Frequently Asked Questions

ZoptEC Phase 3 Clinical Trial
of
Zoptrex™

May 17, 2017

Q. Was ZoptEC a large Phase 3 study? When did it begin?

A. Yes. The study involved approximately 512 patients and was conducted at approximately 125 medical centers in North America, Europe and Israel. We announced on July 31, 2013 that the first patient had been recruited and dosed. Dosing was completed in December 2015.

Q. The design of the study permitted patients who were randomized into the Zoptrex™ arm to receive up to nine cycles of the compound at a dose of 267 mg/m^2. Patients randomized into the doxorubicin arm received 60 mg/m^2 up to a cumulative lifetime dose of 550 mg/m^2. Why was the dose of Zoptrex™ so much larger than the dose of doxorubicin?

A. The recommended dose for ZoptrexTM was established at the highest tolerable dose as evidenced by dose-limiting hematotoxicity studies and contained a concentration of doxorubicin that was slightly increased compared to the dose of doxorubicin given to patients in that arm of the study.

Q. What did the DSMB say following its second interim review of the preliminary data from the ZoptEC trial?

A. The DSMB stated: "There are currently no safety concerns noted by the Committee nor is there any significant reason based upon efficacy differences to justify discontinuation of assigned therapy in the 43 patients who remain on active therapy."

Q. Why did the DSMB permit the trial to continue?

A. We believe that the DSMB permitted the trial to continue because the data they examined suggested that there was a chance that Zoptrex™ could achieve its primary endpoint.

Q. The trial was stopped and the median overall survival was calculated following 384 events. How many patients were in the Zoptrex arm of the trial when the trial was stopped? Is it correct to assume that the remaining patients were in the doxorubicin arm?

A. Of the 384 events, 196 were enrolled in the Zoptrex™ arm and 188 in the doxorubicin arm. When the trial was stopped, 60 and 67 patients were still alive in the Zoptrex™ and in the doxorubicin treatment arms, respectively.

Q. A total of 512 patients were enrolled in the trial, yet it was stopped at 384 events. Why?

A. The study was designed to achieve a high level of statistical confidence following 384 events.

Q. If 127 patients were surviving when the study was stopped, weren't they excluded from the calculation of median overall survival?

A. For the construction of survival time probabilities and curves, the survival times for individual subjects are arranged from the shortest to the longest, without regard to when they entered the study. By this procedure, all subjects within the group begin the analysis at the same point and all are surviving until something happens to one of them. The two things that can happen are: 1) a subject can have the event of interest or 2) they are censored.

Censoring means the total survival time for that subject cannot be accurately determined. This can happen when something negative for the study occurs, such as the subject drops out, is lost to follow-up, or required data is not available or, conversely, something good happens, such as the study ends before the subject had the event of interest occur, i.e., they survived at least until the end of the study, but there is no knowledge of what happened thereafter.

In the case of the ZoptEC study, the median survival time was computed taking into account the patients who were censored because they were still alive at the end of the study. The computation was performed using a common statistical tool called the "Kaplan–Meier estimator". An explanation of this tool is beyond the scope of this document. Suffice it to say, however, that the Kaplan–Meier estimator is one of the most frequently used methods of survival analysis because it is useful to examine recovery rates, the probability of death, and the effectiveness of treatment.

Q. How do you explain the delay in the completion of the trial? You announced during the fall of 2016 that the rate of events had slowed greatly. How do you explain that?

A. Whereas recruitment and treatment period were performed according to plan and reached the anticipated milestones, the follow-up phase after completion of treatment and until the 384 events were reached was longer than initially estimated based on reasonable assumptions and statistical prediction. In other words, the length of time it took to actually complete the trial was longer than was originally estimated.

Q. How is it possible that the median overall survival of participants was only 10.9 months for Zoptrex™, considering (i) the last patient admitted to the trial received his or her final dose of the assigned therapy in December 2015; (ii) the 384th event did not occur until around the end of January 2017; and (iii) at that time, 127 patients were still alive?

A. In our study, median overall survival is the length of time from the respective date of patient randomization, when half of the patients in a treatment arm are still alive.

Q. Is it true that patients whose tumor did not express the LHRH receptor were enrolled in the study? Why?

A. *It is true that patients whose tumor may not express the LHRH receptor were enrolled in the study. This was done because the FDA required us to admit all patients with the disease specified in the protocol. There were two reasons for the FDA's position. First, at the start of the trial there was no validated companion diagnostic tool available to determine whether a tumor expresses the LHRH receptor (and we were not able to develop such a tool during the trial). Second, the consensus among oncologists is that most tumors associated with the disease specified in the protocol express LHRH receptors.*

Q. Is it possible that some undetected differences between the patients in the Zoptrex™ arm of the study and the doxorubicin arm of the study caused the study to fail?

A. *We do not believe so. The study populations in both treatment arms were remarkably similar in all aspects: age, weight, ethnicity and history and stage of endometrial cancer.*

Q. Mr. Dodd made a point of mentioning during a conference call that patients might have received treatment with another therapy in addition to either Zoptrex™ or doxorubicin. Do you have any evidence that this happened? If it did, could the outcome of the study have been influenced?

A. *Anticancer therapy in addition to Zoptrex™ and doxorubicin was excluded per study protocol. However, post-study anticancer therapy at the discretion of the respective investigator was an option. This means that following completion of the dosing of either Zoptrex™ or doxorubicin, the investigator had the option of providing additional anticancer therapy to the respective patient. However, since we do not have an indication that post-study anticancer therapy varied in the treatment arms, it is unlikely to have influenced the outcome of the study biased for one treatment arm, only.*

Q. You announced in January that you had a very positive pre-NDA meeting with the FDA regarding Zoptrex™. How could you have had such a positive meeting if the results of the study were so negative?

A. *The January meeting was a pre-NDA meeting, the purpose of which was to discuss the presentation of data in the NDA. The results of the study were not discussed with the FDA during the January meeting because the results were not known at that time.*

Q. When did you first learn of the results of the study?

A. *After the close of business in Germany on April 28th.*

Q. Why did you decide to halt further work on other indications for Zoptrex™?

A. *We made this decision because the outcome of the ZoptEC trial placed significant doubt on the concept for the mode of action of Zoptrex™. The doubt is so strong that we don't think that expenditure of substantial funds to pursue other indicatives is warranted. Instead, we will use our remaining funds to pursue the successful regulatory approval and commercialization of Macrilen™.*

Q. Will the results of the study be published in a scientific journal?

A. *Yes. The investigators of the study intend to publish the results of the study in appropriate medical scientific journals. Aeterna Zentaris will support them in such efforts.*