



with deletion 13q and deletion 11q treated with alemtuzumab compared with chlorambucil. Infections, including CMV, were reported in 76% of patients receiving alemtuzumab compared with 50% of chlorambucil patients while on study. Grade 3 and 4 lymphopaenia and neutropaenia were more common with alemtuzumab, but anaemia and thrombocytopenia were similar in the two treatment groups. Episodes of bacterial sepsis and febrile neutropaenia were comparable and the increase in infection in the alemtuzumab arm was almost entirely attributable to CMV reactivation. Although CMV reactivation occurred in half the patients, it was only symptomatic in 16%. This toxicity was therefore manageable by screening and pre-emptive treatment. Grade 3 or 4 infusion-related events were seen in 13% of patients receiving alemtuzumab and these were largely confined to the first few weeks of therapy. In contrast, adverse events increased over time in the chlorambucil arm where the median duration of treatment was twice as long. The toxicity profile of alemtuzumab in previously untreated patients appears to be much more acceptable with no increased treatment-related mortality compared with chlorambucil in the CAM307 randomised study. The Lundin study showed that efficacy for 18 weeks of subcutaneous alemtuzumab was equivalent to 12 weeks of intravenous therapy. Since subcutaneous administration results in fewer infusion-related side effects, this may be the preferable route.

Several studies, using a variety of treatment regimens, have confirmed the observation that those patients achieving minimal residual disease (MRD)-negativity have prolonged remissions compared with those patients who are MRD-positive at the end of therapy.

**Alemtuzumab Consolidation Therapy**

Studies of alemtuzumab treatment of CLL, particularly in the relapsed/refractory setting, have consistently shown that patients with bulky nodal disease are less likely to respond to treatment compared with those patients who have low volume or no lymph node enlargement. This is in contrast to the excellent clearance of disease from the blood and bone marrow. In addition, in the Moreton study<sup>3</sup> patients who achieved complete remissions and who were also negative for minimal residual disease (MRD) using a sensitive four-colour flow cytometry<sup>9</sup> had significantly prolonged PFS and overall survival (OS). Several studies, using a variety of treatment regimens, have confirmed the observation that those patients achieving MRD-negativity have prolonged remissions compared with those patients who are MRD-positive at the end of therapy.<sup>10-12</sup> These observations have provided a rationale for using alemtuzumab as consolidation of remissions achieved using fludarabine-based induction regimens. Four groups have published their results for this strategy using various treatment schedules, doses and routes of administration (see Table 2).<sup>13-16</sup> Although not comparable, all have demonstrated the efficacy of such an approach in improving responses in

**Table 1: Response Rates for Single Agent Front-line Therapy in Chronic Lymphocytic Leukaemia**

Agent	OR (%)	CR (%)	Ref
Chlorambucil	55	2	7*
Alemtuzumab (IV)	83	24	7*
Alemtuzumab (SC)	87	19	5
Fludarabine	6%	20	6
Rituximab	51	4	8

\* CAM307 phase III prospective randomised trial comparing chlorambucil and alemtuzumab. CR = complete response; IV = intravenous; OR = overall response; SC = subcutaneous.

**Table 2: Alemtuzumab Consolidation Therapy**

Study	Median Interval from Chemo-therapy to Maintenance	Route	Dose	Improved Response
Wendtner (2004) <sup>13</sup>	67 days (45-90)	IV	30mg TIW	45%; improved PFS
O'Brien (2003) <sup>14</sup>	6 months (1-40)	IV	10mg TIW	39%
Rai (2002) <sup>15</sup>	~2 months	IV/SC	30mg TIW	92% OR: 42% CR: 44%
Montillo (2004) <sup>16</sup>	At least 8 weeks after F	SC	10mg TIW	51%

CR = complete response; F = fludarabine; IV = intravenous; OR = overall response; PFS = progression-free survival; SC = subcutaneous; TIW = three times a week.

around 50% of patients receiving consolidation. There has only been one randomised study which was reported by the German study group in 2004<sup>13</sup> and updated at ASH in 2006.<sup>17</sup> Patients who had been treated to maximum response with fludarabine or fludarabine plus cyclophosphamide were randomised to receive alemtuzumab at the standard dose of 30mg three times per week for 12 weeks given intravenously at a median of two months following induction treatment or to have no further treatment. The trial was stopped prematurely having recruited 21 patients (11 to alemtuzumab and 10 to observation) because of a high infection rate in the alemtuzumab arm. However, despite the small numbers of patients, this trial did show a significant improvement in PFS for patients receiving alemtuzumab consolidation (median not reached) compared with 27.7 months for the observation arm. Factors contributing to the toxicity of alemtuzumab in this setting may be the dose and duration of therapy and, most importantly, the short interval between completing induction treatment and introduction of consolidation.

Consolidation after first induction treatment of CLL is therefore feasible and can deepen remission and increase PFS in a proportion of patients. However, there is a risk of toxicity and there are also financial implications. It may therefore be prudent to reserve this strategy for those patients with higher risk disease. Furthermore, a larger randomised study needs to be completed in such a group to confirm safety and efficacy as well as establishing the optimal timing, dose and delivery (intravenous or subcutaneous).

**Alemtuzumab for High-risk Chronic Lymphocytic Leukaemia**

It is well recognised that patients who have deletions of chromosome 17p resulting in dysfunction of the p53 pathway have resistance to conventional chemotherapy such as alkylating agents or purine

analogues and also have significantly shortened survival compared with those patients without this abnormality.<sup>18</sup> Although p53 deletion in CLL is infrequent at initial presentation – occurring in 5–10% of patients – this abnormality becomes increasingly common as the CLL advances and becomes chemo-resistant. There has now been a number of reports showing that alemtuzumab has efficacy in this subgroup, probably by killing cells through a p53-independent mechanism.<sup>19–21</sup> The only other therapy shown to be effective in this way is high-dose steroids.<sup>22</sup> In CLL

Alemtuzumab has been shown to be an effective monotherapy in both first-line and refractory chronic lymphocytic leukaemia.

patients with p53 deletion who do not have bulky nodal disease, single-agent alemtuzumab may be an appropriate treatment choice either at first or subsequent line of therapy. However, in those patients with enlarged nodes it would seem logical to combine alemtuzumab with high-dose steroids, and this regimen does appear to be effective in a small number of patients who have been treated.<sup>23</sup> It is now critical that patients who are about to embark on treatment, whether this is first- or subsequent-line, should have analysis to detect the presence of the p53 deletion since this will affect selection of treatment. The knowledge of specific genetic abnormalities will allow the prospective selection of appropriate treatments in order to reduce the damage caused by ineffective chemotherapy and to maximise the opportunity for achieving a good remission.

## Alemtuzumab Combination Regimens

To date, experience with alemtuzumab in combination regimens is somewhat limited, and has been explored only in the relapsed patient setting. Single-centre data of combinations with fludarabine (FluCam – fludarabine and alemtuzumab<sup>24</sup>; C-FAR – cyclophosphamide, fludarabine, alemtuzumab and rituximab<sup>25</sup>) have all shown improved efficacy compared with alemtuzumab as a single agent in an equivalent clinical setting. There are currently a number of trials examining fludarabine/alemtuzumab-based combinations in the first-line setting and the results of these are awaited. Studies of high-dose steroids and alemtuzumab in high-risk CLL are ongoing.

## Conclusion

There have been major advances in the management of CLL over the past decade. This includes the ability to stratify patients according to biological risk parameters such as genetic abnormalities, the introduction of novel therapies such as monoclonal antibodies and the ability to achieve a high proportion of good remissions, including eradication of minimal residual disease. All these strategies have resulted in improved selection of patients for appropriate therapy and better PFS. Alemtuzumab has been shown to be an effective monotherapy in both first-line and refractory CLL and it is now clear from several studies that toxicity is much reduced and more manageable when alemtuzumab is used earlier in therapy. More data are now needed on the use of alemtuzumab in front-line combination regimens. The most compelling data for alemtuzumab efficacy are in the high-risk cytogenetic group exhibiting p53 deletion when used either as a single agent or in combination with high-dose steroids. In addition, this antibody therapy has been shown to be effective in eradicating residual disease after completion of induction therapy, although the optimal regimen (dose, schedule and route of administration) is still to be determined. ■

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**MabCampath®:**  
**Unique CD52-targeted**  
**monoclonal antibody**  
**therapy for patients**  
**with CLL**

- First drug with proven efficacy in Fludara® refractory patients<sup>1</sup>
- Clears both blood and bone marrow with no effect on stem cells<sup>2</sup>
- Median survival of 16 months (32 months in responders)<sup>2</sup>
- Use of MabCampath® can eliminate minimal residual disease (MRD), which may lead to an increase in survival<sup>3</sup>
- Beneficial overall safety profile in relation to disease severity and prognosis in patients with fludarabine-refractory B-cell CLL<sup>4</sup>

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Target-specific treatment for CLL

**Prescribing information: Name of the medicinal product:** MabCampath® 30 mg/ml concentrate for solution for infusion. **Qualitative and quantitative composition:** Each vial contains 30 mg alemtuzumab. Alemtuzumab is a genetically engineered humanised IgG1 kappa monoclonal antibody specific for a 21-28 kD lymphocyte cell surface glycoprotein (CD52). The antibody is produced in mammalian cell (Chinese Hamster ovary) suspension culture in a nutrient medium.

**Therapeutic indications:** MabCampath® is indicated for the treatment of patients with chronic lymphocytic leukaemia (CLL) who have been treated with alkylating agents and who have failed to achieve a complete or partial response or achieved only a short remission (less than 6 months) following fludarabine phosphate therapy. **Contraindications:** Hypersensitivity or anaphylactic reactions to alemtuzumab, to murine proteins or to any of the excipients; in patients with active systemic infections; in patients infected with HIV; in patients with active secondary malignancies; pregnancy and breast-feeding. **Undesirable effects:** More than 80% patients may be expected to experience adverse reactions; the most commonly reported reactions usually occur during the first week of therapy. The frequencies of the adverse reactions are based on clinical trial data in the B-CLL study population (n = 149). The frequencies are defined according to CIOMS III + V guidelines (very common  $\geq 1/10$ , common  $\geq 1/100$  -  $< 1/10$ , uncommon  $\geq 1/1,000$  -  $< 1/100$ ). No information is available for events that occur at lower frequency, due to the size of the population studied (n = 149). The most appropriate MedDRA term is used to describe a certain reaction. Synonyms or related conditions are not listed, but should be taken into account as well. **Infusion-related reactions:** very commonly reported reactions (due to release of cytokines) have been acute infusion-related reactions including fever, rigors, nausea, vomiting, hypotension, fatigue, rash, urticaria, dyspnoea, headache, pruritus and diarrhoea. The majority of these reactions are mild to moderate in severity. Serious reactions, including bronchospasm, hypoxia, syncope, pulmonary infiltrates, acute respiratory distress syndrome, respiratory arrest, myocardial

infarction, arrhythmias, acute cardiac insufficiency and cardiac arrest, have occurred in association with cytokine release, with fatal outcome in rare cases. Acute infusion-related reactions usually occur during the first week of therapy and substantially decline thereafter. Grade 3 or 4 infusion-related reactions are uncommon after the first week of therapy. Severe anaphylactic and other hypersensitivity reaction, including anaphylactic shock and angioedema, have been reported rarely following MabCampath® administration. These symptoms can be ameliorated or avoided if premedication and dose escalation are utilised. **Infections and Infestations:** grade 3 or 4 infections have been reported very commonly including Herpes simplex and pneumonia of grade 3 or 4 severity. Opportunistic infections, including those due to reactivation (e.g. *Pneumocystis carinii* pneumonia (PCP), cytomegalovirus (CMV), *Aspergillus* pneumonia and herpes zoster) occur commonly. Rhinocerebral mucormycosis has been reported but is uncommon. Other serious and sometimes fatal viral (e.g. adenovirus, parainfluenza, hepatitis B, Progressive Multifocal Leukoencephalopathy (PML)), bacterial (including tuberculosis and atypical mycobacterioses, nocardiosis), protozoan (e.g. toxoplasma gondii), and fungal infections, including those due to reactivation of latent infections have occurred during post-marketing surveillance. The recommended anti-infective prophylaxis treatment appears to be effective in reducing the risk of PCP and Herpes zoster infections. The prolonged decrease in T-lymphocytes that can be associated with MabCampath® treatment may lead to an increased risk for latent viral reactivation of Epstein Barr Virus (EBV). Evolution of EBV infection/reactivation into EBV-associated lymphoproliferative disorder has been observed in immunocompromised patients in rare cases. **Blood and lymphatic system disorders:** severe bleeding reactions have been reported commonly. Pancytopenia has been reported commonly and may be grade 3 or 4 in severity or serious in nature. Common: neutropenic fever, purpura. **Immune system disorders:** autoimmune phenomena have been reported uncommonly during or after treatment with MabCampath® (e.g. autoimmune haemolytic

anaemia, autoimmune thrombocytopenia, aplastic anaemia, Guillain Barré syndrome and its chronic form, chronic inflammatory demyelinating polyradiculoneuropathy). In rare cases these can be life-threatening or fatal. A positive Coombs test is also a common event. **Metabolic and nutritional disorders:** very common: anorexia; common: hyponatraemia, dehydration, weight decrease, hypocalcaemia, thirst; tumour lysis syndrome with fatal outcome has been rarely reported. **Nervous system disorders:** very common: headache; common: taste loss, tremor, hypoaesthesia, paresthesia, hyperkinesias, dizziness, vertigo; intracranial haemorrhage has occurred in patients with thrombocytopenia with fatal outcome in rare cases. **Cardiac disorders:** common: tachycardia, palpitation; congestive heart failure, cardiomyopathy, and decreased ejection fraction have been reported uncommonly in patients previously treated with potentially cardiotoxic agents. **Psychiatric disorders:** common: confusion, anxiety, somnolence, depression, insomnia. **Eye disorders:** common: conjunctivitis. **Vascular disorders:** very common: hypotension; common: hypertension, vasospasm, flushing. **Respiratory, thoracic and mediastinal disorders:** very common: dyspnoea; common: bronchospasm, coughing, hypoxia, haemoptysis. **GI disorders:** very common: nausea, vomiting, diarrhoea; common: GI haemorrhage, stomatitis, constipation, dyspepsia, ulcerative stomatitis, flatulence, abdominal pain. **Hepatobiliary disorders:** common: hepatic function abnormal. **Skin and subcutaneous tissue disorders:** very common: pruritus, urticaria, rash; common: erythematous rash, bullous eruption. **Musculoskeletal and connective tissue:** common: arthralgia, skeletal pain, back pain, myalgia. **General disorders and administration site conditions:** very common: chest pain, asthenia, malaise, influenza-like symptoms, oedema, oedema mouth, temperature change sensation, injection site reaction. **Date of revision of the text:** July 2006 Please note! For current prescribing information refer to the package insert and/or contact your local Bayer Schering Pharma Organization. Bayer Schering Pharma AG, 13342 Berlin, Germany