fondazione GIMEMA onlus
per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche. FRANCO MANDELLI

Ponatinib for the management of minimal residual disease (MRD) and hematologic relapse in adult Ph+ acute lymphoblastic leukemia (Ph+ ALL) patients

GIMEMA ALL XXXX

EudraCT number XXXXXX
Clinicaltrial.gov Number XXXXXXXXXX

Study Responsabilities:

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Study and Project Management:	GIMEMA Data Center, Rome
ALWP GIMEMA Chairman:	Sergio Amadori
Legal representative of the GIMEMA Foundation:	Marco Vignetti

Full version of the protocol approved by Incyte

Study design

This is a **phase II interventional** multicenter study for adult patients with Ph+ ALL who:

- Are **MRD+** (i.e. BCR-ABL1/ABL1 >0.01) (or loose their molecular response) **after whichever** kind of **previous treatment**; MRD positivity is indeed regarded as a relapse, since it represents the early recognition of cases who will eventually experience an hematologic recurrence of disease.
- Are in **hematologic relapse after whichever kind of previous treatment.**
- Have **never** achieved a **hematologic remission.**

Objectives

Primary:

- To evaluate the rate of patients obtaining a **CMR/MRD reduction** following treatment with either ponatinib alone or in combination with systemic chemotherapy **after 3 months of treatment.**

Secondary:

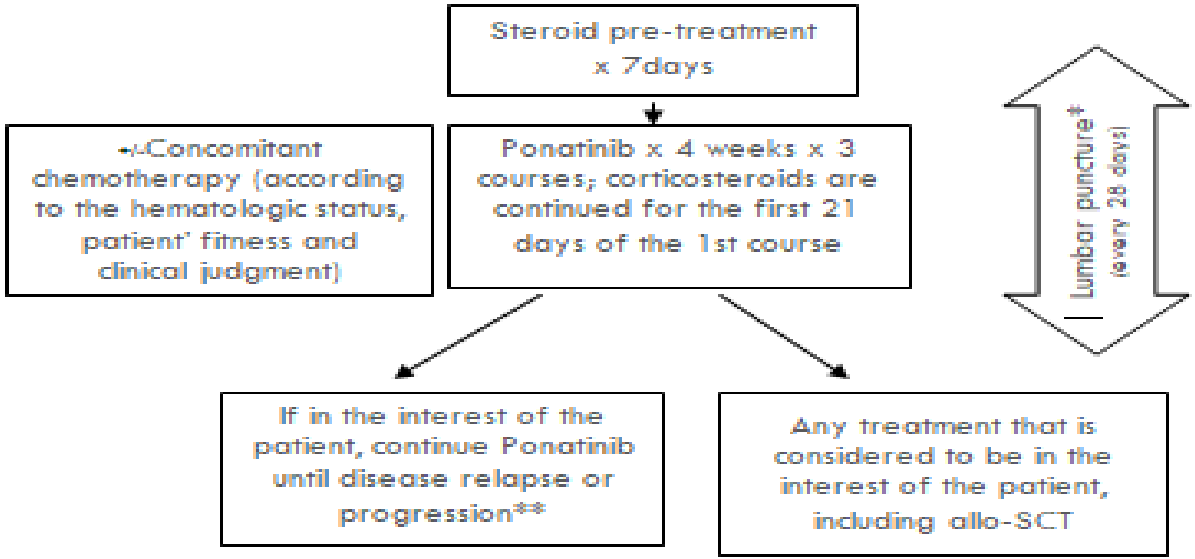
- Duration of CMR
- CIR
- Achievement of hematological remission in patients treated for an hematological relapse and for a refractory disease
- Mutation analysis and correlation between achievement and duration of CMR (or MRD reduction) with the type of fusion protein (eg p190 or p210) and the potential occurrence of mutations
- DFS and OS after Ponatinib administration
- Best molecular response
- Safety profile - AEs and SAEs
- Role of clinical and biological parameters on survival outcomes

Inclusion criteria

- Ph+ ALL patients with evidence of MRD disease, or in hematologic and extra-hematologic relapse/refractoriness after any previous treatment
- Age ≥18 years old with no upper age limit.
- Adequate hepatic function as defined by the following criteria:
- Adequate pancreatic function as defined by the following criterion:
- For females of childbearing potential, a negative pregnancy test must be documented prior to enrollment.
- Female and male patients who are fertile must agree to use an effective form of contraception with their sexual partners from enrollment through 4 months after the end of treatment.
- Signed written informed const according to ICH/EU/GCP and national local laws.

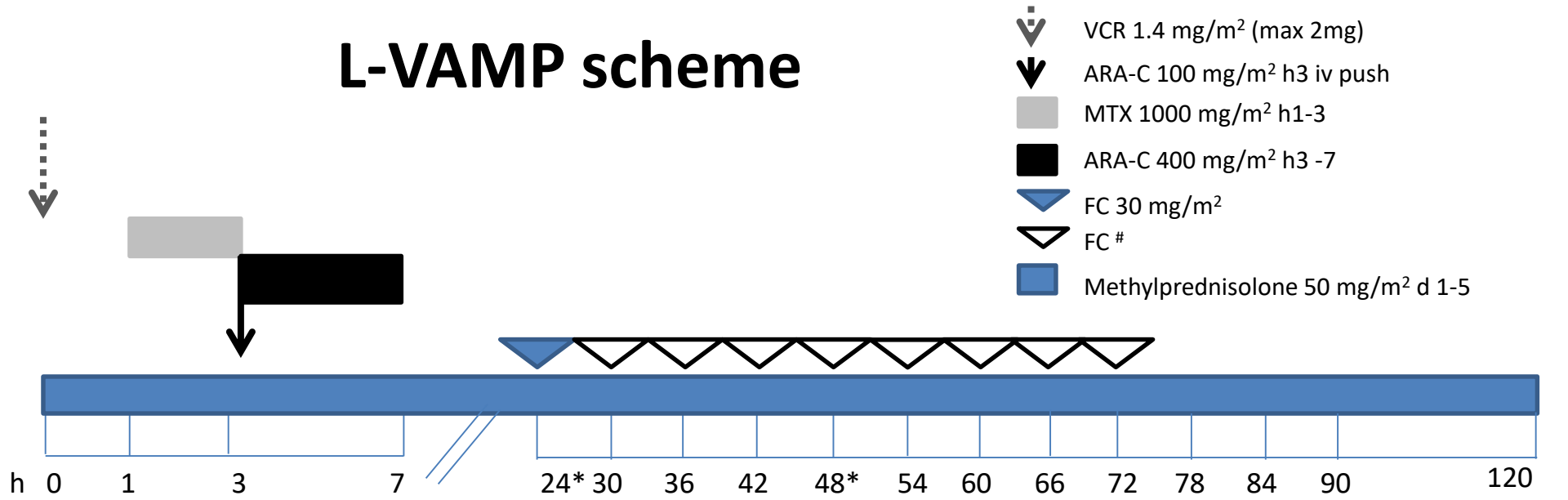
Sample size and scheme

67 patients



* Lumbar punctures should be administerd according to investigator discretion and number of previous lumbar punctures.

L-VAMP scheme



VCR= vincristine; ARA-C= aracytin; MTX= methotrexate; CF = cytofolic acid; * MTX dosing: see schema for folic acid

Cytofolic folic acid scheme:

If MTXemia of the 24° hour is:

<1.5 mM/L→15 mg/m² h 30, 36, 42, 48

Between <1.5 -5 mM/L→30mg/m² h 30, 36, 42, 48, then 15 mg/m² every 6 hours (h 54, 60, 66, 72) until levels are <5 µM/L

>5 mM/L→ 60 mg/m² h 30, 36, 42, 48, then 30 mg/m² every 6 hours (h 54, 60, 66,72) until levels are between 1.5 -5 mM/L; then 15 mg/m² every 6 hours until levels are <5 µM/L

Ponatinib is provided free-of-charge by Incyte Pharmaceutical Inc., under written agreement between GIMEMA and Incyte Pharmaceutical for patients enrolled in MRD+
or hematologic/extra-hematologic relapse, if previously treated with imatinib and/or chemotherapy (and not dasatinib).
Ponatinib is provided by National Health System for patients who are resistant to dasatinib; who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation.
Treatment with ponatinib will be provided as described above for the whole duration of the study, and upon study closure
(27 months: 3 of treatment and 24 of follow-up), in case of clinical benefit until progression or relapse.