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Case report

Long term treatment of advanced endometrial cancer with lenvatinib and pembrolizumab

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ABSTRACT

Objective: To describe a case of sustained disease control for over five years in a patient with recurrent, advanced endometrial cancer treated with lenvatinib and pembrolizumab, despite significant treatment-related toxicities.
Methods: We present a 49-year-old patient with grade 3, stage IVB endometrioid endometrial adenocarcinoma. After cytoreductive surgery, carboplatin and paclitaxel chemotherapy, and radiation therapy, the patient experienced progression with widespread metastases. She was then treated with lenvatinib (20 mg daily) and pembrolizumab (200 mg every three weeks). The patient experienced multiple treatment-related adverse events, including hypertension, colitis, hypothyroidism, adrenal insufficiency, and ocular toxicity, requiring dose adjustments and treatment interruptions.
Results: Despite frequent toxicities, the patient achieved a durable response to lenvatinib and pembrolizumab. Five years after treatment initiation, imaging showed no metabolically active disease, with only minimal stable residual lesions. Careful management of adverse effects, including supportive care, dose modifications, and temporary treatment pauses, enabled continued therapy.
Conclusion: This case underscores the potential for long-term disease control with lenvatinib and pembrolizumab in advanced endometrial cancer, even in patients with proficient mismatch repair (pMMR) and low tumor mutational burden. Although toxicities can require treatment adjustments, they can often be effectively managed, allowing for prolonged therapy. Further research is needed to determine the optimal treatment duration and strategies to mitigate long-term side effects.

1. Introduction

Endometrial cancer is the fourth most common cancer and the sixth most common cause of death among women in the United States (Cronin et al., 2018; American Cancer Society, 2024). It is the most frequent gynecologic cancer in the United States, with an estimated 67,880 new cases and 13,250 deaths in 2024 (American Cancer Society, 2024). Approximately 10–15 % of patients with endometrial cancer present with advanced-stage disease (Brooks et al., 2019), and 5-year survival among patients with distant metastases has been reported to be 17 % (Howlader et al., 2020). While the standard first-line therapy for advanced endometrial cancer is platinum-based chemotherapy now frequently combined with immune checkpoint inhibition, there are limited options for treatment in the recurrent setting.

Lenvatinib acts as a multiple kinase inhibitor which targets vascular endothelial growth factor receptors (VEGFR1, VEGFR2, and VEGFR3), fibroblast growth factor receptors (FGFR), platelet-derived growth factor receptor (PDGFR) alpha, c-Kit, and the rearranged during transfection (RET) proto-oncogene. Treatment of patients with advanced endometrial cancer using lenvatinib in combination with the programmed cell death protein 1 (PD-1) inhibitor pembrolizumab has shown significant clinical benefits. In the KEYNOTE-146 study, the combination of lenvatinib and pembrolizumab showed objective response rate of 39.8 % (95 % CI, 30.5 to 49.7), with a median duration of response of 22.9 months (95 % CI, 10.2 to not estimable). The median progression-free survival and overall survival were 7.4 months (95 % CI, 5.2 to 8.7) and 17.7 months (95 % CI, 15.5 to 25.8), respectively. (Makker et al., 2020). The KEYNOTE-775 trial demonstrated the efficacy of lenvatinib plus pembrolizumab in patients with advanced endometrial cancer previously treated with platinum-based therapy (Makker et al., 2022). In this phase III study, the combination therapy significantly improved progression-free and overall survival compared to physician's choice of single-agent, non-platinum chemotherapy (doxorubicin or paclitaxel), which was the standard of care at the time

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(Makker et al., 2022).

These findings established lenvatinib and pembrolizumab as the standard treatment of mismatch-repair proficient (pMMR), recurrent endometrial cancers following platinum-based chemotherapy. However, limited data exist on the optimal duration of this treatment in clinical practice, as significant side effects can impact quality of life and lead to high discontinuation rates. We present a unique case of a patient with recurrent, advanced endometrial cancer who has been receiving lenvatinib and pembrolizumab with continuous excellent disease control for over 5 years.

2. Case

This is a 49-year-old patient with no significant medical or family history who was diagnosed with International Federation of Gynecology and Obstetrics (FIGO) grade 3, stage IVB endometrial, endometrioid adenocarcinoma. Her body mass index (BMI) at the time of diagnosis was 19 kg/m^2, and germline genetic testing did not reveal any pathogenic variants associated with hereditary cancer syndromes. The patient underwent a total abdominal hysterectomy, bilateral salpingo-oophorectomy, and pelvic and *para*-aortic lymphadenectomy. The intraoperative findings showed bulky pelvic and *para*-aortic lymphadenopathy extending to the level of the renal arteries. Final pathology confirmed grade 3 endometrioid adenocarcinoma and cytoreduction was optimal. Tumor molecular profiling and next-generation sequencing revealed a p53 wild-type status, positive expression of estrogen and progesterone receptor, proficient mismatch repair (pMMR), aberrant beta-catenin expression, wild-type POLE, microsatellite stability, low tumor mutational burden (4 mutations/megabase), and somatic mutations in *ARID1A, CTNNB1, KDM6A, PIK3R1, PTEN, TP53,* and *U2AF1*.

Following surgery, the patient underwent six cycles of adjuvant chemotherapy with carboplatin and paclitaxel, followed by external beam radiation to the pelvis and *para*-aortic region and vaginal brachytherapy. The pelvic radiation field included the bony pelvis to treat osseous metastases. In addition, she received radiation treatment to the right supraclavicular region (metastatic disease confirmed on fine needle aspiration biopsy) and right occiput for metastatic disease. A positron emission tomography-computed tomography (PET/CT) scan following completion of initial adjuvant treatment revealed widespread metastatic disease, with numerous hypermetabolic osseous lesions, metastasis to cervical, axillary, and mediastinal lymph nodes, bilateral adrenal masses, pulmonary nodules, hepatic lesions, a possible pancreatic mass, and multiple subcutaneous lesions on her scalp indicating marked progression compared to prior imaging (Fig. 1). Treatment with lenvatinib 20 mg P.O. daily and pembrolizumab 200 mg intravenously every 3 weeks was initiated.

Shortly after initiating lenvatinib and pembrolizumab treatment, the patient developed lenvatinib-induced hypertension, which required antihypertensive therapy. Two months after initiation of treatment, she was diagnosed with colitis, requiring steroid therapy and dose reduction of lenvatinib to 14 mg daily. Over the next few months, she developed hypothyroidism and adrenal insufficiency, prompting initiation of thyroid hormone replacement therapy and further dose reduction of lenvatinib to 10 mg daily.

At 10 months post-treatment initiation, a PET/CT showed complete resolution of the previously hypermetabolic lymph nodes, osseous lesions, soft tissue nodules, and left adrenal mass. Residual low-level uptake in osseous lesions was noted, consistent with treated metastases. The patient was continued on lenvatinib 10 mg daily and pembrolizumab. However, 18 months after initiation of therapy, imaging demonstrated disease progression including enlargement of a right adrenal mass. Lenvatinib was increased to 14 mg daily, and a biopsy of the right adrenal mass confirmed metastatic disease. She subsequently underwent laparoscopic bilateral adrenalectomy and was started on steroid replacement therapy. Ocular side effects, including light sensitivity required steroid ocular injections at that time. Due to these side effects,

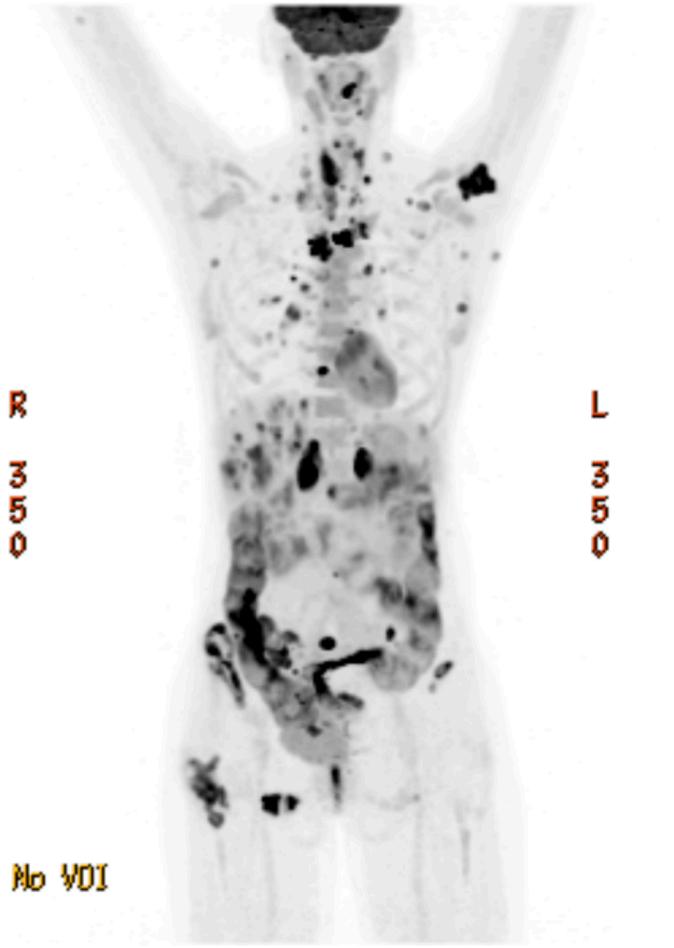

Fig. 1. PET/CT scan after completion of primary treatment (surgery followed by chemotherapy, radiation, and brachytherapy) demonstrating widespread metastatic disease, consistent with disease progression.

treatment was interrupted for two months followed by resumption of pembrolizumab and lenvatinib at a reduced dose of 10 mg.

Ten months later, she developed recurrent ocular symptoms prompting another treatment interruption of 2 months. Following the treatment break, computed tomography (CT) imaging revealed mild new lymphadenopathy prompting re-initiation of treatment with lenvatinib and pembrolizumab. The treatment was again interrupted eight months later due elevated liver enzymes due to transaminitis. Following normalization of liver function within two months, treatment was resumed with PET/CT scan demonstrating mostly treated disease with minimal residual fluorodeoxyglucose (FDG) uptake. The patient was then diagnosed with left-sided otitis externa and ulcerations of the ear canal likely related to treatment. Her systemic treatment was again paused and resumed after two months after recovery. PET/CT imaging performed five years after initiation of treatment showed no metabolically active disease. Stable calcified sub-centimeter lymph nodes and scattered sclerotic osseous lesions with mild FDG uptake were noted, consistent with treated disease. Currently, the patient remains on lenvatinib and pembrolizumab treatment with PET/CT imaging indicating minimal and stable residual disease (Fig. 2). While she has tolerated long-term therapy well, she has experienced mild weight loss over time, though not severe enough to warrant treatment discontinuation. Treatment timeline is summarized in Fig. 3.

3. Discussion

This case highlights the potential of lenvatinib and pembrolizumab

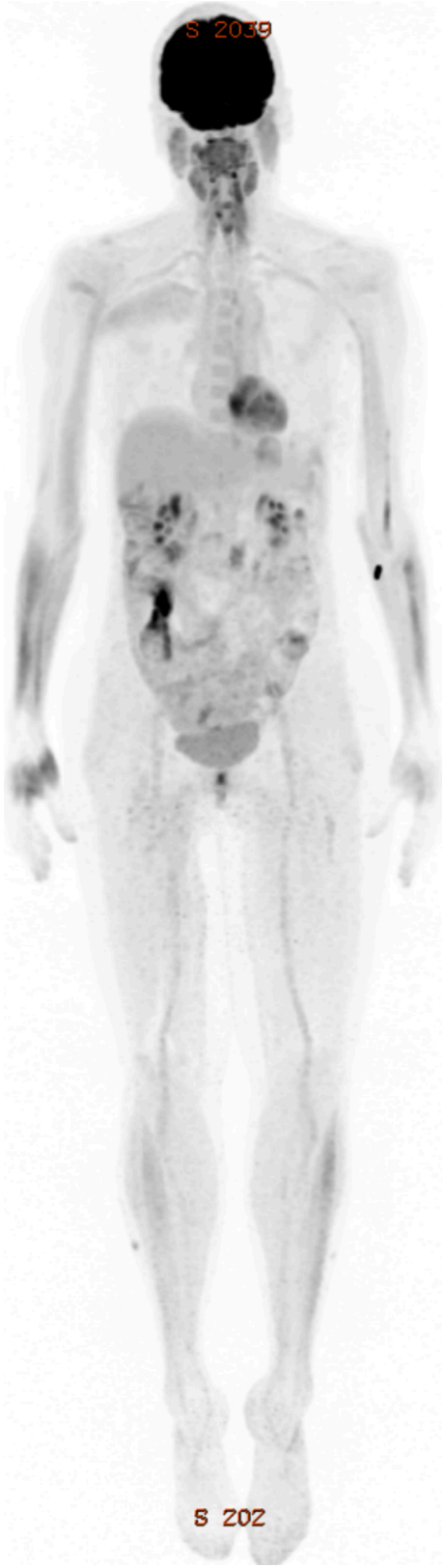

Fig. 2. PET/CT scan after > 5 years treatment with lenvatinib and pembrolizumab demonstrating minimal and stable residual disease.

to result in long term control of advanced endometrial carcinoma. Our patient initially presented with advanced stage disease and progressed with widespread metastasis after adjuvant chemotherapy and radiation. Combination treatment with lenvatinib and pembrolizumab resulted in an outstanding and ongoing response to treatment for over 5 years despite challenging side effects.

The combination of lenvatinib, an oral tyrosine kinase inhibitor, and pembrolizumab, an anti-PD-1 immune checkpoint inhibitor, has shown significant clinical efficacy in patients with advanced endometrial carcinoma (Makker et al., 2020). While pembrolizumab monotherapy has tumor-agnostic approval for tumors with high tumor mutational burden (≥10 mutations/megabase), this patient had a low TMB of 4 mutations/megabase. Given this finding, single-agent pembrolizumab was not considered an optimal approach. Instead, the combination of lenvatinib and pembrolizumab was selected due to its demonstrated efficacy in advanced endometrial cancer, particularly in cases without microsatellite instability or high TMB.

Discontinuation of lenvatinib and pembrolizumab due to treatment-related adverse events has been a notable concern. In KEYNOTE-775, 33.0 % of patients discontinued at least one of the drugs due to adverse events (Makker et al., 2022), while in KEYNOTE-146, the initial analysis reported a 17.7 % discontinuation rate (Makker et al., 2020). However, an updated safety analysis of KEYNOTE-146 later reported a higher discontinuation rate of 21.3 % (Makker et al., 2023), highlighting the ongoing challenge of managing toxicities associated with this regimen. Discontinuation rates have been reported as 17.7 % in the KEYNOTE-146 study (Makker et al., 2020), and 33.0 % reported in KEYNOTE-775 (Makker et al., 2022). In our case, the patient experienced multiple toxicities, including hypertension, colitis, hypothyroidism, adrenal insufficiency, and ocular side effects. These side effects were managed successfully with dose reduction, treatment interruption, and steroid therapy.

There is insufficient data on long term anti-tumor responses and sides effect of lenvatinib and pembrolizumab combination treatment. Our case, however, should be considered as exceptional response with ongoing excellent disease control of over 5 years. The KEYNOTE-775 study reported a median progression-free survival of 7.2 months and overall survival of 18.3 months for patients with endometrial cancer on lenvatinib and pembrolizumab. The median exposure to treatment was 231 days. Notably, 30.5 % of patients in the lenvatinib-pembrolizumab group were still receiving treatment at the data cutoff at 24 months, in contrast to only 2.6 % of chemotherapy-treated patients. The median duration of response was 9.2 months for lenvatinib-pembrolizumab in the pMMR population and 14.4 months in the overall population, with the longest reported durations of response being 23.7 months in the pMMR population and 24.2 months in the overall population. Our patient, now on therapy for 5 years with minimal, stable residual disease, far exceeds these medians.

The biological mechanisms underlying this exceptional and prolonged duration of response to lenvatinib and pembrolizumab are unclear. The patient's tumor was found to be microsatellite stable and had a low tumor mutational burden, molecular characteristics usually associated with a lower likelihood of response to immune checkpoint inhibitors. The molecular profile of the patient's tumor though revealed various activating mutations in genes involved in the PI3K/AKT/mTOR and Wnt/β-catenin pathways, suggesting that these pathways might play a central role in driving tumor growth and survival.

Mutations in *PIK3R1* and *PTEN* are known to dysregulate the PI3K/AKT/mTOR pathway, leading to enhanced cell proliferation and survival via constitutive pathway activation (Rascio et al., 2021). Specifically, mutations in *PIK3R1* can result in constitutive PI3K activation, leading to continuous production of PIP3 and downstream activation of AKT and mTOR, independent of growth factor signals. Similarly, mutations in *PTEN* can result in PIP3 accumulation, causing hyperactivation of AKT and mTOR. Together, these mutations create a state of constitutive PI3K pathway activation, driving enhanced cell

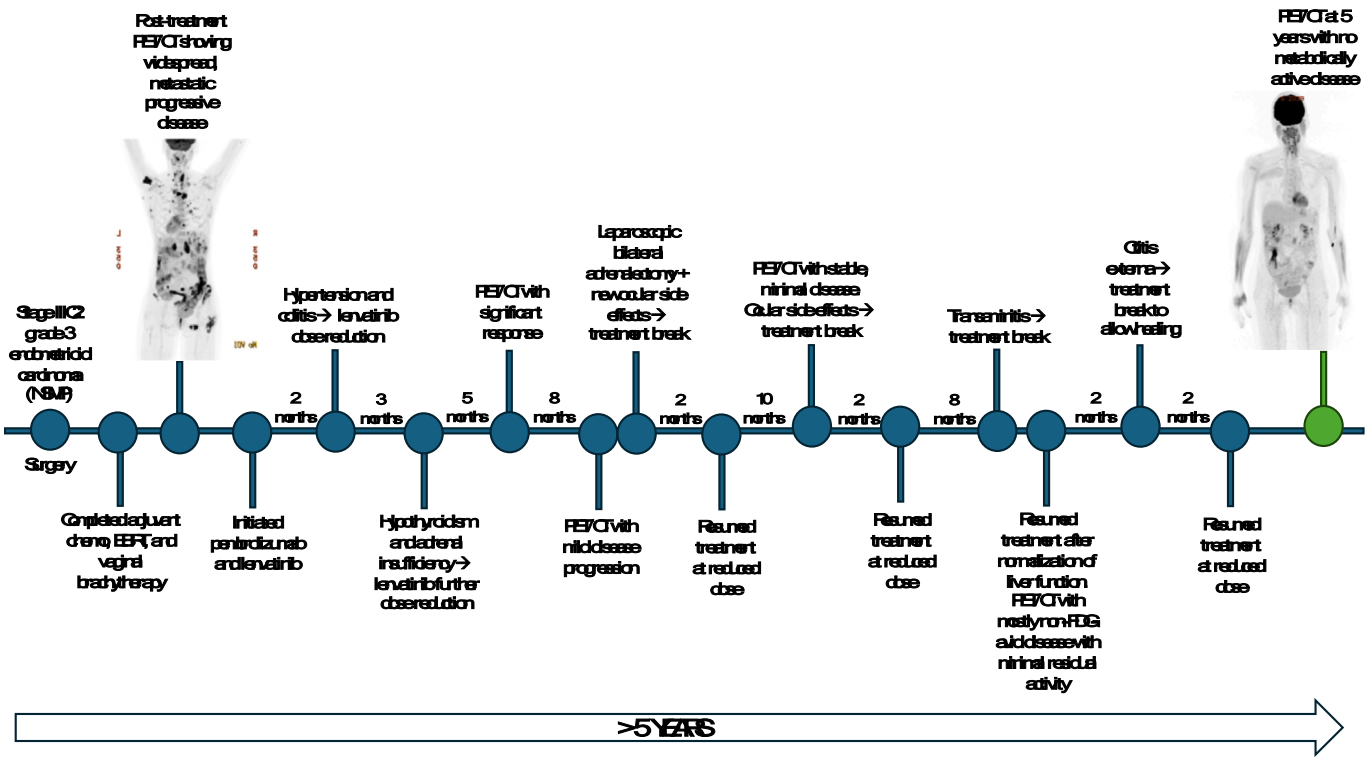

Fig. 3. Timeline of Treatment Course with Key Treatment Breaks.

proliferation, survival, and metabolic adaptation. Inhibition of VEGFR and RET by lenvatinib blocks key upstream signals in the PI3K/AKT/mTOR pathway (Mei et al., 2023). Targeting the PI3K/Akt/mTOR pathway in tumors with activation of this important pathogenic pathway like in our case can reduce cell proliferation, angiogenesis and metastasis.

An alternative explanation of the synergistic effects between lenvatinib and pembrolizumab in our case might be related to Wnt/β-catenin pathway activation possibly induced by the somatic *CTNNB1* mutation. The Wnt/β-catenin pathway has been shown to induce an immune-excluded tumor microenvironment by reducing immune cell infiltration (Luke et al., 2019). Lenvatinib can block β-catenin-driven immunosuppression by inhibition of *VEGFR* and *FGFR* signaling. Targeting the Wnt/β-catenin pathway can lead to enhanced immune effector cell infiltration into tumor tissue and therefore enhance pembrolizumab induced T-cell-mediated anti-tumor responses (Mei et al., 2023). While the exact mechanism of response remains uncertain in our case, the identification of molecular mechanisms provides important insights into predictive response pathways for individualized treatment. The ability to achieve and maintain disease control over an extended period underscores the potential for long-term efficacy of lenvatinib and pembrolizumab combination treatment in selected patients.

A key consideration in this patient's treatment course was balancing disease control with quality of life. While she experienced multiple treatment-related adverse effects, toxicity was managed successfully through dose alterations, enabling continued therapy with minimal treatment interruptions and minimal disruption to the patient's quality of life. Quality of life is inherently subjective, and while this patient experienced multiple treatment-related toxicities requiring intervention—including ocular injections, surgical procedures, and corticosteroid courses—she was able to maintain treatment and continue daily activities without requesting permanent discontinuation. Her continued adherence to therapy over several years suggests that she perceived the benefits of treatment to outweigh the associated toxicities. However, the absence of formal patient-reported quality of life measures limits the ability to draw definitive conclusions regarding her experience.

Given her overall stability and the durable response observed with lenvatinib and pembrolizumab, alternative regimens were discussed but not pursued, as the patient strongly preferred to continue a regimen that was effectively controlling her disease. The patient's recurrent ocular symptoms were most likely an immune-related adverse event associated with pembrolizumab, as checkpoint inhibitors have been reported to cause ocular toxicities, including uveitis and keratoconjunctivitis. While lenvatinib has been linked to some ocular side effects, immune-mediated toxicities are more commonly associated with pembrolizumab. Given the severity of symptoms, treatment was temporarily interrupted, but her symptoms improved with supportive care.

This case not only exemplifies the substantial therapeutic benefits that can be achieved with lenvatinib and pembrolizumab but also highlights the importance of individualized management strategies to mitigate treatment-related adverse events, where tolerability, patient preference, and clinical benefit must be weighed carefully. It is important to acknowledge that in the clinical trials evaluating lenvatinib and pembrolizumab, patients were discontinued from study treatment at the time of progression, and surgical resection of metastases was not permitted per protocol. However, in clinical practice, treatment decisions are often individualized, particularly in cases where patients exhibit continued clinical stability or derive ongoing benefit despite radiographic progression. In this case, the decision to continue therapy post-progression was based on the patient's maintained disease control, manageable toxicity profile, and personal preference. This highlights the complexities of treatment beyond trial settings and underscores the need for further studies to define optimal management strategies in such scenarios. Additionally, this patient's long-term stable disease with minimal residual burden further supports the role of this combination in controlling advanced disease, even beyond the treatment durations reported on clinical trials.

4. Conclusions

Our case describes the potential for long term treatment of advanced endometrial cancer patient with lenvatinib and pembrolizumab. While

the management of treatment-related toxicities is crucial to maintaining quality of life and ensuring continuity of care, most side effects can be successfully mitigated with appropriate interventions.

Statement of consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

CRediT authorship contribution statement

Sahana Somasegar: Writing – review & editing, Writing – original draft, Visualization, Data curation, Conceptualization. **Becky Sousa MSN:** Writing – review & editing. **Arati Jairam-Thodla:** Writing – review & editing. **Oliver Dorigo:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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