

Appendix 1:

In the ----- teleconferences between the FDA and Corixa, the FDA identified issues involving specific patients in their review of iodine I 131 tositumomab. The following table summarizes the concerns identified by FDA's review for confirmation of the long-term response in individual patients and provides Corixa's responses to these concerns for each patient. The page numbers reference the page of the patient's CRF file submitted as part of Item 12 in the ----- partial response to the complete review letter.

004-013-008	Question of progression at study day 425 based on new lesion with dimensions 2.2 x 1.8 cm (3.96 cm ²)	<p>Early versions of the MIRROR panel charter defined measurable disease as any lesion $\geq 2 \times 2$ cm. This came to be interpreted operationally as any lesion with product of perpendicular diameters (PPD) ≥ 4.0 cm². MIRROR2 and later charters have explicitly used PPD measurements. In every review, some lower limit must be set for measurable disease since normal lymph nodes have mass and normal lymph nodes fluctuate in size in association with immunoinflammatory reactions. In this case, the rule facilitated a correct description of the patient's course, because, without further treatment for lymphoma the pelvic lymph node in question becomes smaller and the patient remains in clinical complete response almost 1000 days afterward.</p> <p>Corixa believes that this patient should be included in the durable responders population.</p>
004-014-001	Patient appears to be responding to prior chemotherapy at time of study entry	<p>Patient received fludarabine from 03 June through 02 August 1996. CT scans prior to fludarabine were read by MIRROR panel as having an SPPD of 66.66 cm². Scans after fludarabine on 21 Aug 1996 were read with an SPPD of 43.16 cm². Baseline scans on study entry on --- December 1996 were read with an SPPD of 22.00 cm², a decrease of 67%. Thus the patient had a PR to fludarabine at study entry. The SPPD at week 7 was 9.24 cm².</p> <p>Corixa agrees that this patient is non-informative. In the primary efficacy analysis for study RIT-II-004 this patient is excluded, but included in long-term durable responders. However, inclusion of the patient in analyses of secondary endpoints in the study and in the durable responders population does not diminish the fundamental findings. For the purposes of labeling, Corixa will correct all analyses to reflect exclusion of this patient</p>
004-016-001	Question of progression 9/25/97. Axillary node noted on PE. Oncology assessment PD later changed to PR.	<p>Patient had documented axillary adenopathy on physical exam at baseline. The oncologist had called PD based on a left axillary node, which was interpreted as new disease. Upon the radiologist's and oncologist's review, the left axillary node on 9/25/97 was noted to not have been a new lesion. Refer to CRF18A (page 137) -- all radiographs reviewed and radiologist concluded that the small axillary node was unchanged. Node measured 0.8 x 1.5 cm. After radiology review, the Oncologist revised his assessment to PR and documented his reasoning on CRF</p>

		<p>18C, page 196 of the case report forms, “palpable (L) axillary node also seen on old CT. Therefore, not progression.”</p> <p>Corixa believes that this patient is correctly considered to be in PR on the date in question and not to have evidence of progressive disease.</p>
004-016-001	FDA questioned why the investigator-assessed withdrawal for PD on --- June 1999 had been lined out.	<p>CRF form dated 24 June 1999 (p 338) denotes PD and states “patient also had bx of colonic polyp demonstrating a diffuse large cell lymphoma “. The same CRF (p 339) is crossed out without explanation and dated 25 July 2000 when patient records were obtained from the investigator which stated: “During a routine screening colonoscopy, a lesion was found on the ileocecal valve that was biopsied and came back with a diagnosis of B cell lymphoma. But a CT scan failed to demonstrate any evidence of disease. In addition, the pathology report from the hemicolectomy revealed only lymphoid hyperplasia associated with the villous adenoma which was completely resection”. The outpatient progress note stated: “the findings of DLCL within the villous adenoma may have been artifactual secondary to evaluation of a small biopsy sample”. Two issues were resolved. The patient did not have any 2x2 cm lesions on CT to justify the PD assessment and after the partial colectomy, the pathology was read as lymphoid hyperplasia and not lymphoma. The patient was not withdrawn from study. The patient remains in CR as of 25 Oct 2001. We will attempt to obtain the pathology report from the biopsy and surgical resection. The monitor’s trip report quoted above can be provided at your request.</p> <p>Corixa believes that the patient’s course has been appropriately described in the analyses provided.</p>
004-014-008	FDA questioned whether the patient had PD in July 1998 and not October 1998.	<p>On the date in question, July 1998, the SPPD of all lesions decreased to 37.44 from 37.6 at the previous response visit. No new sites of disease were recognized. While the left axillary lesion became evaluable at 1.0 x 2.2 cm (2.2 cm²) from BDL x BDL at the previous response visit, this increase in isolation does not constitute progression as defined by the MIRROR Panel charter.</p> <p>Corixa believes that this patient’s course has been accurately described in the analyses provided.</p>
004-016-003	FDA questioned why the PD at Week 19 assessment was changed to SD.	<p>The original MIRROR Panel was based on indicator lesions, which for this patient were left (L) femur and right (R) femoral head. The patient was classified as having PD on Week 19 based on the indicator lesions (p. 104). Upon discussion with the FDA, the MIRROR Panel charter was revised and an expanded review was conducted for all patients in study RIT-II-004. Per the new charter, all lesions were included in the lesion inventory. This led to inclusion of one additional lesion (inguinal node) in the expanded MIRROR Panel review. The response assessment was changed to SD (page 150: see documentation on CRF 18A) as the change in SPD of 22% did not meet the 25% increase in SPPD requirement for PD.</p>

		Corixa believes that this patient's course has been appropriately characterized in the analyses provided.
002-030-925 002-030-926	CRFs for Arm B (prior to crossover) were requested by FDA.	Corixa will provide bookmarked hypertext linked CRFs for patients 002-030-025 and 002-030-026.
002-032-001	FDA suggested that patient had PD on 17 August 2000. The MIRROR Panel assessed the patient as continuing in CR on -- August 2001.	<p>Patient entered study with large (3 – 4 cm) bilateral inguinal nodes. These decreased to the point that they were not detected on 2 physical exams prior to 17 Aug 2000.</p> <p>The physical examination note on 17 August 2000 (page 90) identifies left inguinal adenopathy, which was classified as stable (page 91). No measurements were reported. The previous physical examination (page 88) did not report any inguinal adenopathy and the subsequent examination on 09 Nov 2000 (page 92) identifies 1 cm bilateral inguinal lymph nodes which were non-tender. The next examination (page 94) on 15 Feb 2001 reported no palpable adenopathy.</p> <p>The MIRROR Panel tracked the two left inguinal nodes; these were reported as <1 x <1 cm on the 14 August 2000 radiographic evaluation. The MIRROR Panel radiologist and oncologist reported the patient to be in CR. The Investigator continued to follow patient as if in response.</p> <p>Corixa believes that this patient is correctly considered to be in CR on 14 August 2000 and not to have evidence of progressive disease.</p>
002-011-915	FDA reviewer identified a 1 cm cervical node in May 1997. The MIRROR2 Panel reported that the patient was in CR in April and July 1997 and developed PD on -- March 1998.	<p>The medical notes (page 111) from 27 May 1997 reported a 1 cm right mid posterior cervical node. Bilateral cervical 1.5-2.0 cm nodes were noted at Dec 1996 baseline (page 100). In Jan 1997 1.5 cm cervical nodes were present. On 18 March 1997 the maximum diameter of cervical and supraclavicular nodes was 1.0 cm (page 106). The 30 April 1997 medical notes (page 109) reported a small 0.5 cm posterior cervical node. Subsequent medical notes (page 113) reported cervical and supraclavicular nodes, measuring at most 0.5 cm. The referenced 27 May 1997 node does not appear to be a new node.</p> <p>The Investigator identified the right posterior cervical node at baseline (page 40) as 2.0 x 1.2 cm. On 15 July 1997 the lesion was 0.7 x 0.5 cm (page 53). On 25 July 1999 (page 62) the lesion was no longer present.</p> <p>Both MIRROR and MIRROR2 Panels assessed the patient. Both reported that by radiographs the patient had all lesions BDL at the April and July assessments. Neither tracked the posterior cervical node.</p> <p>Corixa believes that this patient is correctly considered to be in CCR on the date in question and not to have evidence of progressive disease.</p>
002-011-016	FDA reviewer was	Open lung biopsy in April 1995 was positive for follicular

	<p>concerned that the patient had a complex medical course: confounding lung involvement, abdominal lesions associated with infection and surgery, and ovarian carcinoma with associated lesions and surgical intervention.</p>	<p>small cell lymphoma. After chemotherapy failed, repeat bronchoscopy was positive for lymphoma in 1996.</p> <p>At baseline, the Investigator noted disease in lung and “midline abdominal lesion anterior to the liver and superior to the kidney”; but stated only measurable disease is in right base. MIRROR and MIRROR2 Panels (pages 85 and 91) note disease in same areas, but state only measurable disease is in abdomen [called mesenteric or presplenic]. MIRROR2 panel states on baseline CRF “disease in the lungs probably sequelae”. Investigator Response: lung lesion decreases to 6.8 cm² at week 7 [called a PR]. Lesion remains between 5.6 cm² and 7.1 cm² for the next 10-11 measurements over 4 years and thus may well have been scarring rather than active lymphoma.</p> <p>The Investigator, MIRROR Panel, and MIRROR2 Panel all report that the patient never developed PD. All identified a baseline lesion and all noted tumor response and the absence of PD.</p> <p>On study day 80 the patient was admitted for acute abdominal pain secondary to ascending cholangitis. Cholecystectomy was performed with full resolution of problem.</p> <p>On -- May 2001 the patient had a hemicolectomy and partial omentectomy that identified poorly differentiated adenocarcinoma, most compatible with Stage III ovarian carcinoma. The patient was withdrawn from study for treatment of the ovarian carcinoma with chemotherapy.</p> <p>Corixa believes that the patient’s lymphoma course has been appropriately documented by the Investigator, MIRROR Panel and MIRROR2 Panel, despite the complexity of the patient’s medical history and co-morbidities.</p>
002-011-009	<p>FDA reviewer reported that the patient had small baseline disease, poor quality of scans, and didn’t know what to make of patient.</p>	<p>This patient was described in an email to George Mills on 19 September 2002 as follows:</p> <p>The 47 year old patient with a history of follicular, small cleaved cell lymphoma presented in 1989 with stage III-A disease. He received 2 cycles of CVP with excellent response and treatment was discontinued. He recurred 5 years later with cervical adenopathy. A brief course of chlorambucil produced another remission. He again developed inguinal and cervical lymphadenopathy 2 years later. Daily chlorambucil was given for 6 months. Approximately one year later he developed rapidly enlarging inguinal adenopathy. Biopsy demonstrated histological</p>

		<p>transformation to follicular, large cell lymphoma. He presented to ----- Medical Center with a single abnormality on physical exam – a submandibular mass that measured 2.5 x 2.0 cm by physical exam. An FNA was performed prior to study entry. Aspirated material was consistent with low grade lymphoma (small cleaved cell type). MIRROR2 review noted two evaluable lesions on baseline CAT scan, a (R) jugular node with product of perpendicular diameters of 1.12 cm² and a (R) infraparotid (submandibular) node of 3.52 cm². Both lesions promptly became BDL x BDL following treatment with Bexxar. The patient was without evidence of progression at 371+ days. Assessments at year two were considered not assessable.</p> <p>Pathologically proven baseline disease was observed to regress after iodine I 131 tositumomab therapy. Corixa believes that the patient's course has been appropriately documented by the Investigator, MIRROR Panel and MIRROR2 Panel.</p>
002-034-906	<p>FDA reviewer reported that he did not have adequate pre-treatment measures to assess patient.</p>	<p>The patient was randomized to Arm B and developed Investigator-assessed PD and MIRROR Panel-assessed PD on --- Dec 1998 (see MIRROR Panel listing for study RIT-II-002 study report [BLA submission -----] and CRF for Week 7 submitted as part of the original BLA). The Investigator-assessed PD at Week 7 was based on a new lesion >2 x 2 cm.</p> <p>The crossover baseline examination was obtained one month later and identifies extensive disease prior to treatment on the ---- January 1999 assessment (page 49). The MIRROR Panel radiologist reported eleven lesions. At the -- May 1999 (Month 3) evaluation, all lesions were BDL and continued to be reported as BDL through the last evaluation on 24 Nov 2000.</p> <p>Corixa believes that the patient's course has been appropriately documented by the MIRROR Panel and other submitted CRFs and lesion listings. This case was the subject of a conversation between Corixa (Stewart Kroll) and the Agency on ----- . It was agreed that the Arm B pretreatment measurements were adequate for the assessment of the patient.</p>
012-035-006	<p>FDA reviewer suggested that the patient had PD on --- August 1999.</p>	<p>The MIRROR Panel identified 13 baseline lesions including a 3.8 x 2.8 cm right neck lesion on the -- Jan 1999 baseline assessment (page 46). At the following assessment the right neck lesion was 1.0 x 1.2 cm. No neck CT was available for --- May 1999 and at the --- August 1999 assessment, the right neck lesion was reported as 1.0 x 2.5 (< 4 cm²). The MIRROR Panel reported the patient as a PR. At the next evaluation on --- Feb 2000 the neck lesion was 2.7 x 1.8 cm and the MIRROR Panel reported PD. At future MIRROR Panel evaluations the neck lesion waxed and waned. The Investigator reports the patient to continue in CR as of -- August 2001.</p> <p>Corixa believes that this patient's course has been</p>

		accurately described by the MIRROR Panel with PD on 15 Feb 2000.
012-037-001	FDA reviewer suggested that the patient had PD on 22 June 2000.	<p>The MIRROR Panel identified 3 baseline lesions including a 1.7 x 1.5 cm right lower lobe lesion on the 22 June 1998 baseline assessment (page 55). At the following assessments the right lower lobe lesion was 1.5 x 2.3 cm, 2.5 x 2.0, 2.2 x 1.7, 2.0 x 1.5, 2.5 x 2.0 (22 June 2000), and then BDL x BDL for all subsequent assessments. Under the MIRROR panel charter in effect, the oncologist had access to the lesion measurements. Employing clinical judgement, he documented in a joint response assessment for 22 June 2000 that his assessment should be changed to CCR. He commented "please note that the RLL lesion is unchanged within error of radiographic measurement" (page 111).</p> <p>PD was documented by both the Investigator and MIRROR Panel in May 2001, based on the appearance of a new preauricular lymph node.</p> <p>Corixa believes that this patient's course has been accurately described by the MIRROR Panel.</p>
012-036-007	FDA reviewer suggested that the patient had PD on 23 May 2000.	<p>A 0.5 cm palpable lymph node was identified on the 23 May 2000 PE. On 13 June 2000 and 30 June 2000 the lesion was reported as 1 cm. The MIRROR Panel reported the patient to have PD on 26 June 2000.</p> <p>As the 0.5 cm lesion does not represent PD based on the MIRROR Panel response definitions (≥ 4.0 cm² radiographically, or ≥ 1 cm by physical examination), Corixa believes that this patient's course has been accurately described by the MIRROR Panel with PD on 26 June 2000.</p>
000-002-006	FDA reviewer suggested that the patient had significant response prior to the therapeutic dose and questioned if the patient should be included as a durable responder.	<p>Both the MIRROR Panel and MIRROR2 Panel assessed the patient to respond to therapy and have PD on 27 August 1993.</p> <p>Numerous patients have been reported to have tumor response subsequent to the dosimetric dose and prior to the therapeutic dose. In fact, the observation that some patients experience tumor regression prior to the therapeutic dose, when a 475 mg predose of unlabeled antibody preceded the dosimetric dose, was one of the reasons for the selection of the 485 mg tositumomab dose as a standard part of the dosing scheme for iodine I 131 tositumomab. (see the Rationale for Treatment Regimen in the Clinical Pharmacology section of the original BLA; Section 8.3.6.3.1 (page 57)). Durable responders with multiple dosimetric doses are summarized in Table 2. While multiple dosimetric doses were administered to some patients, no patient received more than a single predose at the highest level.</p> <p>Corixa believes that this patient's course is informative, and is accurately described by the results provided by the MIRROR panel.</p>

000-002-056	<p>FDA reviewer commented that the concomitant Breast CA made the case confusing.</p>	<p>Jan 1989 node biopsy demonstrated follicular small cell lymphoma. Second biopsy in Dec 1990 demonstrated follicular large cell. Treatment with 5 different chemotherapy regimens was delivered over the next 5 years. During evaluation for recurrence in May 1994, mammogram showed small lesion right breast. Lumpectomy demonstrated infiltrative ductal carcinoma. In July 1994 the patient received more chemotherapy for lymphoma, plus 4000 cGy RT to thoracic spine, mediastinum and upper abdomen but not breast/axillary nodes. In March 1995 the patient had relapse in neck nodes. Biopsy confirmed large cell lymphoma and an abdomen CT was positive. In Sept 1995 the patient had a recurrence of breast cancer in right breast and underwent modified radical mastectomy on 31 Oct 1995 (a 2.5 cm lesion, with 4/11 nodes positive with extranodal extension). The patient entered study RIT-I-000 on 04 Dec 1995. Note that the protocol did not exclude patients who had a prior malignancy.</p> <p>MIRROR 1 and 2 panel response assessments: followed baseline lesions in axillae, aortocaval, and retrocaval areas. In both response evaluations, disease quickly became BDL x BDL and then 0x0 until a mesentery recurrence in mesentery in Jan 1998 (page 77). In MIRROR 2 a new pulmonary lesion in right apex measuring 6.4 cm² was noted at week 13 evaluation. Radiologist stated "In my opinion lung lesion is much more likely from breast cancer or a secondary lesion from therapy". At the 6 mo visit the same lesion measured 1.65 cm and at the one yr BDL x BDL. At 9 months radiologists notes "lesion at apex is probably scar from therapy. In my opinion the patient is still a PR".</p> <p>Corixa agrees that the confounding effects of metastatic breast cancer in this patient make assessment of lymphoma response problematic. Corixa will remove this patient from the durable responder population.</p>
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