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Letter
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Durable Responses and Survival in High-risk Myelodysplastic Syndrome and Acute Myeloid Leukemia Patients Receiving the Allogeneic Leukemia-derived Dendritic Cell Vaccine DCP-001

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Durable responses to therapy are unfortunately rare in elderly patients with high-risk myelodysplastic syndrome (HR-MDS) and acute myeloid leukemia (AML).[1,2] Maintenance therapy options are urgently needed especially for those who are ineligible for allogeneic hematopoietic stem cell transplantation (HSCT).[3] Immunotherapeutic strategies to treat cancer are widely investigated.[4] One of these comprises dendritic cell (DC) vaccines, that are able to activate T cells against tumor-specific antigens.

DC-based anti-cancer immunotherapy relies mostly on vaccination strategies whereby tumor antigens are loaded onto DC to induce anti-tumor-specific T cells. These DC can either be autologous or allogeneic, the latter with or without host HLA matching. Both have been used clinically with variable results.[5] Previously, we reported results from a clinical phase I study (NCT01373515) in which patients with HR-MDS or AML, who were ineligible for HSCT, received an allogeneic leukemia cell line (DCOne)-derived DC vaccine, DCP-001.[6] Data showed the vaccine to be safe, biologically active, and able to induce both humoral and cellular immune responses.[6] Prolonged survival was demonstrated in patients with peripheral circulating blasts <5% at study entry, ranging from 7 to 63 months from the start of vaccination; patients with circulating blasts >5% died within 6 months.[6]

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Here, we report on the updated clinical follow-up of this phase I trial, including additional baseline characteristics such as blast counts, cytogenetics, mutation burden, and pre- and post-vaccination therapies (Suppl. Table S1). All patients received high-dose induction chemotherapy according to The Hemato-Oncology Foundation for Adults in the The Netherlands (HOVON) protocols; studies HOVON 81, 102, 103 (see: www.hovon.nl) with standard 7+3 conventional regimen consisting of cytarabine and an antracycline with or without emerging new drugs in experimental arms. Some patients received additional lines of therapy, that is, azacitidine. We included results of targeted next-generation sequencing and cytogenetics to determine molecular risk factors according to the 2017 European Leukemia Net (ELN) recommendations in AML as well as the Revised International Prognostic Scoring System (IPSS-R) in MDS for risk assessment.[7] Responses until day 126, as endpoint of the study according to protocol, were defined by 2017 ELN criteria.[8] Since this is a small data set we simplified the response criteria into 2 groups: non-responders and responders, according to previously published data.[6] Non-responders were defined as disease progression within 126 days by an increase in leukemic blasts; responders were defined as persistence of complete remission (CR)/complete remission with incomplete count recovery (CRi), a decreased or stable blast count as compared to baseline at study entry. The study population comprised 12 patients: 6 patients with AML, 3 patients with AML with prior MDS, and 3 patients with MDS with excess of blasts. Seven out of twelve patients showed a response to treatment; 5 patients showed progression of disease (Figure 1). In the 7 responders, a median relapse-free survival (RFS) of 420 days (range 90–1849 days) and a median overall survival (OS) of 1090 days (range: 90–2160 days) was observed as compared to a median OS of 144 days (range 59–209 days) (P = 0.03, Mann-Whitney U) in the 5 non-responders.

Subsequently, we investigated the baseline characteristics of the responders to those of non-responders (Table 1), as these would help identify patients most likely to respond to DCP-001. Non-parametric tests were performed and P values <0.05 were interpreted as statistically significant. We considered variables with $P \leq 0.1$ as a trend. Discriminating variables in favor of response were a lower percentage of blasts in bone marrow at study entry (P = 0.022) and a complete remission and/or stable disease status at study entry (P = 0.003). We observed no association between response and risk groups as established by

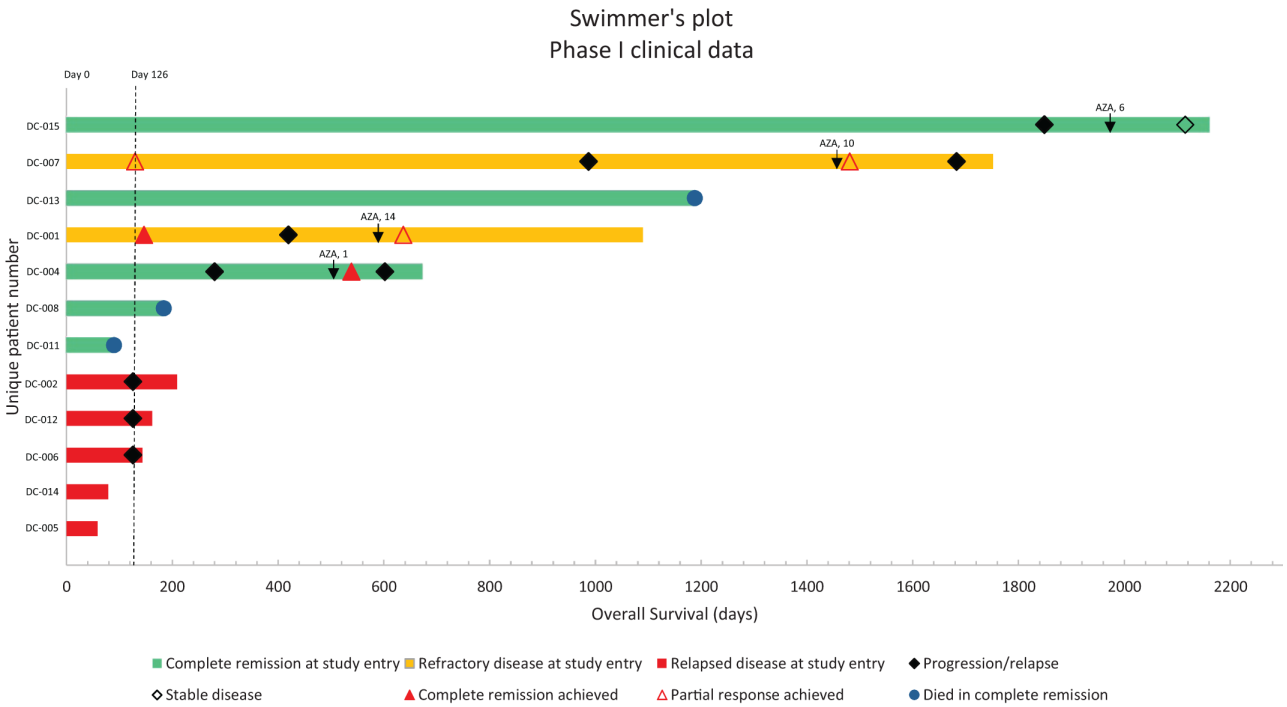

Figure 1. Swimmer's plot showing long-term follow-up data upon DCP-001 phase 1 trial. Each bar represents one patient in the study; every bar starts at the first vaccination (day 0) and ends with the death of the patient. Day 126 is the end of the official study evaluation according to protocol. The bars are ordered based on response and subsequently on survival. Patients DC-008 and DC-011 died in complete remission of the disease due to infections (sepsis and candida endocarditis, respectively). Patient DC-013 received euthanasia. Patients DC-001, DC-004, DC-007, and DC-015 received Azacitidine (AZA) post-vaccination. The start of cycles is indicated with an arrow in the figure. DC-001 received 14 cycles, DC-004 received 1 cycle, DC-007 received 10 cycles and DC-015 received 6 cycles. AZA = azacitidine.

the 2017 ELN, 2022 ELN, or IPSS-R criteria, diagnosis (WHO 2008, WHO 2022), dose cohort, adverse events (only local skin reactions), cytogenetic aberrancies and mutations.

Next, we determined the clinical potential of DCP-001 as maintenance/consolidation therapy by comparing the 5 DCP-001 responders in CR at study entry to a historical cohort from the HOVON97 trial (EudraCT 2008-001290-15) and QUAZAR study (QUAZAR AML-001, NCT01757535).[9,10] Both studies included patients that were >55 years of age (>60 years for HOVON97-trial), in CR with or without complete hematologic recovery after intensive chemotherapy, and ineligible for HSCT. The HOVON97 phase-3 trial comprised 116 patients with intermediate-2 to high-risk MDS and/or AML who were randomized to receive either no maintenance therapy (observation, n = 60) or AZA (subcutaneously [s.c.], n = 56) as post-remission therapy.[9] The median OS for the observation group was ~18 months and the median OS for the group receiving AZA s.c. as maintenance was ~24 months.[9] The QUAZAR study comprised 472 patients who were randomized to receive oral-AZA (CC-486, n = 238) or placebo (n = 234).[10] The placebo group in this study had a median OS of 14.8 months and the oral-AZA group of 24.7 months.[10] The median OS of the patients in the DCP-001 phase I trial who were in CR at study entry was 22.4 months (672 days) and for patients in CR or with bone marrow blasts <10% at study entry was 35.8 months (1090 days), which is higher than in the observation groups in the HOVON97 and QUAZAR studies and comparable to patients treated with AZA. This observation points to the clinical potential of DCP-001 vaccination as maintenance therapy.

Response to AZA post-vaccination was evaluated in 3 patients initially responding to DCP-001 with available follow-up data. Treatment with AZA was initiated in these patients when they showed progression of disease at day 126 (n = 1) or progression after a period of stable disease (n = 2). Post-vaccination treatment with AZA resulted in a partial response in 2 patients: 1 patient after 14 cycles of AZA (15 months duration of response [DC-001]) and 1 patient after 10 cycles of AZA with a 13-month duration of response (DC-007). A complete remission was achieved with only 1 cycle of AZA, after a previous duration of response of 4.5 months upon DCP-001 (DC-004) (Figure 1). These data suggest that AZA can be applied as rescue therapy upon progression after DCP-001. Interestingly, patient DC-004 who achieved CR after only 1 cycle of AZA, was treated with AZA before DC-vaccination. The mechanism of action of AZA is reported to be partially immune-mediated through its effect on T cells, and it may prove most effective in tumors with an immune evasion gene expression signature.[11,12] Notably, the DCP-001 vaccine was recently reported to initiate a tumor-specific T cell priming process.[13] We contemplate that vaccination with DCP-001 may have the potential to overcome resistance to AZA via its effect on T cells.

Taken together, our post-hoc analysis indicates the potential utility of the allogeneic DC vaccine DCP-001 as maintenance/consolidation therapy in high-risk MDS and AML. Although we observed no benefit of DCP-001 in patients with a relatively high disease burden, we observed durable responses in patients in CR or with low blast counts before the start of DCP-001 vaccination. A higher response rate was associated with vaccine administration shortly after achieving CR and not with prognostic risk factors according to 2017ELN or IPSS-R. Further investigations may identify patients most likely to benefit from DCP-001 vaccination. Responders showed a median OS comparable to reported OS in patients with MDS and AML with similar baseline characteristics who received AZA as maintenance

Table 1

Comparison of Baseline Characteristics of Responders to Non-responders

Variable	Non-responder, N = 5[a]	Responder, N = 7[a]	*P*[b]
Age			0.2
Median (IQR)	70 (69–70)	66 (64–70)	
Sex			0.3
Female	1 (20%)	4 (80%)	
Male	4 (57%)	3 (43%)	
Diagnosis			0.2
AML	4 (67%)	2 (33%)	
AML with prior MDS	0 (0%)	3 (100%)	
MDS IB-2	1 (33%)	2 (67%)	
Risk score			>0.9
Adverse	3 (43%)	4 (57%)	
Intermediate	2 (40%)	3 (60%)	
Unfavorable cytogenetics yes/no	2 (50%)	2 (50%)	>0.9
Dosis cohort			0.8
DC1	1 (33%)	2 (67%)	
DC2	2 (67%)	1 (33%)	
DC3	2 (33%)	4 (67%)	
Disease status			0.003
Complete remission	0 (0%)	5 (100%)	
Refractory	0 (0%)	2 (100%)	
Relapsed	5 (100%)	0 (0%)	
Blasts in bone marrow (%)			0.022
Median (IQR)	29 (14–53)	2 (1–6)	
Time between diagnosis and study entry (months)			0.12
Median (IQR)	20 (18–22)	8 (6–12)	
Azacitidine pre-DC vaccination yes/no	4 (80%)	1 (20%)	0.072

Responses until day 126, as endpoint of the study according to protocol, were defined by 2017 ELN criteria. Since this is a small data set we simplified the response criteria into 2 groups: non-responders and responders. Non-responders were defined as disease progression within 126 days by an increase in leukemic blasts; responders were defined as persistence of CR/CRi, a decreased or stable blast count as compared to baseline at study entry.

[a]n (%).

[b]Wilcoxon rank sum test; Fisher's exact test.

AML = acute myeloid leukemia; BM = bone marrow; DC1 = 10 million cells DCP-001; DC2 = 25 million cells DCP-001; DC3 = 50 million cells DCP-001; IQR = interquartile range; MDS =myelodysplastic syndrome; MDS IB-2 = MDS with an increase of blasts according to WHO2022; PB = peripheral blood.

therapy. In addition, our data suggest that DCP-001 followed by AZA can re-induce durable remissions after progression. Due to the limited size of our cohort, we were unable to draw definitive conclusions on variables that did not show a correlation to treatment response. These variables should be considered in future studies with larger cohorts. It's worth noting that data on measurable residual disease (MRD) in this phase I/II trial was incomplete, mainly due to a lack of leukemia-associated immune phenotypes. The major advantages of DCP-001 might be the off-the-shelf applicability, easy use as intradermal injection and a relatively short treatment period. In general, maintenance therapy with classical or emerging new drugs needs continuous compliance to optimize clinical benefits. Currently, an international multi-center phase 2 study (ADVANCE II; NCT03697707) evaluates the effect of DCP-001 on MRD in AML patients in CR, aiming to induce conversion to the absence of MRD.[9,14] Exploring the combination of DCP-001 therapy with other treatments such as AZA or CD47 blocking therapies holds therapeutic interest and should be investigated further.

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AUTHOR CONTRIBUTIONS

AAvdL and TDdG were the principal investigators of the study. LLGJ had primary responsibility for the paper and wrote the article. LLGJ, TMW, JR, TDdG, and AAvdL designed the study and interpreted the results. LLGJ collected the clinical data. PJMV was responsible for the mutational data. All authors contributed to the revising of the article.

DISCLOSURES

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