the 11 patients randomized to alemtuzumab consolidation; that results compares with a 24.7-month mean PFS in the 10 patients randomized to observation (p = 0.036). O'Brien *et al.* [23] reported a median TTP of more than 24 months in patients who demonstrated a response to alemtuzumab consolidation.

Survival: Survival data associated with the use of alemtuzumab consolidation therapy were reported in the RCT published by the German CLL Study Group [20]. Median OS had not been reached in either the alemtuzumab arm or the observation arm. No other studies reported survival data.

4.2.2 Question 2

What toxicities are associated with the use of alemtuzumab?

Toxicities associated with the administration of alemtuzumab were reported in most studies (Table IV). The most common adverse events can be broadly grouped into these categories:

- Infusion-related side effects
- Myelosuppression
- Infection-related toxicities

Infusion-related side effects: Infusion-related side effects were reported in sixteen studies [5–7,9,11,12,14–20,22–24]. They occurred in most patients treated with intravenous alemtuzumab, were usually grade 1 or 2 in severity, and were manageable with appropriate supportive care. The prophylactic use of pre-medications was reported in about one third of the studies and usually consisted of orally administered acetaminophen and antihistamines; corticosteroids were generally reserved for more severe reactions. Grade 3 or 4 fever, rigour, and nausea were reported in up to 20% of patients; other serious infusion-related toxicities were less common. The incidence of infusion-related side effects was similar regardless of the population evaluated, tended to be higher and more severe with the first infusion, and improved with subsequent courses of treatment.

The subcutaneous administration of alemtuzumab was reported in three trials [10,15,21], and this route was generally much better tolerated than the intravenous route used in similar patients (Table IV). Grade 1 or 2 fever (68%) and local injection site reactions (88%) were reported; grade 3 or 4 reactions of any kind were rarely reported (fewer than 2% of patients) [15].

Myelosuppression: Data regarding myelosuppression associated with the use of alemtuzumab were reported in 10 trials [6,7,9–12,15,18–20]. Results for studies evaluating various disease populations were analyzed separately.

Grades 3 and 4 myelosuppression were common in studies evaluating alemtuzumab monotherapy for patients with relapsed or refractory disease [6,7,9–12]. The pooled estimates for grades 3 and 4 neutropenia, thrombocytopenia, and anemia were 39% (range: 22%–66%), 31% (range: 23%–46%), and 8% (range: 0%–28%) respectively. Similar rates of grades 3 and 4 myelosuppression were reported for studies evaluating alemtuzumab in combination and in maintenance or consolidation regimens. Data regarding the co-administration of hematopoietic growth factors were not well reported.

Infection-Related Toxicity: Data regarding the incidence of infections in patients treated with alemtuzumab were reported in twenty publications [5–20,22,23,25,28]. In thirteen studies, antimicrobial prophylaxis was administered during alemtuzumab therapy. The most frequently cited combination was cotrimoxazole together with antiviral therapy (acyclovir, valacyclovir, famciclovir) for the prevention of *Pneumocystis carinii* pneumonia (PCP) and herpes virus infections. For the present systematic review, data relating to infection-related toxicity were analyzed and reported separately for various study populations.

Single-Agent Alemtuzumab for Relapsed or Refractory CLL: Data pertaining to infection-related morbidity in patients with relapsed or refractory CLL were reported in eight studies [5–12]. The per capita incidence of all infections ranged from 30 to 93 per 100 patients (46 per 100 patients across studies). The incidence of grades 3 and 4 infections ranged from 7 to 36 per 100 patients (18 per 100 across studies), and infection-related mortality ranged from 0 to 10 per 100 patients (4.5 per 100 across studies).

Grades 3 and 4 infections included disseminated viral infections [for example, varicella–zoster virus and herpes simplex virus (HSV)], systemic *Candida* infections, mycobacterial reactivation, and invasive fungal infections (for example, pulmonary aspergillosis, rhinocerebral mucormycosis, and cryptococcal meningitis and pneumonia). Infection with PCP was reported, but these cases generally occurred in patients not receiving prophylaxis.

The incidence of CMV reactivation was reported in seven of the above-mentioned trials [5,6,8–11,13] and ranged from 1% to 29% (9% across studies); CMV pneumonitis was reported in 4 patients (0.8% across studies). The actual risk of CMV reactivation in this patient population was not clear because most studies did not prospectively screen all patients.

Williams *et al.* [28] retrospectively pooled safety data in 1538 patients with lymphoid malignancies treated with alemtuzumab in five single-arm trials and reported that 3.6% of patients experienced "symptomatic" CMV reactivation, CMV pneumonitis (0.8%), and CMV-related death (0.2%). Routine prospective screening of all patients for CMV reactivation was not performed in those studies. Patients who developed CMV reactivation were usually treated with intravenous ganciclovir until evidence of viremia resolution. Ganciclovir therapy was highly effective for treating CMV reactivation, but because ganciclovir-induced neutropenia was common, myeloid growth factors