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MANAGEABLE LONGER-TERM SAFETY WITH THE HIGHLY-SELECTIVE COLONY STIMULATING FACTOR-1 RECEPTOR (CSF-1R) INHIBITOR PIMICOTINIB IN PATIENTS WITH TENOSYNOVIAL GIANT CELL TUMOR (TGCT) IN THE GLOBAL MANEUVER TRIAL

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CONCLUSIONS

- **Safety data from the Phase III MANEUVER trial provide insight into the safety of pimicotinib after >1 year of treatment, confirming that adverse events were generally manageable, reversible, and consistent with known CSF-1R inhibitor class effects**
- **In MANEUVER, rash, pruritus, and edema (including periorbital and facial edema) were primarily Grade 1 or 2 in severity and managed with short treatment interruptions, enabling patients to continue their pimicotinib treatment**
- **Laboratory adverse events of clinical interest (AECIs) had early onset with relatively quick resolution, whereas clinical AECIs were generally slower to occur and resolve**
- **For patients treated with pimicotinib, no patients discontinued treatment due to serum enzyme elevations (creatine phosphokinase [CPK], aspartate aminotransferase [AST], alanine aminotransferase [ALT])**
  - **Serum elevations were consistent with the known mechanism of CSF-1 pathway inhibition and cases were asymptomatic and reversible**
- **Longer-term pimicotinib treatment continued to provide sustained, robust antitumor activity with few adverse event (AE)-related treatment discontinuations[1]**

PLAIN LANGUAGE SUMMARY

- **Pimicotinib has previously been shown to shrink most patients' tumors over time and improve the ability for patients to carry out daily activities.[1] This trial reports the side effects associated with pimicotinib**
- **Most side effects in patients who were treated with pimicotinib were mild to moderate**
- **Laboratory side effects (i.e., detected by blood tests) appeared within 3 weeks of starting treatment with pimicotinib, but went away within 63 days**
- **Clinical side effects (e.g., rash and swelling) took longer to appear and went away within 14 to 103 days**
- **Swelling lasted for an average of 103 days and swelling around the eyes lasted for an average of 91 days**

INTRODUCTION

- TGCT is a rare and locally aggressive soft tissue tumor associated with functional impairment and reduced quality of life[2–4]
- Current treatment options for TGCT include surgery (standard of care) and systemic treatments; however, surgery can be limited by high recurrence rates, potential complications, and significant morbidity while current systemic treatments can be associated with toxicity concerns, modest tumor reduction, and lack of global access[3–5]
- Pimicotinib is a once-daily, oral, highly selective and potent small molecule CSF-1R inhibitor that has been investigated for the treatment of patients with TGCT[6]
- In the primary analysis of the Phase III MANEUVER trial, pimicotinib met its primary endpoint of objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1) at Week 25 versus placebo, and provided robust tumor responses, clinically significant symptomatic and functional improvements, and a manageable safety profile[1,7]
- With a median follow-up of 14.3 months, patients treated with pimicotinib achieved an ORR of 76.2% (RECIST v1.1) and 93.7% experienced a reduction in tumor size by Blinded Independent Review Committee (BIRC) per RECIST v1.1[1]
  - Pimicotinib continued to demonstrate clinically meaningful improvements across clinical outcome assessments (Relative Range of Motion, Worst Stiffness, Worst Pain, and physical function), including improvements in quality of life, as assessed by the EuroQol Visual Analog Scale

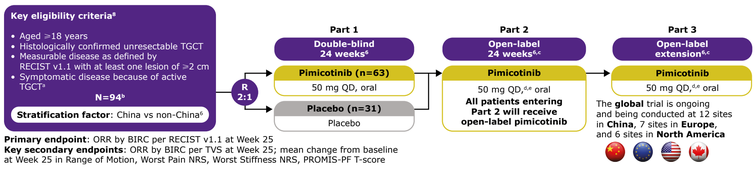
OBJECTIVE

- To report the incidence and timing of key AECIs in the Phase III MANEUVER trial for patients randomized to receive pimicotinib

METHODS

- MANEUVER (NCT05804045) is an ongoing global, Phase III, randomized, placebo-controlled trial investigating the efficacy and safety of pimicotinib in patients with TGCT
- In Part 1 (double-blind), patients were randomized 2:1 to receive either oral pimicotinib 50 mg once daily or placebo for 24 weeks. In Part 2, eligible patients continued or switched to open-label pimicotinib for a further 24 weeks; all patients who completed Part 2 were eligible to enter the Part 3 open-label extension (**Figure 1**)
- Safety evaluations in this analysis included AECI grade, time to first event, time from onset to resolution, and time from discontinuation to resolution
- AEs were monitored for 30 days after the last pimicotinib dose and graded using the Common Terminology Criteria for Adverse Events, version 5.0
- Grouped terms for key AECIs were defined as:
  - Elevation of blood CPK – blood CPK increased, blood CPK-MB increased
  - Elevation of aminotransferase – AST increased, ALT increased
  - Periorbital edema – periorbital edema, eyelid edema, eye edema
  - Edema (excluding periorbital edema) – face edema, edema peripheral, generalized edema, edema, swelling, peripheral swelling
  - Pruritus – not a grouped term
  - Rash – rash, rash maculo-papular, dermatitis, eczema, rash erythematous, rash macular, dermatitis allergic, intertrigo
  - Hypertension – hypertension, blood pressure increased

Figure 1. MANEUVER: A global Phase III, randomized, double-blind, placebo-controlled trial of pimicotinib in TGCT



Primary endpoint: ORR by BIRC per RECIST v1.1 at Week 25
Key secondary endpoints: ORR by BIRC per TVS at Week 25; mean change from baseline at Week 25 in Range of Motion, Worst Pain NRS, Worst Stiffness NRS, PROMIS-PF T-score

[a]Defined as one or more of the following: (i) a Worst Pain score of ⩾4 within 2 weeks prior to randomization (based on scale of 0 to 10, with 10 representing "pain as bad as you can imagine"), (ii) a Worst Stiffness of ⩾4 within 2 weeks prior to randomization (based on a scale of 0 to 10, with 10 representing "stiffness as bad as you can imagine"); [b]Between April 27, 2023 and March 29, 2024, 94 adults with TGCT underwent randomization: 63 were assigned to pimicotinib 50 mg QD and 31 to matching placebo; [c]All patients who completed 24 weeks of dosing in Part 2 were eligible to enter the open-label extension treatment phase (i.e., Part 3) for a longer treatment period and safety follow-up; [d]If a patient had a dose modification in Part 1/Part 2, the patient will continue to be administered at the modified dose in Part 2/Part 3; [e]63 patients were eligible to enter the open-label extension; 52 patients received treatment
NRS, Numeric Rating Scale; PROMIS-PF, Patient-Reported Outcomes Measurement Information System-Physical Function; QD, once daily; R, randomized; TVS, tumor volume score

RESULTS

- In total, 94 patients were randomized to receive pimicotinib (n=63) or placebo (n=31)
- Patient demographics and baseline characteristics were previously reported[7]
  - Median age was 40 years (range 18–69), 68% were female, and 50% had disease in the knee
- At data cutoff, patients randomized to receive pimicotinib had a median exposure duration of 14.2 months

AECIs BY GRADE

- In patients randomized to pimicotinib (N=63), the most common any-grade AECIs were elevated blood CPK (71.4%; n=45) and edema (61.9%; n=39) (**Table 1**)
  - Most AECIs were mild to moderate, and there were no reported Grade ⩾3 cases of elevated aminotransferase or edema
  - 31 out of 39 cases of edema were facial edema

Table 1. Overview of AECIs by grade

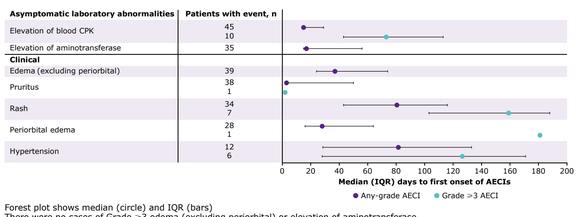
AECIs, n (%)	Any grade	Grade 1	Grade 2	Grade ≥3
Asymptomatic laboratory abnormalities				
Elevation of blood CPK	45 (71.4)	20 (31.7)	15 (23.8)	10 (15.9)
Elevation of aminotransferase	35 (55.6)	33 (52.4)	2 (3.2)	0
Clinical				
Edema (excluding periorbital)	39 (61.9)	27 (42.9)	12 (19.0)	0
Pruritus	38 (60.3)	26 (41.3)	10 (15.9)	2 (3.2)
Rash	34 (54.0)	21 (33.3)	6 (9.5)	7 (11.1)
Periorbital edema	28 (44.4)	21 (33.3)	6 (9.5)	1 (1.6)
Hypertension	12 (19.0)	1 (1.6)	3 (4.8)	8 (12.7)

N=63

TIMING OF AECIs

- Laboratory AECIs were asymptomatic and had early onset with relatively quick resolution
  - Elevation of any-grade blood CPK and aminotransferase had median time to onset of 15.0 and 17.0 days, respectively (**Figure 2**)
  - The median duration (onset to resolution) of elevation of blood CPK and aminotransferase were 63.0 and 43.0 days, respectively (**Figure 3**)

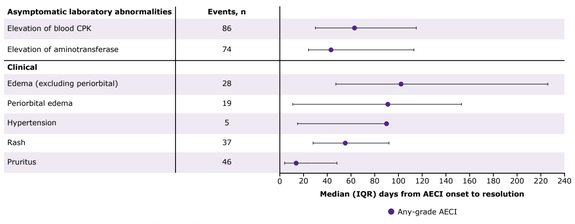
Figure 2. Median time to first onset of AECIs



Forest plot shows median (circle) and IQR (bars)
There were no cases of Grade ⩾3 edema (excluding periorbital) or elevation of aminotransferase
IQR, interquartile range

- Clinical AECIs generally had a longer median time to first onset, with the exception of pruritus, and took longer to resolve than laboratory AECIs (**Figure 2**)
  - Any-grade edema, rash, periorbital edema, and hypertension had median time to onset of 37.0, 80.5, 28.0, and 81.5 days, respectively
  - The median time to first onset of pruritus was 3.0 days and the median duration was 14.0 days
  - The longest median durations of clinical AECIs were observed in edema (102.5 days), periorbital edema (91.0 days), and hypertension (90.0 days) (**Figure 3**)

Figure 3. Median duration (onset to resolution) for any-grade AECIs



Forest plot shows median (circle) and IQR (bars)
Disclaimer: The specific cause of resolution (e.g., dose interruptions/reduction, discontinuation of treatment, concomitant medication) for each AECI was not available and resolution may have been due to multiple factors

- Grade ⩾3 AECIs generally had a longer median time to first onset compared with any-grade AECIs (**Figure 2**)
- Median time from treatment discontinuation to resolution was 12.0–31.0 days for AECIs (**Table 2**), although analysis was limited by the small number of events

Table 2. Median time to resolution of any-grade AECIs after treatment discontinuation

AECI	Time from treatment discontinuation due to any reason to resolution	
	Number of events	Median days
Asymptomatic laboratory abnormalities		
Elevation of blood CPK	1	22.0
Elevation of aminotransferase	1	12.0
Clinical		
Edema (excluding periorbital)	1	31.0
Rash	1	31.0
Hypertension	0	—
Periorbital edema	0	—
Pruritus	0	—

DOSE ADJUSTMENTS DUE TO AECIs

- Dose interruptions and reductions due to AECIs were infrequent in patients treated with pimicotinib (**Table 3**)
  - The median duration of dose interruptions for all AEs was 11.0 days
- One case of Grade 3 pruritus resulted in treatment discontinuation; no other AECIs resulted in treatment discontinuation (**Table 3**)

Table 3. Dose adjustments for AECIs

AECIs, n (%)	Dose interruption	Dose reduction	Treatment discontinuation due to AECI
Asymptomatic laboratory abnormalities			
Elevation of blood CPK	10 (15.9)	3 (4.8)	0
Elevation of aminotransferase	2 (3.2)	0	0
Clinical			
Rash	11 (17.5)	6 (9.5)	0
Edema (excluding periorbital)	8 (12.7)	2 (3.2)	0
Pruritus	7 (11.0)	4 (6.3)	1 (1.6)
Periorbital edema	6 (9.5)	2 (3.2)	0
Hypertension	3 (4.8)	0	0

N=63

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ACKNOWLEDGMENTS

We would like to thank the patients who agreed to participate in the MANEUVER trial, their families and caregivers, and the investigating teams at all participating sites

Medical writing support, under the direction of the authors, was provided by Emily Pinter, PhD, of the Publications Company, Ares Trading S.A. (an affiliate of Merck KGaA, Darmstadt, Germany) (CrossRef Funder ID: 10.13039/100009945) in accordance with Good Publication Practice (GPP 2022) guidelines

Abbisko Therapeutics designed and funded this trial and collected and analyzed the primary data

Pimicotinib (ABSK021) is being developed by Abbisko Therapeutics Co. Ltd., Shanghai, China

In April 2025, the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945) gained exclusive rights to commercialize pimicotinib worldwide. The healthcare business of Merck KGaA, Darmstadt, Germany reviewed this poster for medical accuracy only before submission. The authors are fully responsible for the content of this poster, and the views and opinions described in the poster reflect solely those of the authors

PRESENTER DISCLOSURES

Hans Gelderblom was a site Principal Investigator for Abbisko Therapeutics (fees paid to institution)

Presented at the European Society for Medical Oncology Sarcoma and Rare Cancers (ESMO SRC) Annual Congress; 12–14 March 2026; Lugano, Switzerland