2 SYNOPSIS

Title of Study:

Antitumoral activity and safety of AEZS-108 (AN-152), a LHRH agonist linked doxorubicin, in women with LHRH receptor positive gynecological tumors.

Note: The following synopsis pertains to ovarian cancer patients (Stratum A of the study). Stratum B of the study (endometrial cancer patients) is presented in report AEZS-108-040(EC)_01.

Investigators:

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Publication (reference):

Emons G, Kaufmann M, Gorchev G, Tsekova V, Gründker C, Günthert AR, Hanker LC, Velikova M, Sindermann H, Engel J, Schally AV.
Dose escalation and pharmacokinetic study of AEZS-108 (AN-152), an LHRH agonist linked to doxorubicin, in women with LHRH receptor-positive tumors.
Gynecol Oncol. 2010;119(3):457-61.

Emons G, Tomov S, Harter P, Sehouli J, Wimberger P, Staehle A, Hanker LC, Hilpert F, Dall P, Gruendker C and AGO Study Group.
Phase II study of AEZS-108 (AN-152), a targeted cytotoxic LHRH analog, in patients with LHRH receptor-positive platinum resistant ovarian cancer.
J Clin Oncol 2010 ASCO Annual Meeting Proceedings;28(15s): Abstract 5035

Study period:	**Phase of development:**
First patient enrolled: 05-Feb-2008 Last patient competed: 27-May-2011	II

Objectives:

- To evaluate the efficacy of the study treatment by assessing the partial or complete response rate according to RECIST and/or GCIG guidelines
- To evaluate time to progression and overall survival
- To characterize the profile of adverse reactions, including remarkable changes of laboratory parameters

Methodology:

Open-label, non-comparative multicenter trial; stratified two-stage Simon design.

Number of patients (planned/analyzed):

Stratum A (ovarian cancer): Step 1: 21 / 21
Step 2 (if ≥ 2 responders in step 1): 20/ 21

Diagnosis and main criteria for inclusion:

- Women ≥ 18 years of age
- LHRH receptor positive tumor status: positive receptor status determined by immunohistochemistry from primary tumor

Stratum A - ovarian cancer:

- Histologically confirmed epithelial ovarian cancer (will include primary fallopian tube or primary peritoneal cancer)
- Advanced (FIGO III or IV) or recurrent disease
- Progression during treatment with a platinum-based regimen or within 6 months after receiving a platinum-based regimen
- Previous treatment with a taxane-containing regimen
- No previous anthracycline-based chemotherapy and not more than 2 previous chemotherapies or cytostatic therapies (e.g. monoclonal antibodies, cytokines, and small molecule inhibitors of signal transduction)
- At least one measurable target lesion (RECIST criteria) OR CA125 level higher than twice the upper limit of normal range (GCIG criteria)

Test product, dose and mode of administration, batch number:

AEZS-108 was administered intravenously at a dose of 267 mg/m^2 every Day 1 of a 21-day (3-week) cycle.

Dose reduction to 160 mg/m^2 when dose-limiting drug-related AEs occurred.

Recommended prophylactic anti-emetic: 8 mg dexamethasone

Batch number: P03807, P08706, P05907

Duration of treatment: planned maximum of six cycles (allowing on a case by case up to eight cycles based on tumor response and tolerability)

Reference therapy, dose and mode of administration, batch number:

Not applicable

Criteria for efficacy evaluation:
Tumor response per RECIST 1.0 (and GCIG criteria for patients without evaluable target lesion at screening), TTP and OS.

Criteria for safety evaluation:
Adverse Events, (per CTCAE), clinical laboratory, vital signs, left ventricular ejection fraction (LVEF) and electrocardiogram (ECG)

Statistical Methods:
Kaplan-Meier analysis for TTP and OS. Frequency tables and descriptive statistics for safety parameters.

Summary:
A total of 42 patients were exposed to AEZS-108. All patients were Caucasian and the mean age was 59 years (range = 37 to 77 years). The mean time since diagnosis was 24 months (range = 7 to 90). All patients had undergone prior surgery for their disease and 73.8 % of them had received 2 previous chemotherapies. All patients received the combination of platinum/taxane.

Efficacy results:
In the ITT population, the ORR when combining RECIST and CA 125 criteria was 1 CR (per CA 125) + 6 PR (per RECIST) and 1 response (per CA 125) for a total of 8 out of 42 patients (19.0 %) (see table below. Note: responders per combined criteria are indicated in bold cells). A more conservative estimate of the combined ORR would be 4 PR (per RECIST and confirmed) + 2 responder (per CA 125 and confirmed) for a total of 6 out of 42 patients (14.3 %).

Best overall response – Per RECIST and CA 125 (ITT population)

RECIST	**CA 125**			**Total RECIST**
	Yes	**No or PD**	**N/E**	
CR	0	0	0	0
PR	2[a]	0	4[b]	6
SD	0	7	7	14
PD	0	13	3	16
N/E	2[c,d]	3[e,f,g]	1[h]	6
Total CA 125	4	23	15	42

[a]: SD (up to and) at cycle 6, PR not confirmed prior to start of follow-up therapy: patient 239001.
[b]: PR not confirmed at a subsequent time point: patient 236003.
[c]: No measurable and non-measurable disease at screening and no new lesion up to cycle 6. CA 125 (U/mL): ULN = 35, baseline = 507.6, 3-month follow-up (nadir and last value) = 18.2. Combined response assessed as CR (not confirmed): patient 500111.
[d]: No measurable and non-measurable disease at screening (not evaluable per reviewer) and no new lesion up to cycle 6 (SD per investigator): 500104.
[e]: No measurable and non-measurable disease at screening (not evaluable per reviewer) and no new lesion up to cycle 6 (SD per investigator): 500102.
[f]: No measurable and non-measurable disease at screening (not evaluable per reviewer) and no new lesion up to cycle 2 (SD per investigator). However, progression per CA 125 at cycle 1: patient 500112.
[g]: Discontinued prior to cycle 2 due to a cause other than progressive disease, CA 125 cycle 1(nadir and last value) = -30.4 % change from baseline: patient 500103.

[h]: Discontinued prior to cycle 2 due to a cause other than progressive disease, no post-baseline CA 125 assessment: patient 239018.

Treatment outcome for 14 patients met SD criteria, for a confirmed clinical benefit rate (CBR) of 22 out of 42 patients (52 %). In 8 of the 14 patients with SD based on lesions and CA 125, the SD was still present after 4 or more cycles. Thus, a more conservative estimate for the combined (and confirmed) CBR would be 14 of 42 patients (33 %). Median TTP was approximately 3 months and median OS was 12 months.

Safety results:

Sixteen patients out of 42 (38.1 %) completed at least 6 cycles of treatment. The most frequent AEs judged related to AEZS-108 were nausea (73.8 %), alopecia (50.0 %), vomiting (38.1 %) and fatigue (31.0 %). The most frequent possibly drug-related CTCAE grade 3 or 4 severity AEs were leukopenia (14.3 %), neutropenia (9.5 %), febrile neutropenia (7.1 %) and abdominal pain 7.1 %.

One patients out of 42 (2.4 %) died within 30 days of the last dose of AEZS-108. Progressive disease was an underlying cause of the death. No deaths were judged as possibly related to AEZS-108.

SAEs other than death were observed in 18 patients out of 42 (42.9 %). Ten patients out of 42 (23.8 %) experienced a SAE (other than death) judged as possibly drug-related (possible, likely or not assessable). They consisted of abdominal pain, constipation, fatigue, febrile neutropenia, general physical health deterioration, hemoglobin, hypersensitivity, injection site erythema, leukopenia, nausea, neutropenia, neutrophil count, pyrexia and vomiting.

No AEs (other than deaths or SAEs) led to AEZS-108 discontinuation.

Leukopenia of grade ≥ 3 was observed in 25 % to 45 % of the patients, at each cycle and only on Day 15.

Neutropenia, of grade ≥ 3 was observed in roughly 41 % to 75 % of the patients, at each cycle on Day 15 and in near 15 % of the patients on cycle 5 and 6 on Day 22.

Lymphocytopenia of grade ≥ 3 was observed in roughly 10 % to 20 % of the patients at near each cycle on Day 15 most of the time and in some cases on Day 8 and 22.

No laboratory abnormalities led to study drug discontinuation.

No cardiac toxicity was reported based on LVEF.

Conclusion:

AEZS-108 given as a 2-hour IV infusion at 267 mg/m^2 every 3 weeks was active in 42 advanced or recurrent ovarian cancer patients with LHRH receptor positive tumor status, based on a ORR of 19.0 % and a CBR of 52.4 % when combining RECIST and CA 125 criteria. The overall survival after single agent AEZS-108 was 12 months and compared favorably to the survival observed following topotecan and doxorubicin. AEZS-108 was well tolerated: the most frequent AEs judged related to AEZS-108 were nausea (73.8 %), alopecia (50 %), vomiting (38.1 %), and fatigue (31 %). The most frequent hematotoxicities were leukopenia (nadir mostly on Day 15), neutropenia (nadir mostly on Day 15 and 22) and lymphocytopenia (nadir mostly on Day 8 and 15). These hematotoxicities were easily manageable as none led to AEZS-108 discontinuation.

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