CLINICAL STUDY RESULTS

A study to learn about the effects and safety of tazemetostat in people with integrase interactor-1 (INI-1) negative tumours or relapsed or refractory synovial sarcoma

Overall, the results suggest that 11% of participants had tumours that completely disappeared or became at least 30% smaller after treatment. No major safety findings were reported for tazemetostat.

The results shown in this summary represent one clinical study. Other clinical studies either singularly or combined may produce different results.

What was the study about?

The purpose of this study was to learn about the effects and safety of tazemetostat in people with integrase interactor-1 (INI-1)-negative tumours or relapsed or refractory synovial sarcoma.

A tumour is an abnormal growth of cells in the body that starts in an organ, muscle, soft tissue or bone.

INI-1-negative tumours lack a specific protein called INI1, which normally helps to control cell growth. Without this protein, cells can grow uncontrollably leading to cancer. **Synovial sarcoma** is a type of soft tissue cancer that usually forms in tissues around joints in the arms or legs. **Relapsed or refractory** means a cancer that has either come back after treatment or did not respond to the last treatment.

In this study, participants were enrolled into 1 of 8 treatment groups depending on the type of tumour they had:

GROUPS	TUMOUR OR CANCER TYPE
Group 1	**Rhabdoid tumours:** cancer that usually forms in the kidney, brain, spinal cord, or soft tissues
Group 2	**Relapsed/ refractory synovial sarcoma**
Group 3	**INI-1-negative tumours** or **solid tumours** with a mutation (change) in a protein called 'enhancer of zeste homolog 2 (EZH2)'. These tumours usually start in kidneys, brain, and soft tissues, and are more common in children and young adults.
Group 4	**Renal medullary carcinoma:** a type of kidney cancer
Group 5	**Epithelioid sarcoma:** a cancer that usually starts in soft tissues such as muscles or skin of the arms, hands, or fingers
Group 6	Participants with **epithelioid sarcoma** who had optional tumour biopsy which means a small sample of tissue was taken from the body to check the cancer cells
Group 7	**Chordoma:** a type of bone cancer that usually starts in the lower part of the backbone or at the base of the skull
Group 8	Participants with **epithelioid sarcoma** who received a different dose of tazemetostat in this study

Currently, the treatment available for these cancers include surgery, radiation therapy, and chemotherapy. Radiation therapy uses radiation to kill cancer cells. Chemotherapy uses medicine to kill cancer cells or stop them from growing and dividing. However, current treatment options do not work for everyone.

Tazemetostat was approved for use in the United States in 2020 and in Japan in 2021 for the treatment of certain types of solid tumours. It works by blocking the activity of the EZH2 protein. Blocking EZH2 slows down or stops the growth of cancer cells. Researchers wanted to check the effect of tazemetostat in different types of cancers.

The aim of this study was to find out:

- How many participants in Groups 1, 3, 4, 5, 6 and 7 had tumours that completely disappeared or became at least 30% smaller after treatment?
- How many participants in Group 2 had tumours that completely disappeared or became at least 30% smaller, or neither grew nor shrank after 16 weeks of treatment?
- What could be learned about safety of tazemetostat in participants in Group 8 who received a different dose of tazemetostat compared to other groups?

The study took place between December 2015 and February 2024 at 28 study sites in Europe, North America, Asia, and Oceania.

Who took part in this study?

267
PARTICIPANTS

154
MEN

113
WOMEN

40 YEARS
AVERAGE AGE

To take part in the study, participants had to:

- be aged above 18 years, and have measurable tumours
- be able to at least walk and take care of themselves
- be expected to live for at least 3 months

Participants could not take part in the study if they:

- had already taken tazemetostat, or another treatment that works by blocking the EZH2 protein
- had received a study treatment in another clinical study within 30 days before receiving treatment in this study
- had history of certain medical conditions
- had major surgery within 3 weeks before entering the study
- had a weakened immune system; the immune system protects the body from infection and disease

What treatments were used in this study?

Study Treatment

Groups 1 to 7: Tazemetostat 800 mg tablets given twice daily 260 participants
Group 8: Tazemetostat 1600 mg tablets given once daily 7 participants

The treatment was given in repeating 28-day cycles.

This study was “open label”. This means that the researchers and the participants knew which treatment was given to each participant.

This was a Phase 2 study where the study treatment is given to a small number of participants with the disease condition to gather information about the effects and safety of the study treatment in participants.

This study was divided into 3 parts:

Screening: The study doctor checked if participants could take part in this study within 21 days before starting the study treatment.

Treatment: 267 participants who were eligible to take part were divided into 8 groups based on the type of tumour they had.

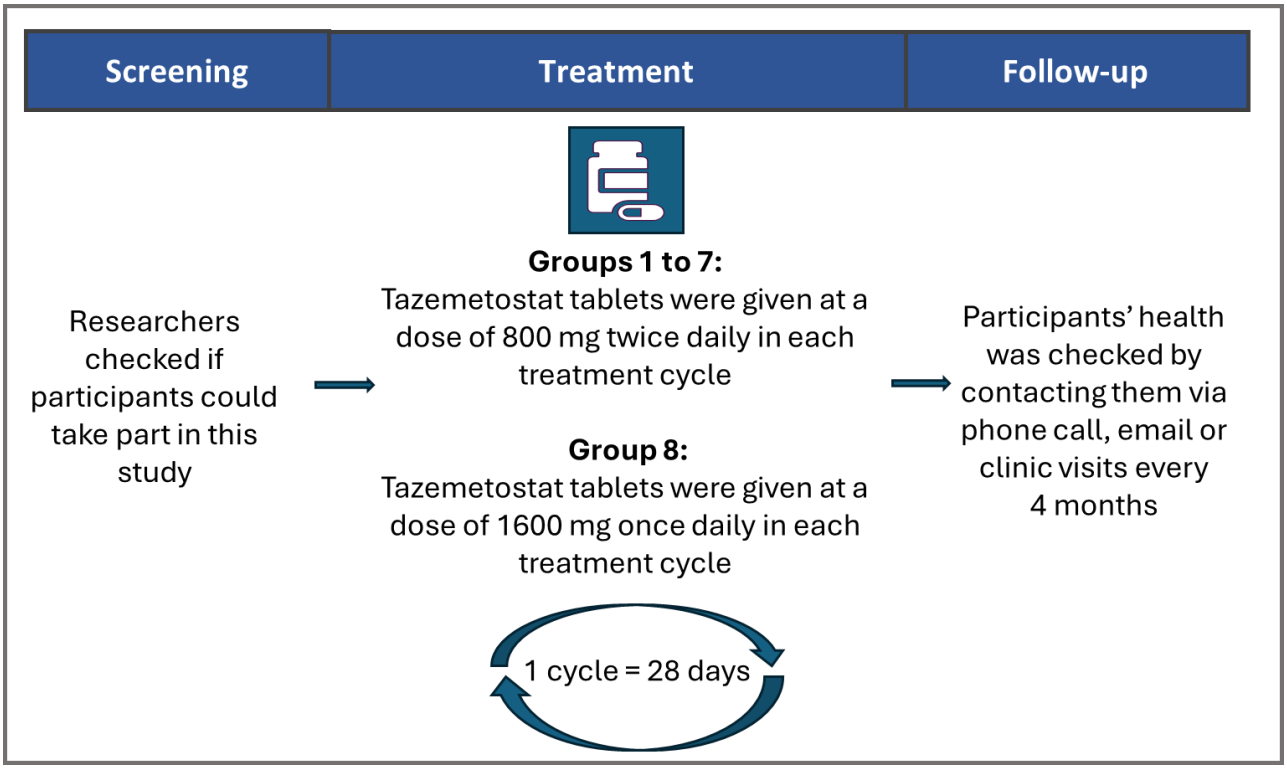
Participants received tazemetostat by mouth as tablets in 800 mg or 1600 mg doses, in repeating 28-day cycles.

Participants continued to receive treatment until their tumour grew, they had unacceptable adverse events, they chose to leave the study, or the study ended.

Participants who discontinued treatment visited the clinic for a final health check 30 days after their last dose of treatment, or before starting a new anti-cancer treatment, whichever happened first.

Follow-up: Researchers checked participants’ health via phone call, email, or clinic visits every 4 months. This follow-up continued for up to 2 years after the first dose of treatment until the participant chose to discontinue follow-up, or they could not be contacted.

After the study ended, eligible participants could choose to continue treatment, or to be monitored for health checks while participating in a new study.

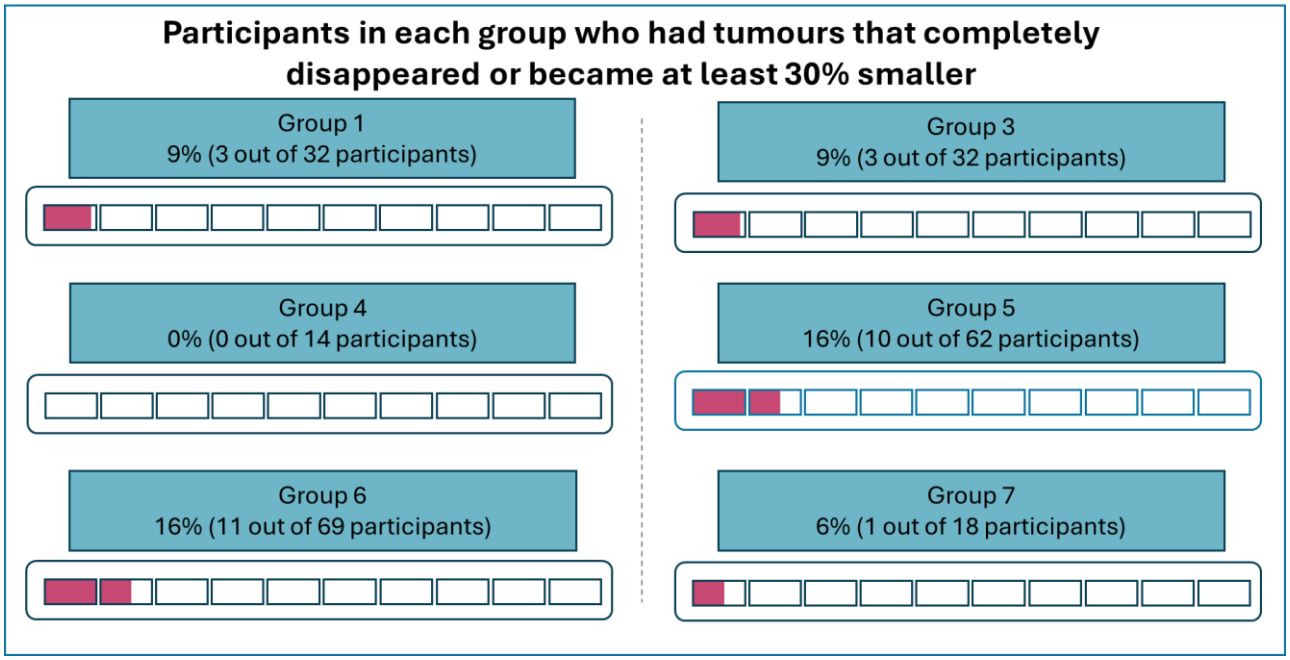


What were the results of the study?

- Treatment with tazemetostat was less effective in participants in Groups 1, 3, 4 and 7, compared to participants in Groups 5 and 6.
- 15% of participants in Group 2 had tumours that did not get worse after 16 weeks of treatment.
- In this study, no new safety concerns were identified following treatment with tazemetostat in Group 8.

How many participants in Groups 1, 3, 4, 5, 6 and 7 had tumours that completely disappeared or became at least 30% smaller after treatment?

In Groups 1, 3, 4, 5, 6 and 7, **12% (28 out of 227)** of participants had tumours that completely disappeared or became at least 30% smaller after treatment.
The results are based on measurements using images of the tumours (scans).



How many participants in Group 2 had tumours that completely disappeared or became at least 30% smaller, or neither grew nor shrank after 16 weeks of treatment?

After 16 weeks of treatment, **15% (5 out of 33)** of participants in Group 2 had tumours that completely disappeared or became at least 30% smaller, or neither grew nor shrank.

What could be learned about safety of tazemetostat in participants in Group 8 who received a different dose of tazemetostat compared to other groups?

During the study, participants were asked to report any 'adverse events', i.e. if they felt unwell, experienced any kind of medical event, or noticed anything different about their body. Researchers recorded all adverse events reported by participants, whatever the cause. For example, some participants caught COVID-19, and this was reported as an adverse event, although it was not related to the study treatment.

All 7 participants in Group 8 had at least 1 adverse event. The most commonly reported adverse events which happened in at least 3 participants were:

- Constipation
- Cough
- Decreased weight
- Feeling sick in the stomach
- Feeling tired
- Shortness of breath
- Vomiting
- Water in the lungs

Overall, 43% (3 out of 7) of participants in Group 8 had a serious adverse event, these were:

- Bacterial lung infection
- Insufficient oxygen in the lungs
- Sharp or stabbing chest pain that worsens during breathing or coughing
- Shortness of breath
- Tumour pain caused by tumour pressing on bones, nerves or other organs in the body
- Water in the lungs

How did the treatment make participants feel?

If the study doctor thinks an adverse event may be related to the study treatment, it is called a 'side effect'. A side effect is considered 'serious' when it is life-threatening, causes lasting problems, or leads to hospitalisation.

- Adverse events that are life-threatening, cause lasting problems or require an individual to go to the hospital are considered serious.
- 3% (7 out of 267) of participants in this study experienced a serious side effect.
- No participants died during the study due to a side effect.

Overall, 66% (175 out of 267) of participants experienced a side effect.

14% (36 out of 267) of participants stopped taking part in the study because of an adverse event.

None of the participants died in this study due to a side effect.

All the reported serious side effects are shown below, as a percentage (%) followed by the actual number of participants in the group [e.g. 3% (1)].

Serious Side Effects	Group 1 (out of 32 Participants)	Group 2 (out of 33 Participants)	Group 5 (out of 62 Participants)	All participants (out of 267 Participants)
At least 1 serious side effect	**6% (2)**	**9% (3)**	**3% (2)**	**3% (7)**
Feeling sick	3% (1)	0	0	Less than 1% (1)
High level of a chemical called bilirubin in the blood which may indicate decreased liver function	3% (1)	0	0	Less than 1% (1)
Vomiting	3% (1)	0	0	Less than 1% (1)
Constipation	0	3% (1)	0	Less than 1% (1)
Lung infection	0	3% (1)	0	Less than 1% (1)
Soft tissue infection	0	3% (1)	0	Less than 1% (1)
Coughing up blood	0	0	3% (1)	Less than 1% (1)
Fits	0	0	3% (1)	Less than 1% (1)

Participants in Groups 3, 4, 6, 7, and 8 had no serious side effects.

The most commonly reported side effects which happened in at least 5% of all 267 participants are shown below.

Side Effects	Group 1 (out of 32 Participants)	Group 2 (out of 33 Participants)	Group 3 (out of 32 Participants)	Group 4 (out of 14 Participants)	Group 5 (out of 62 Participants)	Group 6 (out of 69 Participants)	Group 7 (out of 18 Participants)	Group 8 (out of 7 Participants)	All participants (out of 267 Participants)
At least 1 side effect	**53% (17)**	**64% (21)**	**69% (22)**	**29% (4)**	**76% (47)**	**70% (48)**	**67% (12)**	**57% (4)**	**66% (175)**
Feeling sick	22% (7)	15% (5)	28% (9)	14% (2)	29% (18)	35% (24)	33% (6)	29% (2)	27% (73)
Vomiting	16% (5)	3% (1)	6% (2)	7% (1)	18% (11)	6% (4)	22% (4)	14% (1)	11% (29)
Feeling tired	13% (4)	24% (8)	25% (8)	0	27% (17)	23% (16)	22% (4)	43% (3)	23% (60)
Decreased appetite	9% (3)	6% (2)	0	7% (1)	15% (9)	12% (8)	17% (3)	29% (2)	11% (28)
Altered sense of taste	6% (2)	6% (2)	9% (3)	0	8% (5)	1% (1)	6% (1)	14% (1)	6% (15)
Diarrhoea	6% (2)	6% (2)	9% (3)	0	13% (8)	13% (9)	6% (1)	14% (1)	10% (26)
Weakness	6% (2)	9% (3)	9% (3)	0	7% (4)	9% (6)	11% (2)	0	8% (20)
Constipation	3% (1)	6% (2)	3% (1)	0	8% (5)	6% (4)	0	14% (1)	5% (14)
Hair loss	3% (1)	0	9% (3)	0	7% (4)	7% (5)	0	14% (1)	5% (14)
Low number of red blood cells	3% (1)	12% (4)	6% (2)	0	10% (6)	6% (4)	6% (1)	14% (1)	7% (19)

More information

To learn more about this study, please visit:

- ClinicalTrials.gov and search for study NCT02601950 or
- Clinicaltrialsregister.eu/ctr-search/search and search for study 2015-002469-41

For more information about current treatments available, please speak to your healthcare provider. If you have any questions about this study, please contact the sponsor, Ipsen at:

clinical.trials@ipsen.com

Future research

At the time of this report, future research on tazemetostat were planned.

Study identification and other information

FULL STUDY TITLE: A phase II, multicenter study of the EZH2 Inhibitor tazemetostat in adult subjects with INI-1-negative tumors or relapsed/refractory synovial sarcoma

STUDY NUMBERS: Europe: 2015-002469-41| United States: NCT02601950|

PROTOCOL: EZH-202

OTHER INFORMATION: Phase II studies can take several months to years to complete. Analysis of the study results will show how safe and effective a study treatment was during the study.

We thank all the volunteers who took part in this study. Without their support, advances in treatments for medical conditions would not be possible.

We would also like to thank the people who took the time to review this document to make it easier for a general audience to read.