After the interruption and management of pneumonitis, seven patients discontinued imatinib permanently. In three patient this was in a Neo-adjuvant setting with good response to imatinib and subsequent resection, without continuation of adjuvant imatinib. Two of these three patients developed metastatic disease, 9 and 33 months later, respectively. In the first patient second-line treatment with sunitinib was started, and in the second patient imatinib was reintroduced successfully in combination with prednisolone 20 mg once daily. One patient resumed imatinib after 10 days, resulting in a quick relapse of the

pneumonitis after which imatinib was discontinued permanently. Two patients started with sunitinib after 41 days and 65 days without imatinib respectively, and currently have no signs of disease activity neither of GIST nor of pneumonitis.

Discussion

Here, we describe a series of GIST patients that developed pneumonitis while on treatment with imatinib. The exact mechanism of imatinib-induced pneumonitis is not fully understood, it is suggested to be multifactorial, imatinib may cause direct lung injury as it targets several tyrosine kinases, including platelet-derived growth factor receptor and c-Kit, which are expressed in alveolar epithelial cells (Grimison et al., 2005; He and Zhou, 2019). Furthermore, evidence suggests an immune-mediated reaction with a principal role for T-cells and cytokines (Shah, 2016).

In previous research, different risk factors for imatinib-induced pneumonitis were suggested, such as male sex, older age, history of pulmonary disease (e.g., tuberculosis, pneumonia or chronic obstructive pulmonary disease) and smoking (Ohnishi et al., 2006; Choi et al., 2018; Uchida et al., 2022). However, in our small case series we did not find an association with gender and none of the patients had a history of

Table 1B

Overview of the diagnostics and treatment of the imatinib-induced pneumonitis and management of the GIST treatment.

	Diagnostics pneumonitis			Management pneumonitis		Dose	After treatment of pneumonitis Stop, rechallenge or start new line of TKI	
	CT chest	BAL	AE grade	Stop imatinib	Start prednisolone			
1	Yes	No	2	Yes	Yes	40 mg QD	New line	After 41 days without treatment, sunitinib was started
2	Yes	No	3	Yes	Yes	25 mg BID	Stop	Resection of the GIST after 2 months. Metastatic disease 9 months later, after which sunitinib was started
3	Yes	No	3	Yes	Yes	1 mg/kg QD	Stop	Patient died 5 months later
4	Yes	Yes*	2	Yes	Yes	30 mg QD	Rechallenge	After 10 days without treatment resumed imatinib 300 mg, resulting in a quick relapse of the pneumonitis after which prednisolone was increased to 60 mg QD. and imatinib was permanently stopped
5	Yes	No	1	No	No	–	Continue	Continued imatinib at a lower dose of 200 mg
6	Yes	No	1	Yes	No	–	New line	After 65 days without treatment, sunitinib was started
7	Yes	Yes	2	Yes	No	–	Stop	Still no treatment started
8	Yes	No	2	Yes	Yes	60 mg QD.	Stop	Resection of the GIST after 2 months
9	Yes	No	2	Yes	Yes	30 mg QD**	Rechallenge	Resection of the GIST after 1 months. Metastatic disease 33 months later, after which imatinib was reintroduced in combination with prednisolone 20 mg QD. without a relapse

Abbreviations CT = Computerized Tomography; BAL = bronchoalveolar lavage; QD = once daily; BID = twice daily; TKI = tyrosine kinase inhibitor.

* A BAL was performed during the second episode of imatinib-induced pneumonitis.

** Increased to 30 mg QD, the patient was already on prednisolone 5 mg QD due to the skin toxicity.

pulmonary disease. Furthermore, data collected on smoking was insufficient to investigate any causalities. In addition, patients who tolerate imatinib less, underlined by dose-reductions, may also be more prone to develop imatinib-ILD. In our series this was the case in four of the nine patients, who had dose reductions of imatinib due to other toxicities (e. g., oedema and skin toxicity). In these patients the trough levels of imatinib might be higher, resulting in more exposure to imatinib and therefore more side effects (Zhuang et al., 2018), including imatinib-induced pneumonitis. However, of the patients with known imatinib trough levels, only one patient had a high trough level, which may suggest that imatinib trough levels are not associated with developing imatinib-induced pneumonitis.

What our case series illustrates is that patients can develop pneumonitis on imatinib 400 mg but also at lower doses, both after weeks or even after years of treatment. This means that in case of unexplained fever, dyspnea, (dry) cough and suspected findings on a CT chest, clinicians need to consider pneumonitis as a possible cause. When the medical history, physical examination and CT chest do not raise a high suspicion of a cause other than imatinib related ILD, a BAL does not necessarily have to be performed. Therewith, it is also possible to exclude infections as a possible cause with PCRs and banal cultures. However, if the etiology of the pneumonitis is not clear, then a BAL or lung biopsy is indicated before starting any treatment.

Recognition of imatinib induced pneumonitis may result in timely discontinuation of imatinib, and start of supportive treatment. As one of the mechanisms may be immune-mediated, patients often benefit from corticosteroids (Ohnishi et al., 2006; He and Zhou, 2019; Shah, 2016). In case of a grade 2 or higher grade pneumonitis, prednisolone 40 mg or 1 mg/kg is started in patients with other drug-induced pneumonitis (Willemsen et al., 2016; Swain et al., 2022). There is no reason to deviate from this with imatinib, therefore prednisolone was also started empirically in our patients. Prednisolone is not necessarily indicated in a grade 1 pneumonitis, in which interruption of the imatinib and watchful waiting until the pneumonitis resolves is often sufficient. Since imatinib was deemed to be the cause of the pneumonitis, it was interrupted in the majority of patients, which can pose a clinical dilemma, as was also addressed elsewhere (He and Zhou, 2019). Most GIST patients responded well to imatinib before the pneumonitis developed and a switch to the alternative, second-line sunitinib, will not always result in similar anti-tumor activity and can lead to other side effects (Demetri et al., 2006; van de Wal et al., 2022). Therefore, the indication of imatinib

should be weighed against the severity of pneumonitis in the individual patient. In case of a grade 1 pneumonitis, a rechallenge with imatinib can be considered, if necessary, in a reduced dose or in combination with prednisolone in a mitigated dose (e.g. 30 mg). In the Japanese case series imatinib was resumed in 11 patients with a success rate (i.e., no relapse pneumonitis) of 64 %, however, whether GIST patients belonged to this series was not mentioned (Ohnishi et al., 2006). In addition, two case reports in GIST patients also described a successful rechallenge of imatinib while prednisolone was continued at a high dose of 60 and 50 mg once daily, respectively (Grimison et al., 2005; Ma et al., 2003). In grade 2 or higher-grade pneumonitis, initiating second-line sunitinib, may be the best option given that the risk of getting a relapse pneumonitis might be high and patients have to restart or continue high dose corticosteroids, which may also lead to side effects (Weatherald et al., 2020; Zhang et al., 2019; Orasan et al., 2020; Puckett et al., 2022). Furthermore, in case of a relapse the patient needs to interrupt imatinib therapy again and faces the probability of disease progression in the meantime. The probability of a relapse pneumonitis during sunitinib treatment is low, although sunitinib-induced pneumonitis has been described in patients with metastatic renal cell carcinoma (Ivanyi et al., 2014; Seidel et al., 2010). To date, no cases of GIST patients with sunitinib-induced pneumonitis have been described, nor were they identified in the DGR.

In conclusion, imatinib-induced pneumonitis in patients with GIST is a rare side effect, which may affect their GIST management considerably. As illustrated by this case series, there is no commonality in presentation and treatment of imatinib-induced pneumonitis. Corticosteroids should be considered in the treatment of this uncommon ILD. Before making final treatment decisions, it is important to take into account the indication for imatinib, the availability of alternatives (i.e., possibility of resection, second-line sunitinib), the grade of the pneumonitis, the risks and consequences of a possible relapse or progression of GIST and pneumonitis.

Patient consent statement

The authors declare that they have obtained consent from individual patients for whom identifying information is included in this manuscript.

CRedit authorship contribution statement

Deborah van de Wal: Conceptualization, Methodology, Data curation, Writing – original draft, Writing – review & editing. **Evelyne Roets:** Conceptualization, Methodology, Writing – review & editing. **Roos F. Bleckman:** Conceptualization, Methodology, Writing – review & editing. **Jorn Nützing:** Conceptualization, Methodology, Writing – review & editing. **Birthe C. Heeres:** Conceptualization, Methodology, Writing – review & editing. **J. Martijn Kerst:** Conceptualization, Methodology, Writing – review & editing. **Mahmoud Mohammadi:** Conceptualization, Methodology, Writing – review & editing. **Anna K.L. Reyners:** Conceptualization, Methodology, Writing – review & editing. **Ingrid M.E. Desar:** Conceptualization, Methodology, Writing – review & editing. **Astrid W. Oosten:** Conceptualization, Methodology, Writing – review & editing. **Neeltje Steeghs:** Conceptualization, Methodology, Writing – review & editing. **Winette T.A. van der Graaf:** Conceptualization, Methodology, Writing – review & editing.

Declaration of competing interest

The authors have no relevant conflicts of interest to declare.

Data availability

The data that support the findings of this study are available from the corresponding author, WG, upon reasonable request.

Acknowledgments

The authors would like to thank Thijs Krijger, Thomas van de Zwet and Tom Wal for their help in maintaining the Dutch GIST Registry.

Statement of Ethics

For this study we used data of the Dutch GIST Registry (DGR). The DGR was approved by the local independent ethics committee (IRBd20-212) of the Netherlands Cancer Institute.

Funding

An unrestricted research grant for the DGR to NKI was received from Novartis (3017/13), Pfizer (WI189378), Bayer (2014-MED-12005), and Deciphera (4EE9EEC-7F19-484D-86A4-646CFE0950A5) received for the infrastructure of the DGR. These funding sources did not have any involvement in conducting this research.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.cpcpr.2024.100280](https://doi.org/10.1016/j.cpcpr.2024.100280).

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