

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.

## PRIMA Newsletter N° 10

### Topics

- Interim Analysis - PFS Event Reporting
- Protocol Amendment # 4
- 2nd Monitoring Workshop
- Adverse Events Reporting
- CT Scan Collection Status
- CRF Reception Status
- Queries Turnaround per Country

## Interim Analysis Coming Soon!

**As the Analysis is PFS Events driven, all progressions and deaths must be reported to GELARC immediately!**

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**) **IMMEDIATELY** after the Investigator is informed of the event. These pages must be SDVed and collected during the next monitoring visit.

An accurate calculated events rate is mandatory in order to predict the exact cut-off date for the Interim Analysis!

*Please inform the CRA about any issues impeding the reporting of events on time.*

13 Study Events have been reported in May and 15 in June 2008. However, some of these events occurred more than 4 months before being reported:

### May 2008

- 4 Events from 2007**
- 2 Events from January 2008**
- 2 Events from February 2008
- 1 Event from March 2008
- 3 Events from April 2008
- 1 Event from May 2008**

### June 2008

- 1 Event from October 2007**
- 1 Event from February 2008**
- 6 Events from April 2008
- 6 Events from May 2008
- 1 Event from June 2008**

With these current figures, it is very difficult to calculate an accurate events rate and/or predict the cut-off date for the Interim Analysis.

### Protocol Version 5.0 (Amendment # 4)

The study protocol has been amended in order to incorporate the following key changes:

1. The statistical analysis plan was revised to include only one interim analysis after 75% of the PFS events (258 events) have occurred.
2. The number of independent reviewers was changed to give estimates in order to allow more reviewers during the independent review process as required.
3. SAE reporting was added for Arm B (observation arm) during the 'active' observation period and additional guidance was included for the management of SAEs.

This Protocol Amendment has been submitted to both the FDA and the French Authorities/Ethic Committees. As soon as approval is received, it will need to be submitted to the Health Authorities/Ethic Committees in all other countries participating in PRIMA as required.

### 2nd Monitoring Workshop

The second Monitoring Workshop took place in Vienna during May, 19/20 2008. 30 Monitors from 22 countries participated at the training.

CRAs have been trained in the Cleaning and Safety Processes and requirements and have been provided with updated information regarding timelines.

We are confident all CRAs are well trained to answer all your questions and will provide valuable support to all sites.

### Adverse Events Reporting

**Real time reporting of Adverse Events (AE)** is required in this study as data are **reviewed on an ongoing basis by Data Safety Monitoring Committee (DSMC)**.

Please do not delay reporting of AEs, even incomplete CRF AE pages (e.g. missing end date) are processed and follow up information can then be reported on the **Complementary Information of Adverse Event** CRF page (pages 58-61).

## CT Scan Collection Status - June 30, 2008

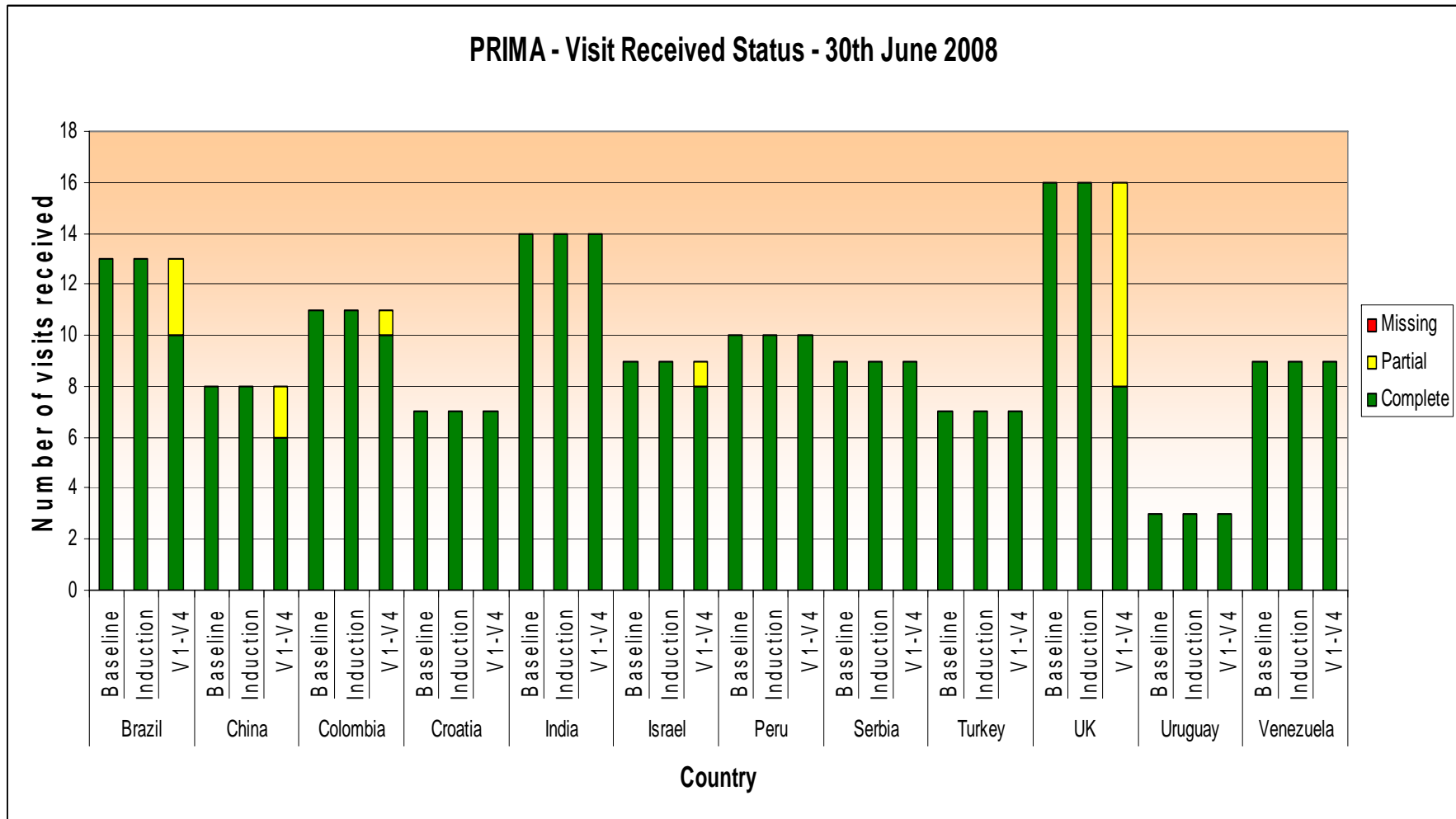
Please ensure that all patients sign the ICF related to Protocol version 4.0 in order to be allowed to collect their CT Scans. Furthermore, all outstanding CT Scans must be submitted to Bio-Imaging as soon as possible.

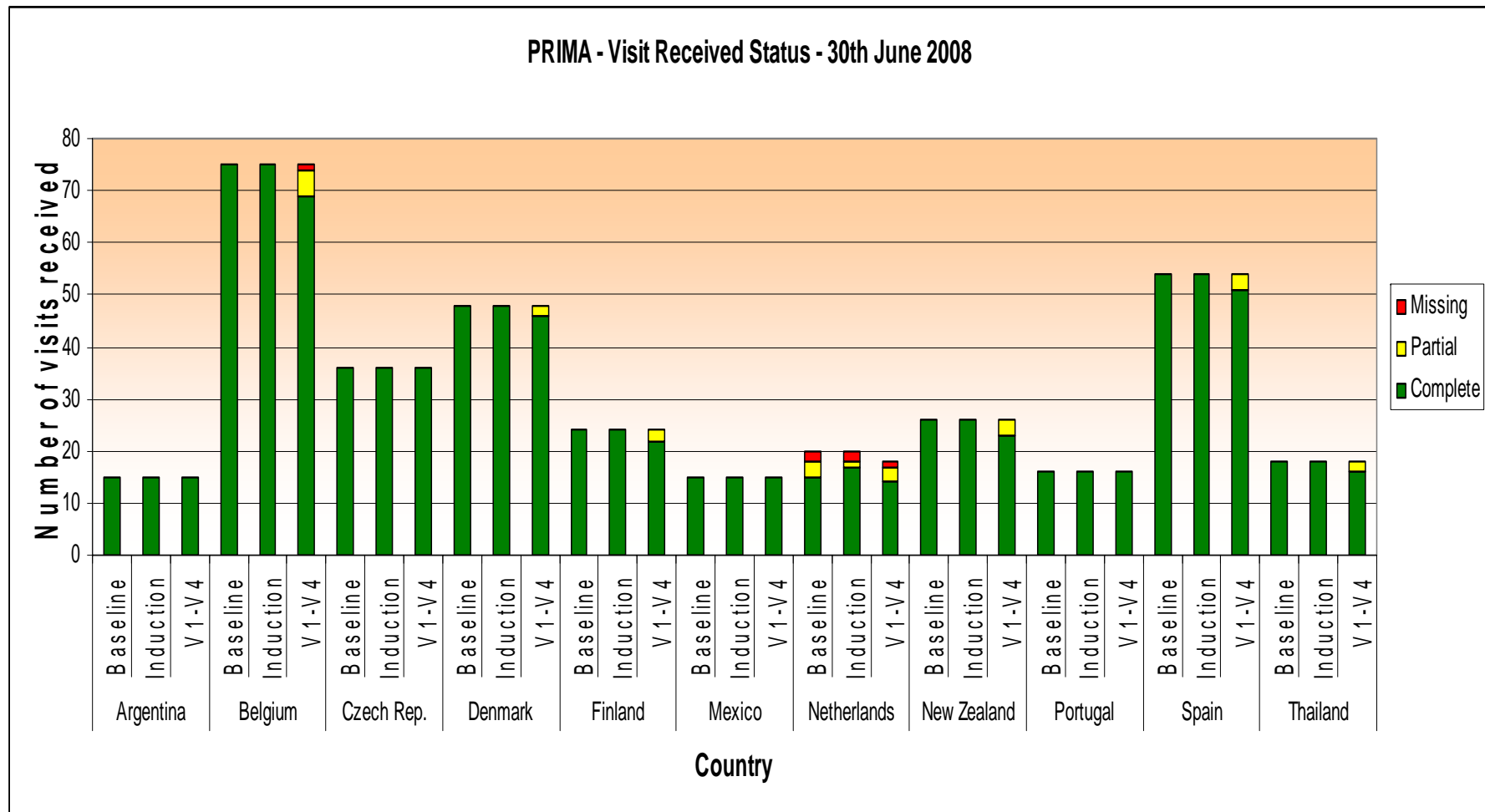
*All CT Scans performed after January, 31<sup>st</sup> 2008 must be sent to Bio-Imaging within 5 days after being performed (prospective collection kit).*

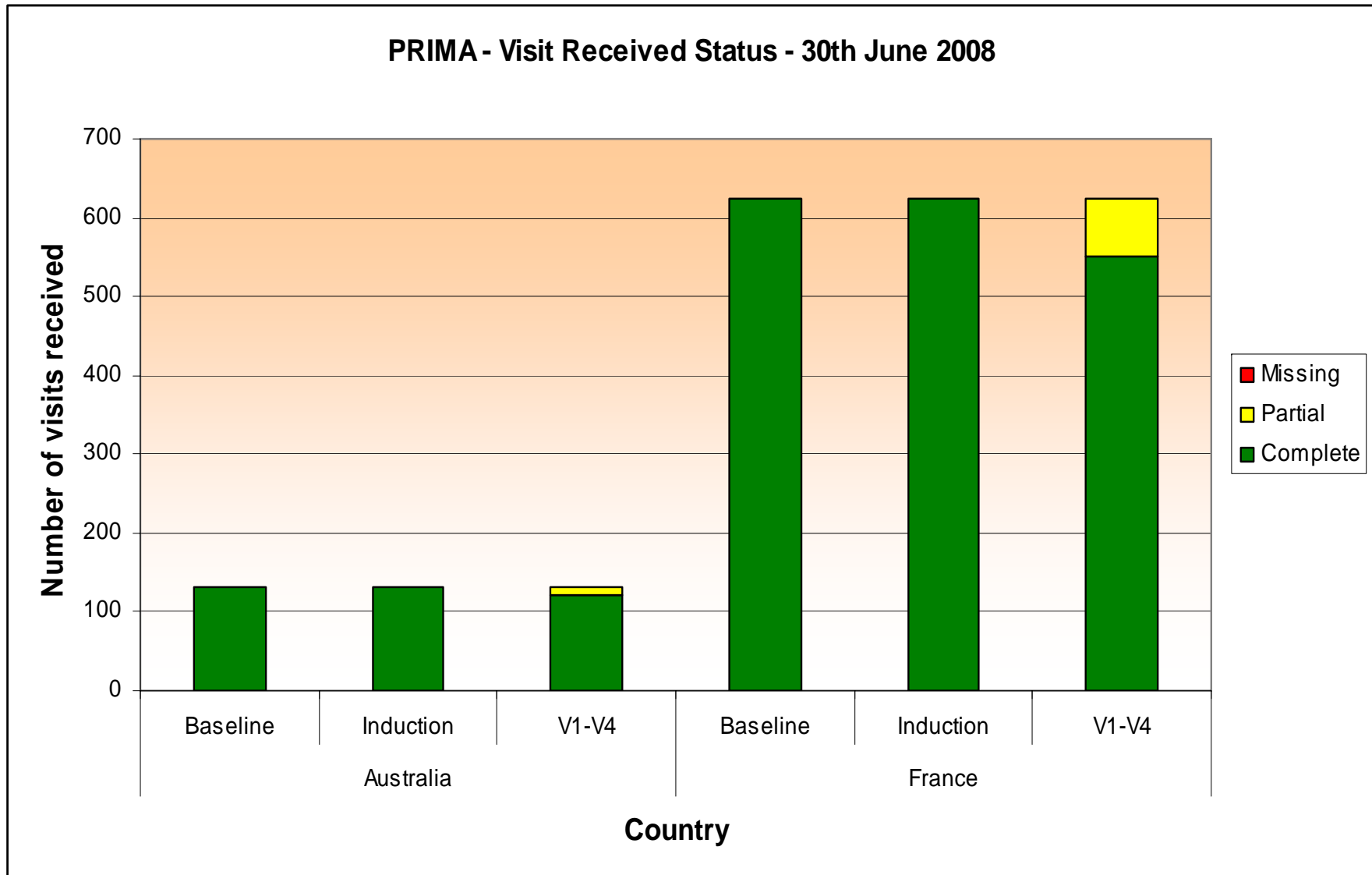
Country	Number of randomised patients	N° of patients outstanding to sign ICF to CT Scan collection	Number of patients received	Number of patients missing	Timepoints (TP) received	Timepoints (TP) missing
Argentina	13	0	5	8	19	60
Australia	112	37	49	22	232	413
Belgium	63	2	39	18	212	170
Brazil	12	0	12	0	61	0
China	6	0	6	0	24	6
Colombia	5	0	5	0	26	4
Croatia	7	0	7	0	24	15
Czech Republic	30	0	28	0	191	15
Denmark	43	0	42	0	232	23
Finland	22	0	22	0	110	9
France	543	32	297	197	1193	1706
India	9	0	7	0	43	1
Israel	8	0	9	-1	34	8
Mexico	11	5	0	6	0	24
Netherlands	14	2	5	5	19	27
New Zealand	22	3	14	4	58	67
Peru	9	0	7	0	27	21
Portugal	16	0	16	0	84	8
Serbia	6	0	4	1	12	8
Spain	37	0	29	7	137	73
Thailand	11	0	11	0	65	2
Turkey	6	0	6	0	36	0
UK	14	0	6	8	21	46
Uruguay	3	0	3	0	13	0
Venezuela	8	0	8	0	41	9
<b>Total</b>	<b>1030</b>	<b>81</b>	<b>637</b>	<b>275</b>	<b>2914</b>	<b>2715</b>

## CRF RECEPTION STATUS

Please ensure that all incomplete or outstanding CRF pages (including AE, PD or premature withdrawal pages) are completed as soon as possible, in order to ensure their collection by the CRA during the next monitoring visit.

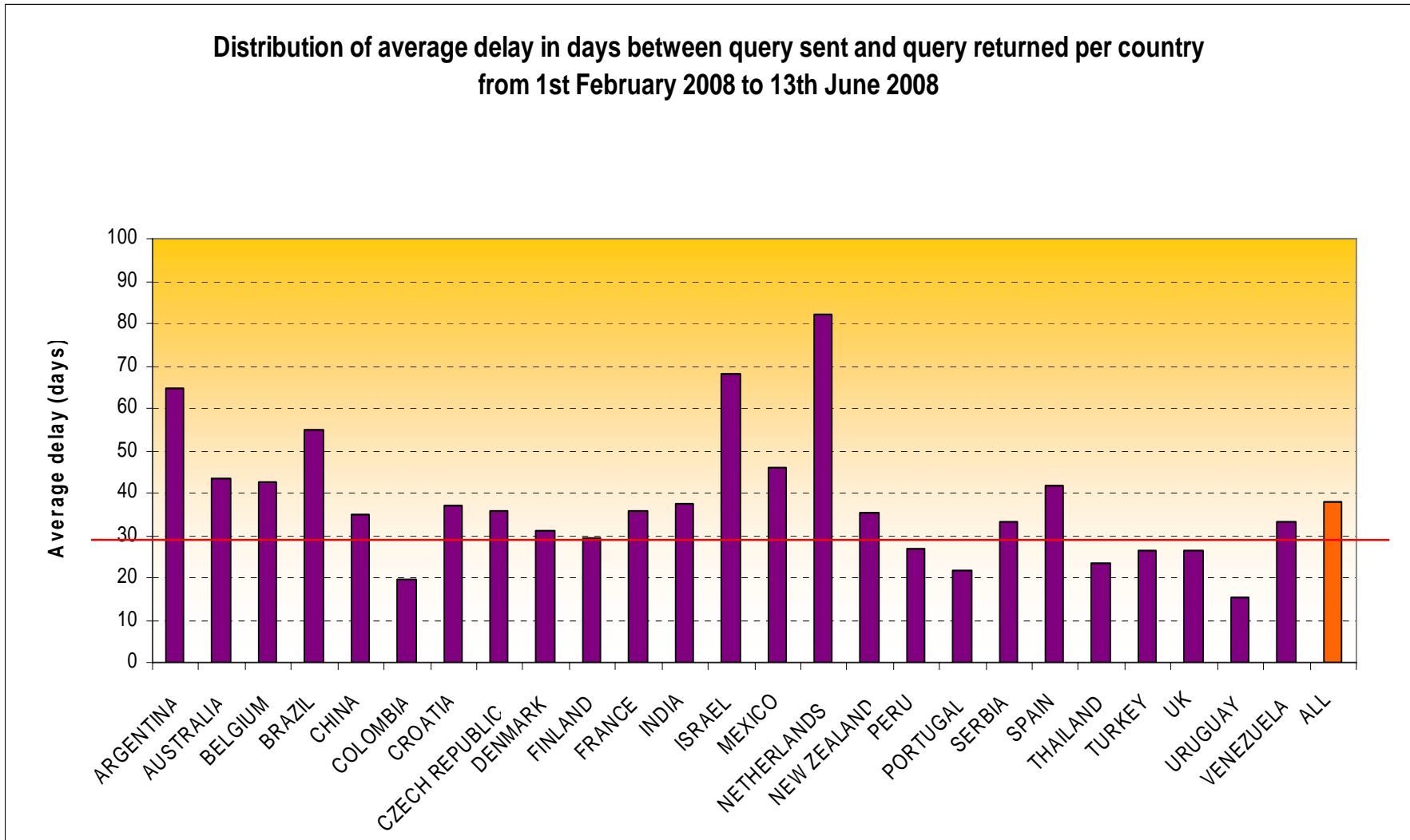






Please be reminded that all queries should be solved within few days after arrival, in order to allow the CRA to perform Source Data Verification and to collect them during the next Monitoring Visit.

**As per agreed Monitoring Frequency of every 4 weeks, the average delay should not be higher than 28 days (red line)!**



### PLEASE REMEMBER

1. During Maintenance period with or without Rituximab, patient must have clinical visits every 8 weeks. It is critical to maintain this evaluation as planned in the protocol to avoid any biases between the 2 arms. Refer also to DSMC feedback letter distributed early this year.
2. After 24 months maintenance period the Evaluation at the End of Treatment forms (CRF pages 34, 35, 36) need to be completed independently of how many visits have been done.
3. If a patient is withdrawn due to Treatment Toxicity (AE or SAE reporting action taken with study drug as *discontinued*) the withdrawal page needs to be completed as soon as possible, with reason due to toxicity.

### IN CASE OF QUESTIONS

#### Medical questions: please contact

- Prof. Gilles Salles at GELA  
([gilles.salles@chu-lyon.fr](mailto:gilles.salles@chu-lyon.fr))
- Delphine Germain at GELARC  
([delphine.germain@gelarc.org](mailto:delphine.germain@gelarc.org) or +33 4 72 66 93 33) or
- Elisabeth Wassner-Fritsch at Roche  
([elisabeth.wassner\\_fritsch@roche.com](mailto:elisabeth.wassner_fritsch@roche.com) or +41 61 688 50 31)

#### Data Management questions: please contact

- Laurence Girard  
([laurence.girard@gelarc.org](mailto:laurence.girard@gelarc.org) or +33 4 72 66 93 33) or
- Delphine Germain or your DM at GELARC

#### SAE questions: please contact

- Larissa Mege at GELARC  
([larissa.mege@gelarc.org](mailto:larissa.mege@gelarc.org))

**THANK YOU FOR YOUR CONTINUOUS SUPPORT AND COMMITMENT!**