

TRANSFORMED LOW-GRADE NHL

At the initiation of the major efficacy trial (RIT-II-004) FDA informed the sponsor, in the End-of-Phase 2 meeting and in subsequent correspondence, that extending the efficacy date obtained in the treatment of patients with low grade and follicular NHL without evidence of transformation to the treatment of patients with NHL with transformation to a higher grade histology may not be appropriate. The sponsor was asked to provide a justification for pooling the results from these two populations. In addition, the sponsor was informed that subset analyses should be conducted in patients with and without evidence of transformation. At the conclusion of RIT-II-004, the results of the subset analyses showed a marked difference in the response rates in the two subsets (62% vs. 21%). Based on a demonstration of durable responses in patients with low grade and follicular NHL with transformation, recurrent after combination chemotherapy, the sponsor requested Fast Track designation and received for treatment of patients with transformed NHL, that was recurrent or refractory to standard chemotherapy. FDA asked the sponsor to supplement the data from RIT-II-004, which enrolled 23 patients with transformed NHL. The sponsor identified a total of 71 patients with a diagnosis of transformed NHL at the time of study entry who were enrolled in the 4 activity/efficacy trials conducted by the sponsor.

The integrated efficacy analyses of the transformed low-grade NHL patient population include data on the 78 patients who had a diagnosis of transformed low-grade NHL at some point prior to study entry and who received study drug in the 4 studies (RIT-I-000, RIT-II-001, RIT-II-002, and RIT-II-004). In order to be included in the dataset, FDA stated that the histologic diagnosis be confirmed for each subject. Central pathologic review was conducted by Dr. Charles Ross at the University of Michigan of 60 patients with a diagnosis of transformed NHL who were enrolled in studies RTI-I-000, RIT-II-001, RIT-II-002, and RIT-II-004. Dr. Elaine Jaffe performed central pathologic review for 12 patients a diagnosis of transformed NHL who were enrolled in study CP 97-012.

The independent (MIRROR) panel conducted a retrospective review of the clinical data to establish the response rates and duration for this subpopulation.

FDA conducted a review of the information in the case report forms, pathology reports (initial and central review) and the central pathologic review process for the 60 patients who were centrally reviewed at the University of Michigan. FDA has not yet completed its review of the information and central pathologic review process for those subjects assessed by Dr. Jaffe. This report will cover the review of the 60 patients and an updated report on all 72 subjects will be provided as supplemental information and presented at the Dec. 17, 2002 ODAC meeting.

Among the 60 patients reviewed, FDA determined that a diagnosis of low grade NHL with evidence of histologic transformation could be documented for 42 patients. Biopsy material was available for central pathological review at all critical timepoints for each of these 42 patients. There were 31 patients in whom low grade NHL was documented histologically at the time of original diagnosis and intermediate grade NHL was documented histologically at a later time; both diagnoses were confirmed by the central pathologist. There were 11 patients in whom lymphoma with transformed features (low grade and intermediate grade) was documented histologically at the time of diagnosis and confirmed by the central pathologist.

FDA believes that the remaining 18 should be excluded from analysis of the transformed subpopulation due to inability to confirm the pathologic diagnosis. The reasons for exclusion from the dataset are listed in the table below. For most of these 18 patients, the pathologic material (slides) was not available or was inadequate at one or more critical times. In three of the patients where the slides were available for central review, the central reviewing pathologist disagreed with the diagnosis of transformation.

Classification of Transformed Lymphomas From the Transformed Dataset

Reason for exclusion from the subpopulation	Number of patients excluded
Original histological diagnosis of NHL not documented. Transformed (low grade and intermediate grade) documented histologically at a later time.	7
Low grade NHL documented histologically at the time of original diagnosis. Transformation diagnosed by pathologist at a later time, but diagnosis of transformation not upheld by central pathologist.	3
Transformation diagnosed at time of original diagnosis, but slides not available for central pathologic review. Subsequent biopsy(s) show low grade NHL.	1
Insufficient pathologic material for central pathologist to diagnose low grade lymphoma. No material submitted to support diagnosis of transformation.	1
Low grade NHL documented histologically at the time of original diagnosis. Slides documenting transformation not available for central review.	1
Slides documenting original diagnosis of low grade NHL not available for central review. Slides documenting histologic transformation not available for central review. (1 case)	1
No transformation of NHL diagnosed at either original biopsy, or on any subsequent biopsies.	1
Original diagnosis of transformation not documented. Slides not available. No evidence of pre-existing low grade lymphoma. (1 case)	1
Histologic subtype of NHL does not Eligibility Criteria and diagnosis of transformation not upheld by central pathologist.	1
Histologic subtype of NHL does not meet Eligibility Criteria and no transformation diagnosed either at original biopsy or any subsequent biopsies.	1
TOTAL	18

Among the 42 patients, with adequate information to confirm the diagnosis, there were two patients who had been enrolled in single patient IND trials. The sponsor has provided minimal data and has not audited the clinical data for these two patients. These two patients have been excluded from the FDA confirmed group because there was

insufficient clinical information to conduct analyses and the quality of the data available are unknown. The baseline entry characteristics for the remaining 40 patients are summarized in the following table.

Baseline Entry Characteristics	Sponsor Identified*	FDA Confirmed
Median time from diagnosis to study entry (years) (range)	6.2 (0.7, 27.8)	5.0 (0.7, 27.8)
Median time from diagnosis to transformation date (years) (range)	59 (37.80) (-0.3, 10.3)	58 (37.80) (0.02, 9.9)
Male (% male)	41 (58%) (0, 24.5)	23 (58%) (0, 24.5)
Ann Arbor Stage at entry		
1	1 (1%)	1 (2%)
2	7 (10%)	1 (2%)
3	17 (24%)	11 (28%)
4	46 (65%)	27 (68%)
Modified IPI Score	(n = 67)	(n = 38)
0-1	9 (13%)	2 (5%)
2	23 (34%)	14 (37%)
3	23 (34%)	16 (42%)
4-5	12 (18%)	6 (16%)
Number of prior chemotherapies	4	4
Median	(3, 5)	(3, 5)
IQ	(1, 11)	(1, 9)
Range		
Maximum unidimensional lesion measurement (cm)		
0 to ≤5 cm	24 (34%)	12 (30%)
>5 to ≤10 cm	34 (48%)	20 (50%)
> 10 cm	13 (18%)	8 (20%)
Response to last chemotherapy	35 (49%)	22 (55%)
Response (CR+CCR+PR)	16 (23%)	10 (25%)
Complete Response (CR+CCR)		
Tumor grade at the study entry		
Low	9 (13%)	2 (5%)
Intermediate	59 (83%)	35 (88%)
High	3 (4%)	3 (8%)
Last qualifying chemotherapy end day to study day (yrs)	(n = 66)	(n = 35)
Median	0.5	0.5
Range	(0.1, 5.4)	(0.1, 3.1)

Most of the baseline data for these patients is typical for patients with transformed disease. Such patients have had multiple courses of chemotherapy (median 4). Transformation is often suspected clinically when a patient with known lymphoma presents with a rapidly enlarging node, so the presence of nodes greater than 7 cm in 40% of the FDA confirmed study patients is not surprising.

An atypical statistic in this group is the median time from transformation until study entry, which was 3.3 years (range of 0 to 24.5). The literature states that transformed low grade NHL has a poor prognosis, with a median survival of less than one year after transformation. Yuan, et al (JCO 13:1726, 1995) described a group of patients with histologic transformation who had a median survival duration of 81 months after transformation. The predictors of good survival in this study were lack of prior chemotherapy, complete response to chemotherapy after transformation and limited disease. Such factors are not present in the FDA confirmed patients, who, as mentioned above, have had a median of 4 chemotherapy regimens, did not tend to have limited disease, and were less likely to have had a complete response to chemotherapy once they transformed. The implication is that the transformed patients who received iodine ¹³¹I tositumomab had already demonstrated a tendency towards a favorable natural history.

Analyses of Baseline Entry Characteristics

FDA performed an analysis of the baseline entry characteristics (as variables) that were associated with a diagnosis of transformed disease. A stepwise selection using PROC LOGISTIC in SAS was used to identify the variables associated with patients who had a diagnosis of transformed disease. A significance level of 0.10 was used to allow a baseline variable into the model and a significance level of 0.15, was used to allow a baseline variable to stay in the model. The baseline variables that entered into the model significantly were tumor grade at the study entry (GRADEE), days between the last qualifying chemotherapy regiment and study day (LQCEDAY), number of prior chemotherapy and Ann Arbor Stage at study entry. Other baseline variables such as age, sex, IPI category, study day of diagnosis of NHL, maximum unidimensional lesion measurement (cm) at baseline, Ann Arbor stage at study entry, number of prior chemotherapy received, duration of response to first chemotherapy, etc. did not enter into the model (all p-values ≥ 0.25).

The following table summarizes the baseline entry characteristics of the 271 patients enrolled in the 5 efficacy/activity studies, according to the presence or absence of a reported pathologic diagnosis of histologic transformation.

Baseline Entry Characteristics	Non-transformed-ISE Pop	Transformed Population - Sponsor	Transformed Population - FDA
N	200	71	40
Tumor grade at the study entry			
Low	179 (89%)	9 (13%)	2 (5%)
Intermediate	19 (10%)	59 (83%)	35 (88%)
High	2 (1%)	3 (4%)	3 (8%)
Ann Arbor Stage at the study entry			
1	3 (2%)	1 (1%)	1 (3%)
2	17 (9%)	7 (10%)	1 (3%)
3	41 (21%)	17 (24%)	11 (28%)
4	139 (70%)	46 (65%)	27 (68%)
Response to last qualifying chemotherapy (investigator)			
CR	32 (16%)	15 (21%)	9 (23%)
CCR	5 (3%)	1 (1%)	1 (3%)
PR	68 (34%)	19 (27%)	12 (30%)
ORR	105 (53%)	35 (49%)	22 (55%)
Duration of response to last qualifying chemotherapy (years)			
Median (Years)	0.5	0.4	0.3
95% CI	(0.4, 0.6)	(0.2, 0.6)	(0.2, 0.5)
IQ Range	(0.2, 0.9)	(0.2, 0.7)	(0.2, 0.6)
Range	(0.1, 4.5)	(0.0, 2.2)	(0.1, 1.3)
Number of prior chemotherapies			
Median	3	4	4
IQ Range	(2, 4)	(3, 5)	(3, 5)
Range	(1, 13)	(1, 11)	(1, 9)
Last qualifying chemotherapy end day to study day (years)			
Median	0.6	0.5	0.5
95% CI	(0.4, 0.8)	(0.4, 0.7)	(0.3, 0.7)
IQ Range	(0.3, 1.2)	(0.3, 1.1)	(0.3, 1.0)
Range	(0.01, 9.3)	(0.01, 5.4)	(0.1, 3.1)

Efficacy Outcomes and Analyses

The pooled efficacy outcomes (response rates and durations) are provided for the subpopulations of the 271 patients enrolled in the 5 efficacy/activity studies, according to sponsor-reported histologic diagnosis (without [n=200] and with [n=71] evidence of histologic transformation) and in the subset of patients where FDA confirmed that there were adequate evidence to establish a diagnosis of transformed histology on central pathologic review (n=40). The outcome measures are summarized in the following table

Outcome Measures	Non-transformed-ISE Pop	Transformed Population - Sponsor	Transformed Population - FDA
N	196*	71	40
Response		(n=71)	(n=40)
CR (%)	36 (18%)	7 (10%)	3 (8%)
CCR (%)	21 (11%)	11 (15%)	7 (18%)
PR (%)	57 (29%)	10 (14%)	6 (15%)
ORR (%)	114 (58%)	28 (39%)	16 (40%)
Response Duration			
Median (Years)	1.0	1.2	1.6
95% CI	(0.8, 1.5)	(0.9, 3.4)	(0.6, ---)
IQ Range	(0.4, ---)	(0.8, 3.4)	(0.7, 3.4)
Range	(0.1, 7.8+)	(0.1+, 4.9)	(0.1+, 4.9)

* Data not available for 4 of the 200 patients identified by sponsor as without histologic transformation

The response rates for the FDA-confirmed population were 8% CR, 18% CCR (combined CR rate 26%), and 15% PR, for an overall response rate of 41%. The median duration of response to iodine ¹³¹I tositumomab was 1.6 years (range: 0.1—4.9 years). While these are impressive responses for patients with transformed NHL, the prolonged median survival after transformation and before study entry needs to be taken into account.

FDA conducted an analysis to assess whether there were predictors of response to iodine ¹³¹I tositumomab in this subpopulation. The results of the analysis of the

relationship between response to last qualifying chemotherapy and response to iodine ¹³¹I tositumomab in the FDA confirmed transformed subpopulation is summarized in the table below.

Last Qualifying Chemotherapy Overall Response (ORR = CR+CCR+PR)	Overall Response (ORR = CR+CCR+PR) to iodine ¹³¹ I tositumomab		
	Yes	No	Total
Yes	11	11	22
No	5	13	18
Total	16	24	40

There were 11 of 22 (50%) patients responding to chemotherapy and 5 of 18 (28%) who did not respond to chemotherapy who achieved a response to the iodine ¹³¹I tositumomab regimen. There is no significant difference in the overall response rates following the last qualifying chemotherapy regimen and ORR following the iodine ¹³¹I tositumomab regimen in the FDA-confirmed transformed population (p-value using two-sided McNemar's test for paired samples = 0.2101).