Drug 1

Treatment for infantile hemangioma

Off-label used in hospitalized infants

randomised, controlled, multidose, multicentre, adaptive phase II/III study in infants with proliferating infantile hemangiomas

Endpoint: investigator global assessment of the evolution of the target hemangioma at W24 as compared to baseline

Adaptive element : dose selection and sample size re-assessment

MAA - 2013

Trial design

- NT dose 1 duration 1 (regimen 1),
- NT dose 1 duration 2 (regimen 2),
- NT dose 2 duration 1 (regimen 3),
- NT dose 2 duration 2 (regimen 4),
- Placebo for duration 2

- Randomization ratio: 2:2:2:2:1 and then 2:1

- 90 patients by treatment arm + 45 in placebo to be randomized rounded up to a total of 450 patients (10% withdrawal)

Statistical analysis

- Test of superiority to placebo

- Interim analysis by IDMC planned at mid term of to select the best dose group(s) and re-assess sample size;

- P-values from both stages computed using a one-sided pooled Z test

- Closed-test principle applied at each stage with the Simes method to test for the intersection of canonical hypotheses containing the dose group considered.

- The final p-value maximizes the weighted inverse normal combination function over the p-values of intersection of hypotheses at both stages.

Stop for futility wrapped in the sample re-assessment :

Maximum number of patients limited to 100 under placebo and 200 per treatment arm

- If conditional power < 80% then sample size is re-assessed to achieve 80% if respecting the sample size limit ;

- If conditional power < 80% and cannot be increased without respecting the sample size limit

  - If conditional power > 50% could be guaranteed recruiting the maximum number of patients allowed, then study continues.

  - otherwise the study is stopped for futility

Simulations ensured power > 98% if one arm selected and control of the Type 1 error at 0.005

Results

- 456 patients on treatment.
- Interim analysis was conducted after the first 188 infants enrolled ;
- The IDMC decided to perform the interim analysis although all planned patients were already included, in order to allow sample size re-assessment if necessary.
- Only one arm selected : regimen 4 (62.8% vs 8% success, $p<0.001$), although regimen 3 months was also significant, $p=0.004$
- Phase 2, combined $p < 0.001$ (60% and 4%) on ITT

Drug 2

Previous MAA in soft tissue sarcoma (STS) under exceptional circumstances => specific obligation of investigation in STS subtypes linked to chromosomal translocations, especially Myxoid Round Cell Lyposarcoma

multicentre, randomized phase-3 study of single-agent NT vs AC

Endpoint : PFS

Duration : Evaluation of survival every 3 months during the first 2–year period of follow-up and every 6 months thereafter

Adaptive element: sample size re-assessment

Design

Arm A: NT

Arm B: AC

Randomization : 1:1

Sample size : 80 patients randomized to detect a hazard ratio of 0.45 with 80% power, with a Type I error of 0.05. Median survival in the control group was set to 11 months.

Interim Analysis

_ Interim analysis will be conducted by IDMC with approximately 45 independently assessed PFS events in order to re-assess the sample size (expected to be 30 months after start of enrolment).

_ The hypothesis H0:HR=1 will be tested and, with an information fraction of 80% and using Pocock's alpha spending function, its p-value should be lower than 0.0432 to reject it.

_ The sample sized will be increased if the HR was significant and the expected power was not reached, provided the conditional Type I error was maintained.

Results of MAA - 2015

- At interim analysis at 30 months : 88 patients enrolled with 26 events << 45 events
- HR non significantly different of 1
- Under powered trial because of censoring -> stopped since needed sample size impossible to reach (ca 500 patients) ;
- HR=0.86 [0.4,1.8], p=0.6992 ;
- No question as regards AD ;
- CHMP acknowledged recruitment constraints and useful trend of efficacy in rare cancers
- Specific obligation was considered fulfilled

Drug 3

Already approved for different indications in patients with Multiple Myeloma (MM)

Open-labelled, randomised, controlled, multicentre, phase III study in newly diagnosed Mantle Cell Lymphoma who are not eligible for bone marrow transplantation

Trial design

Arm 1 : NT + combination

Arm 2 : AC + combination

Endpoint: PFS

Randomization : 1:1

Adaptive element: sample size re-assessment and diagnostic concordance

MAA - Interim analyses :

1. If the discordance rate is found to be <=5% in the first 100 patients, no sample size re-assessment will be performed ; Otherwise sample size will be re-assessed to observe the required number of events

2. The second evaluation is for safety only ;

3. when approximately 50% of the planned number of PFS events have been observed, aiming at stopping the trial if p < 0.003 (2-sided) ; O'Brien-Fleming function ; p final = 0.049

A stop for futility is included if HR < 1.03 (conditional power<30%)

Safety is reviewed as well

Results

_ Trial not changed or stopped at none of the interim analyses ;

_ HR=0.63 [0.50,0.79] (p<.001 on ITT)

_ No specific comment as regards the interim analysis

_ drug accepted

Conclusions

_ Different conditions ;

_ Different regulatory questions ;

_ Different types of adaptation ;

_ Drugs accepted with convincing results ;

_ Referral to the reflection paper ;

_ Need to justify rational for adaptation, type 1 error control, study integrity (IDMC) ;

_ First of all, choice of inclusion criteria, doses, treatment duration etc must be fully mastered ;

_ Go to Scientific Advice when use of complex statistical is planned.

References

_Léauté-Labrèze, Christine, et al. "A randomized, controlled trial of oral propranolol in infantile hemangioma." *New England Journal of Medicine* 372.8 (2015): 735-746.

_ Heritier, Stephane, Serigne N. Lô, and Caroline C. Morgan. "An adaptive confirmatory trial with interim treatment selection: Practical experiences and unbalanced randomization." *Statistics in medicine* 30.13 (2011): 1541-1554.

_ Blay, Jean-Yves, et al. "Randomised phase III trial of trabectedin versus doxorubicin-based chemotherapy as first-line therapy in translocation-related sarcomas." *European Journal of Cancer* 50.6 (2014): 1137-1147.

_ Robak, Tadeusz, et al. "Bortezomib-based therapy for newly diagnosed mantle-cell lymphoma." New England Journal of Medicine 372.10 (2015): 944-953.

_ Public Assessment Report drug 1 : http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002621/WC500166912.pdf

_ Public Assessment Report drug 3 : http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000539/WC500184919.pdf