

May 10, 2010

Submission Request c/o NCCN NHL Panel Members
National Comprehensive Cancer Network
275 Commerce Dr, Suite 300
Fort Washington, PA 19034

RE: Request for NCCN Guidelines Panel on NHL regarding Campath® (alemtuzumab) in CLL with del(17p)

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Dear NCCN NHL Panel Members,

We respectfully request that the NCCN NHL panel consider the following changes to the Practice Guidelines for CLL with del(17p) with >20% cells:

1. Consider adding Campath® (alemtuzumab) monotherapy as a treatment option for patients with relapsed/refractory CLL with del(17p) in >20% of cells
2. Consider re-evaluating order of alemtuzumab on the list of suggested treatment regimens in patients with first-line CLL with del(17p) in >20% of cells based on current clinical data

The clinical rationale for these requests is summarized below.

Request to add alemtuzumab monotherapy as a treatment option for patients with relapsed/refractory CLL with del(17p) in >20% of cells

Five studies document the response of relapsed/refractory (R/R) CLL patients with del(17p) to alemtuzumab monotherapy (Table 1)^{1,2,3,4,5}. The body of evidence supporting these regimens is similar if not greater than the evidence supporting some of the regimens recommended in the current NCCN guidelines for CLL (Table 2)^{7,8,9,10,11}. The largest prospective study is described in greater detail below.

In a multicenter, prospective, CLL2H study of the German Chronic Lymphocytic Leukemia Study Group (GCLLSG), responses were documented in del(17p) patients with fludarabine-refractory CLL receiving alemtuzumab monotherapy¹. After dose escalation, patients received 30 mg of s.c. Campath three times a week for up to 12 weeks. 31 of the 103 evaluable patients had del(17p). In patients with del(17p), the observed ORR was 39%, median OS was 18.3%, median PFS was 5.8 months and median TTTF was 5.8 months. These results were statistically indistinguishable from patients with normal 17p status. Grades 3 to 4 neutropenia, thrombocytopenia, and anemia occurred in 56%, 57%, and 49% of patients, respectively. Grades 3 to 4 infections occurred in 29% and 8% of patients, respectively. All cytomegalovirus (CMV) episodes were successfully treated with anti-CMV therapy, and there were no CMV-related deaths. The authors concluded that “in contrast to chemotherapy-based therapy, alemtuzumab treatment overcomes the adverse prognostic impact of *VH* mutation status, *TP53* mutation, and genomic aberrations.”

Table 1. Alemtuzumab in R/R CLL with del (17p)

Regimen	No. Patients with del(17p)	ORR	CR	PFS (Months)	OS (Months)	Reference
Alemtuzumab	31	39%	0%	6	18	Stilgenbauer S, et al. J Clin Oncol. 2009;27:3994-4001.
	46	44%	0%	7	19	Fiegl M, et al. Blood. 2008;112. Abstract 3164.
	15	40%	0%	-	-	Lozanski G, et al. Blood. 2004;103:3278-3281.
	10	60%	0%	-	-	Cortelezzi A, et al. Leukemia. 2009;Epub.
	8	50%	0%	-	-	Osuji NC, et al. Haematologica. 2005;90:1435-1436.
Total: 110		39-60%				

Table 2. Current Relapsed/Refractory Therapies as Listed in v.1.2010 NCCN Guidelines for CLL/SLL

Regimen	No. Patients with del(17p)	ORR	CR	PFS	OS	References Currently Listed in NCCN Practice Guidelines for CLL
CHOP+R	-	-	-	-	-	No reference listed (Leporrier study does not include subset analysis for 17p deletion)
CFAR	-	-	-	-	-	No reference listed (Wierda study is frontline only)
HyperCVAD+R	-	-	-	-	-	No reference listed
OFAR	14	33%	7%	36% 6-month failure-free survival	86% 6-month survival	Tsimberidou AM, et al. <i>J Clin Oncol.</i> 2008;26(2):196-203.
Ofatumumab	17 fludarabine + alemtuzumab-refractory	41%	0%	-	-	Wierda WG, et al. <i>J Clin Oncol.</i> 2010;28(10):1749-1755. Coiffier B, et al. <i>Blood.</i> 2008;111:1094-1100.
	14 fludarabine-refractory bulky disease	14%	0%	-	-	Wierda WG, et al. <i>J Clin Oncol.</i> 2010. 28(10):1749-1755. Coiffier B, et al. <i>Blood.</i> 2008;111:1094-1100.
Alemtuzumab + rituximab	10	50%	10%	-	20.5 months	No reference listed, but data are available from: Badoux X, et al. <i>Blood.</i> 2009;14. Abstract 1248, and a poster by Badoux X, et al. presented at ASH 2009.
HDMP	10	50%	0%	8 months	20 months	Thornton PD, et al. <i>Ann Hematol.</i> 2003; 82:759-765.
Bendamustine	0	-	-	-	-	No reference listed; there are no published studies of bendamustine monotherapy in 17p deletion
Total: 65		14-50%				

Request to re-evaluate order of alemtuzumab on the list of suggested treatment regimens in patients with first-line CLL with del(17p) in >20% of cells based on current clinical data

Efficacy data for alemtuzumab and other suggested treatment regimens for first-line patients with del(17p) are summarized in Table 3^{6,12,13,14,15,16}.

In a randomized, multicenter phase III trial comparing alemtuzumab to chlorambucil in front-line CLL⁶, 11 patients were found to have del(17p) upon study entry. 7 out of 11 (64%) patients responded, including 3 (27%) who achieved complete responses. Adverse events profiles were similar between the two arms, except for more infusion-related and CMV events with alemtuzumab and more nausea and vomiting with chlorambucil. CMV events had no apparent impact on efficacy.

Table 3. Current First-Line Therapies as Listed in v.1.2010 NCCN Guidelines for CLL/SLL

Regimen	No. Patients with del(17p)	ORR	CR	PFS (Months)	OS (Months)	Relevant References
FCR	30*	74%	11%	15**	52	Zenz T, et al. <i>Blood.</i> 2009;114. Abstract 1267
FR	29	76%	48%	-	-	Tam C, et al. <i>J Clin Oncol.</i> 2008; 26. Abstract 7035.
	3	-	0%	20***	-	Byrd J, et al. <i>J Clin Oncol.</i> 2006; 24:437-443.
HDMP + R	1	100%	0%	-	-	Castro JE, et al. <i>Leukemia.</i> 2009; 23:1779-1789.
CFAR	14	78%	57%	18	N/A	Parikh S, et al. <i>Blood.</i> 2009; 114. Abstract 208.
Alemtuzumab	11	64%	27%	11	N/A	Hillmen P, et al. <i>J Clin Oncol.</i> 2007;25:5616-5623
Bendamustine	0	-	-	-	-	No published studies of bendamustine monotherapy in del(17p)

*Patients with mutated TP53, deleted in del(17p) patients.

**Addition of rituximab did not result in significant improvement in PFS (PFS for FC and FCR were 12.1 months and 15.4 months, respectively, P = 0.19).

***17p deletion and 11q deletion combined; data for 17p deletion were not reported separately.

We appreciate the efforts of the NCCN NHL Panel in advancing patient care and your specific consideration of alemtuzumab in this regard.

FDA status

Campath is indicated as a single agent for the treatment of B-CLL.

Literature support

Alemtuzumab in relapsed/refractory CLL with del(17p) > 20% cells

1. Stilgenbauer S, et al. *J Clin Oncol.* 2009;27:3994-4001.
2. Fiegl M, et al. *Blood.* 2008;112. Abstract 3164.
3. Lozanski G, et al. *Blood.* 2004;103:3278-3281.
4. Cortelezzi A, et al. *Leukemia.* 2009;Epub.

5. Osuji NC, et al. *Haematologica*. 2005;90:1435-1436.
- Alemtuzumab in first-line CLL with del(17p) > 20% cells
6. Hillmen P, et al. *J Clin Oncol*. 2007;25:5616-5623

Additional References

Relapsed/Refractory therapies currently listed NCCN Guidelines for R/R CLL with del(17p) > 20% cells

7. Tsimberidou AM, et al. *J Clin Oncol*. 2008;26(2):196-203.
8. Wierda WG, et al. *J Clin Oncol* 2009. 2010;28(10):1749-1755.
9. Coiffier B, et al. *Blood*. 2008;111:1094-1100.
10. Badoux X, et al. *Blood*. 2009;14. Abstract 1248 and poster board I-270.
11. Thornton PD, et al. *Ann Hematol*. 2003; 82:759-765.

First-line therapies currently listed NCCN Guidelines for CLL with del(17p) > 20% cells

12. Zenz T, et al. *Blood*. 2009;114. Abstract 1267
13. Tam C, et al. *J Clin Oncol*. 2008; 26. Abstract 7035.
14. Byrd J, et al. *J Clin Oncol*. 2006; 24:437-443.
15. Castro JE, et al. *Leukemia*. 2009; 23:1779-1789.
16. Parikh S, et al. *Blood*. 2009; 114. Abstract 208.