CHLORAMINOPHENE 2 mg, capsule
B/30 (CIP code: 3369906)

Applicant: TECHNI-PHARMA

chlorambucil
ATC code: L01AA02

List I

Date of Marketing Authorisation: 5 June 1956, validated on 4 December 1997

Reason for request: Assessment of IAB level in chronic lymphocytic leukaemia.
1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
Chlorambucil

1.2. Indications
“- Chronic lymphocytic leukaemia
- Hodgkin’s and non-Hodgkin’s lymphomas
- Primitive chronic glomerulonephritis with optically normal glomeruli and corticosteroid-dependent (threshold > 1 mg/kg prednisone) or corticoid-refractory nephrotic syndrome.
- Extramembranous primitive chronic glomerulonephritis with nephrotic syndrome.”

1.3. Dosage
“Lymphoid line disorders:
1 to 6 capsules every day or in cycles of 6-10 mg/m²/day for 5 days every 30 days.”
2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC classification (2009)

L   Antineoplastic and immunomodulating agents
L01  Antineoplastic agents
L01A  Alkylating agents
L01AA Nitrogen mustard analogues
L01AA02 Chlorambucil

2.2. Medicines in the same pharmaco-therapeutic category

Comparator medicines
LEVACT (bendamustine) “First-line treatment of chronic lymphocytic leukaemia (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate.”

2.3. Medicines with a similar therapeutic aim

- FLUDARA (fludarabine)
- MABTHERA (rituximab)
- MABCAMPATH (alemtuzumab), indicated when fludarabine combination chemotherapy is not appropriate
- ARZERRA (ofatumumab) in patients refractory to fludarabine and alemtuzumab
- combination chemotherapies such as CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) and CVP (cyclophosphamide, vincristine, prednisone)....
3. ANALYSIS OF AVAILABLE DATA

Chlorambucil (CHLORAMINOPHENE) was granted marketing authorisation in June 1956 (national procedure validated on 4 December 1997) in the treatment of chronic lymphocytic leukaemia (CLL). It was included on the list of medicines refundable by National Health Insurance and approved for use by hospitals on 1 January 1962 as the tablet form, which was subsequently substituted by the capsule form on 22 February 1995. The ACB was graded as high in the initial listing and this was confirmed in successive re-assessments. Because of the date of the initial listing, the transparency Committee (TC) was unable to assess the IACB of the product. The company therefore requests that the TC gives its opinion on the IACB of chlorambucil in CLL.

The company has submitted the results of two comparative studies, which are analysed below. Two other comparative studies taken from the literature data are also presented in this document.

3.1. Efficacy and tolerance

A. Data submitted by the company

Study by Eichhorst et al. (2009)\(^1\)

Randomised, open-label phase III study that compared fludarabine with chlorambucil solely as first-line treatment of chronic lymphocytic leukaemia (CLL) in patients aged over 65.

Inclusion criteria included:
- age between 65 and 80;
- not previously treated for CLL;
- estimated life expectancy > 6 months;
- general condition of 0 to 2 on the Eastern Cooperative Oncology Group scale.

Primary efficacy endpoints:
- overall survival, defined as the time between randomisation and death
- progression-free survival, defined as the interval between randomisation and disease progression according to the National Cancer Institute (NCI) definition or death

Secondary endpoints:
- response to treatment. Full response was defined as the combination of a normal physical examination, normal blood count and a bone marrow lymphocyte count of less than 30%.
- quality of life
- tolerability
- occurrence of secondary cancer

Patients were randomised to two treatment groups:
- One group comprising 93 patients was given a 30-minute i.v. infusion of 25 mg/m\(^2\) fludarabine for 5 days every 28 days for a maximum period of 6 cycles.
- The second group comprising 100 patients received an initial oral dose of 0.4 mg/kg chlorambucil. The dosage was increased by 0.1 mg/kg at each cycle up to 0.8 mg/kg,

\(^1\) Eichhorst BF et al; German CLL Study Group (GCLLSG). First-line therapy with fludarabine compared with chlorambucil does not result in a major benefit for elderly patients with advanced chronic lymphocytic leukemia. Blood. 2009;114:3382-91.
provided treatment was well tolerated. In this group a maximum of 24 cycles of 14 days was carried out.

Results:
A total of 193 patients, with a median age of 70, underwent randomisation. The analysis was based on 185 patients (8 lost to follow-up).

Table 1: Initial patient characteristics:

<table>
<thead>
<tr>
<th></th>
<th>Chlorambucil group (n = 100)</th>
<th>Fludarabine group (n = 93)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (min-max)</td>
<td>70 (65-78)</td>
<td>71 (65-78)</td>
</tr>
<tr>
<td><strong>Age group [%]</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65 to 69 years</td>
<td>47</td>
<td>45</td>
</tr>
<tr>
<td>70 to 74 years</td>
<td>31</td>
<td>33</td>
</tr>
<tr>
<td>75 to 79 years</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td><strong>Binet stage [%]</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>16</td>
<td>13</td>
</tr>
<tr>
<td>B</td>
<td>44</td>
<td>51</td>
</tr>
<tr>
<td>C</td>
<td>40</td>
<td>36</td>
</tr>
<tr>
<td><strong>Rai stage [%]</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>I or II</td>
<td>52</td>
<td>55</td>
</tr>
<tr>
<td>III or IV</td>
<td>43</td>
<td>40</td>
</tr>
<tr>
<td><strong>General condition (ECOG score)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>42</td>
<td>46</td>
</tr>
<tr>
<td>1</td>
<td>49</td>
<td>52</td>
</tr>
</tbody>
</table>

No difference between the two groups was observed in the two primary efficacy endpoints:
- median overall survival (46 months in the fludarabine group versus 64 months in the chlorambucil group, p = 0.15);
- median progression-free survival (19 months in the fludarabine group versus 18 months in the chlorambucil group, p = 0.7).

This study did not achieve its objective; the results for the secondary endpoints are given for information purposes.

The patients treated with chlorambucil had a shorter time to treatment failure than the patients treated with fludarabine (11 months versus 18 months; p = 0.004). The overall response rate was higher in the fludarabine group than in the chlorambucil group (72% versus 51%; p = 0.003). Treatment with fludarabine brought about a higher number of full remissions (as defined by the NCI-WG criteria) than treatment with chlorambucil (7% versus 0%; p = 0.011).

A subgroup analysis was carried out as a function of classification and prognostic risk. However, the numbers in each group are small and do not allow any conclusions to be drawn. Recourse to second-line treatment was less common in the fludarabine group than in the chlorambucil group: 50% versus 77%; p = 0.006.

There are no available data comparing quality of life between the two groups.
**Adverse effects**

Discontinuation of treatment due to adverse events was more common in the chlorambucil group (26%) than in the fludarabine group (19%).

Grade 3-4 haematological toxicity was less common in the chlorambucil group (CTC classification) 42% vs. 23%.

Infections occurred with similar frequency in the two groups: 32% vs. 26% in the chlorambucil group.

**Study by Catovsky C. et al. (2007)²**

Randomised, open-label study that compared the efficacy and tolerance of the combination fludarabine/cyclophosphamide with fludarabine and chlorambucil monotherapy in patients with previously untreated chronic lymphocytic leukaemia.

Patients were randomised to three treatment groups:
- A group comprising 194 patients was given a 30-minute i.v. infusion of 25 mg/m² or an oral dose of 40 mg/m² fludarabine for 5 days every 4 weeks for a duration of 6 cycles;
- A second group comprising 196 patients was treated with the fludarabine/cyclophosphamide combination and received daily doses of 25 mg/m² fludarabine and 250 mg/m² cyclophosphamide (i.v. protocol) or daily oral doses of 24 mg/m² fludarabine and 150 mg/m² cyclophosphamide. The combination was given for a maximum duration of 6 cycles.
- Finally, a third group comprising 387 patients received a daily oral dose of 10 mg/m² chlorambucil for 5 days every 28 days until maximum response or for a maximum duration of 12 cycles.

In the event of remission after 3 months of treatment or a life-threatening occurrence linked to an adverse effect, treatment was stopped. In patients who developed neutropenia or thrombocytopenia with haemorrhagic complication, the dose in the following cycle was reduced compared with the initial dose.

The primary efficacy endpoint was overall survival defined as the time between randomisation and death.

Secondary endpoints:
- response to treatment (a good response is defined as the sum of full remissions and partial nodular remissions)
- progression-free survival
- tolerability

**Results:**

A total of 777 patients, with a median age of 65 years, underwent randomisation. About one-third of patients (30%) were aged 70 or older.

A quarter of patients were at Binet stage A, with a progressive form. Stage B accounted for 40% of cases and stage C for 30% of cases.

No difference between the three groups was observed in the primary efficacy endpoint overall survival. Comparing the groups treated with fludarabine and fludarabine plus cyclophosphamide with the group treated with chlorambucil, a hazard ratio of 1.18 (95% CI [0.92-1.51]; p = 0.2) is observed.

This study did not achieve its objective; the results for the secondary endpoints are given for information purposes.

The percentage overall response was higher in the fludarabine monotherapy group (80% vs. 72%, 0.04) or in combination with cyclophosphamide (94% vs. 72%, p < 0.0001) than in those treated with chlorambucil. The percentage achieving a full response was higher in the fludarabine monotherapy group (15%) or in combination with cyclophosphamide (38%) than in the chlorambucil group (7%).

Adverse effects
The combined incidence of neutropenia of all grades was higher in the groups of patients treated with fludarabine on its own or in combination with cyclophosphamide than in the chlorambucil group: 41% in the fludarabine monotherapy group vs. 56% under fludarabine+cyclophosphamide vs. 28% under chlorambucil. There are no data available on the frequency of febrile neutropenia. Haemolytic anaemias were more common in the chlorambucil group (12%) than in the fludarabine monotherapy group (11%) or in combination with cyclophosphamide (5%).

B. Literature data

CALGB study
Open-label randomised crossover study that evaluated the efficacy of fludarabine versus chlorambucil and versus the fludarabine-chlorambucil combination in 509 patients with type B CLL newly diagnosed at different stages in the disease.

The recruited patients were randomised to three groups:
- fludarabine (N = 179) 25 mg/m² i.v. once daily for 5 days in every 28;
- chlorambucil (N = 193) 40 mg/m² p.o. once every 28 days;
- fludarabine-chlorambucil combination (N = 137) (fludarabine 20 mg/m² for 5 days in every 28 and chlorambucil 20 mg/m² once every 28 days).

Treatments were repeated in cycles of 28 days for a maximum of 12 cycles. Treatment was stopped in the event of disease progression, full remission or stabilisation of the disease without progression for 2 months.

The efficacy endpoints employed were full remission, partial remission and disease progression according to the NCI criteria.

Primary efficacy endpoint: time to disease progression
Secondary endpoints: response rate, duration of response, time to treatment failure and overall survival.

Results:
The group treated with the fludarabine-chlorambucil combination was terminated prematurely owing to the high number of deaths observed in an interim analysis.
Of the 509 patients who underwent randomisation, 474 patients were evaluated for treatment response.
The median ages of the groups ranged from 62 to 64.

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4 Opinion on FLUDARA of 24 March 2004
Table 2: Efficacy of FLUDARA versus chlorambucil

<table>
<thead>
<tr>
<th></th>
<th>FLUDARA N = 170</th>
<th>Chlorambucil N = 181</th>
<th>FLUDARA + chlorambucil N = 123</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total clinical response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Full remission</td>
<td>20%</td>
<td>4%</td>
<td>20%</td>
</tr>
<tr>
<td>- Partial remission</td>
<td>43%</td>
<td>33%</td>
<td>41%</td>
</tr>
<tr>
<td>- Full and partial remission</td>
<td>63%</td>
<td>37%</td>
<td>61%</td>
</tr>
<tr>
<td>- Disease stable or in progression</td>
<td>37%</td>
<td>63%</td>
<td>39%</td>
</tr>
<tr>
<td>Patients in stages I and II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Full remission</td>
<td>26%</td>
<td>6%</td>
<td>22%</td>
</tr>
<tr>
<td>- Partial remission</td>
<td>41%</td>
<td>40%</td>
<td>42%</td>
</tr>
<tr>
<td>- Full and partial remission</td>
<td>67%</td>
<td>46%</td>
<td>64%</td>
</tr>
<tr>
<td>Patients in stages III and IV</td>
<td>67%</td>
<td>70%</td>
<td>46%</td>
</tr>
</tbody>
</table>

The median time to disease progression (primary efficacy endpoint) under fludarabine monotherapy was 20 months versus 14 months under chlorambucil, i.e. an absolute difference of 6 months in favour of fludarabine (p < 0.001).

The percentages for full remission and overall remission (full and partial) in the fludarabine monotherapy group are superior to those observed with chlorambucil monotherapy.

The median duration of remission (full or partial) was longer under fludarabine monotherapy (25 months) than under chlorambucil monotherapy (14 months), with an absolute difference of 9 months in favour of fludarabine (p < 0.001).

The percentage achieving full remission was higher under fludarabine than under chlorambucil, irrespective of prognostic risk: 26% vs. 6% for intermediate risk (Rai stages I and II) and 10% vs. 1% for high risk (Rai stages III or IV).

The median duration of overall survival did not differ between fludarabine and chlorambucil monotherapy: 66 months vs. 56 months in the chlorambucil group (NS).

Study 02CLLIII⁵

Randomised open-label study that compared the efficacy and tolerance of bendamustine with that of chlorambucil in first-line treatment in 319 patients with stage B or C chronic lymphocytic leukaemia according to the Binet classification.

Inclusion criteria:
- chronic lymphocytic leukaemia of stage B or C according to the Binet classification
- patients under 75 years of age
- no previous treatment for chronic lymphocytic leukaemia
- WHO performance index ≤ 2
- life expectancy of at least 3 months.

Treatments (up to a total of 6 cycles):
- bendamustine group: 100 mg/m² i.v. on day 1 and day 2 every 4 weeks (n = 162);
- chlorambucil group: 0.8 mg/kg p.o. on day 1 and day 15 every 4 weeks (n = 157), i.e. a dosage regimen different to that employed in France.

Primary efficacy endpoints:
- percentage overall response rate, determined by an independent committee (cf. Annex 1);
- progression-free survival, defined as the time between randomisation and occurrence of one of the following events: tumour progression, recurrence after intercurrent remission or death from any cause.

This second endpoint was analysed only if a significant difference was observed in the first primary efficacy endpoint.

Secondary endpoints:
- time to progression, defined as the time between randomisation and occurrence of one of the following events: tumour progression, recurrence after intercurrent remission or death linked to chronic lymphocytic leukaemia;
- duration of remission, defined as the time between the observed improved response and disease progression or death from any cause;
- overall survival, defined as the time between randomisation and death from any cause.

Results
The median age of the patients was 63 years in the bendamustine group (45-77 years) and 66 years in the chlorambucil group (35-78 years). Two-thirds of patients were in good general condition and almost one-third had a maintained general state. Approximately 71% of patients had stage B chronic lymphocytic leukaemia.
This study did not specifically include patients “for whom fludarabine combination chemotherapy is not appropriate” (wording of the indication in the marketing authorisation for bendamustine).

The results described below are taken from a third interim analysis scheduled in the protocol (after recruitment of the 300th patient), which resulted in the termination of the study.

• Primary efficacy endpoints:
The percentage overall response rate was 68% in the bendamustine group (of which 31% showed a full response) versus 31% (of which 2% showed a full response) in the chlorambucil group (p < 0.00016). The median progression-free survival was 21.5 months in the bendamustine group versus 8.3 months in the chlorambucil group (p = 0.0001). The observed values for these two criteria are probably overestimated, taking into account the termination of the study after an interim analysis.

• Secondary endpoints:
The median time to progression, as evaluated by the independent committee, was 23.9 months in the bendamustine group and 8.3 months in the chlorambucil group (p < 0.001). The median duration of remission was 19 months in the bendamustine group and 6 months in the chlorambucil group (p < 0.0001). No difference between the two groups was observed in median overall survival (65.4 months in the chlorambucil group and not reached in the bendamustine group). The subgroup results are not described, as these analyses were not scheduled in the protocol.

Adverse effects
Discontinuation of treatment due to adverse events was reported in 9.3% (15/162) of patients in the bendamustine group and in 3.2% (5/157) in the chlorambucil group.
Grade 3-4 adverse events were more common with bendamustine than with chlorambucil (52.8% vs. 31.1%), in particular haematological adverse events (40.4% vs. 19.2% of which neutropenia: 23% vs. 10.6%) and infections (8.7% vs. 3.3%).

6 The required value for the significance test in the interim analysis was p = 0.016.
3.2. Conclusion

The company has submitted the results of two studies that compared chlorambucil with fludarabine in the first-line treatment of CLL in patients with a median age of 65 years in one study (Catovsky study) and 70 years in the other (Eichhorst study). Overall survival, which was the primary efficacy endpoint in both these studies, did not differ between the two groups. The results for the secondary endpoints suggest that the percentage overall response is lower with chlorambucil than with fludarabine (51% vs. 72% in the Eichhorst study and 72% vs. 94% in the Catovsky study).

On the other hand, grade 3-4 haematological toxicity (CTC classification) was less common in the chlorambucil group than in the fludarabine group, with incidences of 23% vs. 42% (Eichhorst study). Neutropenia (of all grades) was less common in the group treated with chlorambucil (28%) than in the fludarabine monotherapy group (41%) or in combination with cyclophosphamide (56%) (Catovsky study).

The scientific literature data mentioned two other studies that evaluated the efficacy and tolerance of chlorambucil versus either fludarabine or bendamustine in patients under 65. These confirm the poorer performance of chlorambucil compared with these drugs in terms of progression-free survival and haematological response, but with no difference in overall survival.

Overall, the available data show that the therapeutic benefit of chlorambucil in the first-line treatment of CLL is inferior to that of available treatment options, i.e. fludarabine on its own or in combination with cyclophosphamide or bendamustine, in terms of percentage overall response and progression-free survival. However, the results for overall survival do not demonstrate any difference between chlorambucil and these comparator drugs. This poorer efficacy is counterbalanced by the better haematological tolerability of chlorambucil, particularly in patients aged over 65 (Eichhorst study and Catovsky study).
4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Chronic lymphocytic leukaemia (Binet stages B and C), characterised by the proliferation and accumulation of a malignant clone of mature B lymphocytes in the bone marrow, blood and lymphoid organs, is a life-threatening condition.

This proprietary product is intended as curative therapy.

The efficacy/adverse effects ratio is high;

Public health benefit:

Chronic lymphocytic leukaemia (CLL) constitutes a moderate public health burden. Improving its therapeutic management is a public health need in the fight against cancer.

Based on the available data, the proprietary product CHLORAMINOPHENE is not expected to have any impact on progression-free survival. Given the non-significant difference in overall survival versus the comparator drug (fludarabine) and the absence of quality of life data, it is not possible to evaluate the impact of CHLORAMINOPHENE on morbidity/mortality and quality of life. The transferability of the results of these studies to current practice is acceptable.

The proprietary product CHLORAMINOPHENE does not meet the identified public health need. As a result, CHLORAMINOPHENE is not expected to benefit public health in the treatment of CLL.

The drug is intended to be used as first-line therapy.

There are alternative drugs available;

The actual benefit remains substantial.

4.2. Improvement in actual benefit (IAB)

CHLORAMINOPHENE provides a moderate improvement in actual benefit (IAB III) in terms of tolerability in the first-line treatment strategy for chronic lymphocytic leukaemia in a limited population comprising patients aged over 65 years and/or with comorbidities that make it difficult or impossible to use fludarabine on its own or in a combination regimen.

4.3. Therapeutic use\textsuperscript{7,8}

The decision whether to treat the patient (or wait) depends on the patient’s general condition (age and comorbidities), on the stage of the disease and on the presence of factors pointing to a poor prognosis (peripheral lymphocyte doubling time < 12 months, elevated $\beta_2$-microglobulin, p53 mutation, etc.). The most numerous cases of the disease, i.e. Binet stage A or Rai stages 0, I and II, are asymptomatic and do not justify any specific treatment.

When treatment of CLL is undertaken, first-line treatment options are:

- an alkylating agent: chlorambucil either on its own or in combination with corticosteroids, cyclophosphamide;
- a purine analogue, particularly fludarabine phosphate (on its own or in combination), which can be used as a first-line or second-line treatment;
- COP or CVP (cyclophosphamide, vincristine, prednisone) and CHOP (cyclophosphamide, adriamycin, vincristine, prednisone) combination regimens;
- a monoclonal antibody (rituximab).

\textsuperscript{7} http://hematologie.net/hematolo/UserFiles/File/REFERENTIEL\%20COMPLET\%20VERSION\%20FINALE%20SFH20082009(1).doc

\textsuperscript{8} EPAR CEPLENE 2008
Autologous stem cell transplantation may be proposed, particularly in young individuals who have achieved full remission. In patients with few comorbidities, the first-line reference treatment is the combination rituximab + fludarabine + cyclophosphamide (R-FC)\textsuperscript{9,10}. Alemtuzumab is used in refractory disease or in the event of early progression, particularly where 17p deletion is present. For subsequent recurrence, other treatments, such as bendamustine, are given. Preliminary data, not validated by the marketing authorisation of bendamustine, point to the efficacy of bendamustine in combination with rituximab\textsuperscript{11}.

Because of its lower bone marrow toxicity compared with the available first-line treatment options, chlorambucil is the treatment of choice in patients aged over 65 years and/or with comorbidities. In practice, the available alternatives may be, in particular, combinations based on a low-dose purine (fludarabine + cyclophosphamide or R-FC or pentostatin + cyclophosphamide + rituximab). However, the data from studies carried out with these drugs concerned only individuals under 65 and without comorbidities.

4.4. Target population

The incidence of CLL in 2005\textsuperscript{12} in France was estimated at 3224 cases. Stages B and C account for almost 45% of cases\textsuperscript{13}, i.e. 1450 patients. The target population of CHLORAMINOPHENE in the indication of the marketing authorisation is therefore 1450 patients per year. Approximately half of patients are aged over 65 and/or have comorbidities (expert opinion). The target population of CHLORAMINOPHENE in the context of the treatment strategy, i.e. restricted to patients aged over 65 with/without comorbidities, is of the order of 700 patients per year.

\textsuperscript{10} Société Française d’Hématologie [French Haematology Society], 2009 guidelines
\textsuperscript{11} Fisher, ASH 2009, Abstract 205; Fisher, ASH 2008, Abstract 330
\textsuperscript{12} Presentation of the most recent data on cancer incidence and mortality in France and the trends over the past 25 years (1980-2005) - Press conference held on 21 February 2008. INVS/Hôpitaux de Lyon/FRANCIM/INCA
APPENDIX 1: Response criteria according to NCIWG 1996 (Cheson et al, 1996)  
(chronic lymphocytic leukaemia)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Complete Remission</th>
<th>Partial Remission</th>
<th>Progressive Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocytes</td>
<td>&lt;4.0 x 10^9/L</td>
<td>≥50% reduction from baseline</td>
<td>≥50% increase to at least 5.0 x 10^9/L</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>Absence by physical exam</td>
<td>≥50% reduction (physical examination)</td>
<td>≥50% increase for at least 2 weeks or new palpable node ≥1cm</td>
</tr>
<tr>
<td>Organomegaly</td>
<td>Normal size spleen and liver by physical exam</td>
<td>≥50% reduction if abnormal at baseline</td>
<td>≥50% increase</td>
</tr>
<tr>
<td>Constitutional Symptoms</td>
<td>None</td>
<td>Not defined</td>
<td>Not defined</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>≥1.5 x 10^9/L</td>
<td>≥1.5 x 10^9/L or 50% improvement from baseline</td>
<td>Not defined</td>
</tr>
<tr>
<td>Platelets</td>
<td>&gt;100 x 10^9/L</td>
<td>&gt;100 x 10^9/L or 50% improvement from baseline</td>
<td>Not defined</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>&gt;11.0 g/dL (untransfused)</td>
<td>&gt;11.0 g/dL or 50% improvement from baseline (untransfused)</td>
<td>Not defined</td>
</tr>
<tr>
<td>Bone Marrow</td>
<td>Normocellular for age, &lt;30% lymphocytes, no B-lymphoid nodules.</td>
<td>If done, ≥30% lymphocytes and/or B-lymphoid nodules</td>
<td>Not defined</td>
</tr>
</tbody>
</table>
| Response Definition     | All above to be met for at least 2 months.  
If persistent nodules in bone marrow = nPR | Meets criteria for first 3 for at least 2 months, and at least 1 other of above to be met | At least 1 of above to be met, or transformation to more aggressive histology |