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A phase II, double-masked, randomized, placebo-controlled evaluation of a human monoclonal anti-Cytomegalovirus antibody (MSL-109) in combination with standard therapy versus standard therapy alone in the treatment of AIDS patients with Cytomegalovirus retinitis

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Abstract

ACTG 266 was designed as a randomized study to evaluate two doses of the human monoclonal antibody directed against CMV gH (MSL-109) versus placebo, each in combination with standard antiviral therapy for the treatment of newly diagnosed Cytomegalovirus (CMV) retinitis in AIDS patients. A total of 82 subjects were enrolled and received either placebo (n = 28), or MSL-109 at 15 mg (n = 26) or 60 mg (n = 28) every 2 weeks until disease progression was diagnosed. The primary endpoint, disease progression, was determined by masked reading of retinal photographs taken every 4 weeks read by a single investigator. The median time to progression was 8.0, 8.3, and 12.1 weeks in the placebo, MSL-109 15 mg and MSL-109 60 mg cohorts, respectively (P = 0.087, placebo versus 60 mg cohort). There were 22 deaths during the study period (9, 9, and 4 in the placebo, MSL-109 15 mg and MSL-109 60 mg cohorts, respectively (P = 0.0058, placebo versus 60 mg cohort)). MSL-109 was well tolerated with no significant adverse events attributable to study medication. The unexplained survival advantage in the higher dose cohort was discordant with the findings of the parallel Studies of Ocular Complications of AIDS Research Group (SOCA)-

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Monoclonal Anti-CMV Retinitis Trial (MACRT), which was prematurely halted because of increased mortality in subjects treated with high-dose MSL-109, recognizing that A266 enrolled subjects with newly diagnosed, whereas the MACRT enrolled subjects with relapsed, CMV retinitis.

Keywords: MSL-109; AIDS; Cytomegalovirus retinitis; Cytomegalovirus; Monoclonal antibody

1. Introduction

CMV infection has been a leading cause of morbidity and mortality in patients with AIDS, typically occurring during profound and prolonged immunosuppression with $CD4^+$ T-lymphocytes below 50 cells/mL (Egbert et al., 1980; Kuppermann et al., 1993; Pertel et al., 1992). Therapy with ganciclovir, foscarnet, or cidofovir became standards of care for treating CMV disease, administered intravenously during a 2-week induction dose followed by indefinite maintenance therapy (Anon., 1986, 1997b, 1994; Spector et al., 1993; Walmsley et al., 1988). Failure to achieve an initial remission was common, and relapse generally occurred within a period of less than four months with a median survival of approximately 1 year (Anon., 1992c; Gallant et al., 1992). With the introduction of highly active antiretroviral therapy (HAART) in the second half of the 1990s, the incidence of CMV disease fell (Murphy et al., 2001), but remains an important opportunistic infection (Drew, 2003; See and Rao, 2002). However, even in the HAART era, CMV disease still presents in patients with incomplete immune reconstitution (Jacobson et al., 1997; Johnson et al., 2001; Weinberg et al., 2001) or as a manifestation of the immune reconstitution syndrome shortly after the initiation of HAART (Mallolas et al., 1997; Shelburne et al., 2002). In addition, infections caused by CMV continue to cause morbidity and mortality in patients undergoing bone marrow and solid organ transplantation, where immunosuppression is profound (Gorensek et al., 1988a, 1988b; Rubin, 2001; Snydman, 1988; Zaia, 2002). Thus, seeking alternative strategies for the treatment of human CMV disease has remained a high priority (Hoffman and Skiest, 2000).

MSL-109 (Protein Design Laboratories, Mountain View, CA, USA) is an IgG_1 κ subclass human monoclonal antibody directed against cytomegaloviral surface glycoprotein gH. In vitro studies demonstrated potent neutralizing activity against both laboratory and clinical strains of CMV (Lakeman et al., 1991). MSL-109 also exhibited additive anti-CMV activity, in vitro, when combined with ganciclovir or foscarnet (Nokta et al., 1994). Phase I studies in humans with hematogenous malignancies found that the agent was safe at doses up to a 5 mg/kg dose (Drobyski et al., 1991). Pharmacokinetic studies suggested that administration every other week would be sufficient to maintain MSL-109 serum levels above the ED_{50} (median effective dose that produces the desired effect in 50% of a population) for typical CMV isolates (Aulitzky et al., 1991a; Drobyski et al., 1991). In phase II studies of AIDS patients with CMV retinitis, the median time to relapse was over 28 weeks in those subjects who received standard anti-CMV therapy and adjunctive MSL-109 (Pollard et al., 1992). ACTG 266 was designed to obtain additional data on the influence of MSL-109 on prolongation of the time to progression of CMV retinitis, compared to standard therapy in subjects with AIDS and newly diagnosed CMV retinitis in a carefully controlled, multicentered, blinded clinical trial. An additional primary objective was to examine the safety of MSL-109 in this population with secondary endpoints including survival advantages of the treatment group and pharmacodynamic correlates of response to treatment.

2. Materials and methods

Individuals with AIDS and newly diagnosed, initial episodes of CMV retinitis were eligible for enrollment. All subjects provided informed consent approved by their respective institutions' IRB. Eligibility criteria included documented HIV infection, age greater than 13 years, and a Karnofsky score of 60 or greater. Only subjects with first episodes of CMV retinitis were eligible for study entry, and entry had to occur promptly following the diagnosis. Enrollees may not have had prior CMV end organ disease at any site and may not have received intravenous cidofovir, foscarnet, or ganciclovir within six months prior to study entry. Subjects who met eligibility criteria were randomized 1:1:1 to receive infusions of either placebo or MSL-109 at either 15 mg or 60 mg every other week in conjunction with standard anti-CMV therapy selected by the subject and their primary care physician. The randomization was stratified by the anti-CMV therapy chosen. The induction therapy was based upon standard-of-care dosing; cidofovir (5mg/kg, i.v., weekly), foscarnet (90 mg/kg, i.v., every 12 h or 60 mg/kg, i.v., every 8 h), and ganciclovir (5 mg/kg, i.v., every 12 h), and was continued for 2 weeks. Similarly, the maintenance dosing reflected the standard-of-care; cidofovir (5 mg/kg, i.v., every 2 weeks), foscarnet (120 mg/kg, i.v., daily), ganciclovir (5 mg/kg, i.v., daily or 1000 mg orally, daily). Subjects continued to receive their assigned study medication every other week for the remainder of their time on study with CMV disease progression as the primary end point. Subjects were followed until a study end-point was met or until the study was closed to enrollment following the decision by the parallel SOCA study DSMB.

Progression of retinitis was defined as any one of the following: (a) advancement of the edge of an existing area of CMV retinitis by a fixed distance, 750 μm (roughly half the diameter of the optic nerve), (b) development of new lesion(s)

at least 750 μm in diameter (contralateral disease or ipsilateral disease unrelated to pre-existing lesions), (c) retinal detachment in the presence of active retinitis, or (d) optic nerve involvement associated with loss of visual acuity to 20/400 or worse (Anon., 1992b). The University of Wisconsin served as the retinal reading center for all retinal photographs obtained from subjects every 4 weeks which were read by a masked investigator (LH). Once progression of CMV retinitis had occurred, the subject was taken off study as a treatment failure, and was treated with anti-CMV salvage therapy.

Urine cultures for CMV were obtained at baseline and at pre-specified intervals during the study period. Urine cultures were processed using standard tissue culture methodology at the clinical laboratories of each institution. Pharmacokinetic levels were measured by an anti-idiotype assay specific for MSL-109.

This study was originally designed to provide an 80% power to detect a two-fold difference in the median time to CMV progression, the primary efficacy endpoint. Based on the sample size needed to achieve that level of power for the primary endpoint, the power analysis also provided a 25% versus 59% probability of detecting the safety endpoint (a grade 3 or higher adverse event possibly or definitely due to MSL-109 within the first 11 months on study) in an MSL-109 arm versus the placebo arm. The study team elected to terminate ACTG 266 prematurely on February 4, 1997 because of a parallel study's DSMB's findings (see Section 4). Since only 82 of the 167 subjects were accrued, the statistical power of this study was 39% for efficacy and 48% for safety.

The safety and efficacy hypothesis tests are considered to be independent. For each pair of tests a Bonferroni adjustment ($k = 2$) was employed to account for testing of the two MSL-109 groups against a common placebo group; the type I error is set at 2.5% so that the probability of incorrectly rejecting at least one primary null hypothesis is 5%.

The statistical approach for the primary efficacy endpoint was tested using a stratified log-rank test and for safety, exact tests for categorical data were employed. We first tested homogeneity (across the strata) of the odds ratio of having a primary safety endpoint in the placebo versus each MSL-109 group. Since homogeneity was not rejected, we assumed a common odds ratio and tested the null hypothesis that it is unity versus the two-sided alternative.

3. Results

The first subject was randomized in July 1995, and the last in August 1996. Eighty-two subjects were enrolled at 17 participating AIDS Clinical Trials Group sites (placebo: $n = 28$; MSL-109 15 mg: $n = 26$; and MSL-109 60 mg: $n = 28$). The subjects were well balanced for gender, ethnicity, injection drug use history, distribution of age, and baseline $CD4^+$ T-lymphocyte count (Table 1). Urine cultures recovered CMV at baseline in 66 (80%) subjects (placebo: $n = 20$; MSL-109 15 mg: $n = 23$; and MSL-109 60 mg: $n = 23$).

Adverse events were evenly distributed between all three treatment groups. There were 28, 26, and 28 grade III or IV adverse events recorded during the first 11 months of the study for the placebo, MSL-109 15 mg, and MSL-109 60 mg cohorts, respectively. Most of these adverse events were judged 'not related' to study medication, as they often represented recognized toxicities of the primary anti-CMV therapy.

All subjects who were CMV urine culture positive at baseline became negative within the first 4 weeks of therapy except one from each cohort. No subject who was culture negative at baseline became culture positive at follow-up. A limited number of subjects from each cohort were CMV urine culture negative at baseline and remained so during follow-

Table 1
Baseline characteristics

	Total ($n = 82$)	Placebo ($n = 28$)	15 mg ($n = 26$)	60 mg ($n = 28$)	Placebo vs. 15 mg[a]	Placebo vs. 60 mg[a]
Gender						
Male	67 (82%)	21 (75%)	22 (85%)	24 (86%)	$P = 0.505$	$P = 0.503$
Female	15 (18%)	7 (25%)	4 (15%)	4 (14%)		
Drug use (i.v.)						
Never	69 (84%)	21 (75%)	24 (92%)	24 (86%)	$P = 0.144$	$P = 0.503$
Previous	13 (16%)	7 (25%)	2 (8%)	4 (14%)		
Race						
Asian	3 (4%)	1 (4%)	1 (4%)	1 (4%)	$P = 1.00$	$P = 0.640$
Black	22 (27%)	6 (21%)	5 (19%)	11 (39%)		
Hispanic	18 (22%)	7 (25%)	6 (23%)	5 (18%)		
Native American	1 (1%)	1 (4%)	0	0		
White	38 (46%)	13 (46%)	14 (54%)	11 (39%)		
Age (year)						
Median	38	34	38	39	$P = 0.256$	$P = 0.261$
CD4 (cells/mL)						
Median	13 ($n = 77$)	9 ($n = 27$)	11 ($n = 24$)	21 ($n = 26$)	$P = 0.850$	$P = 0.236$

[a] Fisher's Exact Test for gender, drug use (i.v.), and race; Wilcoxon Test for age and $CD4^+$ T-cell count.

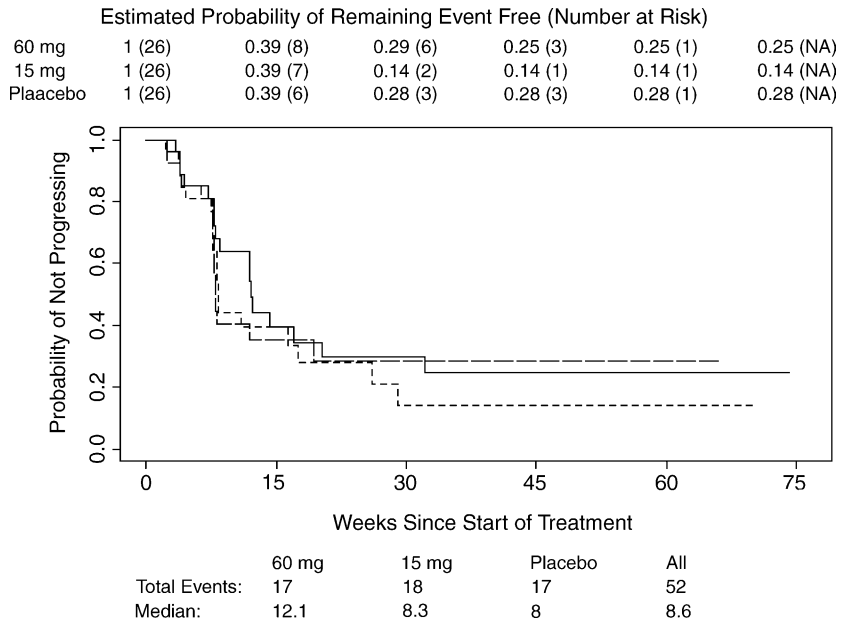

Fig. 1. Time to CMV progression (60 mg, ——; 15 mg, - - - -; placebo, — —).

up (placebo: $n = 8$; MSL-109 15 mg: $n = 4$; and MSL-109 60 mg: $n = 4$). One subject, who received placebo, was CMV urine culture positive through out the treatment period.

The primary endpoint of time to progression of CMV disease, showed a trend towards an advantage for the high-dose MSL-109 cohort compared to the placebo group ($P = 0.087$), but no difference between the low-dose MSL-109 group and placebo ($P = 0.33$) (Fig. 1). The median time to relapse was 8 weeks for the placebo cohort, 8.3 weeks for the low-dose MSL-109 15 mg cohort, and 12.1 weeks for the high-dose MSL-109 60 mg cohort. Similarly, analyses of the time to last follow-up and of the time to permanent treatment discontinuation failed to demonstrate any differences among the treated and placebo recipients (data not shown).

Overall, there were 22 deaths among study participants during the conduct of this trial: 9 from the placebo cohort, 9 from the low-dose MSL-109 cohort, and 4 from the high-dose MSL-109 cohort. The Kaplan–Meier survival plot (Fig. 2)

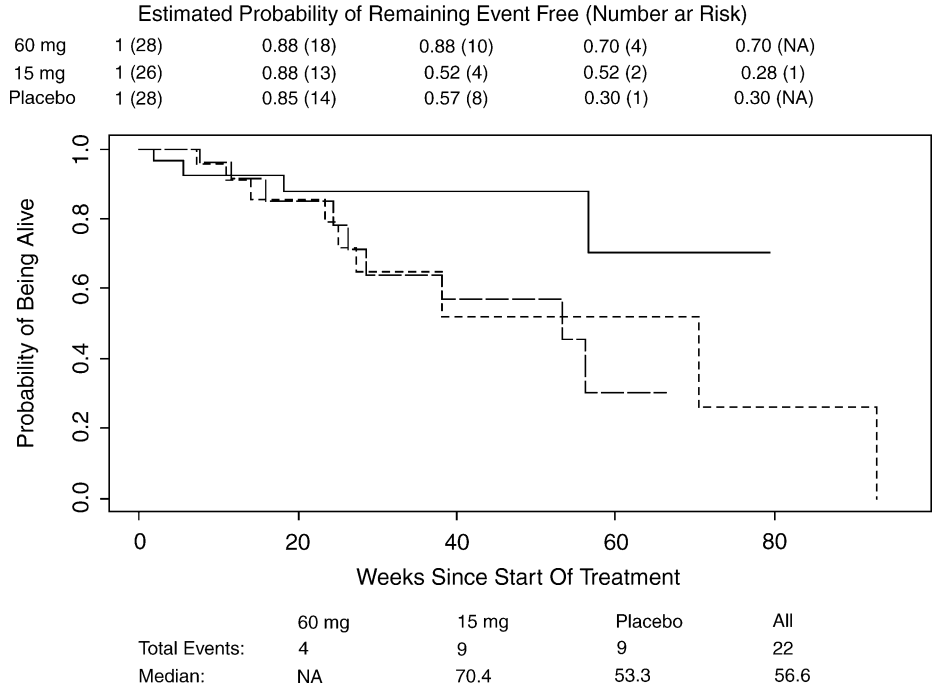

Fig. 2. Time to death from any cause (60 mg, ——; 15 mg, - - - -; placebo, — —).

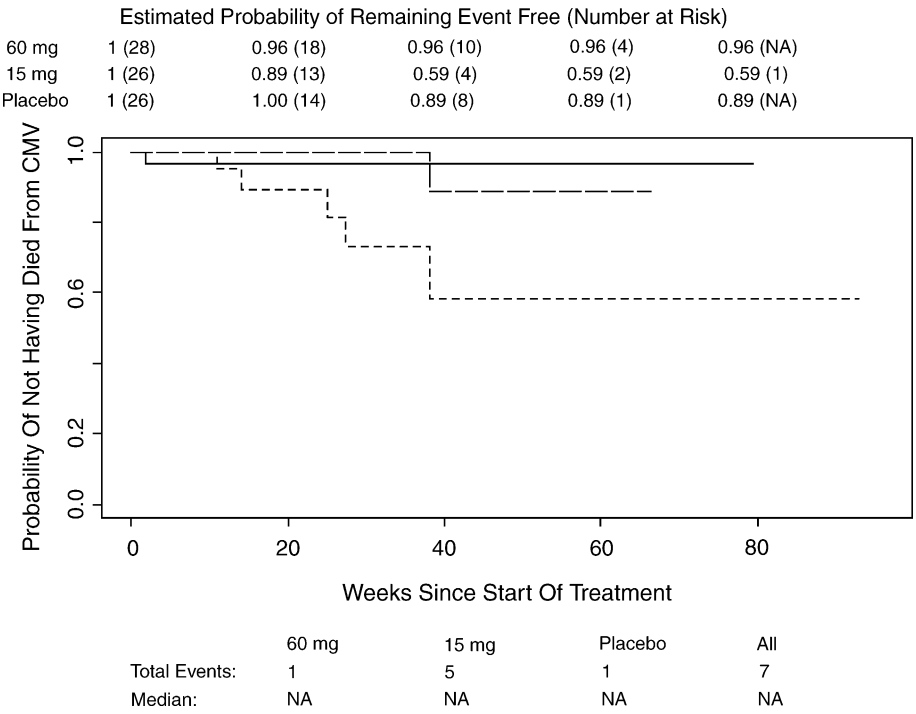

Fig. 3. Time to death attributable to CMV (60 mg, ——; 15 mg, - - - -; placebo, — —).

suggests a survival benefit for the high-dose MSL-109 treatment group compared to placebo (P = 0.0058). The low-dose MSL-109 treatment group was not different from the placebo group (P = 0.42). Mortality data were also examined for the number of deaths attributed to CMV (Fig. 3). The Kaplan–Meier and log-rank analysis demonstrated no differences between the high-dose MSL-109 or the low-dose MSL-109 when compared to placebo (P = 0.87 and P = 0.17, respectively). Only seven deaths of the 22 on-study deaths were attributed to CMV, which significantly limits the CMV-attributable mortality analysis. A further analysis using the endpoints of time to progression of CMV disease or death found a nearly equal distribution for these clinical endpoints among the three groups: 20 events in the placebo

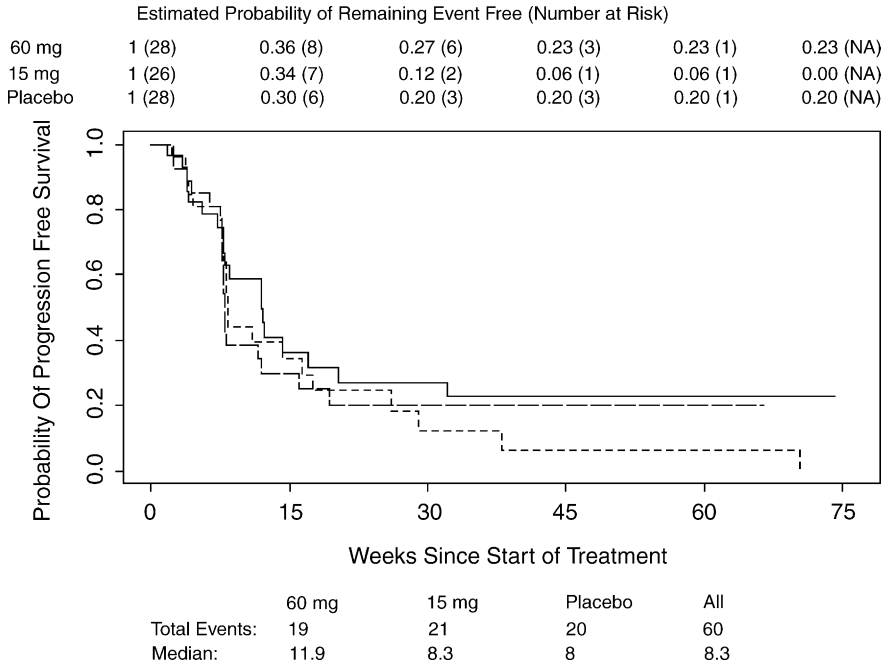

Fig. 4. Time to CMV progression or death (60 mg, ——; 15 mg, - - - -; placebo, — —).

cohort, 21 events in the low-dose MSL-109 cohort ($P = 0.14$), and 19 events in the high-dose MSL-109 cohort ($P = 0.056$) (Fig. 4).

Pharmacokinetic/pharmacodynamic parameters were measured on a subset of study participants. Among 31 of 34 subjects who experienced CMV progression and who were randomized to an MSL-109 regimen, the correlation between time-averaged trough level of MSL-109 prior to CMV progression, and time to progression was not significantly different from zero (Spearman $\rho = 0.21$, $P = 0.24$; Pearson $\rho = 0.18$, $P = 0.32$) (data not shown). The study had an 80% power to detect a non-zero correlation if the true correlation were 0.50 (Spearman test) or 0.48 (Pearson test).

4. Discussion

ACTG 266 was conducted in parallel with the Studies of Ocular Complications of AIDS (SOCA)-Monoclonal Anti-CMV Retinitis Trial (MACRT), which was similar in design with respect to end points but had two important differences. First, SOCA subjects were stratified by newly diagnosed and relapsing CMV retinitis (whereas ACTG 266 enrolled only subjects with newly diagnosed CMV retinitis), and second, for the SOCA study, there was only one treatment cohort at 60 mg MSL-109 intravenous every 2 weeks plus standard anti-CMV therapy compared to a control arm of standard anti-CMV therapy alone (Anon., 1997a). In SOCA-MACRT, the combined median times to disease progression were nearly 10 weeks in both the placebo and 60 mg MSL-109 treatment cohorts, compared to 8 and 12 weeks, respectively, in ACTG 266. Among subjects enrolled at the time of their initial episode of CMV retinitis in the SOCA-MACRT, the mortality rates were similar between the two groups; 0.41/person-year versus 0.42/person-year for the placebo and MSL-109 treatment cohort, respectively. However, among subjects with relapsing CMV retinitis in the same study, the mortality rate was greater in the MSL-109 cohort as compared to the placebo cohort (0.83/person-year versus 0.24/person-year, $P = 0.03$) for the MSL-109 and placebo cohorts, respectively. Interestingly, in the two stratified placebo groups' mortality rates were 0.42/person-year and 0.24/person-year for those with an initial diagnosis of CMV and those with relapsing CMV, respectively. This finding of a lower mortality rate in the stratified subgroups of placebo treated subjects is particularly difficult to explain and is in sharp contrast to previous studies (Anon., 1992a). Similarly, historical data for mortality rate among AIDS patients with relapsing CMV retinitis were significantly higher than that occurred during the MACRT. No differences in baseline variables or in concurrent antiretroviral therapy explained the high mortality rates in the treatment group. Nonetheless, the DSMB recommended to prematurely close the MACRT (Gilpin et al., 2003), which in turn, resulted in the premature discontinuation of ACTG 266. In addition, analysis by treatment group noted no effect of MSL-109 on clearance of CMV-DNA or CMV antigen from the plasma in MACRT participants (Jabs et al., 2002).

Since the completion of these two trials of MSL-109 for the treatment of AIDS patients with CMV retinitis, a clinical trial for the prevention of CMV infection after allogeneic hematopoietic stem cell transplantation (HSCT) has been completed (Boeckh et al., 2001). This prospective, double-blind study of HSCT recipients with positive donor and/or positive recipient serology for CMV randomized subjects to receive either 60 mg/kg MSL-109 ($n = 59$), 15 mg/kg MSL-109 ($n = 60$), or placebo ($n = 60$) intravenously every 2 weeks from day 1 until day 84 after transplantation. There was no significant difference in the fraction of subjects who became positive for CMV-DNA or CMV antigen (CMV pp65) in the high-dose MSL-109 (15% CMV-DNA+; 47% CMV antigen+), low-dose MSL-109 (23% CMV-DNA+; 52% CMV antigen+), and placebo (17% CMV-DNA+; 45% CMV antigen+) cohorts over the period of observation. Subgroup analysis for survival revealed somewhat divergent findings. There was a transient survival advantage at 100 days for the high-dose MSL-109 in CMV seronegative recipients of seropositive donors that did not persist at the end of the study. In contrast, there was a survival advantage for the placebo group compared to MSL-109 groups in the combined seropositive recipients (seropositive or seronegative donors). The authors concluded that MSL-109 appeared safe and well tolerated, but survival differences could not be explained and there were no data supporting benefit of MSL-109 treatment among CMV seropositive HSCT recipients.

Taken in the context of the other clinical trials testing MSL-109 for the treatment or prevention of CMV disease in immunocompromised hosts, the results of ACTG 266 are compromised by the decision to terminate the study early. The delay in recurrence of CMV retinitis observed for the high-dose MSL-109 cohort compared to the standard of care only cohort did not reach significant levels in the setting being underpowered to detect a significant difference at the time of its termination (12 weeks versus 8.1 weeks for MSL-109 60 mg versus standard of care alone, respectively, $P = 0.087$). This is compared to earlier phase II trials where the delay in relapse was over 28 weeks in the MSL-109 plus anti-CMV viral therapy where higher doses of MSL-109 were used in an unmasked study design (Pollard et al., 1992). At the time the MACRT was terminated, the mean time to recurrence in the newly diagnosed CMV cohort was approximately 10 weeks in the both the treatment and control arms without a survival difference between them. The unanticipated and unexplainable reduction in mortality in the standard of care only arm of the MACRT cohort with recurrent CMV retinitis is what prompted the DSMB recommendations. There was no comparable arm within ACTG 266. However, the improved survival in the high-dose MSL-109 arm of ACTG 266 (Fig. 2) also remains unexplained in the context of available pharmacokinetic measurements performed for this study. This lack of a correlation between plasma level of MSL-109 and treatment outcome suggests that any differences seen between

cohorts cannot be explained by the treatment intervention. However, without an assessment of the trough levels in subjects who did not develop CMV progression, this assessment cannot be definitively determined.

Despite the preclinical and early clinical promise for MSL-109 monoclonal anti-CMV antibody (Nokta et al., 1994; Pollard et al., 1992), there are several possible explanations for its failure to demonstrate a virologic or consistent clinical benefit in larger trials. First the MSL-109 epitope may not be the optimal design for this strategy; second, insufficient antibody concentrations in the aqueous and vitreous humors may explain the failure to affect the clinical course of CMV retinitis (but not as a prophylaxis for CMV diseases in transplant patients); and third, immunomodulatory therapy targeting the humoral immune system in isolation may be an insufficient strategy in the setting of coincident profound cellular immune defects as occurs with advanced HIV infection or post-ablative bone marrow chemotherapy.

The first two of the potential explanations seems unlikely. MSL-109 is the product of a hybrid cell line constructed by fusion of a non-antibody producing murine × human hybrid myeloma to a human B lymphocyte stimulate in vitro by human CMV antigens isolated from the Towne strain of CMV (Lakeman et al., 1991). MSL-109 recognizes an 82,000 Da molecule (gH) identified as the target for a neutralizing murine monoclonal antibody against human CMV (Britt and Mach, 1996; Urban et al., 1996). The overall size of the molecule is approximately 150,000 Da. Since the blood–eye barrier is essentially like the blood–brain barrier, this size molecule would be expected to diffuse to the site of CMV-induced inflammation. In addition, neutralizing activity was not detected against MSL-109 during the preclinical or phase I trials (Aulitzky et al., 1991b; Drobyski et al., 1991), and the construct demonstrated excellent neutralization of CMV in in vitro experiments (Nokta et al., 1994). Nevertheless, an antibody to gB or other epitopes may be more critical, despite early trials with a gB monoclonal antibody demonstrating a 10-fold inferior level of activity in comparison to the gH monoclonal antibody used in this trial (Ostberg, 1992; Ostberg and Queen, 1995).

Infection with CMV is accompanied by both humoral and cell-mediated immune responses. Studies of individuals with severe or fatal CMV infections have demonstrated that antibody responses to the virus are nearly always intact, indicating that depressed cell-mediated immunity may especially contribute to both the reactivation and severity of the disease (Schoppel et al., 1997). Although CMV-specific antibody responses may not protect against the development of a severe infection, evidence suggests that they can modify the disease outcome under certain circumstances. Administration of immunoglobulins from hyperimmune sera to bone marrow allograft recipients does not protect against infection but appears to modify the severity of the infection-related symptoms (Bowden et al., 1991; Meyers et al., 1983). However, it is likely that cell mediated immunity in the form of CMV-specific T-lymphocyte responses dominate the immune control of CMV infection (Quinnan et al., 1982). In the setting of severe immunodeficiency, as occurs in patients with HSCT and late stage AIDS, the absence of a reliable $CD4^+$ T-lymphocyte response likely masks any incremental benefit of monoclonal antibody therapy (Lilleri et al., 2003; Reusser et al., 1991). In our study, there appeared to be a survival benefit in the high-dose MSL-109 recipients by an unexplained mechanism, which is in contrast to the findings of the SOCA-MACRT. The survival benefit is not directly attributable to a reduction in CMV-attributable mortality, but this is not unexpected given that CMV causes increased mortality in patients with AIDS that is not directly attributable to CMV-related mortality.

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