

Immune checkpoint inhibitor-associated TTP: can patients be rechallenged with immunotherapy?

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Case Report

Keywords: Immune checkpoint inhibitors, purpura, thrombotic thrombocytopenic, ADAMTS13 protein, nivolumab, ipilimumab

Posted Date: September 28th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-11154096/v1>

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Additional Declarations: The authors declare no competing interests.

Abstract

Immune checkpoint inhibitors (ICIs) are increasingly used to treat advanced malignancies and can cause a wide spectrum of immune-related adverse events. Immune thrombotic thrombocytopenic purpura (iTTP) is a rare but life-threatening complication, with little evidence to guide subsequent oncological management. We report a 49-year-old woman who developed ADAMTS13-confirmed iTTP following combination nivolumab and ipilimumab for metastatic melanoma. Treatment with plasma exchange, corticosteroids, rituximab and caplacizumab achieved clinical and ADAMTS13 remission. Given an excellent radiological response after a single cycle and limited alternative effective therapeutic options, ICI therapy was reintroduced following multidisciplinary discussion, initially with nivolumab monotherapy followed by escalation to combination nivolumab and ipilimumab, with serial ADAMTS13 and haematological monitoring. No iTTP recurrence occurred despite re-exposure. To our knowledge, this is the first reported successful ICI rechallenge following ICI-associated, ADAMTS13-confirmed iTTP. This case suggests that carefully selected patients may undergo ICI rechallenge with multidisciplinary assessment and close ADAMTS13 surveillance.

Introduction

Immune checkpoint inhibitors (ICIs) have transformed the management of advanced malignancies by enhancing T-cell mediated anti-tumour responses. Although generally well tolerated, these agents can cause a wide spectrum of immune-related adverse events (irAEs) through dysregulation of self-tolerance.[1] Haematological irAEs are uncommon but can be severe, including autoimmune haemolytic anaemia, immune thrombocytopenia, neutropenia, pure red cell aplasia, hemophagocytic lymphohistiocytosis and thrombotic microangiopathy.[2]

Immune-mediated thrombotic thrombocytopenic purpura (iTTP) is a rare but life-threatening thrombotic microangiopathy caused by severe acquired ADAMTS13 deficiency due to anti-ADAMTS13 autoantibodies. Prompt treatment with plasma exchange, immunosuppression and caplacizumab have substantially improved outcomes.[3] A small number of cases of ADAMTS13-confirmed iTTP following ICI therapy have been reported, suggesting that checkpoint blockade may precipitate anti-ADAMTS13 autoimmunity in susceptible individuals (Table 1).[4–17] However, there is little evidence to guide subsequent oncological management, with no reported successful ICI rechallenge following ICI-associated iTTP. It therefore remains uncertain whether immunotherapy can be reintroduced in selected patients, particularly following a substantial tumour response or when alternative treatment options are limited.

We report a patient who developed ADAMTS13-confirmed iTTP following combination ipilimumab (anti-cytotoxic T-lymphocyte-associated protein 4 [CTLA-4]) and nivolumab (anti-programmed cell death protein 1 [PD-1]) therapy for metastatic melanoma. Following iTTP remission, she underwent carefully monitored ICI rechallenge with serial ADAMTS13 measurements and remained free from iTTP relapse while maintaining an excellent oncological response.

Case

A 49-year-old woman with no significant past medical history was diagnosed with BRAF V600-mutated, pT2a N1 M0 malignant melanoma of the left flank in 2021. She underwent surgical excision followed by adjuvant BRAF/MEK-targeted therapy with dabrafenib and trametinib, completed in 2022. A second melanoma in situ of the right arm was excised in 2023, with no invasive malignancy identified on subsequent wide local excision.

In February 2026, surveillance computed tomography suspected local recurrence at the left flank, with enlarged precarinal lymph nodes and pulmonary nodules concerning for metastatic disease. Endobronchial ultrasound-guided biopsy confirmed BRAF V600E-positive metastatic melanoma. Other than mild chest discomfort, she remained asymptomatic. On 30 March 2026, combination ICI therapy with ipilimumab and nivolumab was commenced.

Routine blood tests 14 days after the first cycle demonstrated new thrombocytopenia (platelet count $10 \times 10^9/L$) and anaemia (haemoglobin 93 g/L), with occasional red cell fragments on peripheral blood film. She was clinically well, with minor bruising and a petechial rash but no significant bleeding. ICI-associated immune thrombocytopenia was initially suspected, and intravenous methylprednisolone 1 mg/kg was commenced. Despite three daily doses, thrombocytopenia persisted and the anaemia worsened, with increasingly marked red cell fragmentation prompting referral to the regional TTP Specialist Centre.

At presentation on 17 April 2026, haemoglobin was 85 g/L and platelet count $23 \times 10^9/L$. Laboratory investigations demonstrated haemolysis, with lactate dehydrogenase 864 U/L, bilirubin 41 $\mu\text{mol/L}$, reticulocyte count $142 \times 10^9/L$ and undetectable haptoglobin. Creatinine was 81 $\mu\text{mol/L}$ and troponin 8 ng/L, with no focal neurological findings. ADAMTS13 activity was 1.3%, confirming iTTP, with anti-ADAMTS13 antibody subsequently quantified at 19% (reference range 0-6.1%).

Treatment comprised daily plasma exchange for three days, prednisolone 1 mg/kg/day, rituximab 375 mg/m² twice weekly for four doses and caplacizumab 10 mg daily until 12 May 2026, in accordance with British Society for Haematology guidance.[18] She achieved rapid clinical and haematological remission, with resolution of haemolysis and normalisation of platelet count and ADAMTS13 activity.

The case was reviewed within national immuno-oncology and TTP forums. Interval imaging after a single combination ICI cycle demonstrated complete response of the left flank recurrence and marked partial response of the metastatic lymph nodes and pulmonary nodules. Given the magnitude of response, the risks and benefits of ICI rechallenge were carefully considered. Relatively low disease burden and minimal cancer-related symptoms allowed time to establish sustained iTTP remission and a prospective monitoring and relapse-management strategy before resuming systemic therapy.

Following recovery of ADAMTS13 activity and multidisciplinary consensus, ICI was cautiously reintroduced using a stepwise approach. Nivolumab alone (1 mg/kg, as used in the combination regimen) was administered as cycle 2 on 26 May 2026, with planned reintroduction of ipilimumab from cycle 3 if tolerated. With no clinical or biochemical evidence of iTTP recurrence, combination ipilimumab and nivolumab was resumed at standard doses for cycles 3 and 4, on 18 June and 17 July 2026, respectively. During rechallenge, full blood count, haemolysis parameters and ADAMTS13 activity were monitored weekly, with anti-ADAMTS13 antibody also measured periodically (Fig. 1). A predefined relapse management strategy was established: ADAMTS13 relapse would prompt further B-cell-directed immunosuppression with obinutuzumab, selected in view of recent rituximab exposure.[19] Clinical iTTP relapse would prompt caplacizumab and immunosuppression, with consideration of a plasma exchange-free approach in clinically stable disease and immediate initiation of plasma exchange if deterioration occurred.[20]

The patient remained in clinical and ADAMTS13 remission throughout rechallenge. ICI was well tolerated aside from low-grade transaminitis and a probable lower respiratory tract infection requiring oral antibiotics. Imaging on 5 August 2026 demonstrated an ongoing favourable oncological response, with resolution of pulmonary and nodal metastases; new borderline abdominal lymphadenopathy was considered potentially inflammatory and remains

under surveillance. She subsequently transitioned to maintenance subcutaneous nivolumab every 4 weeks. Full blood count, haemolysis parameters and ADAMTS13 activity continue to be monitored fortnightly, with plans to extend to 4-weekly for the duration of nivolumab therapy if remission is maintained.

Discussion

Although rare, iTTP should be considered in patients developing thrombocytopenia during ICI therapy, particularly when accompanied by anaemia and red cell fragmentation. Evidence to guide subsequent oncological management is limited. As summarised in Table 1, previously reported cases have resulted in permanent discontinuation of ICI or death during the acute episode. ICI has previously been successfully administered to a patient with relapsing iTTP; however, TTP pre-dated ICI exposure and was not considered an irAE in that case.[21] To our knowledge, this is the first reported successful ICI rechallenge following ICI-associated, ADAMTS13-confirmed iTTP. Although no conclusions can be drawn from a single case, ICI-associated iTTP may not necessarily represent an absolute contraindication to further immunotherapy.

Establishing causality between ICI and iTTP is challenging. In our patient, thrombocytopenia developed within two weeks of commencing combination nivolumab and ipilimumab, consistent with the temporal relationship reported in previous cases. Although the underlying malignancy represented an alternative cause of thrombotic microangiopathy, severe ADAMTS13 deficiency with anti-ADAMTS13 antibodies supported iTTP. By contrast, malignancy-associated thrombotic microangiopathy is typically characterised by preserved or only moderately reduced ADAMTS13 activity and generally responds poorly to plasma exchange.[22]

The decision to recommence ICI required balancing oncological benefit against the risk of recurrent iTTP. At 10-year follow-up of CheckMate 067, melanoma-specific survival was 52% with combination ipilimumab and nivolumab, compared with 44% with single-agent nivolumab and 23% with ipilimumab; among patients with BRAF V600-mutated tumours, rates were 56% and 42% with combination therapy and nivolumab, respectively.[23] These data demonstrate the potential for durable disease control with ICI, including in BRAF V600-mutated melanoma.

In our patient, the rationale for rechallenge was strengthened by the marked radiological response after a single combination cycle. The principal alternative was BRAF/MEK-targeted therapy, previously received in the adjuvant setting. However, durability of response was an important consideration; in COLUMBUS, encorafenib plus binimetinib achieved a median response duration of 18.6 months.[24] At the time rechallenge was considered, she was in clinical and ADAMTS13 remission. Following multidisciplinary review, the anticipated oncological benefit was considered to outweigh the risk of iTTP recurrence, and a predefined monitoring and relapse-management strategy was established.

A key aspect of this case was serial ADAMTS13 monitoring during rechallenge. ADAMTS13 activity during remission can identify relapse before clinical recurrence and is increasingly incorporated into longitudinal iTTP surveillance.[25] Persistently normal ADAMTS13 activity provided objective evidence of maintained iTTP remission despite renewed ICI exposure. Anti-ADAMTS13 antibody levels were also monitored, as reduced ADAMTS13 activity combined with elevated anti-ADAMTS13 antibody levels during remission have been associated with increased risk of clinical relapse.[26]

One explanation for successful rechallenge is that preceding rituximab therapy suppressed the pathogenic anti-ADAMTS13 response through B-cell depletion, potentially reducing susceptibility to recurrence despite renewed ICI exposure. Rituximab is established in acute iTTP and as pre-emptive therapy for recurrent ADAMTS13 deficiency

during remission.[25, 27] Notably, a recent small randomised study in advanced melanoma found that rituximab-mediated B-cell depletion during combination ipilimumab and nivolumab was associated with fewer severe irAEs without an apparent adverse effect on tumour response or survival.[28]

Importantly, this approach is unlikely to be appropriate for all patients. Decisions should consider the severity of the initial iTTP episode, confirmation of clinical and ADAMTS13 remission, alternative anti-cancer therapies and anticipated oncological benefit. ICI regimen and sequencing may also be relevant. In our patient, rechallenge was undertaken in a stepwise manner, initially with nivolumab alone before reintroducing combination therapy once iTTP remission had been maintained. This approach is consistent with the lower overall toxicity of nivolumab monotherapy compared with combination ipilimumab and nivolumab, although whether it reduces the risk of recurrent iTTP is unknown.[29] More broadly, ICI rechallenge should involve multidisciplinary haematology and oncology assessment, shared decision-making, and prospective monitoring with a predefined strategy for ADAMTS13 or clinical relapse. Although these principles require evaluation in further cases, they may provide a pragmatic framework for managing this rare but clinically challenging scenario.

Table 1

Published cases of immune checkpoint inhibitor-associated thrombotic thrombocytopenic purpura. ICI - immune checkpoint inhibitor; iTTP - immune thrombotic thrombocytopenic purpura; PEX - plasma exchange; IVIg – intravenous immunoglobulin. Cases of ICI-associated thrombotic microangiopathy without severe (< 10%) ADAMTS13 deficiency were excluded.

Report	Malignancy	ICI	Onset	ADAMTS13 activity and inhibitor	iTTP treatment and outcome	ICI rechallenge
King et al., 2017 [4]	Melanoma	Ipilimumab	3 weeks after cycle 3	Activity < 3%; inhibitor 3.7 BEU/ml	Corticosteroids, PEX, IVIg, rituximab → remission	No
Youssef et al., 2018 [5]	Renal cell carcinoma	Ipilimumab + nivolumab	4 days after cycle 1	Activity < 3%; inhibitor 9.9 BEU/ml	Corticosteroids, PEX, rituximab → remission	No
Dickey et al., 2020 [6]	Non-small cell lung cancer	Pembrolizumab	2 weeks after cycle 5	Activity 3%; inhibitor not reported	Corticosteroids, plasma as a bridge to PEX → initial remission; recurrence 2 weeks later and died	Not
Lafranchi et al., 2020 [7]	Melanoma	Ipilimumab + nivolumab	18 days after cycle 2	Activity < 5%; inhibitor > 2 (units not reported)	Corticosteroids → died within 24 hours of admission	Not applicable
Ali et al., 2020 [8]	Renal cell carcinoma	Ipilimumab + nivolumab	2 weeks after cycle 4	Activity < 2%; inhibitor > 186 U/ml (reference < 12 U/ml)	Corticosteroids, PEX, rituximab, caplacizumab → remission	No
Gergi et al., 2020 [9]	Anal squamous cell carcinoma	Nivolumab	41 days after cycle 3	Activity 9%; inhibitor 0.6 inhibitor units	Corticosteroids, PEX, rituximab → remission	No
Lancelot et al., 2021 [10]	Melanoma	Ipilimumab + nivolumab	1 month after cycle 4	Activity < 5%; inhibitor 3.7 BEU/ml	IVIg (initially for suspected immune thrombocytopenia), corticosteroids, PEX, IVIg, rituximab, bortezomib → multiple TTP relapses, died from progressive malignancy	No
Nelson et al., 2022 [11]	Urothelial carcinoma	Pembrolizumab	After 3 cycles	Activity 8%; inhibitor 8% (reference > 80%)	TTP-directed treatment declined because of comorbidities → died	Not applicable

Report	Malignancy	ICI	Onset	ADAMTS13 activity and inhibitor	iTTP treatment and outcome	ICI rechallenge
Mullally et al., 2022 [12]	Melanoma	Ipilimumab + nivolumab	11 days after cycle 1	Activity < 5%; inhibitor not reported	Corticosteroids → fatal cardiac arrest during first PEX	Not applicable
Kozak et al., 2023 [13]	Lung adenocarcinoma	Pembrolizumab	After 6 cycles	Activity < 5%; inhibitor 31 AU (arbitrary units; reference < 18 AU)	Corticosteroids, PEX rituximab → remission	No
Yoshida et al., 2024 [14]	Oesophageal adenocarcinoma	Nivolumab	After 15 cycles	Activity < 1%; inhibitor 2.7 BEU/ml	Corticosteroids, PEX, rituximab → remission	No
Parekh et al., 2025 [15]	Melanoma	Ipilimumab + nivolumab	2 weeks after cycle 3	Activity < 5%; inhibitor not reported	Corticosteroids, PEX, rituximab, caplacizumab → remission	No
Palega et al., 2026 [16]	Renal cell carcinoma	Pembrolizumab	11 days after cycle 1	Activity 3.8%; inhibitor not reported	Corticosteroids, PEX not undertaken due to poor clinical condition → patient died	Not applicable
Ke et al., 2026 [17]	Triple-negative breast cancer	Atezolizumab	During cycle 4	Activity < 3%; inhibitor 1.4 BEU/ml	Corticosteroids, PEX, rituximab → remission	No

Figure 1. Clinical course of immune checkpoint inhibitor-associated immune thrombotic thrombocytopenic purpura and subsequent rechallenge. iTTP - immune thrombotic thrombocytopenic purpura. Serial platelet count, ADAMTS13 activity and anti-ADAMTS13 antibody levels are shown from initiation of combination ipilimumab and nivolumab through acute iTTP treatment, staged ICI rechallenge and subsequent nivolumab maintenance therapy. The upper limit of quantification for the ADAMTS13 activity assay was 109%.

Declarations

The patient has given written consent for publication of her clinical case.

Conflicts of interest:

The authors have no conflicts to declare.

Author contributions

All authors were involved in the clinical care of the patient. KB drafted the manuscript. KH, AK, AC and EY critically reviewed and edited the manuscript. All authors approved the final version.

Funding statement:

KB is funded by an NIHR Academic Clinical Lectureship.

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Figures

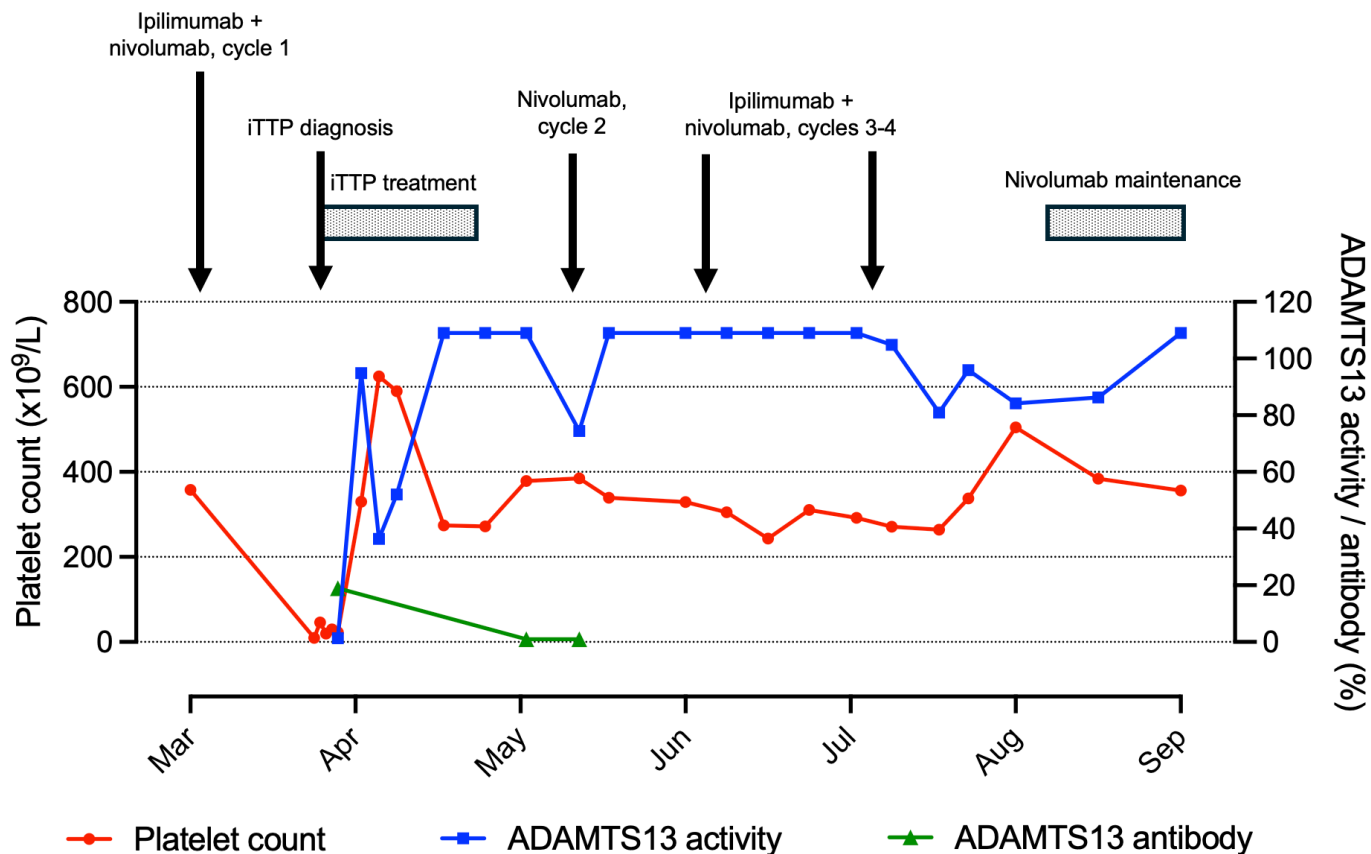


Figure 1

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