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A phase I study of MAGE-A1-targeted T1367 T-cell receptor-based cell therapy in patients with advanced multiple myeloma

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Running title: MAGE-A1-targeted TCR therapy in myeloma
Key words: Multiple myeloma; MAGE-A1; T cell receptor (TCR); TCR T cell therapy

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Contribution
J. Krüger collected and analyzed the IHC expression data and created the graphs. I.A., K.J., J.B. and A-C.B. provided the immunohistochemistry slides of MAGE-A1 expression. M.O., A.P., T.B., U.K., J. Krönke, I.W.B., A.B. and A.N. designed the study. M.O., D.H., V.S., G.W., T.B. and A.P. contributed the preliminary work for TCR-1367 and designed the manufacturing process with M.V. and H.R.. M.V. and H.R. manufactured the TCR-1367 T cells. M.O., T.B., A.P., V.S. and E.K. designed the clinical trial. J. Krüger and A.N. wrote the manuscript. All authors revised the manuscript and approved the final version which was submitted.

LETTER TO THE EDITOR

Cancer/testis (C/T) antigens are genes whose expression is silenced in healthy adult tissues except for male germ cells. Because C/T antigens are expressed in various cancers, they are potential targets for targeted therapies[1]. MAGE-A1, the first identified C/T antigen, was characterized as the target of an autologous cytotoxic T cell clone recognizing the melanoma cell line MZ2E[2]. MAGE-A1 expression was described in biopsies from patients with multiple myeloma (MM)[3], an aggressive plasma cell malignancy, and was associated with poor prognosis in one study[4]. Despite recent advances in the treatment of MM, such as chimeric antigen receptor (CAR-)T cell therapy and Bispecific T cell engagers (BiTEs)[5], MM remains incurable, and antigen loss has been described as resistance mechanism for immunotherapies[6]. Therefore, there is a high need for new treatment options and therapeutic targets. T cell receptor (TCR) therapy represents another T cell-based immunotherapeutic approach in cancer[7]. TCR-T cell therapy allows to target intracellular proteins presented by major histocompatibility (MHC) class I molecules with a higher antigen sensitivity compared to CAR-T cells[8,9]. We have previously described TCR-T1367 with optimal affinity against MAGE-A1 for development of TCR-based cellular immunotherapy[10]. In this study, we present the analysis of a large cohort of MM patients for MAGE-A1 expression and its association with specific clinical and disease characteristics. Furthermore, we describe TCR-1367 T cell production in an academic setting, and present clinical data from the phase 1 study (EudraCT: 2017-001208-30) investigating TCR-1367 T cells in two patients.

MAGE-A1 expression was investigated by immunohistochemistry (IHC) in 252 formalin-fixed, paraffin-embedded histological samples from 213 patients, collected from 2012 to 2022, using the commonly used anti-MAGE-A1 antibody MA454. The study was approved by the ethical committee of Charité-Universitätsmedizin Berlin (EA4/133/23). Statistical tests included Mann-Whitney test for comparing two categories and Kruskal-Wallis test for more than two categories. Clinical and genetic characteristics of our cohort are presented in Suppl. Table 1. Out of the 252 samples, 27% presented with ≥30% MAGE-A1+ MM cells, 23% with a lower fraction and 50% without MAGE-A1 expression (Fig. 1A). An exemplary slide of MAGE-A1 expressing MM cells is shown in Fig. 1B. The fraction of MAGE-A1 positive samples (≥30% of MAGE-A1+ MM cells), increased from 18% at diagnosis to 33% during relapse (Fig. 1B) with a significant increase of the mean proportion of MAGE-A1+ MM cells in all samples (15% vs. 26%; p=0.0002). For 131 patients cytogenetics and FiSH results were available, with 59 classified as standard risk and 72 as high risk based on cytogenetic aberrations defined as del(17p), t(4;14), t(14;16), gain or amplification (1q21)[11,12]. High-risk patients presented with a slightly higher proportion of MAGE-A1 positive samples (31%)

compared to the standard risk group (23%), but without significant difference in mean MAGE-A1 expression (24% vs. 18%, p=0.0788, Fig. 1C).

Furthermore, we investigated the association of MAGE-A1 expression with extramedullary disease (EMD). In BM samples, 22% had ≥30% MAGE-A1+ cells, compared to 55% in bone-related extramedullary myeloma (EM-B) and 46% in extraosseous extramedullary myeloma (EM-E) samples. The mean proportion of MAGE-A1+ MM cells in positive samples was higher in EM-B (83%, p=0.3918) and EM-E (85%, p=0.0417) samples compared to BM (68%) as shown in Fig. 1D. A significant higher proportion of MAGE-A1+ MM cells in positive BM samples were found in patients with documented EMD compared to patients without EMD (82% vs. 58%, p=0.0017; Fig. 1E). Analyzing 11 matched EMD and BM samples collected from the same time point and same patient we found only a weak correlation between the proportion of MAGE-A1+ cells between these samples (R2=0.3883; p=0.0405). Survival data were available for 99 newly diagnosed MM patients of which 83 were MAGE-A1 negative (<30% MAGE-A1+ MM cells) and 16 positive (≥30% MAGE-A1+ MM cells). Kaplan-Meier survival analysis revealed that MAGE-A1 expression at diagnosis was associated with impaired OS resulting in 2-year survival rates of 95% for negative and 54% for positive patients (median OS not-reached for both; HR 0.21, 95% CI 0.04-1.16; p=0.0015, log-rank test; Fig. 1F).

To investigate MAGE-A1 as a therapeutic target, we applied the MAGE-$A1_{278-286}$- epitope directed TCR-T1367 sequence[10] and transduced autologous T cells from patients with MM with retrovirus encoding TCR-T1367. TCR-1367 T cells were manufactured at Zellkulturlabor für Klinische Prüfung (ZKP), the GMP Facility of the Experimental and Clinical Research Center (ECRC), Charité-Universitätsmedizin Berlin. An overview of the manufacturing process is shown in Fig. 2A. The manufacturing process was validated in three healthy donor validation runs. TCR-1367 T cells were manufactured for three patients (patients 001, 004, 006). T1367 expresses Vß3, which was used as marker for T1367 transduced cells. The transduction rates, estimated by flow cytometry detection of Vß3+/CD8+ cells four days after transduction, were 18.6% (001), 32.7% (004) and 31.6% (006) of all CD45+/7-ADD- cells, and were stable throughout the freezing and thawing process. Only the product from patient 006 experienced a 10% decrease (Fig. 2B). For patients 004 and 006 a sufficient cell proliferation after transduction was observed, reaching proliferation rates of 57-fold and 13-fold on day 12 (Fig. 2C). In contrast, product 001 showed a proliferation rate of only 2-fold on day 12 (Fig. 2C). We observed a strong correlation between the proliferation rate from day 2 to day 5 and the transduction rate in the final product (R^2=0.9441, p=0.0012, Fig. 2D). The cell viability after thawing, determined by trypan blue staining, was 76.0% (001), 97.5% (004) and 93.5% (006). Due to the proliferation and viability data, the TCR-1367 T cells (patient 001) were not considered for therapy.

To evaluate safety and efficacy of TCR-1367 T cells, we conducted a one-armed, single-center, open-label, phase 1 clinical trial (EudraCT: 2017-001208-30). The summarized study design is shown in Fig. 3A. The main inclusion criteria were age ≥18 years, relapsed and/or refractory disease requiring therapy, at least 3 prior lines of therapy, HLA-A*02:01 genotype, and at least 30% of MAGE-A1+ MM cells assessed by IHC. The primary objective was to evaluate the safety and tolerability of TCR-1367 T cells. It was planned to enroll 12 patients in four cohorts with ascending doses of TCR-1367 T cells (10^5; 10^6; 10^7 and $5x10^7$ cells/kg body weight (BW) ± 20%). However, based on limited recruitment potential upon availability of BCMA-CAR-T cells, and competing clinical studies investigating BiTEs, the trial was closed by the sponsor after treating 2 patients (patients 004 and 006). All patients provided written informed consent and the trial was approved by the local ethical committee in Berlin, Germany (17/0259-EK13). The study was conducted in accordance with principles of good clinical practice and the Declaration of Helsinki. The patient characteristics are shown in Suppl. Table 2. Both patients were treated in the first dosing cohort and were eligible for safety and efficacy analysis. The time between apheresis to application of TCR-1367 T cells was 64d (004) and 55d (006). Altogether, we observed 18 treatment-emergent adverse events (TEAEs) in the 2 patients with 11 classified as possibly study treatment related. Four of the TEAEs were CTCAE (version 4.03)[13] grade 3 or 4 and two were serious AEs (febrile neutropenia and cancer pain), both likely related to chemotherapy and disease progression, respectively. All AEs are listed in Suppl. Table 3. The best response according to the IMWG criteria[14] was minimal response for patient 004, while patient 006 experienced progressive disease. The time to next treatment was 110 days for patient 004 and 64 days for patient 006. In patient 004, the proportion of MAGE-A1+ MM cells subsequently decreased from 80% to 60% to 30% 3 months after administration of TCR-1367 T cells (Fig. 3B). MM cell infiltration decreased from 60% to 40%. However, the fraction of MAGE-A1+ MM cells started to rise again seven months after the administration of TCR-1367 T cells, reaching 40% (Fig. 3B). As shown in Fig. 3C for patient 006, no measurable effect of the TCR-1367 therapy on the MAGE-A1 expression was found. Patient 004 achieved a complete response under following BiTE treatment and is still alive 35 months after administration of TCR-1367 T cells. Patient 006 further progressed and died three months after receiving the study treatment from myeloma progression and disease-related pancytopenia with an infection of unknown focus, considered not related to the study treatment, resulting in an OS of 91 days. No TCR-1367 T cells could be detected by flow cytometry or qPCR in pharmacokinetics samples, possibly due to the low cell number administered.

MAGE-A1, identified as a frequently expressed antigen in MM in our diagnostic study, could emerge as a valuable new target, especially considering loss of commonly targeted antigens like BCMA and GPRC5D under current therapies[6]. MAGE-A1 expression was associated

with EMD and lower OS, aligning with findings in other MM patient cohorts[3,15]. In the phase 1 clinical trial investigating MAGE-A1-directed TCR-1367 T cells, we treated only two patients due to premature closure of the trial by the sponsor, making it impossible to provide conclusive safety and efficacy data. While we observed no severe TEAEs, durable responses were not achieved, possibly due to the low dose of TCR-1367 T cells administered in the first dose cohort ($1x10^5$ cells/kg BW).

In conclusion, MAGE-A1 is an antigen expressed by a subset of MM patients associated with advanced disease and EMD. MAGE-A1-directed TCR-1367 therapy appears feasible for the tested dose in this patient group. Further clinical studies are required within the multirefractory patient population, especially those relapsing after currently approved T cell redirecting therapies.

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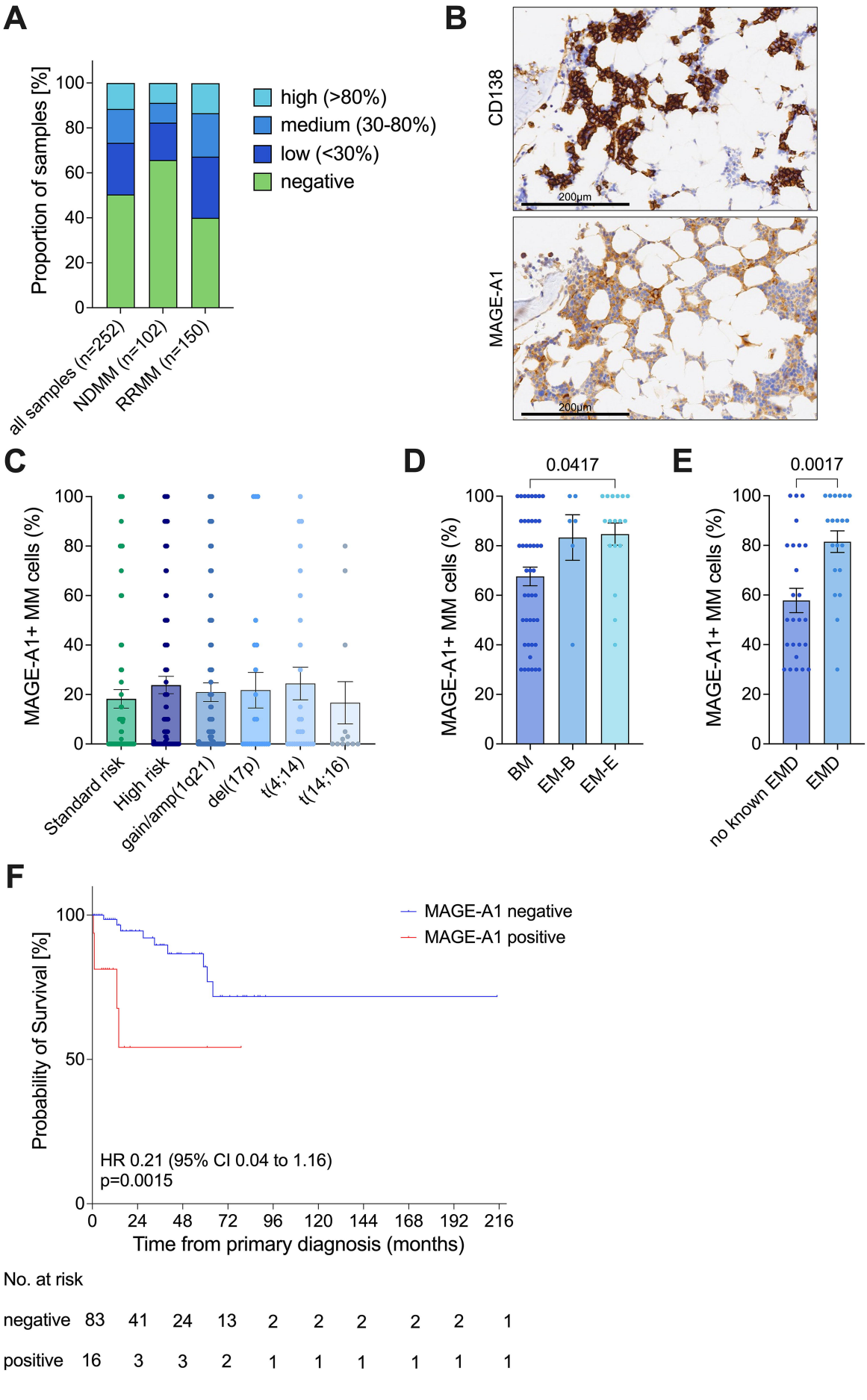
FIGURE LEGENDS

Figure 1. MAGE-A1 expression in multiple myeloma (MM) patient samples is associated with extramedullary disease (EMD) and is a risk factor for overall survival. A. Samples were classified according to the fraction of MAGE-A1+ MM cells (negative; low = 1-29%; medium = 30-80%; high = >80%). Proportion of the different categories of MAGE-A1 expression shown for all samples, NDMM and relapsed/refractory MM (RRMM). **B.** Representative immunohistochemistry staining of MM bone marrow (BM) samples with mAb MA454 and anti-CD138 of a patient with newly diagnosed MM (NDMM). BM is infiltrated with 30% of MM cells of which overall 10-20% are MAGE-A1+. **C.** Proportion of MAGE-A1+ MM cells categorized according to the patients cytogenetics results. Mean and SEM shown. Kruskal-Wallis-test. **D.** Proportion of MAGE-A1+ MM cells depending on sample type in MAGE-A1 positive samples (at least 30% positive MM cells). **E.** Proportion of MAGE-A1+ MM cells depending on the presence of EMD at any time of disease course in MAGE-A1 positive BM samples. **F.** Kaplan-Meier-curves of patients with MAGE-A1 expression (at least 30% positive myeloma cells) and without (<30% positive myeloma cells) at time point of newly diagnosed multiple myeloma.

Figure 2. Production of TCR-1367 T cells and product characteristics. A. Flow chart of manufacturing process of MAGE-A1 directed TCR-1367 T cells. TCR-T1367 sequence was isolated from ABabDII mice (transgenic for the human TCRα/β gene loci and human leukocyte antigen HLA-A*02:01) vaccinated with the MAGE-A1-derived nonamer epitope MAGE-$A1_{278-286}$. IPC=in process control. Created with BioRender.com. **B.** FACS results for the 3 patient cell products to different time points during manufacturing process. Data shown is pregated for CD45+/7-ADD- cells. **C.** Proliferation rate of living cells from d2 to harvest (d12/13), proliferation normalized to cell number from d2. Data shown from the three patients cell products and three validation runs. **D.** Correlation of proliferation rate from d2 to d5 with transduction rate of final cell product from the three patients cell products and three validation runs with simple linear regression.

Figure 3. Phase 1 clinical trial of MAGE-A1 directed TCR-1367 T cells. A. Study design of the phase 1 clinical trial with scheduled sample collection for myeloma response evaluation and pharmacokinetic (PK) analysis. Created with BioRender.com. **B.** Time-coursed MAGE-A1 expression of myeloma cells of clinical trial patient 004 before and after the TCR-1367 T cell administration in bone marrow. Representative immunohistochemistry staining (CD138, MAGE-A1) of sample before (left) and after (right) the TCR-1367 T cell administration. Before myeloma infiltration is overall 60%, shown is an area with higher

myeloma cell infiltration with 80% of cells positive for MAGE-A1. The after sample has 40% myeloma cell infiltration with a decrease to 30% of MAGE-A1 positive myeloma cells. **C.** Time-coursed MAGE-A1 expression of myeloma cells of clinical trial patient 006 before and after the TCR-1367 T cell administration in BM and bone-associated extramedullary (EM-B) samples.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60
40
20
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medium (30-80%)
low (<30%)
negative
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NDMM (n=102)
RRMM (n=150)
B
CD138
MAGE-A1
200µm
200µm
C
MAGE-A1+ MM cells (%)
Standard risk
High risk
gain/amp(1q21)
del(17p)
t(4;14)
t(14;16)
D
0.0417
MAGE-A1+ MM cells (%)
BM
EM-B
EM-E
E
0.0017
MAGE-A1+ MM cells (%)
no known EMD
EMD
F
MAGE-A1 negative
MAGE-A1 positive
Probability of Survival [%]
HR 0.21 (95% CI 0.04 to 1.16)
p=0.0015
0
24
48
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No. at risk
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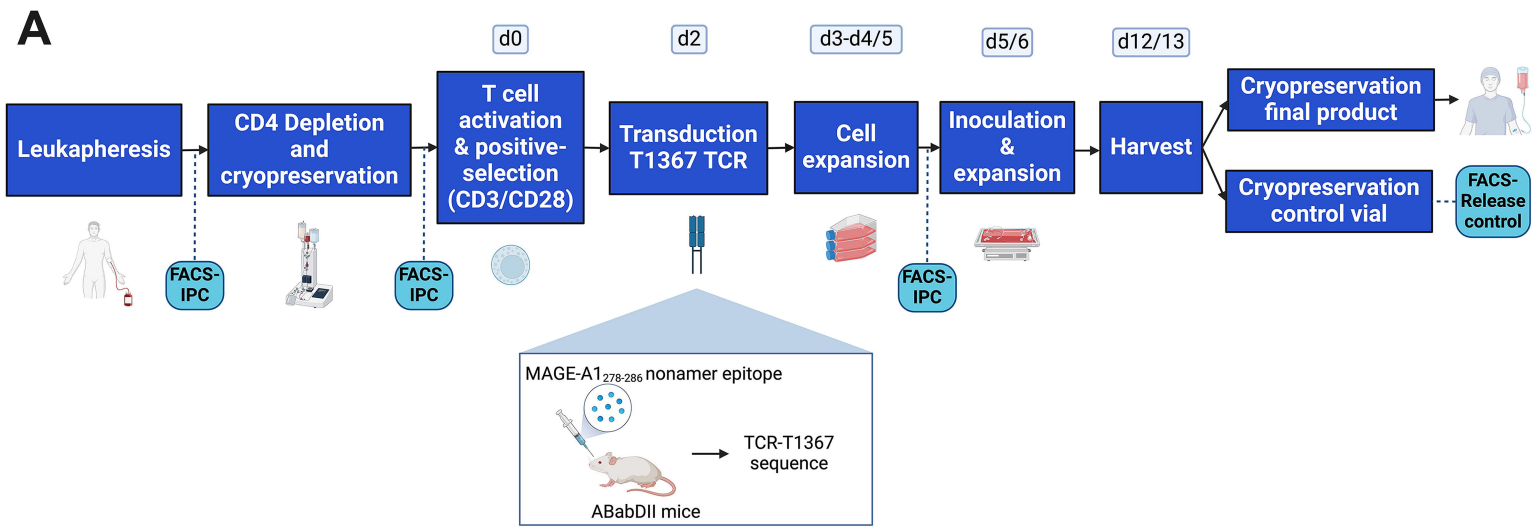
positive 16 3 3 2 1 1 1 1 1 1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d3-d4/5
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d12/13
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CD4 Depletion and cryopreservation
T cell activation & positive-selection (CD3/CD28)
Transduction T1367 TCR
Cell expansion
Inoculation & expansion
Harvest
Cryopreservation final product
Cryopreservation control vial
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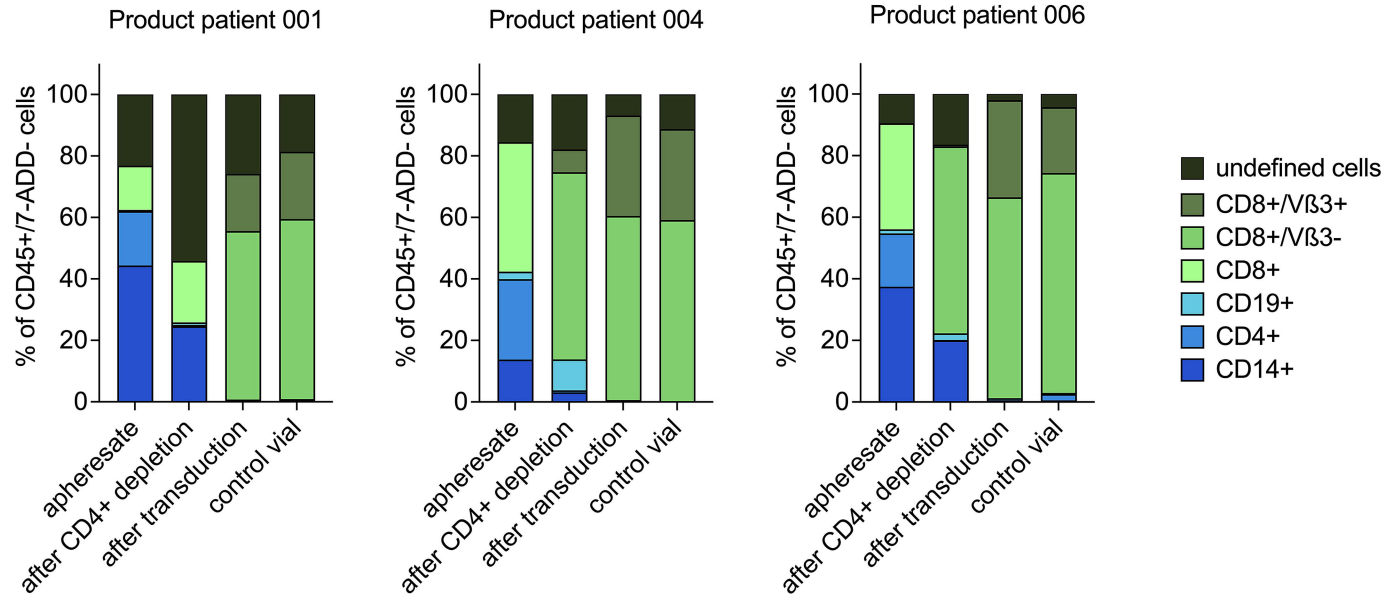
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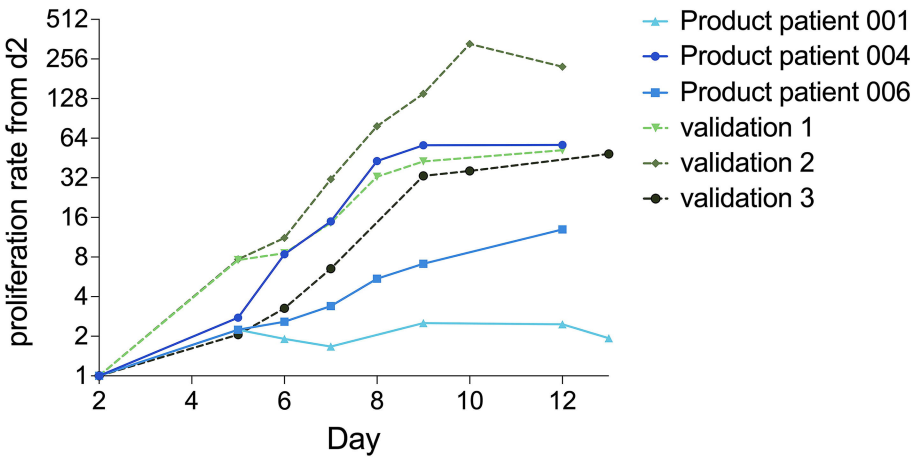
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16
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Product patient 001
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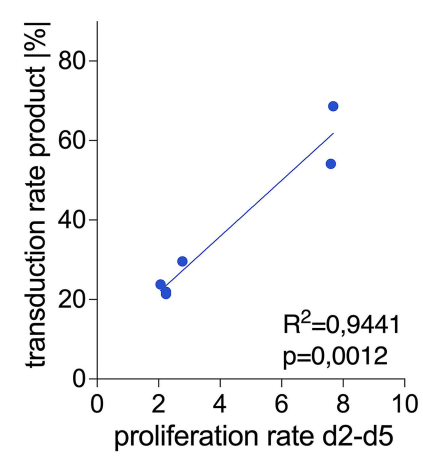
validation 1
validation 2
validation 3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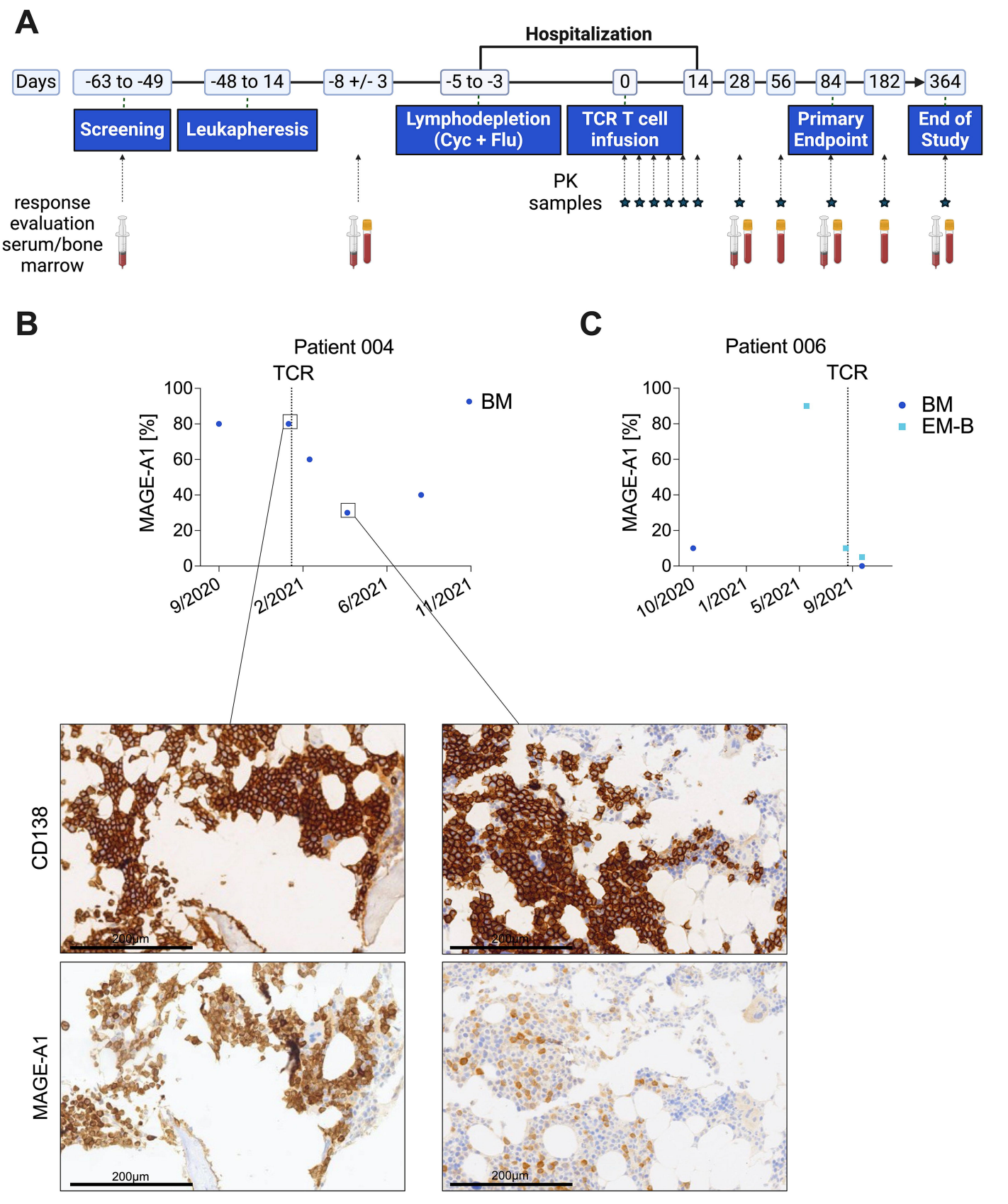
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-48 to 14
-8 +/- 3
-5 to -3
0
14
28
56
84
182
364
Screening
Leukapheresis
Lymphodepletion (Cyc + Flu)
TCR T cell infusion
Primary Endpoint
End of Study
response evaluation serum/bone marrow
PK samples
B
Patient 004
TCR
BM
MAGE-A1 [%]
100
80
60
40
20
0
9/2020
2/2021
6/2021
11/2021
C
Patient 006
TCR
BM
EM-B
MAGE-A1 [%]
10/2020
1/2021
5/2021
9/2021
CD138
MAGE-A1
200µm

A phase I study of MAGE-A1-targeted T1367 T-cell receptor-based cell therapy in patients with advanced multiple myeloma

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Supplementary Data:

Supplementary Tables

SUPPLEMENTARY TABLES

Supplemental Table 1. Patient characteristics of the diagnostic MAGE-A1 expression study.

	n (%)
all patients	213 (100)
female	75 (35)
Disease stage	
first diagnosis	92 (43)
relapse	114 (54)
sequentially primary and relapse	7 (3)
Occurrence of EMD at any time of disease	84 (39)
EM-B	66 (31)
EM-E	18 (9)
FiSH results available	131 (62)
standard risk	59 (28)
high risk, defined as...	72 (34)
Gain(1q21) or amplification(1q21)	55 (26)
del(17p)	18 (8)
t(4;14)	21 (10)
t(14;16)	7 (3)

EMD: extramedullary disease

EM-B: bone-related extramedullary myeloma

EM-E: extraosseous extramedullary myeloma

Supplemental Table 2. Phase 1 study of TCR-1367 T cells, patient characteristics.

Patient ID	**004**	**006**
Sex	female	male
Age	57	62
EMD	no	yes (EM-B)
MAGE-A1+ myeloma cells in BM at screening |%|	80%	90%
Cytogenetics/FiSH	standard risk	high risk (+1q21)
Lines of previous therapies	4	7
Refractory status		
IMiDs	yes	yes
PI	yes	yes
any anti-CD38 antibody	yes	yes
any anti-BCMA directed therapy	no	yes

EMD: extramedullary disease

BM: bone marrow

IMiDs: immunomodulatory drugs

PI: proteasome inhibitors

BCMA: B-cell maturation antigen

Supplemental Table 3. Phase 1 study of TCR-1367 T cells, adverse events.

Patient 004			
Term	**Grade**	**TEAE?**	**Causality to T-cell therapy**
Nausea	2	no	Not related
Pyrexia	1	no	Not related
Pain in extremity	1	yes	Possible
Arthralgia	1	yes	Possible
Cancer pain	1	yes	Possible
Sinus tachycardia	1	yes	Possible
Pyrexia	1	yes	Possible
Pyrexia	1	yes	Possible
Chest pain	1	yes	Possible
Neutropenia	4	yes	Possible
Anemia	2	yes	Possible
Anemia	2	yes	Possible
White blood cell count decreased	2	yes	Not related
White blood cell count decreased	4	yes	Possible

Patient 006			
Term	**Grade**	**TEAE?**	**Causality to T-cell therapy**
Anemia	3	no	Not related
Platelet count decreased	4	no	Not related
Urinary tract infection	2	no	Not related
White blood cell count decreased	3	no	Not related
Nausea	2	no	Not related
Lymphocyte count decreased	4	no	Not related
Dry mouth	1	no	Not related
Depression	2	yes	Not related

Petechiae	1	yes	Not related
Neoplasm progression	1	yes	Not related
Neoplasm progression	3	yes	Not related
Mouth hemorrhage	1	yes	Not related
Monoparesis	3	yes	Not related

TEAE: treatment-emergent adverse events