

A multicentre phase III open-label randomized study in patients with advanced follicular lymphoma evaluating the benefit of maintenance therapy with rituximab after induction of response with chemotherapy plus rituximab in comparison with no maintenance therapy

Welcome to the 1st Edition of the PRIMA Monitors Newsletter

This Newsletter intends to keep you updated on the study progress. We would like this Newsletter to be as useful as possible, so if you have any suggestions, comments or information to share, please send it to any of the persons mentioned in the contacts section.

Status: 1217 patients registered

Induction treatment allocation:

- R-CHOP: 900 patients
- R-CVP: 272 patients
- R-FCM: 45 patients

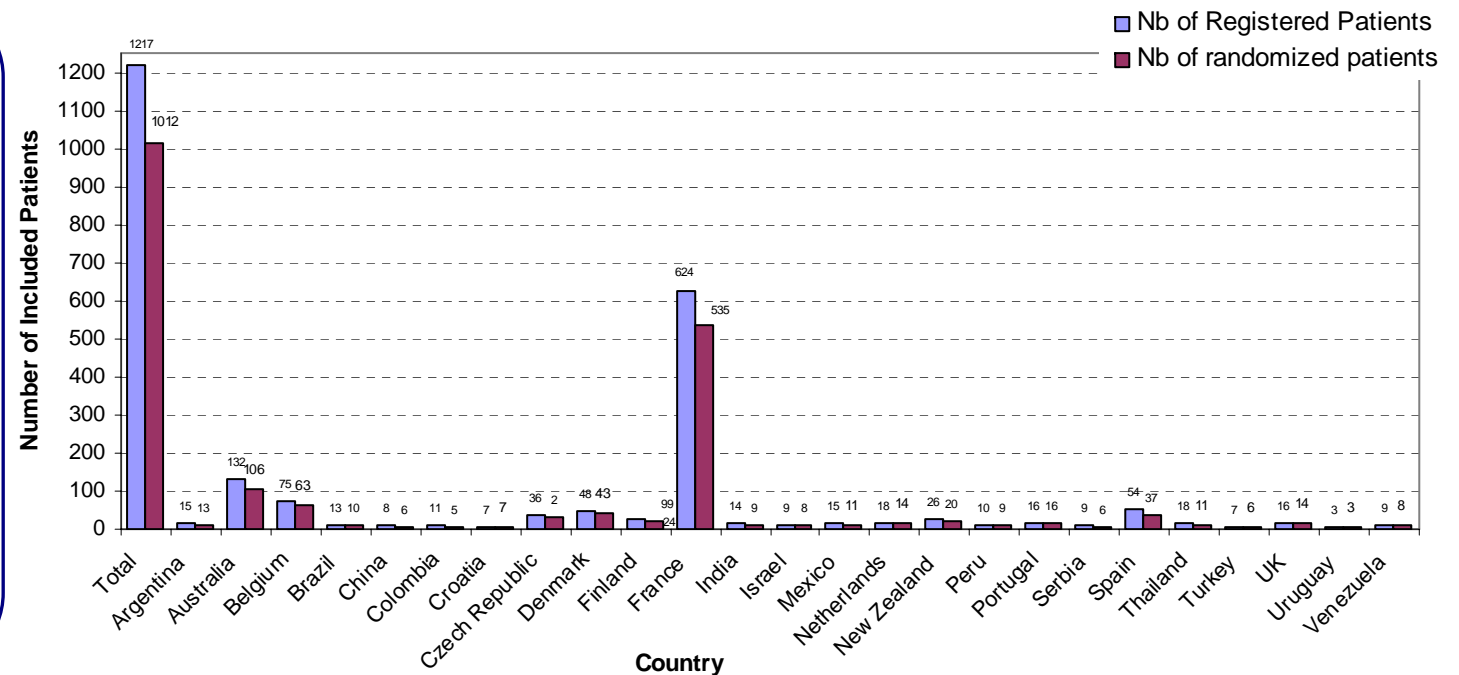
Randomized as of October 5th, 2007:

1012 patients

- Maintenance with Rituximab: 505 patients
- Observation: 507 patients

<http://prima.gela.org>

Country Recruitment - PRIMA study



Timelines 1ST Interim Analysis

172 PFS (Progression Free Survival) events are needed to fulfil the protocol requirements for the **First Interim Analysis**.

Upon estimations based on the current PFS event rate in the PRIMA Trial and data from previous similar trials, the **Cut-Off Date** for the analysis is planned by **March 18th, 2008**. This date will be re-evaluated in January 2008 with more updated data on events occurred. All data related to visits performed until this date will be used for the analysis, and must be entered in the database and clean - this means no open discrepancies.

It is planned to lock the database 4 months after the cut-off date. Database lock date is the day by which a snapshot of the database is taken for the analysis.

Importance of Immediate Event Reporting

Please remind the investigator that **Death or Progression/Relapse** pages (pages 47, 47-2, 48 and 49), if applicable to the patient - need to be faxed to GELARC (**FAX +33 4 72 66 93 71**) as soon as the Investigator is informed of the event. These pages must be SDVed and collected during the next monitoring visit.

DSMC Meeting

The PRIMA Data Safety Monitoring Committee will meet on **December 2007** during the ASH Congress. Demographic and Safety data of the PRIMA Trial will be reviewed and evaluated during this meeting. Therefore it is critical that all baseline data and all adverse events and toxicity information has been reported on the CRF pages immediately after data are obtained and these data is SDVed and sent to GELARC. For the upcoming DSMC Meeting all outstanding baseline data and AEs should be at GELARC by **October 19th, 2007**.

Please remind the investigators that an AE page must be completed for each SAE, immediately after faxing the SAE report to the GELA Safety Desk. In future, CRAs or country contacts will be notified by Pharmacovigilance GELA every time a new SAE is reported. A monitoring visit should be organized ASAP and the corresponding AE page must be SDVed and collected during this visit.

Contact Details

GELARC:	Delphine Germain Tel: +33 472 66 93 33 Email: delphine.germain@gelarc.org
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Monitoring News

- ✓ **Study Coordination in GELA Countries:** Due to an increase of workload and reorganization of resources in order to achieve study goals, GELARC will hand over certain study coordination activities to Roche Basel for all "GELA" countries but France and Belgium. These activities will mainly cover follow-up on monitoring activities (visit dates, outstanding CRF pages and queries), and communication with CRAs. Regular TCs will be planned for all countries.
- ✓ **Monitoring Frequency Increased:** In order to meet the study goals for the First Interim Analysis and the Safety Data Review by the DSMC, and the upcoming work on data cleaning, it has been decided by the Study Management Team to increase the monitoring frequency to **every 4 weeks**. A minimum of one visit every 2 months is acceptable for sites for which no data is outstanding (to be communicated and negotiated on an individual basis with GELARC for France and Belgium and Roche Basel for all other countries).
- ✓ As of October 1st, 2007, Roche has taken over from GELA Pharmacovigilance the responsibility of SUSAR distribution to Health Authorities in all participating countries. **SAEs must still be faxed by the investigators to GELA Safety Desk within 24 hours, as per protocol.**

Monitoring Reminders

- ✓ **CRF verification guidelines:** This document distributed to country contacts in August must be signed by the investigators and a copy of the signature page must be sent to GELARC.
- ✓ **Study Teams contacts:** Any changes should be communicated immediately to **BOTH GELARC and Roche Basel!!** This is also applicable to **Site contact changes**. Existing contact lists will be re-sent to all countries for review and update.
- ✓ Please remember to plan and agree the next monitoring visit date with the Investigator at each of your visits.
- ✓ Data Management Status reports will be provided on a monthly basis. **Feedback on outstanding CRF and queries must be provided to Roche Basel.**
- ✓ All Site Closures need to be approved by GELARC. All regulatory documents, acc. to Monitoring Plan, must be previously collected.
- ✓ Please remind the investigator to obtain all applicable ICF versions signed by all patients. Signature dates must be recorded on CRF page 1 and/or 1-2. This page must then be SDVed and sent to GELARC.

CT Scan Collection Update *by Bio-Imaging*

- ✓ The CT Data Collection for the GELA PRIMA study is well under way! Bio-Imaging is asking you for your continued assistance as we continue our efforts towards collecting all available CT data.
- ✓ Please remember that Bio-Imaging will only be collecting the CT/MRI scans of randomized patients that have approved protocol amendment 3 and signed ICF versions 2.0/2.1. If you cannot locate a patient on the spreadsheet it is likely because we are not able to collect the data yet.
- ✓ Our team at Bio-Imaging is here to assist you with the data collection. Please let us know how we can assist and we will ensure that your needs are met.

FAQ:

- Q: What type of digital data is acceptable at Bio-Imaging?
A: Any digital data should be submitted in uncompressed DICOM format. This is the most widely used format of imaging data.
- Q: I am in need of additional supplies. What do I need to do?
A: In the event that you require additional supplies, please email supplies@bioimaging.com or contact the Project Management team at Bio-Imaging (rcella@bioimaging.com, mvdkooi@bioimaging.com, or rvincenten@bioimaging.com).
- Q: I have collected the patient data from my site. Now what?
A: Firstly, please ensure that the data is from a randomized patient that has signed ICF versions 2.0/2.1 and the site has approved protocol amendment 3. After this is confirmed, the data should be labeled using the protocol specific labels that are found in the Imaging Study Kit. A retrospective Data Transmittal Form (rDTF) should be prepared and submitted to Bio-Imaging. Please remember, one DTF per each patient timepoint.

Questions or concerns: Please contact Ryan Cella (rcella@bioimaging.com), Marieke van der Kooi (mvdkooi@bioimaging.com), Rianne Vincenten (rvincenten@bioimaging.com), and/or Karen Kubacke (kkubacke@bioimaging.com).

SAE Reporting Rules

GELARC Pharmacovigilance (PV) department proceeds a reconciliation between each SAE and a corresponding CRF AE page. For this process the AE pages need to be collected immediately after the SAE report. This is an important step as the Data Safety Monitoring Committee (DSMC) is reviewing on an on going basis the safety AE data. Missing information has a major impact on the quality of the safety assessment performed and can potentially be detrimental to patients.

The following items must be identical on the SAE form and on the corresponding CRF page:

- Registration number
- Gender
- Date of Birth
- SAE diagnosis
- AE ONSET DATE
- Drug-event relationship
- Date of Death if outcome is death

The item drug-event relationship on the AE page must correspond to the worse causality from the SAE form.

By SAE form, only one event (=main diagnosis) should be reported. Symptoms should be reported in the narrative. In case of several serious adverse events, one separate SAE form has to be completed for each event.

In order to simplify the SAE - AE reconciliation procedure and to avoid numerous queries generated following the reconciliation process, **please check that all above mentioned items are identical on the both SAE and AE pages before sending them to GELARC.**

SAE cancellation rules

The SAEs reports which do not qualify as serious adverse events according to the protocol reporting rules (example: lymphoma manifestation, haematological toxicities) are further cancelled by the PV department.

PV department sends a query in order to ask you to proceed a cancellation of the SAE (and the corresponding AE if the event is lymphoma manifestation) in the patient's file.

Please send an answer to this query to the PV department which confirms that a cancellation of the SAE (and the corresponding AE if the event is lymphoma manifestation) has been done.

Help on Source Document Verification on Haematological Lab Value

If hematological toxicity is reported for Hemoglobin, Leukocytes, Neutrophils and Platelets, please use the exact CTCAE v.3 below to assess the grading of a lab value to be reported on the toxicity page.

BLOOD/BONE MARROW						
AE	Short name	Grade				
		1	2	3	4	5
Hemoglobin	Hemoglobin	<LLN – 10.0 g/dL <LLN – 6.2 mmol/L <LLN – 100 g/L	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80 – 65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L	Death
Leukocytes (total WBC)	Leukocytes	<LLN – 3000/mm ³ <LLN – 3.0 x 10 ⁹ /L	<3000 – 2000/mm ³ <3.0 – 2.0 x 10 ⁹ /L	<2000 – 1000/mm ³ <2.0 – 1.0 x 10 ⁹ /L	<1000/mm ³ <1.0 x 10 ⁹ /L	Death
Neutrophils/granulocytes (ANC/AGC)	Neutrophils	<LLN – 1500/mm ³ <LLN – 1.5 x 10 ⁹ /L	<1500 – 1000/mm ³ <1.5 – 1.0 x 10 ⁹ /L	<1000 – 500/mm ³ <1.0 – 0.5 x 10 ⁹ /L	<500/mm ³ <0.5 x 10 ⁹ /L	Death
Platelets	Platelets	<LLN – 75,000/mm ³ <LLN – 75.0 x 10 ⁹ /L	<75,000 – 50,000/mm ³ <75.0 – 50.0 x 10 ⁹ /L	<50,000 – 25,000/mm ³ <50.0 – 25.0 x 10 ⁹ /L	<25,000/mm ³ <25.0 x 10 ⁹ /L	Death

Please also refer to <http://ctep.cancer.gov/forms/CTCAEv3.pdf>