1.Question： Was there a limitation to the conduction of the study other than the limitation of availability of drugs for advanced gastric cancer that led the patient to continue to receive five cycles of nab-PTX combined with S-1 chemotherapy?

In terms of curative effect, the level of detecting common serum tumor markers in gastrointestinal cancer after nab-paclitaxel combined with S-1 chemotherapy is lower than before chemotherapy. According to the result, we think this chemotherapy protocol is effective, and we don't know if the new chemotherapy protocol will be effective.

In terms of safety, after symptomatic treatment, the hemorrhagic cystitis has improved. We believe this is a reversible adverse reaction that can improve after discontinuation of the medication. Based on clinical experience and consultation with relevant departments, we believe it is appropriate to continue using nab-paclitaxel combined with S-1 chemotherapy.

In conclusion, we have continued to use this chemotherapy protocol, other than limitation to the conduction of the study.

2.Question：As the authors stated, "Since 1992, PTX has been approved by the FPA for the treatment of ovarian cancer and various forms, such as docetaxel, albumin-bound PTX, and liposome PTX, have been approved for cancer treatment." Who is the FPA? Please state it more clearly.

I'm so sorry. There is a misspelling. This is FDA (Food and Drug Administration) rather than FPA.

3. Question：Is the nab-paclitaxel related to hemorrhagic cystitis as dose-related?

There is no evidence to prove hemorrhagic cystitis as dose-related. After hemorrhagic cystitis was relieved, the patient continued to receive 5 cycles nab-paclitaxel combined with S-1 chemotherapy that the dosage is the same as the first time. What's different from the first chemotherapy is that the bladder was protected with 2-mercaptoethane sodium sulfonate on the day of intravenous chemotherapy.

4. Question： Owing to demonstrate the causality of adverse events of the drug (Nab-paclitaxel), were there some methods used to support that hemorrhagic cystitis caused by Nab-paclitaxel, such as Naranjo's algorithm (adverse drug reaction probability scale)?

We use Naranjo's algorithm to evaluate the causality of adverse events of Nab-paclitaxel. The total score was 8 points, which is means that hemorrhagic cystitis probably caused by Nab-paclitaxel.

Naranjo's algorithm

Question	Yes	No	Don't know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	0
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	+2
3. Did the adverse reaction improve when the drug was	+1	0	0	+1

	discontinued or a specific antagonist was administered?				
4.	Did the adverse reaction reappear when the drug was re-administered?	+2	-1	0	+2
5.	Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	+2
6.	Did the reaction reappear when a placebo was given?	-1	+1	0	0
7.	Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
8.	Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	+1
9.	Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
10.	Was the adverse event confirmed by any objective evidence	+1	0	0	0
				Total	8

5. Question： According to the pharmacokinetics of Nab-paclitaxel, there is a small amount of renal excretion (4% unchanged, less than 1% changed), then reaches the urinary bladder (reference: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021660s037lbl.pdf). What is the evidence to support that hemorrhagic cystitis is caused by Nab-paclitaxel?

There is no direct evidence to support that hemorrhagic cystitis is caused by Nab-paclitaxel. But through some things, we consider hemorrhagic cystitis associated with nab-paclitaxel: **1)** As you said, according to the pharmacokinetics of Nab-paclitaxel, there is a small amount of renal excretion, the Nab-paclitaxel may cause inflammation directly; **2)** Time correlation: the patient developed hemorrhagic cystitis on the 15th day after first nab-paclitaxel combined with S-1 chemotherapy. **3)** During 5 cycles nab-paclitaxel combined with S-1 chemotherapy, the patient had repeated episodes of frequent urination, urgency, and pain, but no hematuria was observed. It may associate with 2-mercaptoethane sodium sulfonate which can protect bladder. **4)** After 5 cycles nab- paclitaxel combined with S-1 chemotherapy, the patient received radiation therapy and synchronous oral chemotherapy with S-1, the symptoms of cystitis improved significantly and without hemorrhagic cystitis. **5)** Hemorrhagic cystitis probable caused by Nab-paclitaxel evaluated by Naranjo's algorithm. **6)** There is another case that a patient with breast cancer who received nab-paclitaxel chemotherapy developed hemorrhagic cystitis has been reported.

6. Question：what is the possibility of the mechanism of the hemorrhagic cystitis caused by Nab-paclitaxel?

The mechanism of the hemorrhagic cystitis caused by Nab-paclitaxel is not clear. According to the pharmacokinetics and pharmacologic toxicity of Nab-paclitaxel, we have some speculations to explain why it can lead to hemorrhagic cystitis.

1.Oxidative stress: Nab-paclitaxel may induce oxidative stress in bladder cells, leading to cellular damage and inflammation. This oxidative stress can disrupt the normal functioning of blood

vessels and contribute to the development of hemorrhagic cystitis.

2.Inflammatory response: The administration of Nab-paclitaxel can trigger an inflammatory response in the bladder, leading to the release of pro-inflammatory mediators such as cytokines and chemokines. These inflammatory molecules can promote vascular permeability and cause bleeding in the bladder.

3.Disruption of the urothelial barrier: Nab-paclitaxel may disrupt the integrity of the urothelial barrier, which is responsible for maintaining the barrier function of the bladder. This disruption can increase the susceptibility of the bladder to injury and inflammation, resulting in hemorrhagic cystitis.

Patients with a history of cystitis may be more susceptible to experiencing this adverse reaction. Because their bladder mucosa is already damaged, they are more prone to experiencing symptoms after Nab-paclitaxel chemotherapy.

7. Question：Why the other part of the urinary tract is not susceptible to hemorrhagic injury?

The mechanism of the hemorrhagic cystitis caused by Nab-paclitaxel is not clear. According to the pharmacokinetics and pharmacological toxicity of Nab-paclitaxel, we speculate that this may be related to oxidative stress, inflammatory response, disruption of the urothelial barrier, impaired angiogenesis. The patient has a history of cystitis. Although there were no symptoms before the first treatment by Nab-paclitaxel, the Nab-paclitaxel may deteriorate cystitis through the aforementioned mechanism. Presumably, there is no history of cystitis in the other part of the urinary tract in this patient, so the hemorrhagic injury limited to bladder.

8. In Figure 3, some texts are underlined with red as follows: "SMZ, Flavoxate," and "mesna." Please improve them. -In Figure 3, please change the dates "2023-06-20," "2023-09-23," and "2023-11-21" to the day after the given nab-PTX.

The underlined with red ("SMZ, Flavoxate," and "mesna.") has been modified in Figure 3. And the dates have been changed in Figure 3.