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EASIX-guided risk stratification for complications and outcome after CAR T-cell therapy with ide-cel in relapsed/refractory multiple myeloma

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ABSTRACT

Background Chimeric antigen receptor (CAR) T-cell therapy has demonstrated significant benefits in the treatment of relapsed/refractory multiple myeloma (RRMM). However, these outcomes can be compromised by severe complications, including cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome (ICANS) and immune effector cell-associated hematotoxicity (ICAHT), predisposing for life-threatening infections.

Methods This retrospective observational study examined a total of 129 patients with RRMM who had received idecabtagene vicleucel (ide-cel) at two major myeloma centers in Germany and one center in the USA to assess the Endothelial Activation and Stress Index (EASIX) as a risk marker for an unfavorable clinical course and outcome after CAR T-cell therapy. EASIX is calculated by lactate dehydrogenase (U/L) × creatinine (mg/dL) / platelets (10^9 cells/L) and was determined before lymphodepletion (baseline) and at the day of CAR T-cell infusion (day 0). The analysis was extended to EASIX derivatives and the CAR-HEMATOTOX score.

Results An elevated baseline EASIX (>median) was identified as a risk marker for severe late ICAHT, manifesting with an impaired hematopoietic reconstitution and pronounced cytopenias during the late post-CAR-T period. Patients with high EASIX levels (>upper quartile) were particularly at risk, as evidenced by an increased rate of an aplastic phenotype of neutrophil recovery, severe late-onset infections and ICANS. Finally, we found associations between baseline EASIX and an inferior progression-free and overall survival. Moreover, the EASIX at day 0 also demonstrated potential to serve as a risk marker for post-CAR-T complications and adverse outcomes.

Conclusions In conclusion, EASIX aids in risk stratification at clinically relevant time points prior to CAR T-cell therapy with ide-cel. Increased EASIX levels might help clinicians to identify vulnerable patients to adapt peri-CAR-T management at an early stage.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The Endothelial Activation and Stress Index has emerged as a prognostic marker in various hematologic neoplasms and therapies. Most recently, the EASIX has been demonstrated to predict the development of severe cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome (ICANS) following CD19-directed chimeric antigen receptor (CAR) T-cell therapy.

WHAT THIS STUDY ADDS

⇒ This is the first study investigating the EASIX as a risk marker for complications and adverse outcomes following anti-B-cell maturation antigen (BCMA) CAR T-cell therapy with idecabtagene vicleucel. We also describe for the first time associations with hematotoxicity and extend our model to other scoring systems and key pre-CAR-T time points for clinical decision-making. In summary, we found associations between EASIX and severe post-CAR-T cytopenias, late-onset infections, ICANS, inferior progression-free and overall survival.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our EASIX model has the potential to serve as a simple and rapid screening tool for identifying patients at risk for a broad spectrum of post-CAR-T complications and inferior outcomes, who could benefit from more intensive monitoring, prophylaxes and supportive measures. Future studies should further evaluate EASIX-guided risk stratification prior to other cellular and antibody-based immunotherapies.

BACKGROUND

Chimeric antigen receptor (CAR) T-cell therapy revolutionizes the treatment landscape of relapsed/refractory multiple

myeloma (RRMM). Idecabtagene vicleucel (ide-cel) is an autologous anti-B-cell maturation antigen (BCMA) targeting CAR T-cell product. The efficacy and safety of ide-cel in RRMM has been demonstrated in clinical trials[1 2] and in the real-world setting.[3]

The success of CAR T-cell therapy is hampered by the potential risk for severe toxicities including cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS) and immune effector cell-associated hematotoxicity (ICAHT).[4–6] High-grade clinical manifestations of CRS and ICANS after CAR T-cell therapy with ide-cel are rare (5% and 3% grade ≥3 in the phase II trial, respectively),[1] but potentially life-threatening due to circulatory instability, hypoxia or neurological deficits. ICAHT represents the most common CAR T-cell-associated adverse effect and can manifest with severe, protracted and recurrent cytopenias during the early (≤30 days) and/or late (>30 days) post-CAR-T period.[6 7] As the severity of ICAHT is closely linked to prolonged hospitalization and severe infections, the most common cause of non-relapse mortality, it is important to identify risk factors and key drivers of this complication.[5 7–9] An important step towards a reliable risk stratification has been achieved through implementation of the CAR-HEMATOTOX score by Rejeski and colleagues.[5] The score was developed to predict the duration of severe neutropenia in patients with relapsed/refractory large B-cell lymphoma undergoing anti-CD19 CAR T-cell therapy.[5] Recent studies, however, suggested applicability to a broader context, including anti-BCMA CAR T-cell therapy.[10 11]

Additional markers and scoring systems could further improve and facilitate risk stratification and help identify the full spectrum of patients at risk for adverse clinical outcomes after CAR T-cell therapy. Many severe complications following immunotherapies have been reported to be associated with endothelial dysfunction.[12 13] The Endothelial Activation and Stress Index (EASIX) includes high lactate dehydrogenase (LDH), high creatinine and low platelet counts as validated indicators for endothelial dysfunction and is calculated with the simple formula LDH (U/L) × creatinine (mg/dL) / platelets (10^9 cells/L).[12 14–16] The EASIX was originally developed to predict overall survival (OS) in patients with acute graft-versus-host disease,[14] but has since been reported as a prognostic marker in the context of allogeneic stem-cell transplantation in general,[15] sepsis,[16] myelodysplastic syndrome[17] and multiple myeloma.[18] Several groups have demonstrated the potential of the EASIX and its variants to predict the risk for severe CRS, ICANS and inferior survival following CAR T-cell therapy in patients with B-cell neoplasias.[12 19–22] Moreover, recent data points to a link between an aplastic phenotype of neutrophil recovery and progressive endothelial dysfunction.[13]

So far, associations between EASIX and post-CAR-T cytopenias as well as the potential of EASIX-based risk stratification in the context of anti-BCMA CAR T-cell therapy remain unexplored. Moreover, a comparative analysis of the EASIX and other scores as a risk marker at different time points prior to ide-cel infusion has not yet been conducted. Therefore, the aim of this study was to address this knowledge gap and assess the EASIX as a risk marker for major complications and adverse outcomes following BCMA-directed CAR T-cell therapy with ide-cel.

METHODS

Patient selection and data collection

This multicenter retrospective observational study included a total of 129 patients with RRMM. Until May 2023, 63 patients had received ide-cel at Heidelberg University Hospital (n=30) or University Hospital of Würzburg (n=33) (German cohort), and 66 patients at the Dana-Farber Cancer Institute (US cohort). Data cut-off was 25 September 2023. All patients with available data were included in the further analysis. Patients had received prior lymphodepletion with fludarabine/cyclophosphamide (n=125) or bendamustine (n=4). Institutional standard operating procedures for post-CAR-T prophylaxes and toxicity management are listed in online supplemental table S1. Clinical data were extracted from the electronic patient management software and the original medical records whenever available. Laboratory values prior to lymphodepletion and at the day of CAR-T-cell infusion (day 0) were collected with a leniency period of up to 5 and 2 days, respectively. The observation period for post-CAR-T complications between day 0 and day 30 was referred to as the early post-CAR-T period, and the period between day 31 and 90 was referred to as the late post-CAR-T period.[6 9] For analysis of post-CAR-T cytopenias, all patients with repetitive blood cell count measurements (≥2 time points) were included, irrespective of the cause of cytopenia. Missing data on complications were due to an incomplete follow-up period, external follow-up with limited data access or loss to follow-up and are detailed in online supplemental table S3. Study results were reported according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for cohort studies.

Classifications and grading systems

Clinical response, disease stage, drug refractoriness and prior lines of therapy were defined according to international guidelines.[23–25] Extramedullary disease manifestations were classified as bone-associated or extraosseous, bone-independent soft tissue masses.[26] High risk cytogenetic abnormality was defined by the presence of del(17p), t(4;14) and/or t(14;16) as described in previous publications.[1 3] Chromosome 1q gain/amplification was included if explicitly mentioned.[27] CRS and ICANS were graded as recommended by the American Society for Transplantation and Cellular Therapy.[4] Cytopenias and infections were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) V.5.0. CTC grade ≥3 thrombocytopenia (platelets <50 x 10^9/L), anemia (hemoglobin <80g/L) and infections were

defined as severe. Late neutropenia was further specified based on the absolute neutrophil count (ANC) cut-offs for late ICAHT in the current consensus guidelines.[6] Severe late ICAHT included grade 3 and 4.[6] The phenotypes of neutrophil recovery (*quick*, *intermittent*, *aplastic*) were defined according to Rejeski *et al*.[5] Causes of death and non-relapse mortality were classified as previously described.[8 28]

Scores

The EASIX and its derivatives (modified EASIX [m-EASIX], EASIX-F and EASIX-FC) were determined according to the literature.[14 19 20] Log_2-transformed values were used for the primary statistical analysis and data visualization if necessary.[14 15] The median or upper quartile (Q_3) was used to form EASIX groups, with rounding to the second decimal place. The CAR-HEMATOTOX score (CAR-HTX) was determined according to Rejeski *et al*.[5] A score <2 was considered as low, a score ≥2 as high.[5]

Statistical analysis

R (V.4.4.1), GraphPad Prism (V.10.2.3) and Microsoft Excel (V.16.87) were used for statistical data analysis and visualization. The entire dataset with all cohorts was used for the primary analyses.[29] Statistical tests and subgroup analyses were applied to examine differences between the German and US cohorts. Non-parametric Mann-Whitney test was used to compare continuous variables. Percentages were compared with Fisher's exact test. Longitudinal laboratory markers were compared between groups using a linear mixed model with random patient effect and group, time and group–time interaction as fixed effects. Contrast tests based on estimated marginal means were used to compare groups across time points, at individual time points and for interaction between group and time points. P values of pairwise group comparisons were adjusted for multiple testing using Tukey's method, and for testing at individual time points, p values were additionally adjusted using Holm's method. Univariate and multivariate logistic regression analyses were performed using binary or continuous variables. Correlations between continuous variables were described by Spearman correlation coefficient (r). Simple linear regression was used to visualize data and obtain a best-fit line. Receiver operating characteristic (ROC) curve analysis was used to evaluate test characteristics. Optimal cut-off values were selected according to the highest Youden Index. Survival data were analyzed by univariate and multivariate Cox regression and log-rank test. All p-values were two-sided and considered as statistically significant at p<0.05.

RESULTS

Patient and disease characteristics

Patient and disease characteristics are listed in table 1.

In the total cohort (n=129), the median age at CAR T-cell therapy was 64 years (range: 34–83). Forty-two (33%) patients were female. Of the patients with available data, 9% had ISS stage III (n=10/108), 40% had high risk cytogenetic aberrations (n=49/123), 20% had a bone marrow infiltration ≥50% (n=14/71) and 38% had extramedullary disease (n=48/126), including 16 (13%) cases of bone-associated and 32 (25%) cases of extraosseous soft tissue masses. Patients had received a median of five prior therapy lines. Triple-class and penta-drug refractory disease were found in 107 (83%) and 41 (32%) patients, respectively. Patient-related and disease-related differences between the German and US cohorts are outlined in table 1. Of note, official approval requirements for ide-cel and general treatment algorithms are different in both countries.

Efficacy

CAR T-cell therapy with ide-cel induced an overall response rate of 78% (n=101) (online supplemental figure S1A; online supplemental table S2). Forty-seven (36%) patients achieved a complete response or better. At a median follow-up of 9.6 months (95% CI: 7.9 to 11.6), the median progression-free survival (PFS) was 8.6 months (95% CI: 6.7 to 11.9), and the median OS was not reached (online supplemental figure S1D, E). Efficacy results were comparable between the German and US cohorts (online supplemental figure S1; online supplemental table S2).

CRS and ICANS

Detailed information on post-CAR-T complications, supportive and prophylactic measures are provided in online supplemental table S3. One hundred and nine patients (84%) experienced CRS, including mostly grade 1 (n=67; 52%) and grade 2 (n=41; 32%) events (figure 1A). One (1%) patient was affected by CRS grade 3. The US cohort showed a trend towards less pronounced CRS events (p=0.04). ICANS was reported in 11 (9%) patients, including three grade 3 events (2%) and one grade 4 event (1%) (figure 1B). Tocilizumab and dexamethasone were administered in 66 (51%) and 57 (44%) patients, respectively.

Cytopenias

Baseline cytopenias prior to lymphodepletion are summarized in online supplemental table S4 and were mostly limited to CTC grades 1–2. An overview of the frequency and CTC grades of post-CAR-T cytopenias is given in online supplemental table S5. Interestingly, the US cohort had a lower rate of CTC grade ≥3 neutropenia during the early post-CAR-T period (65% vs 92%; p=0.0006), with concurrent evidence of a higher rate of early (p=0.0009) and prophylactic (p<0.0001) granulocyte colony-stimulating factor (G-CSF) use. A significant proportion of patients showed high-grade cytopenias during the late post-CAR-T period, with CTC grade ≥3 neutropenia, anemia and thrombocytopenia occurring in 39% (n=42/107), 14% (n=15/109) and 34% (n=37/109) of evaluable patients in the total cohort, respectively.

Table 1 Patient and disease characteristics

	Total cohort n=129	German cohort n=63	US cohort n=66	P
Age, years				
Median (range)	64 (34–83)	60 (34–77)	66 (35–83)	**0.007**
≥70, No. (%)	36 (28)	14 (22)	22 (33)	0.17
Sex, No. (%)				
Male	87 (67)	45 (71)	42 (64)	0.36
Female	42 (33)	18 (29)	24 (36)	
ECOG*, No. (%)				
0–1	111 (96)	63 (100)	48 (91)	**0.02**
2–3	5 (4)	0 (0)	5 (9)	
Unknown	13	0	13	
ISS stage*, No. (%)				
I	63 (58)	37 (71)	26 (46)	**0.03**
II	35 (32)	11 (21)	24 (43)	
III	10 (9)	4 (8)	6 (11)	
Unknown	21	11	10	
R-ISS stage*, No. (%)				
I	24 (23)	18 (35)	6 (11)	**0.009**
II	75 (71)	31 (61)	44 (81)	
III	6 (6)	2 (4)	4[7]	
Unknown	24	12	12	
Extramedullary disease*, No. (%)				
Yes	48 (38)	30 (50)	18 (27)	**0.01**
Bone-associated	16 (13)	13 (22)	3 (5)	
Extraosseous	32 (25)	17 (28)	15 (23)	
No	78 (62)	30 (50)	48 (73)	
Unknown	3	3	0	
Cytogenetics, No. (%)				
Standard risk	74 (60)	27 (45)	47 (75)	**0.0009**
High risk	49 (40)	33 (55)	16 (25)	
del(17p)	30 (24)	20 (33)	10 (16)	
t(4;14)	19 (15)	12 (20)	7 (11)	
t(14;16)	5 (4)	3 (5)	2 (3)	
High risk with 1q	74 (60)	44 (73)	30 (48)	**0.006**
1q+	54 (44)	30 (50)	24 (38)	
Unknown	6	3	3	
Bone marrow burden†, No. (%)				
<50%	57 (80)	20 (80)	37 (80)	>0.99
≥50%	14 (20)	5 (20)	9 (20)	
Unknown	58	38	20	
Prior lines of therapy, median (95% CI)	5 (5-6)	5 (5-6)	6 (5-6)	0.67
Prior therapies, No. (%)				
Double-class refractory‡	114 (88)	48 (76)	66 (100)	**<0.0001**
Triple-class refractory§	107 (83)	42 (67)	65 (98)	**<0.0001**
Penta-drug exposed¶	100 (78)	50 (79)	50 (76)	0.68

Continued

Table 1 Continued

	Total cohort n=129	German cohort n=63	US cohort n=66	P
Penta-drug refractory¶	41 (32)	11 (17)	30 (45)	**0.0007**
Autologous SCT	116 (90)	61 (97)	55 (83)	**0.02**
Allogeneic SCT	12 (9)	12 (19)	0 (0)	**0.0001**
BCMA-targeted therapy	22 (17)	4 (6)	18 (27)	**0.002**
Belantamab mafodotin	21 (16)	3 (5)	18 (27)	**0.0006**
Bispecific antibody	4 (3)	3 (5)	1 (2)	0.36
Teclistamab	2 (2)	1 (2)	1 (2)	>0.99
Talquetamab	2 (2)	2 (3)	0 (0)	0.24
Systemic bridging therapy**, No. (%)				
Yes	111 (86)	59 (94)	52 (79)	**0.02**
Immunomodulatory agent	50 (39)	36 (57)	14 (21)	**<0.0001**
Proteasome inhibitor	71 (55)	40 (63)	31 (47)	0.08
Anti-CD38 antibody	36 (28)	25 (40)	11 (17)	**0.006**
Classical cytotoxic agent	61 (47)	39 (62)	22 (33)	**0.002**
No	18 (14)	4 (6)	14 (21)	
Radiotherapy	2 (2)	0 (0)	2 (3)	0.50
Watch-and-wait	16 (12)	4 (6)	12 (18)	0.06
Lymphodepletion, No. (%)				
Fludarabine/cyclophosphamide	125 (97)	63 (100)	62 (94)	0.12
Bendamustine	4 (3)	0 (0)	4 (6)	
Vein-to-vein time, days, median (range)	49 (35–138)	56 (42–138)	45 (35–113)	**<0.0001**
Time from initial diagnosis to CAR T-cell therapy, years, median (range)	6.2 (0.6–17.6)	6.4 (1.4–17.6)	5.5 (0.6–14.4)	0.19

*Determined prior to lymphodepletion (baseline).
†Last bone marrow status determined within 90 days prior to CAR T-cell therapy.
‡Refractory to an immunomodulatory agent and a proteasome inhibitor.
§Refractory to an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 monoclonal antibody.
¶ Exposed/refractory to lenalidomide, pomalidomide, bortezomib, carfilzomib and daratumumab.
**Systemic treatment administered between leukapheresis and lymphodepletion (at least one drug).
BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; ECOG, Eastern Cooperative Oncology Group performance status; ISS, International Staging System; R-ISS, Revised International Staging System; SCT, stem cell transplant.

To further characterize late hematotoxicity, patients were classified according to the ICAHT consensus guidelines as described in the Methods section and based on late neutrophil counts (figure 1C). After day 30, 60% of the patients met the definition for late ICAHT (n=64/107) and 21% for severe late ICAHT (grade ≥3; n=22/107). Neutrophil recovery over time and the corresponding ANC nadir values for patients with grade 1–2, grade 3–4 or without late ICAHT are shown in figure 1D and online supplemental figure S2A. The severe late ICAHT group was characterized by a significantly impaired neutrophil recovery, which was already indicated during the early period and led to a pronounced, second drop after a short-term plateau. Since ICAHT grading is based solely on neutrophil counts, we also analyzed the corresponding recovery of platelet and hemoglobin levels over time (figure 1E, F). Similar to neutrophil recovery, we observed a lymphodepletion-associated drop, followed by a recovery tendency. Severe late ICAHT was associated with a pronounced second decline, characterized by significantly lower platelet (median 15 x 10^9/L vs 110 x 10^9/L; p<0.0001) (online supplemental figure S2B) and hemoglobin nadir values (median 84g/L vs 107 g/L; p<0.0001) (online supplemental figure S2C) compared with all others, resulting in a significantly increased rate of severe thrombocytopenia (77% vs 22%; OR: 11.81; 95% CI: 3.86 to 31.34; p<0.0001) and severe anemia (45% vs 6%; OR: 13.33; 95% CI: 3.70 to 41.59; p<0.0001). Average ANC, platelet and hemoglobin levels across time points were significantly different between all three groups. Moreover, there was a significant interaction between group and time points indicating different longitudinal patterns of blood cell counts, driven by the severe late ICAHT group. Further details are provided in online supplemental table S6. Compared with the other patients with available data (n=68), the severe late ICAHT

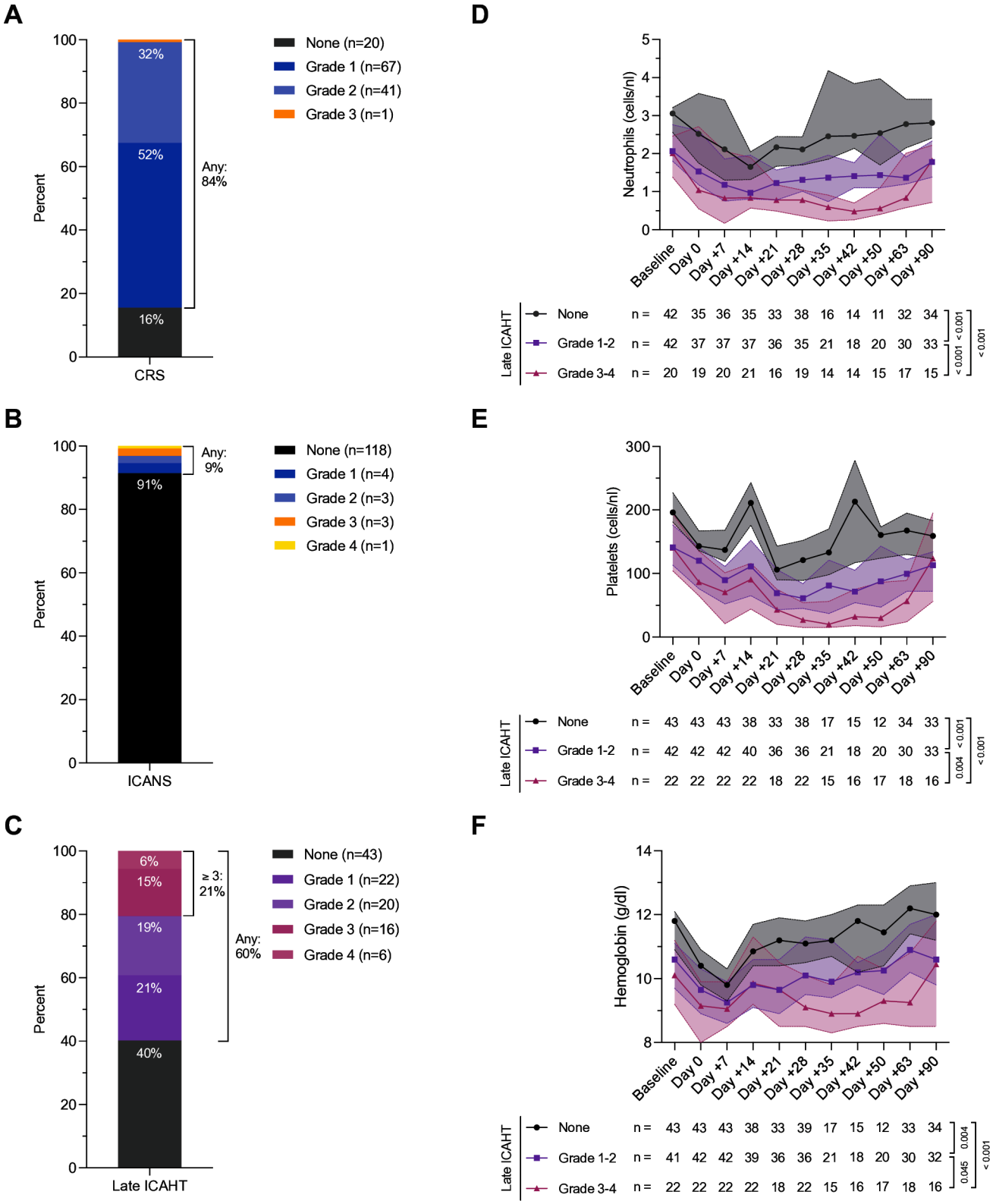

Figure 1 Frequency and severity of toxicities after CAR T-cell therapy in the total cohort. (A) CRS; (B) ICANS; (C) Late ICAHT. (D–F) Median absolute neutrophil count (D), platelet count (E) and hemoglobin levels (F) over time depending on late ICAHT grade. The filled area illustrates the corresponding 95% CIs. Measured events per group and time point are provided in the table below. P values are shown to the right of the table and refer to pairwise group comparisons across time points. Further statistical analyses using a linear mixed model are summarized in online supplemental table S6. Baseline, prior to lymphodepletion. Day 0, day of CAR T-cell infusion. CAR, chimeric antigen receptor; CRS, Cytokine-release syndrome; ICAHT, immune effector cell-associated hematotoxicity; ICANS, immune effector cell-associated neurotoxicity syndrome.

group (n=14) showed a significantly increased need for supportive measures after day 30, including G-CSF stimulation (71% vs 15%; p<0.0001), red blood cell transfusions (29% vs 4%; p=0.01) and platelet transfusions (36% vs 4%; p=0.003).

EASIX is associated with severe late cytopenias

To assess associations between baseline variables and late post-CAR-T cytopenias, we first determined the individual EASIX components, as well as blood cell counts, inflammatory and other laboratory parameters prior to lymphodepletion (baseline) and calculated the EASIX, its derivatives and the CAR-HEMATOTOX for all patients with available data (table 2). As ferritin values were not available for the US cohort, analyses of ferritin-based scores prior to lymphodepletion were restricted to the German cohort unless otherwise stated.

The median baseline EASIX was determined to be 1.26, the upper quartile (Q_3) was 2.15. Accordingly, the following groups were derived: >median (n=62) versus ≤median (n=64) and >Q_3 (n=31) versus ≤Q_3 (n=95), respectively. A comparison of patient and disease characteristics, complications and outcomes between baseline EASIX groups is provided in online supplemental tables S7 and S8. The main disease-related differences among patients with elevated (>median) or high (>Q_3) EASIX levels compared with the others included ISS/R-ISS stage, baseline cytopenias, glomerular filtration rate and the frequency of bridging therapies. The corresponding laboratory values and scores at day 0 are shown in online supplemental table S9.

When testing the correlation of the baseline EASIX components or the EASIX score with the late nadir values of ANC, platelets and hemoglobin, we found significant associations between the EASIX and all three endpoints (r=−0.39, p<0.0001; r=−0.52, p<0.0001; r=−0.38, p<0.0001) (figure 2A–C), whereas the correlations between the individual EASIX parameters and the nadirs were generally weaker. Correlation heatmaps including additional laboratory parameters and time points are shown in online supplemental figure S3. In a logistic regression model, the log_2-transformed baseline EASIX emerged as a significant predictor of late ICAHT (OR: 2.11; 95% CI: 1.33 to 3.65; p=0.004) and severe late ICAHT (grade ≥3) (OR: 1.51; 95% CI: 1.09 to 2.26; p=0.02). Detailed results of the univariate and multivariate analyses are presented in online supplemental tables S10 and S11. Baseline EASIX values were significantly higher in the severe late ICAHT group (n=21) compared with patients without severe late ICAHT (n=83) (median 1.78 vs 1.12; p=0.002) (figure 2D). The corresponding ROC analysis showed an area under the curve (AUC) of 0.72 (95% CI: 0.61 to 0.82; p=0.002), and the median baseline EASIX (1.26) as a cut-off achieved a sensitivity of 71% and a specificity of 58% (figure 2E). The group with an elevated baseline EASIX (>median; n=50/104) was characterized by a higher rate of late ICAHT (80% vs 43%; OR: 5.39; 95% CI: 2.16 to 13.42; p=0.0001) and severe late ICAHT (30% vs 11%; OR: 3.43; 95% CI: 1.24 to 9.76; p=0.03) (figure 2F). The impaired hematopoietic reconstitution in the elevated EASIX group is further illustrated by significantly lower ANC (median 0.96 x 10^9/L vs 1.71 x 10^9/L; p<0.0001), platelet (median 52 x 10^9/L vs 136 x 10^9/L; p<0.0001) and hemoglobin (median 99 g/L vs 109 g/L; p=0.003) nadir values during the late post-CAR-T period (figure 2G–I), resulting in a significantly higher rate of G-CSF stimulation (33% vs 14%; OR: 2.89; 95% CI: 1.00 to 7.41; p=0.05), severe late thrombocytopenia (50% vs 17%; OR: 5.00; 95% CI: 2.10 to 11.39; p=0.0004) and anemia (23% vs 6%; OR: 5.10; 95% CI: 1.43 to 17.61; p=0.01) (online supplemental table S7). Of note, associations between EASIX and severe late ICAHT were not restricted to the baseline time point, but also seen for the log_2-transformed EASIX at day 0 (OR: 1.79; 95% CI: 1.24 to 2.87; p=0.006) (online supplemental table S11). The corresponding ROC analysis showed a comparable AUC value (AUC: 0.77; 95% CI: 0.64 to 0.90; p=0.0004) to the baseline EASIX (figure 2E).

EASIX is associated with the neutrophil recovery phenotype

To further specify associations between EASIX and post-CAR-T cytopenias and consider qualitative differences in neutrophil recovery, we classified the evaluable 104 patients according to the three phenotypes recently proposed by Rejeski and colleagues.[5] Fifty (48%), 46 (44%) and 8 (8%) patients were assigned to the *quick*, *intermittent* and *aplastic* phenotype, respectively. A logistic regression analysis with an aplastic phenotype as a binary endpoint is shown in online supplemental table S12. Patients with an *aplastic* phenotype of neutrophil recovery showed significantly higher baseline EASIX values compared with all other patients (median 2.37 vs 1.22; p=0.004) (figure 3A). The corresponding ROC analysis demonstrated an AUC of 0.80 (95% CI: 0.67 to 0.93; p=0.005) (figure 3B). In the group with high baseline EASIX values (>Q_3), 21% of the patients (n=5/24) exhibited an aplastic phenotype, compared with 4% in the EASIX<Q_3 group (n=3/80) (OR 6.75; 95% CI 1.53 to 26.62; p=0.02) (figure 3C). When evaluating the test characteristics of the EASIX at day 0, we also observed a high AUC (AUC: 0.83; 95% CI 0.66 to 1.00; p=0.002) (figure 3B).

EASIX and CAR-HEMATOTOX score

Given the similar endpoint of both scores, we then compared the baseline EASIX values between the CAR-HTX^{low} (n=43) and CAR-HTX^{high} (n=13) groups in the German cohort and the patients in the US cohort who were attributable to the CAR-HTX^{high} group based on the available laboratory values (n=20). Patients in the CAR-HTX^{high} group showed significantly higher baseline EASIX values (median 2.07 vs 1.18; p=0.009 and median 3.15 vs 1.18; p=0.0001, respectively) (figure 3D). Moreover, we observed significant correlations between the baseline EASIX and the individual CAR-HTX scores (r=0.54; p<0.0001; n=52) (figure 3E), which were also

Table 2 Laboratory parameters and scores prior to lymphodepletion (baseline)

	Total cohort N=129	German cohort n=63	US cohort n=66	P
Laboratory parameters prior to lymphodepletion (baseline), median (range)				
LDH, U/L	213 (101–1717), n=126	228 (101–1131)	204 (117–1717), n=63	0.07
Creatinine, mg/dL	1.0 (0.40–4.13)	1.02 (0.40–1.77)	0.94 (0.49–4.13)	0.28
Platelet count, x10^9/L	168 (8–349)	178 (20–344)	149 (8–349)	0.22
Absolute neutrophil count, x10^9/L	2.54 (0.43–7.67), n=126	2.72 (0.76–7.67), n=60	2.49 (0.43–5.63)	0.18
Hemoglobin, g/L	108 (61–145), n=128	107 (75–143)	109 (61–145), n=65	0.87
CRP, mg/dL	0.27 (0.03–10.85), n=116	0.27 (0.1–5.21)	0.29 (0.03–10.85), n=53	0.91
Ferritin, ng/mL	198 (10–4494), n=58	143 (10–4494), n=55	2684 (1013–3869), n = 3[a]	
B2-MG, mg/L	2.9 (1.29–27.6), n=117	3.0 (1.5–7.9), n=52	2.8 (1.29–27.6), n=65	0.92
eGFR, mL/min	75 (16–117)	75 (38–114)	74 (16–117), n=65	0.58
>60, No. (%)	95 (74)	48 (76)	47 (71)	0.36
30–60, No. (%)	31 (24)	15 (24)	16 (24)	
<30, No. (%)	3 (2)	0 (0)	3 (5)	
Scores prior to lymphodepletion (baseline)				
EASIX, median (Q_1–Q_3)	1.26 (0.90–2.15), n=126	1.26 (0.93–1.80)	1.26 (0.87–2.73), n=63	>0.99
>median (>1.26), No. (%)	62 (49)	31 (49)	31 (49)	>0.99
>Q_3 (>2.15), No. (%)	31 (25)	11 (17)	20 (32)	0.10
Modified EASIX, median (Q_1–Q_3)	0.34 (0.19–1.10), n=115	0.34 (0.23–0.97)	0.36 (0.17–1.70), n=52	0.76
>6.2, No. (%)	11 (10)	5 (8)	6 (12)	0.54
EASIX-F, No. (%)				
Low	30 (50)	30 (55)	0 (0)	
Intermediate	22 (37)	21 (38)	1 (20)	
High	8 (13)	4 (7)	4 (80)	
Unknown	69	8	61[a]	
EASIX-FC, No. (%)				
Low	40 (69)	40 (73)	0 (0)	
Intermediate	11 (19)	10 (18)	1 (33)	
High	7 (12)	5 (9)	2 (67)	
Unknown	71	8	63[a]	
CAR-HEMATOTOX, No. (%)				
Low	43 (56)	43 (77)	0 (0)	
High	34 (44)	13 (23)	21 (100)	
Unknown	52	7	45[a]	

Due to missing data for the US cohort, further analyses of ferritin and ferritin-based scores prior to lymphodepletion were only performed for the German cohort, unless stated otherwise.
B2-MG, beta-2-microglobulin; CAR, chimeric antigen receptor; CRP, C reactive protein; EASIX, Endothelial Activation and Stress Index; eGFR, estimated glomerular filtration rate; LDH, lactate dehydrogenase; Q_1, first/lower quartile (25th percentile); Q_3, third/upper quartile (75th percentile).

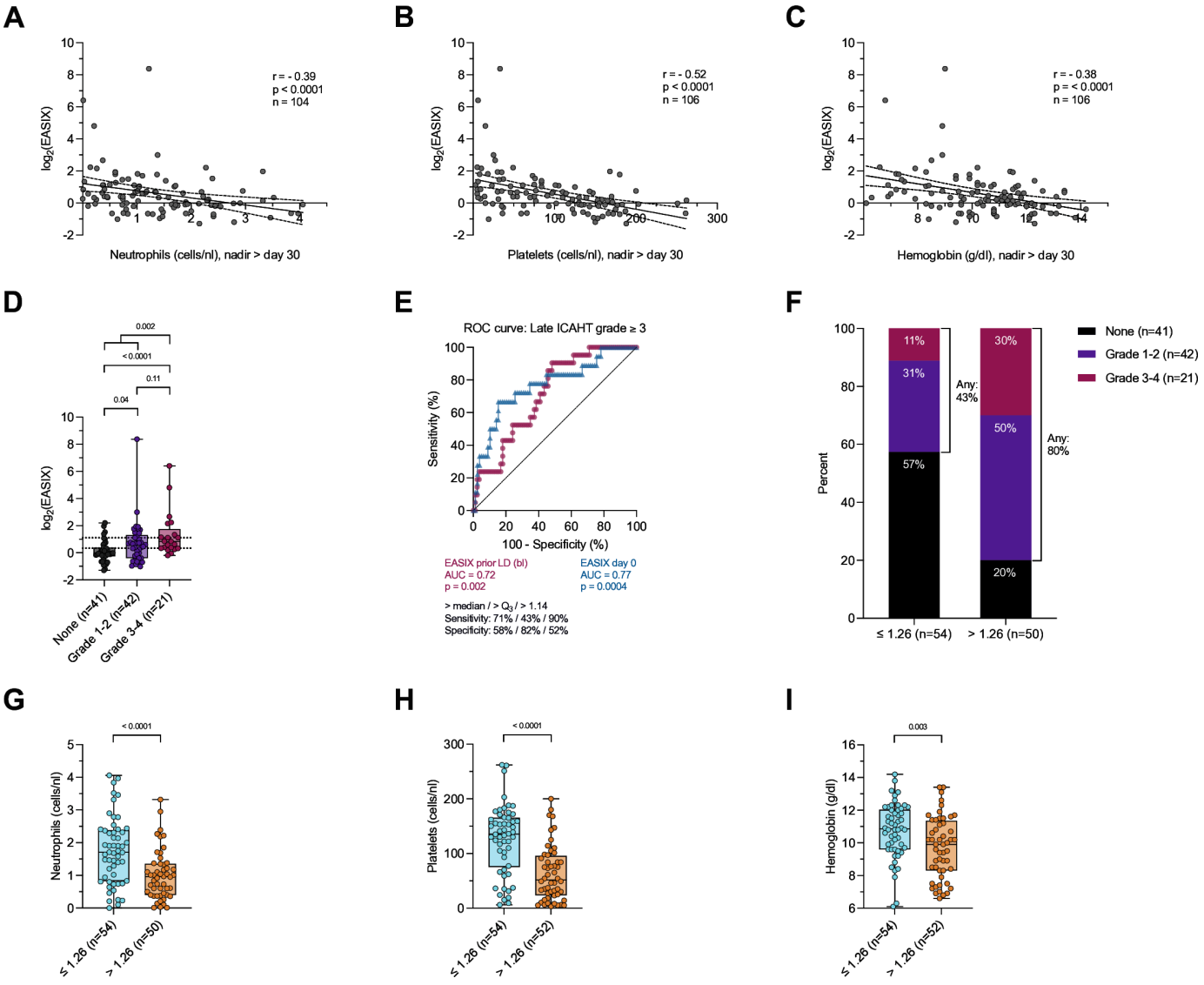

Figure 2 EASIX is associated with severe late cytopenias. (A–C) Graph showing the association between baseline log_2(EASIX) (prior to lymphodepletion) and late ANC (A), platelet count (B) and hemoglobin (C) nadir values. Best-fit line and 95% confidence bands were obtained by simple linear regression. Coefficient (r) and p values are based on Spearman correlation analysis. (D) Baseline log_2(EASIX) values depending on late ICAHT grade. Median (left to right): −0.03 vs 0.63 vs 0.83. P values of the group comparisons are shown at the top. The dashed lines indicate the median and the upper quartile of the baseline EASIX. (E) ROC curves to assess the potential of the baseline (bl) EASIX (prior to lymphodepletion (LD)) (red) and the EASIX at day 0 (day of CAR T-cell infusion) (blue) to identify patients at risk for severe late ICAHT (grade ≥3). AUC values, p values and sensitivity/specificity for selected baseline EASIX cut-off values (median, upper quartile [Q_3], optimal cut-off) are provided below. (F) Frequency and severity of late ICAHT depending on baseline EASIX group (≤median [≤1.26] vs >median [>1.26]). (G–I) Blood cell count nadir values during the late post-CAR-T period depending on baseline EASIX group (≤median [≤1.26] vs >median [>1.26]). P values of the group comparisons are shown at the top. Late ANC nadir values (G), median (left to right): 1.71/nL vs 0.96/nL. Late platelet count nadir values (H), median (left to right): 135.5/nL vs 51.5/nL. Late hemoglobin nadir values (I), median (left to right): 10.85 g/dL vs 9.90 g/dL. ANC, absolute neutrophil count; AUC, area under the curve; CAR, chimeric antigen receptor; EASIX, Endothelial Activation and Stress Index; ICAHT, immune effector cell-associated hematotoxicity; ROC, receiver operating characteristic.

seen at day 0 (r=0.56; p<0.0001; n=92). Significantly increased rates of high CAR-HTX scores were found when comparing evaluable patients with an elevated baseline EASIX (>median; n=11/28; 39%) and an EASIX ≤median (n=2/28; 7%) (OR: 8.41; 95% CI: 1.83 to 40.28; p=0.01) or a high baseline EASIX (>Q_3; n=6/10; 60%) and an EASIX ≤Q_3 (n=7/46; 15%) (OR: 8.36; 95% CI: 2.03 to 30.19; p=0.007), respectively (figure 3F; online supplemental table S7).

Detailed information on associations between the CAR-HTX score at different time points and the post-CAR-T clinical course are provided in online supplemental tables S10 - S18. Despite partial overlaps between CAR-HTX- and EASIX-based groups prior to lymphodepletion,

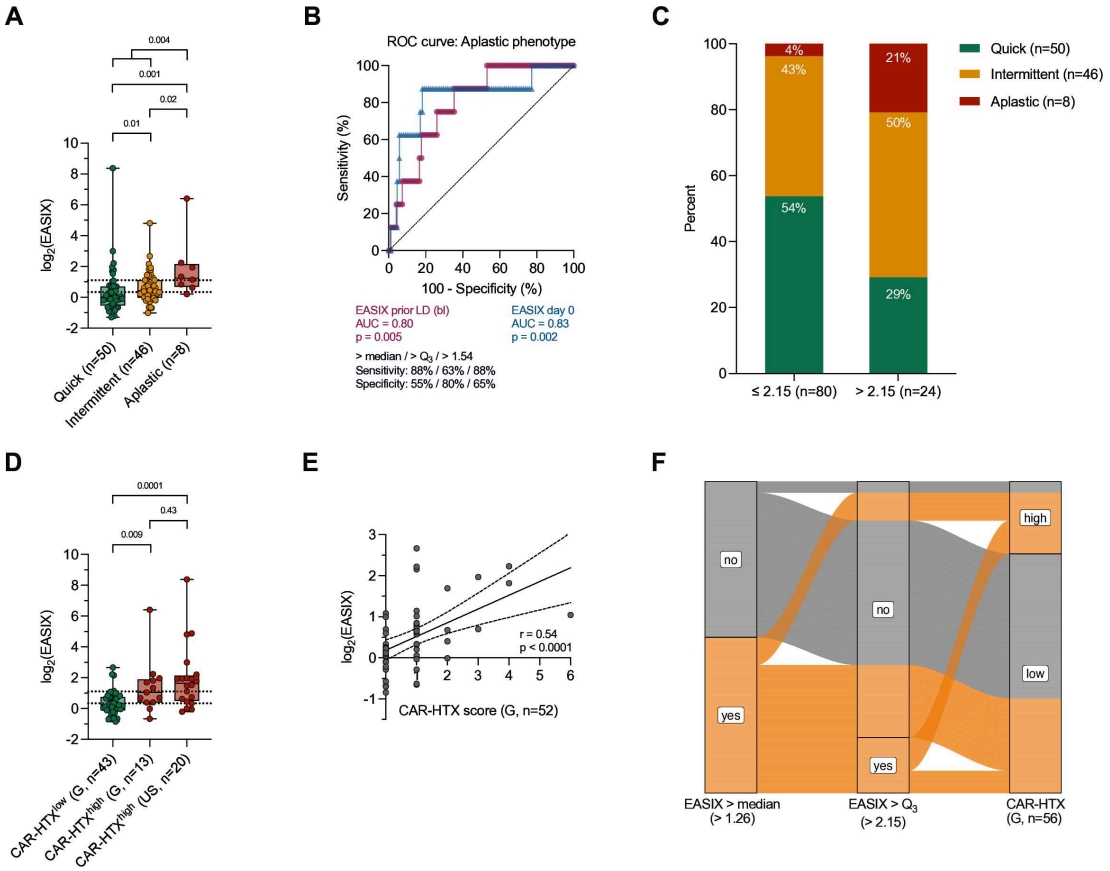

Figure 3 EASIX is associated with the neutrophil recovery phenotype and the CAR-HEMATOTOX (CAR-HTX) score. (A) Baseline log_2(EASIX) values (prior to lymphodepletion) depending on the phenotype of neutrophil recovery (*quick*, *intermittent* or *aplastic*). Median (left to right): −0.03 vs 0.43 vs 1.24. P values of the group comparisons are shown at the top. The dashed lines indicate the median and the upper quartile of the baseline EASIX. (B) ROC curves to assess the potential of the baseline (bl) EASIX (prior to lymphodepletion (LD)) (red) and the EASIX at day 0 (day of CAR T-cell infusion) (blue) to identify patients at risk for an *aplastic* phenotype of neutrophil recovery. AUC values, p values and sensitivity/specificity for selected baseline EASIX cut-off values (median, upper quartile [Q_3], optimal cut-off) are provided below. (C) Distribution of the *quick*, *intermittent* and *aplastic* phenotype of neutrophil recovery depending on baseline EASIX group (≤upper quartile [≤2.15] vs >upper quartile [>2.15]). (D) Comparison of patients with a low (<2) and a high (≥2) CAR-HTX regarding baseline log_2(EASIX) values in the German cohort (G) and the US cohort (US). Median (left to right): 0.24 vs 1.05 vs 1.65. P values of the group comparisons are shown at the top. The dashed lines indicate the median and the upper quartile of the baseline EASIX. (E) Graph showing the association between baseline log_2(EASIX) (prior to lymphodepletion) and exact CAR-HTX score for all patients with available data in the German cohort. (G) Best-fit line and 95% confidence bands were obtained by simple linear regression. Coefficient (r) and p values are based on Spearman correlation analysis. (F) Alluvial plot showing the individual patient distribution and associations regarding (left to right) baseline EASIX group>median (>1.26) (yes (orange) vs no (gray)), baseline EASIX group>upper quartile (>Q_3; >2.15) (yes vs no) and baseline CAR-HTX (high vs low) in the German cohort (G) for all patients with available CAR-HTX. AUC, area under the curve; CAR, chimeric antigen receptor; EASIX, Endothelial Activation and Stress Index; ROC, receiver operating characteristic.

we still observed differences in the associations with the investigated endpoints and assigned risk. For example, a proportion of patients affected by severe cytopenias or other complications had a low CAR-HTX, but elevated or high baseline EASIX levels (online supplemental figure S4).

EASIX and risk for severe late-onset infections, ICANS and medical interventions

We then evaluated associations between the EASIX parameters and other clinically relevant complications following CAR T-cell therapy. The corresponding univariate and multivariate logistic regression analyses including patient and disease characteristics are summarized in online supplemental tables S13–S15. Fifteen out of 113 evaluable patients were affected by a severe late-onset infection (CTC grade ≥3). These patients had significantly higher baseline EASIX values (median 2.21 vs 1.20; p=0.003) compared with non-affected patients (figure 4A). The ROC analysis provided comparable AUC values for the EASIX before lymphodepletion and at day 0 (figure 4B). The frequency of severe late-onset infections was significantly increased in the group with a high baseline EASIX (>Q_3; n=8/25; 32%) compared with patients with an EASIX ≤Q_3 (n=7/88; 8%) (OR:

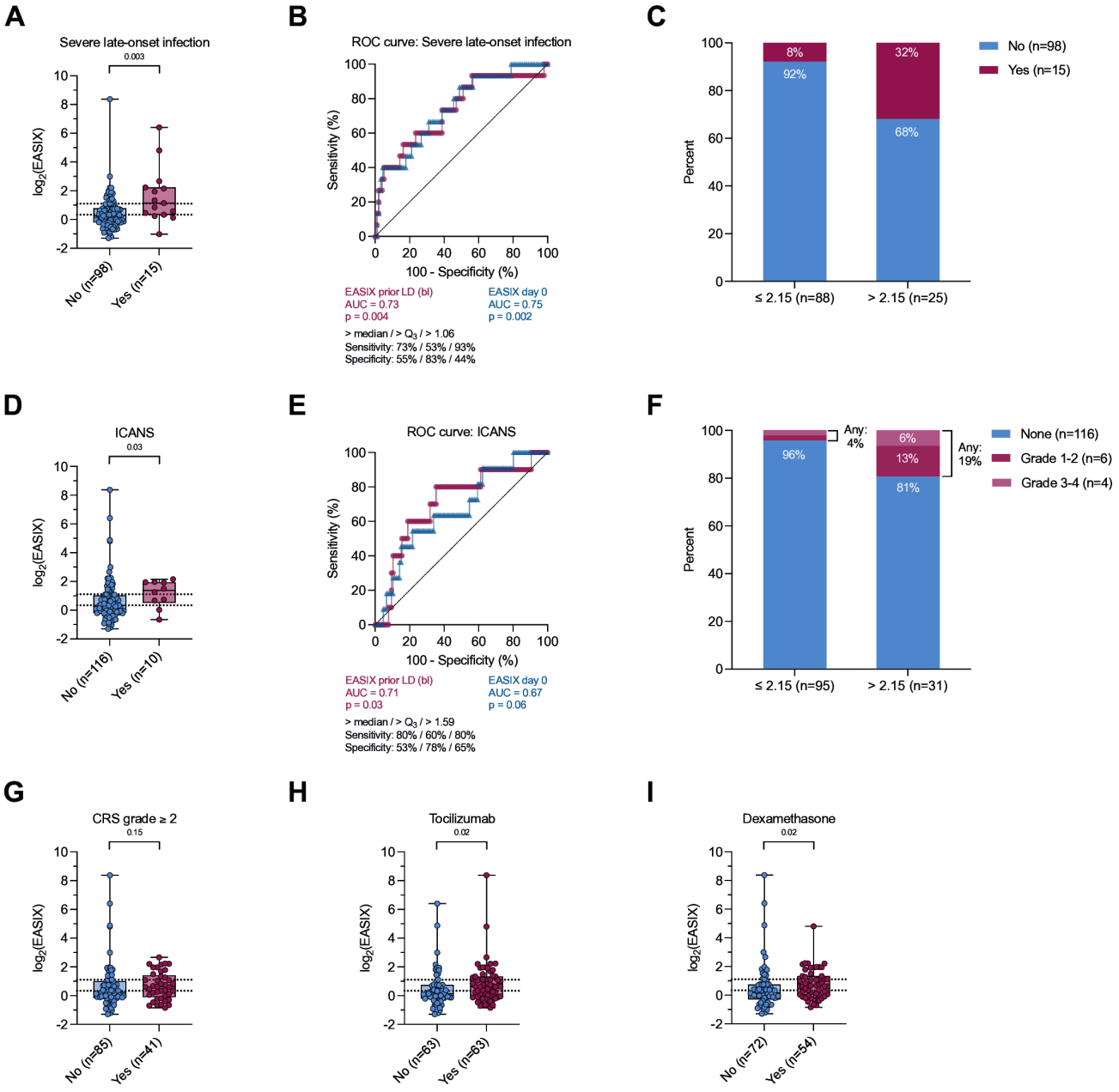

Figure 4 EASIX is associated with severe late-onset infections, ICANS and medical interventions. (A) Comparison of patients with and without late-onset severe infection (Common Terminology Criteria (CTC) grade ≥3) regarding baseline log_2(EASIX) values (prior to lymphodepletion). Median (left to right): 0.26 vs 1.14. P value of the group comparison is shown at the top. The dashed lines indicate the median and the upper quartile of the baseline EASIX. (B.) ROC curves to assess the potential of the baseline (bl) EASIX (prior to lymphodepletion (LD)) (red) and the EASIX at day 0 (day of CAR T-cell infusion) (blue) to identify patients at risk for a severe late-onset infection. AUC values, p values and sensitivity/specificity for selected baseline EASIX cut-off values (median, upper quartile [Q_3], optimal cut-off) are provided below. (C) Frequency of late-onset severe infections depending on baseline EASIX group (≤ upper quartile [≤2.15] vs >upper quartile [>2.15]). (D) Comparison of patients with and without ICANS regarding baseline log_2(EASIX) values. Median (left to right): 0.33 vs 1.38. P value of the group comparison is shown at the top. The dashed lines indicate the median and the upper quartile of the baseline EASIX. (E) ROC curves to assess the potential of the baseline EASIX (prior to LD) (red) and the EASIX at day 0 (day of CAR T-cell infusion) (blue) to identify patients at risk for ICANS (any grade). AUC values, p values and sensitivity/specificity for selected baseline EASIX cut-off values (median, Q_3, optimal cut-off) are provided below. (F) Frequency and severity of ICANS depending on baseline EASIX group (≤upper quartile [≤2.15] vs >upper quartile [>2.15]). (G–I) Comparison of patients with and without CRS grade ≥2, tocilizumab and dexamethasone treatment due to CAR T-cell associated toxicities regarding baseline log_2(EASIX) values. P values of the group comparisons are shown at the top. The dashed lines indicate the median and the upper quartile of the baseline EASIX. CRS grade ≥2 (G), median (left to right): 0.24 vs 0.61. Tocilizumab (H), median (left to right): 0.14 vs 0.63. Dexamethasone (I),median (left to right): 0.17 vs 0.64. AUC, area under the curve; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; EASIX, Endothelial Activation and Stress Index; ICANS, immune effector cell-associated neurotoxicity syndrome; ROC, Receiver operating characteristic.

5.45; 95% CI: 1.80 to 16.11; p=0.005) (figure 4C). Moreover, patients who were affected by ICANS (any grade; n=10) showed significantly higher baseline EASIX values compared with the others (n=116) (median 2.61 vs 1.26; p=0.03) (figure 4D). The results of the ROC analysis favored the baseline EASIX as a risk marker (figure 4E). The group with a high baseline EASIX (>Q_3) was characterized by a significantly increased rate of ICANS events (n=6/31; 19%) compared with the EASIX ≤Q_3 group (n=4/95; 4%) (OR: 5.46; 95% CI: 1.49 to 17.90; p=0.01) (figure 4F). While no association between EASIX and CRS grade ≥2 was found (figure 4G), we observed that patients with a need for medical interventions had significantly higher baseline EASIX values (figure 4H–I), and increased rates of tocilizumab and dexamethasone administrations were found among patients with elevated EASIX levels (61% vs 39%; OR: 2.47; 95% CI: 1.21 to 4.92; p=0.02 and 53% vs 33%; OR: 2.33; 95% CI: 1.13 to 4.70; p=0.03, respectively) (online supplemental table S8). An overview of all ROC analyses performed is given in online supplemental figure S5. A comparison of the test characteristics of the EASIX and the m-EASIX at the two pre-CAR-T time points demonstrated a general superiority of the EASIX score for the investigated endpoints (online supplemental figure S6). Associations between the other EASIX derivatives and complications are shown in online supplemental table S10–S15.

EASIX is associated with inferior outcomes

Finally, we examined associations between patient and disease characteristics, laboratory parameters, scores and clinical outcomes (online supplemental tables S16–S18). No associations between EASIX and response status before or after CAR T-cell therapy were found (online supplemental table S16; online supplemental figure S7). Results of the univariate Cox regression analysis of PFS are summarized in figure 5A. High baseline EASIX levels (>Q_3) were found to be prognostically unfavorable (HR: 2.05; 95% CI: 1.21 to 3.48; log-rank p=0.007; C-index=0.58) (figure 5A, B). The associations between ISS stage III (HR: 2.76; 95% CI: 1.32 to 5.77; p=0.007), extraosseous disease (HR: 2.34; 95% CI: 1.31 to 4.19; p=0.004), high EASIX levels (HR: 2.03; 95% CI: 1.13 to 3.64; p=0.02) and an inferior PFS remained significant in a multivariate model. Moreover, patients with high EASIX levels showed an inferior OS (HR: 4.85; 95% CI: 2.35 to 10.00; log-rank p<0.0001; C-index=0.68) (figure 5C, D), driven by a high rate of death in the first 6 months after CAR T-cell infusion (n=8/15) and also seen in the subcohorts (online supplemental figure S8B, D). A multivariate analysis confirmed the negative prognostic significance of ISS stage III (HR: 4.42; 95% CI: 1.62 to 12.10; p=0.004), extraosseous disease (HR: 3.42; 95% CI: 1.44 to 8.17; p=0.006) and a high baseline EASIX (HR: 3.89; 95% CI: 1.71 to 8.83; p=0.001). Under consideration of the limited case numbers, no significant differences were found in the distribution of causes of death and non-relapse mortality between the EASIX groups (online supplemental table S8). In addition to the baseline time point, we also found strong associations between the EASIX at day 0 and post-CAR-T outcomes (figure 5A, C; online supplemental figure S8E, F). Further analyses of score-based risk groups at different time points are provided in online supplemental tables S17 and S18.

DISCUSSION

Our real-world data analysis confirmed the clinical efficacy and safety of ide-cel in RRMM. We included cohorts from two German centers and one US center, representing two countries with widespread use of CAR T-cells in RRMM. While overall efficacy based on response rates and survival times were similar between the German and US cohorts, we observed significant differences in the incidence of complications. This is most likely explained by differences in patient and disease characteristics, but also by center-specific management of post-CAR-T prophylaxes and toxicities. For example, prophylactic G-CSF administration, as described in the literature,[30] was used in the US cohort and associated with a decreased rate of high-grade neutropenia during the early post-CAR-T period.

With the aim of predicting severe complications following CAR T-cell therapy with ide-cel, we employed the EASIX score originally developed for similar purposes in the allogeneic transplant setting. We demonstrated associations between EASIX at two pre-CAR-T time points and life-threatening complications and inferior outcomes after ide-cel infusion. To our knowledge, this is the first study investigating EASIX-based risk stratification in this context. Former studies have focused on CD19-directed CAR T-cell therapy in lymphomas and associations between EASIX and severe CRS/ICANS.[12 19 20] We extended our analysis by including post-CAR-T cytopenia as an endpoint, the most common adverse event after CAR T-cell therapy.[6]

High-grade cytopenias were frequently observed and not restricted to the early post-CAR-T period. We identified a fraction of patients with severe late ICAHT, defined by deep neutropenia after day 30 and associated with severe anemia and thrombocytopenia, leading to a high need for supportive measures and complicating outpatient care. The EASIX allowed for a simple risk evaluation based on LDH, creatinine and platelet count. Patients with elevated EASIX levels showed a significantly higher rate of severe late cytopenias. The high relevance of baseline platelet count for prediction of post-CAR-T cytopenias is a well-described phenomenon[5 31] and could be related to intensive prior therapies and disease-associated suppression of hematopoiesis. Of note, we observed significantly higher rates of bridging therapies among patients with increased EASIX levels, whereas bone marrow disease burden and baseline remission status were comparable between groups. LDH is a well-established prognostic factor in multiple myeloma and regarded as an indicator of highly proliferative disease activity and extramedullary tumor masses.[23 32 33] Although no correlation between

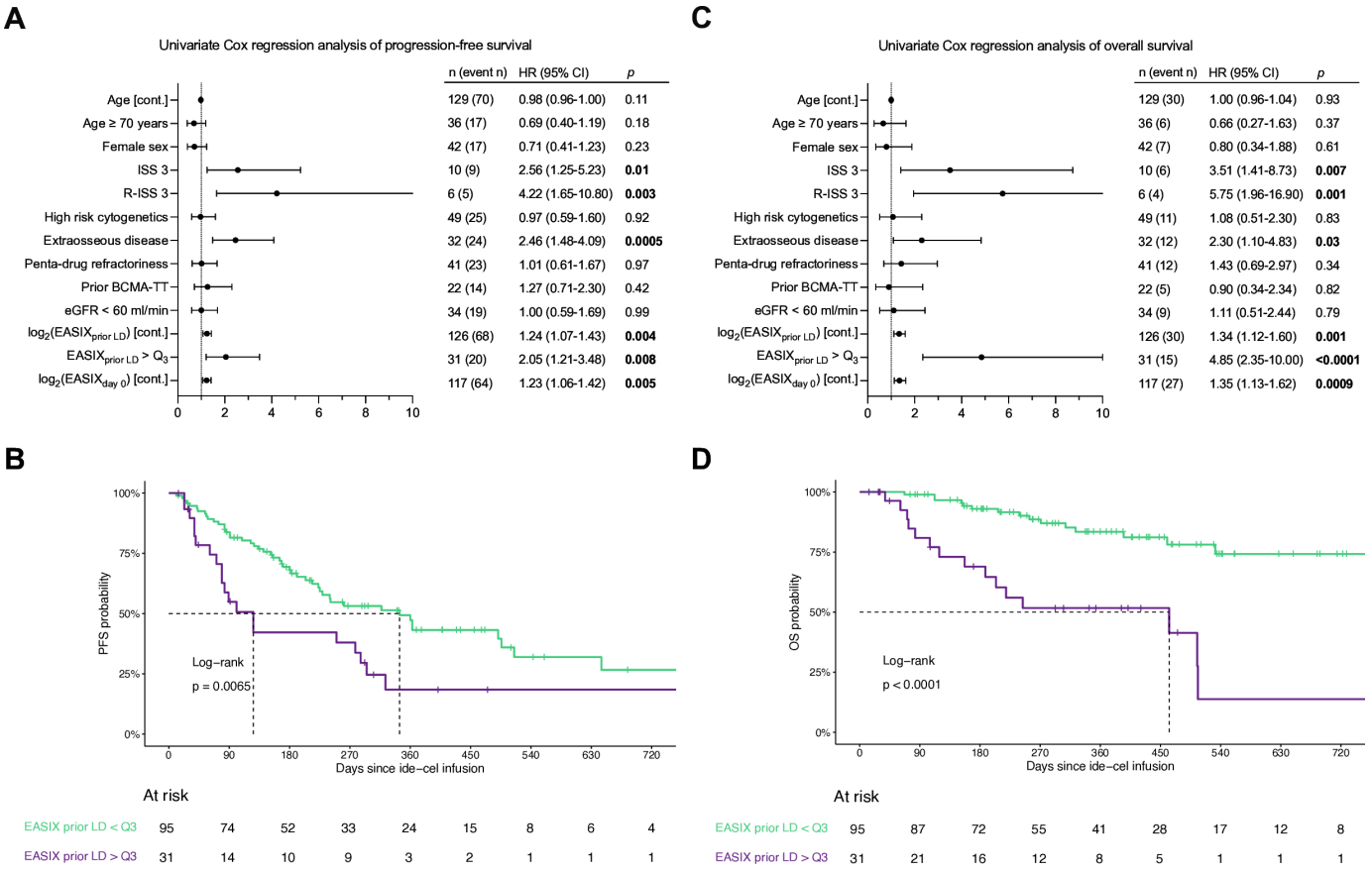

Figure 5 EASIX is associated with inferior outcomes after CAR T-cell therapy. (A) Forest plot showing the results of the univariate Cox regression analysis of PFS in the total cohort. The plot shows the respective HR and 95% CI. Included continuous and binary variables: age (continuous), age ≥70 years, female sex, ISS stage 3, R-ISS 3, high risk cytogenetics, extraosseous disease, penta-drug refractoriness, prior BCMA-TT, eGFR <60 mL/min, log_2(EASIX) prior to lymphodepletion (LD) (continuous), EASIX prior to LD>upper quartile (Q_3) and log_2(EASIX) at day 0 (day of CAR T-cell infusion) (continuous). (B) Kaplan-Meier estimates of the probability of PFS in days since ide-cel infusion for the baseline EASIX (prior to LD) ≤ Q_3 (≤2.15) group (green) (median PFS 344 days; 95% CI: 225 to 515) and the baseline EASIX>Q_3 (>2.15) group (violet) (median PFS 126 days; 95% CI: 79 to 323) in the total cohort. (C) Forest plot showing the results of the univariate Cox regression analysis of OS. The plot shows the respective HR and 95% CI. Included continuous and binary variables are shown above. (D) Kaplan-Meier estimates of the probability of OS in days since ide-cel infusion for the baseline EASIX (prior to LD) ≤ Q_3 (≤2.15) group (green) (median OS NR) and the baseline EASIX>Q_3 (>2.15) group (violet) (median OS 463 days; 95% CI: 188 to NR) in the total cohort. BCMA-TT, B-cell maturation antigen-targeted therapy; CAR, chimeric antigen receptor; EASIX, Endothelial Activation and Stress Index; eGFR, estimated glomerular filtration rate; ide-cel, idecabtagene vicleucel; ISS, International Staging System; NR, not reached; OS, overall survival; PFS, progression-free survival; R-ISS Revised International Staging System stage.

LDH and duration of severe neutropenia during the post-CAR-T phase has been found in the context of anti-CD19 CAR T-cell therapy,[5] Rejeski and colleagues have reported associations between elevated LDH levels and an aplastic phenotype of neutrophil recovery.[11 13] Baseline creatinine showed an impact on late cytopenias and infections in our analysis. Renal impairment might reflect disease type, higher disease aggressiveness, comorbidities and intensive pretreatment. In line with this hypothesis, we observed a correlation between baseline creatinine and beta-2 microglobulin, a marker of high tumor mass in multiple myeloma.[23]

In addition to disease-related factors, the common interpretation of the EASIX as an indicator of endothelial stress and homeostasis provides an additional explanation for the observed associations.[12 15] Endothelial cells represent an important component of the bone marrow niche contributing to maintenance, expansion and regeneration of hematopoietic stem cells,[34–36] and endothelial dysfunction and corresponding serum markers have been found to be associated with an aplastic phenotype of neutrophil recovery after CD19 CAR T-cell therapy.[13] Consistently, patients with high EASIX levels showed a higher rate of aplastic phenotypes in our analysis.

The importance of severe, long-lasting neutropenia and endothelial dysfunction in the development of life-threatening infections has been well demonstrated by Rejeski and colleagues.[8 37] It therefore appears plausible that patients with high EASIX levels had a significantly increased risk for late-onset severe infections. These patients could therefore particularly benefit from prolonged anti-infective prophylaxis, early intravenous

immunoglobulin substitution, more regular monitoring of infection parameters and intensified use of growth factors.

Previous studies have demonstrated the potential of the EASIX and its derivatives as risk markers for advanced CRS and ICANS,[12 19 20] although in a different disease context. In line with these findings, our analysis showed associations between baseline EASIX and increased rates of ICANS and medical interventions. Considering EASIX as a marker of endothelial damage, it is important to note that endothelial and complement dysfunction are regarded as pathogenetic drivers of CAR-T-associated neurotoxicity, and different studies have shown associations with corresponding serum markers.[12 38–40]

Most importantly, we found strong associations between high EASIX levels and an inferior PFS and particularly OS, driven by a high rate of early death. High EASIX levels implicated a higher rate of an aplastic phenotype of neutrophil recovery, which has been shown to be associated with adverse outcomes after CD19-directed CAR T-cell therapy.[13] The link between increased EASIX levels, endothelial dysfunction and non-relapse mortality has been extensively described in the context of allogeneic stem cell transplantation,[15] and more recently, also in the context of CAR T-cell therapy for large B-cell lymphoma.[41] Due to the limited event rate in our cohort, further studies are needed to validate the EASIX as a risk marker specifically for non-relapse mortality after anti-BCMA CAR T-cell therapy.

In addition to the EASIX, we also included established EASIX derivatives and the CAR-HEMATOTOX score in our analysis. We observed partial overlaps between the different score-based risk groups and varying degrees of association with the selected clinical endpoints. For example, the group with high baseline EASIX levels included an increased proportion of patients with a high CAR-HEMATOTOX, which is an established scoring system to risk stratify for an aplastic phenotype. The partial overlap between both risk groups is at least in parts explained by the fact that both scores include platelet count as a marker of hematopoetic reserve. A major difference is that the EASIX includes parameters known to mirror disease burden and aggressiveness in RRMM, whereas the CAR-HEMATOTOX, similarly to the EASIX derivatives, focuses on baseline inflammation. Among evaluable patients, we found significant associations between baseline CAR-HEMATOTOX and late ICAHT. However, no associations were observed between the baseline score and other endpoints of interest, acknowledging a relevant proportion of patients who had to be excluded from the analysis due to missing data. The extent and relevance of inflammation might vary depending on the composition of the patient population, disease, CAR construct and endpoint. For example, the m-EASIX showed a strong association with PFS and OS, but weaker associations with the examined post-CAR-T complications. Compared with the other scores, one of the general strengths of the EASIX is simplicity and the usage of widely available laboratory markers to predict severe late complications affecting survival. The two cut-off values (median and upper quartile) allow for a stepwise risk stratification approach and help to cover a broad spectrum of clinically relevant endpoints. A potential weakness is the integration of laboratory parameters which may be age-, sex- and assay-dependent. Nevertheless, the score has been validated for numerous diseases, treatments and endpoints in the past years.

Key limitations of our study are the retrospective design and the limited case and event numbers. In addition, the lack of baseline ferritin values for the US cohort limited our analysis of ferritin-based scores prior to lymphodepletion. The combined analysis of cohorts from three independent centers for the other endpoints, however, is a strength of the analysis and increases generalizability. Further studies are needed to evaluate the benefits and disadvantages of different scoring systems and to prospectively validate the EASIX and the derived cut-off values in larger, external cohorts prior to implementation in clinical routine.

In conclusion, the EASIX represents a quick and simple screening tool to identify vulnerable patients and predict major complications and adverse clinical outcomes after CAR T-cell therapy with ide-cel. The EASIX could therefore facilitate clinical decision-making prior to lymphodepletion and at day 0 in the future. Patients with low EASIX levels might be suitable candidates for outpatient CAR T-cell therapy. In contrast, patients with elevated, and even more those with high EASIX levels might particularly benefit from hospitalization, closer monitoring after discharge and intensified use of supportive and prophylactic measures. Future studies across different entities and time points should explore the potential of the EASIX as a risk marker in the context of CAR T-cell and other immunotherapies.

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Competing interests JF has received honoraria from BMS and Stemline and travel and congress participation grants from Janssen-Cilag. XZ declares advisory services for and has received travel support from SkylineDx. JK has received honoraria from AstraZeneca. EKM declares a consulting or advisory role for Amgen, BMS/Celgene, GlaxoSmithKline, Janssen-Cilag, Pfizer, Sanofi, Stemline and Takeda. He has received honoraria from Amgen, BMS/Celgene, GlaxoSmithKline, Janssen-Cilag, Pfizer, Sanofi, Stemline and Takeda, research funding from BMS/Celgene, GlaxoSmithKline, Janssen-Cilag, Sanofi and Takeda and travel support from BMS/Celgene, GlaxoSmithKline, Janssen-Cilag, Sanofi, Stemline and Takeda. MJF declares consulting activity for Pfizer and Kerna Ventures. CSM has received honoraria and travel support from Janssen-Cilag. IB has received honoraria from Oncopeptide and travel support from Janssen. ON reports receiving consulting fees from Janssen, BMS, Takeda, GPCR therapeutics, Sanofi and Pfizer. AS has received travel grants from Hexal and Jazz Pharmaceuticals and research grants from Therakos/Mallinckrodt. She is a consultant for Janssen-Cilag and BMS and co-founder of TolerogenixX Ltd. AS is part-time employee of TolerogenixX Ltd. MS declares an advisory role or expert testimony for MSD, Novartis, BMS and Pierre Fabre. He is co-founder and shareholder of TolerogenixX GmbH, Heidelberg. He has received financial support for research on biosimilars and travel grants from Hexal, financial support of educational activities and conference participation and travels grants from Kite and BMS, collaborative research grants from Novartis and funding for collaborative research from Apogenix. MT has received research funding from Kite, Regeneron and Roche. He is an advisory board member for AstraZeneca, BMS, Incyte, Janssen and Novartis. HE declares a consulting or advisory role for BMS/Celgene, Janssen, Amgen, Takeda, Sanofi, GSK, Novartis and Roche. He has received research funding from BMS/Celgene, Janssen, Amgen, GSK, Sanofi and Novartis, honoraria from BMS/Celgene, Janssen, Amgen, Takeda, Sanofi, GSK, Novartis and travel support from BMS/Celgene, Janssen and Amgen. PD reports consultancy for AbbVie, AstraZeneca, Beigene, BMS, Gilead, Miltenyi, Novartis and Riemser. He is member of the speakers' bureau for AbbVie, AstraZeneca, BeiGene, BMS, Gilead, Novartis, Riemser and Roche and has received research support from Riemser (all to institution). NCM reports receiving personal fees from BMS, Janssen, Amgen, Takeda, OncoPep, AbbVie, Karyopharm, Novartis, Legend, Raqia, Adaptive Biotechnology, and Pfizer outside the submitted work. He has intellectual property licensed to OncoPep and held stocks in C4 Therapeutics. ASp reports receiving consulting fees from Novartis and Roche. LR consulted for Janssen, Amgen, GSK, Pfizer, BMS, Sanofi, and received honoraria from Janssen, GSK, Pfizer, BMS, Sanofi and received research funding from Skyline Dx and BMS. SS has received travel grants or honoraria for presentations from Celgene, BMS, Janssen, Takeda and Amgen. MSR declares a consulting or advisory role for BMS, Amgen, GSK, Janssen, Sanofi, Pfizer, AbbVie and Takeda. He has received research funding from BMS, Janssen, Sanofi and Heidelberg Pharma, travel support from BMS, Amgen and Janssen and honoraria from BMS, Janssen, AbbVie and Sanofi.

Patient consent for publication Not applicable.

Ethics approval This study was approved by institutional committees and boards (Ethics Committee of the Medical Faculty of Heidelberg University [S-096/2017] and Dana-Farber IRB [18-340]) and conducted according to the Declaration of Helsinki. Written informed consent was obtained from all patients. Participants gave informed consent to participate in the study before taking part.

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Supplementary Materials for

EASIX-guided risk stratification for complications and outcome after CAR T-cell therapy with ide-cel in relapsed/refractory multiple myeloma

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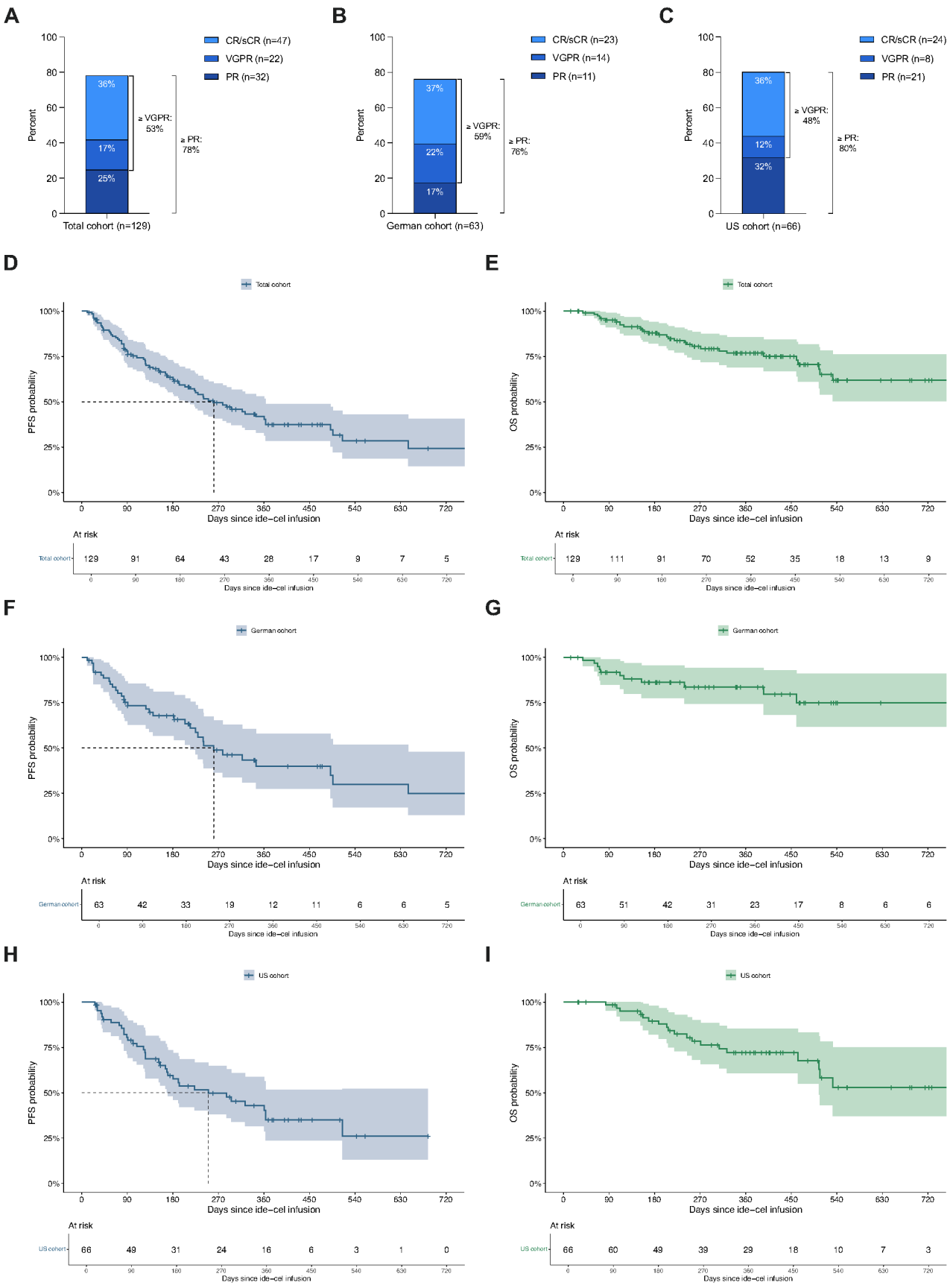
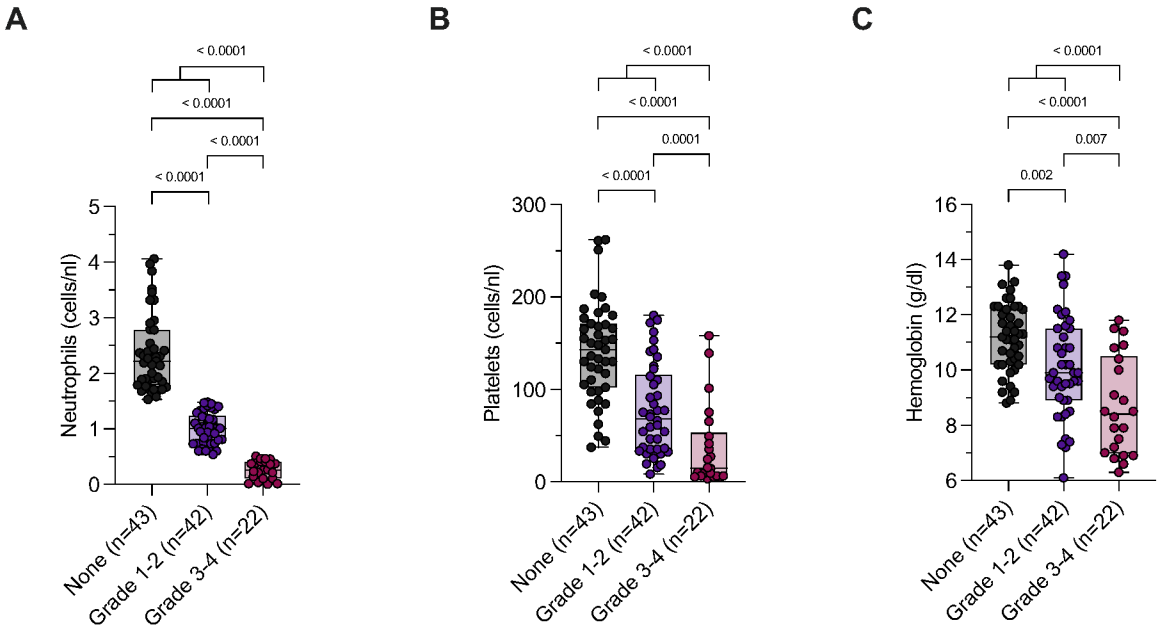
Supplementary Materials

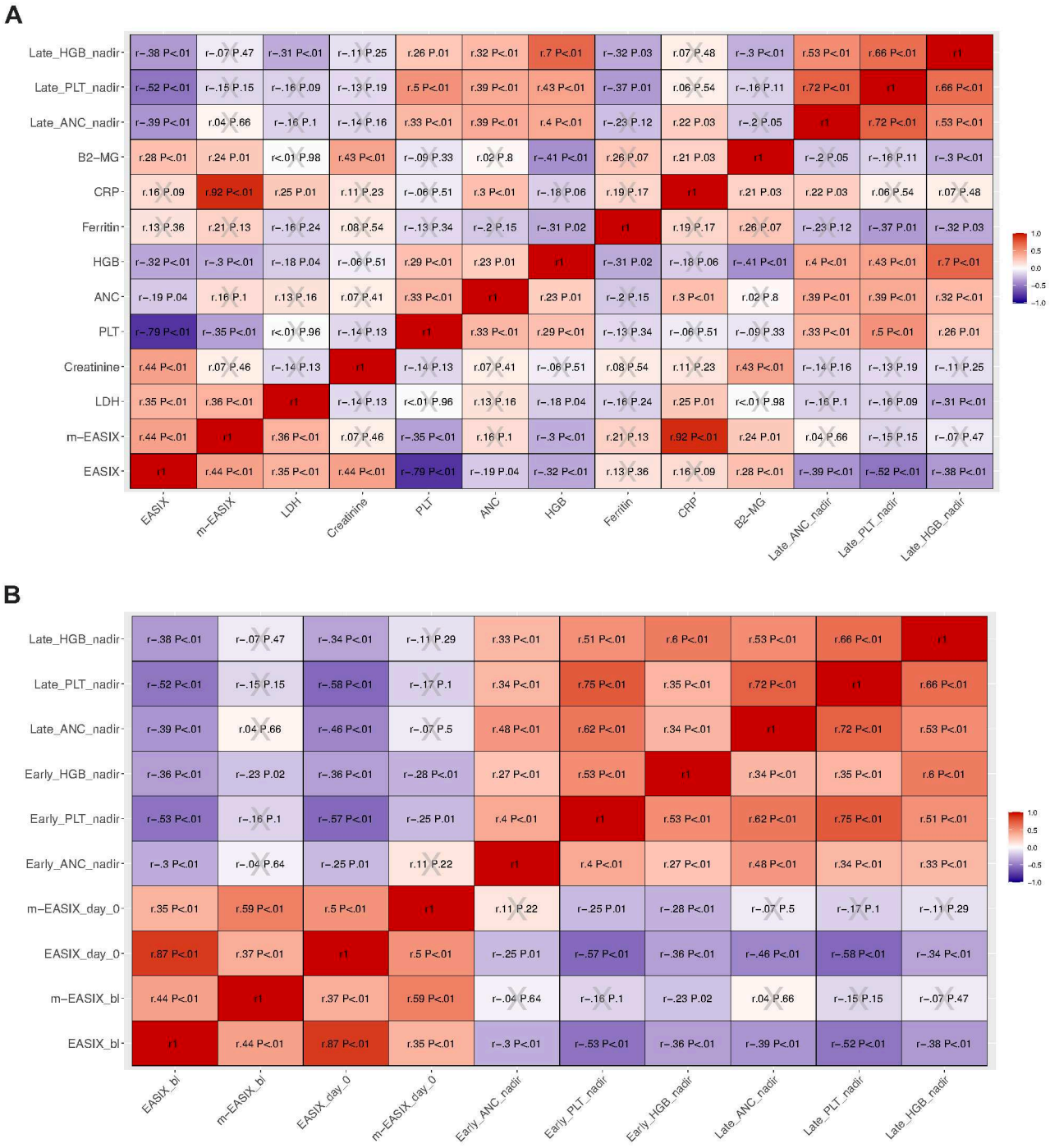
- **Supplementary Figures S1-8**
- **Supplementary Tables S1-18**


A
B
C
CR/sCR (n=47)
VGPR (n=22)
PR (n=32)
CR/sCR (n=23)
VGPR (n=14)
PR (n=11)
CR/sCR (n=24)
VGPR (n=8)
PR (n=21)
Percent
36%
17%
25%
≥ VGPR: 53%
≥ PR: 78%
Total cohort (n=129)
37%
22%
17%
≥ VGPR: 59%
≥ PR: 76%
German cohort (n=63)
36%
12%
32%
≥ VGPR: 48%
≥ PR: 80%
US cohort (n=66)
D
E
F
G
H
I
Total cohort
German cohort
US cohort
PFS probability
OS probability
Days since ide-cel infusion
At risk
Total cohort 129 91 64 43 28 17 9 7 5
Total cohort 129 111 91 70 52 35 18 13 9
German cohort 63 42 33 19 12 11 6 6 5
German cohort 63 51 42 31 23 17 8 6 6
US cohort 66 49 31 24 16 6 3 1 0
US cohort 66 60 49 39 29 18 10 7 3

Supp. Figure S1 | Efficacy of CAR T-cell therapy. A-C. Best overall response in the total cohort (**A**), German cohort (**B**) and US cohort (**C**). CR, complete response. PR, partial response. sCR, stringent complete response. VGPR, very good partial response. **D-E.** Kaplan-Meier estimates of the probability of progression-free survival (PFS) (median PFS 261 days; 95% confidence interval [CI] 204-363) (**D**) and overall survival (OS) (median OS not reached [NR]) (**E**) in days since ide-cel infusion for the total cohort. **F-G.** Kaplan-Meier estimates of the probability of PFS (median PFS 261 days; 95% CI 214-645) (**F**) and OS (median OS NR) (**G**) in days since ide-cel infusion for the German cohort. **H-I.** Kaplan-Meier estimates of the probability of PFS (median PFS 250 days; 95% CI 170-NR) (**H**) and OS (median OS NR; 95% CI 505-NR) (**I**) in days since ide-cel infusion for the US cohort.

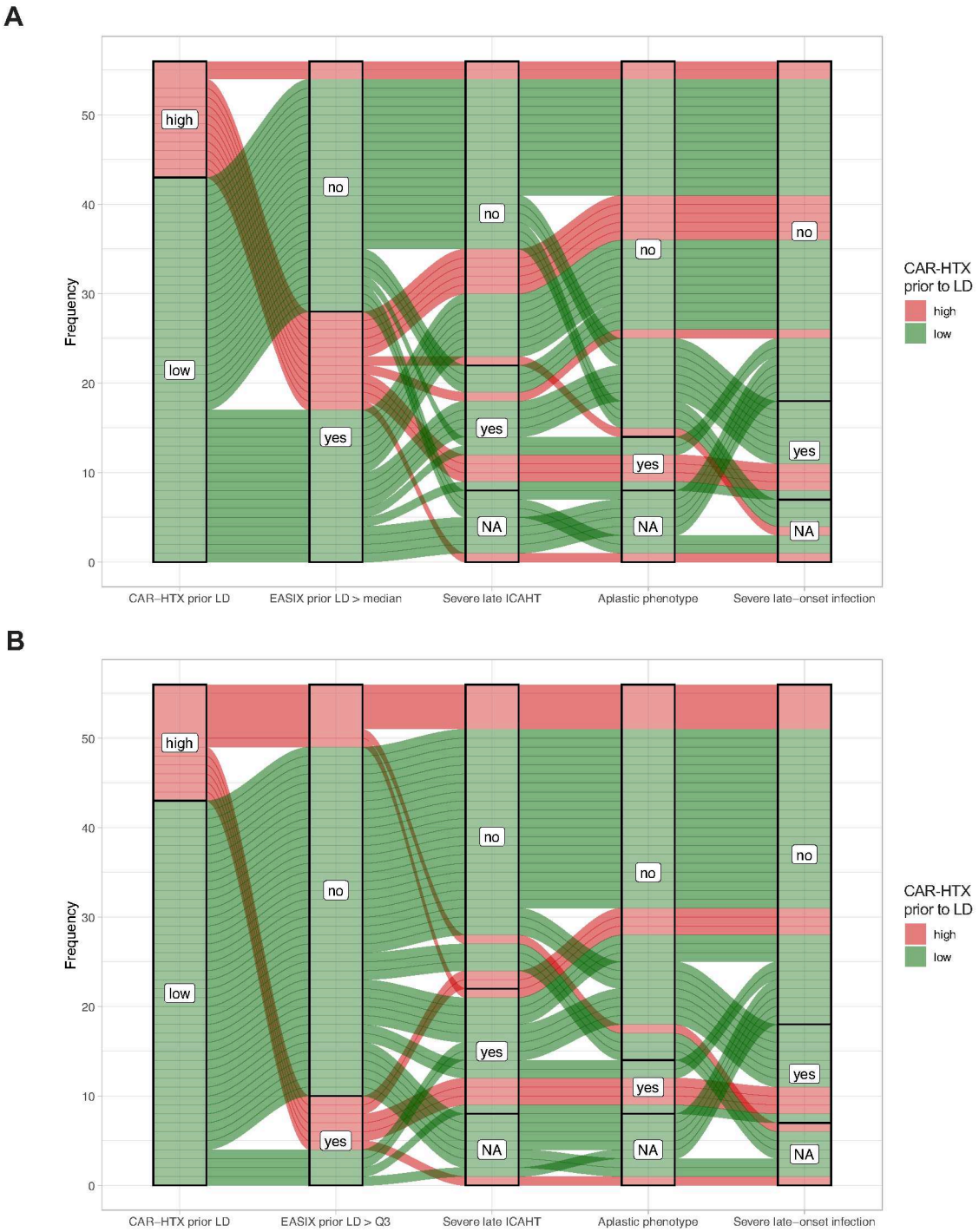


Supp. Figure S2 | Blood cell count nadir values during the late post-CAR-T period depending on late immune effector cell-associated hematotoxicity (ICAHT) grade. P-values of the group comparisons are shown at the top. **A.** Late absolute neutrophil count nadir values. Median (left to right): 2.22/nl vs. 1.01/nl vs. 0.26/nl. **B.** Late platelet count nadir values. Median (left to right): 143/nl vs. 68/nl vs. 14.5/nl. **C.** Late hemoglobin nadir values. Median (left to right): 11.20 g/dl vs. 9.90 g/dl vs. 8.40 g/dl.



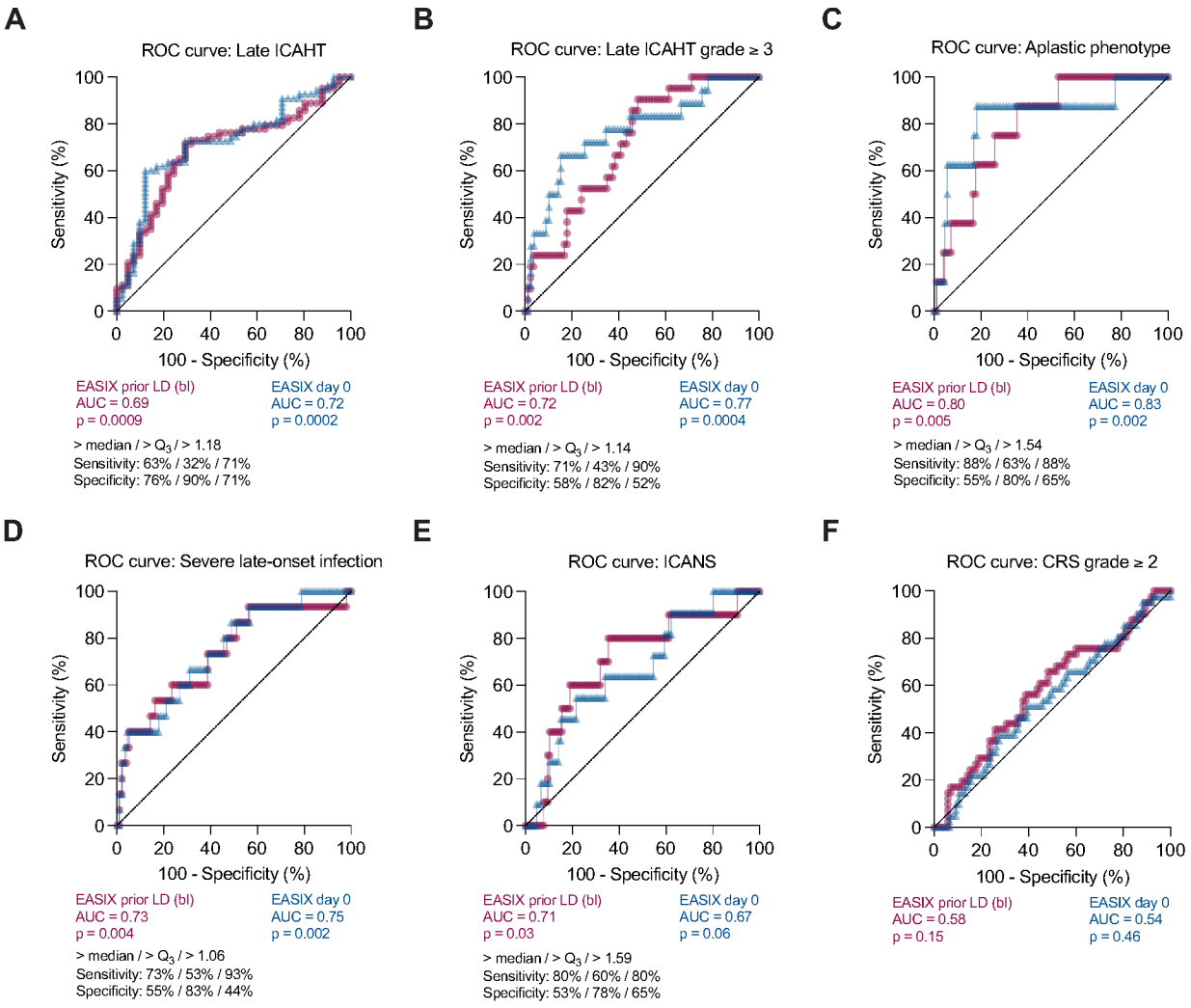
Supp. Figure S3 | Correlation heatmaps showing associations between laboratory parameters and scores and blood cell count nadir values during the post-CAR-T period in the total cohort. Coefficient (r) and p-values are based on Spearman correlation analysis and are shown in the individual fields of the heatmaps. Positive r values are shown in red, negative r values in blue. Non-significant associations are marked with a cross. **A.** Correlation heatmap showing associations between laboratory parameters and scores determined prior to lymphodepletion and nadir values during the late post-CAR-T period. Due to missing data for the US cohort, analyses of ferritin were only performed for the German cohort. **B.** Correlation heatmap showing associations between scores determined prior to lymphodepletion (baseline [bl]) or at day 0 (day of CAR T-cell infusion) and nadir values during the early and late post-CAR-T period. ANC, absolute

neutrophil count. EASIX, Endothelial Activation and Stress Index. HGB, hemoglobin. m-EASIX, modified EASIX. PLT, platelet count.

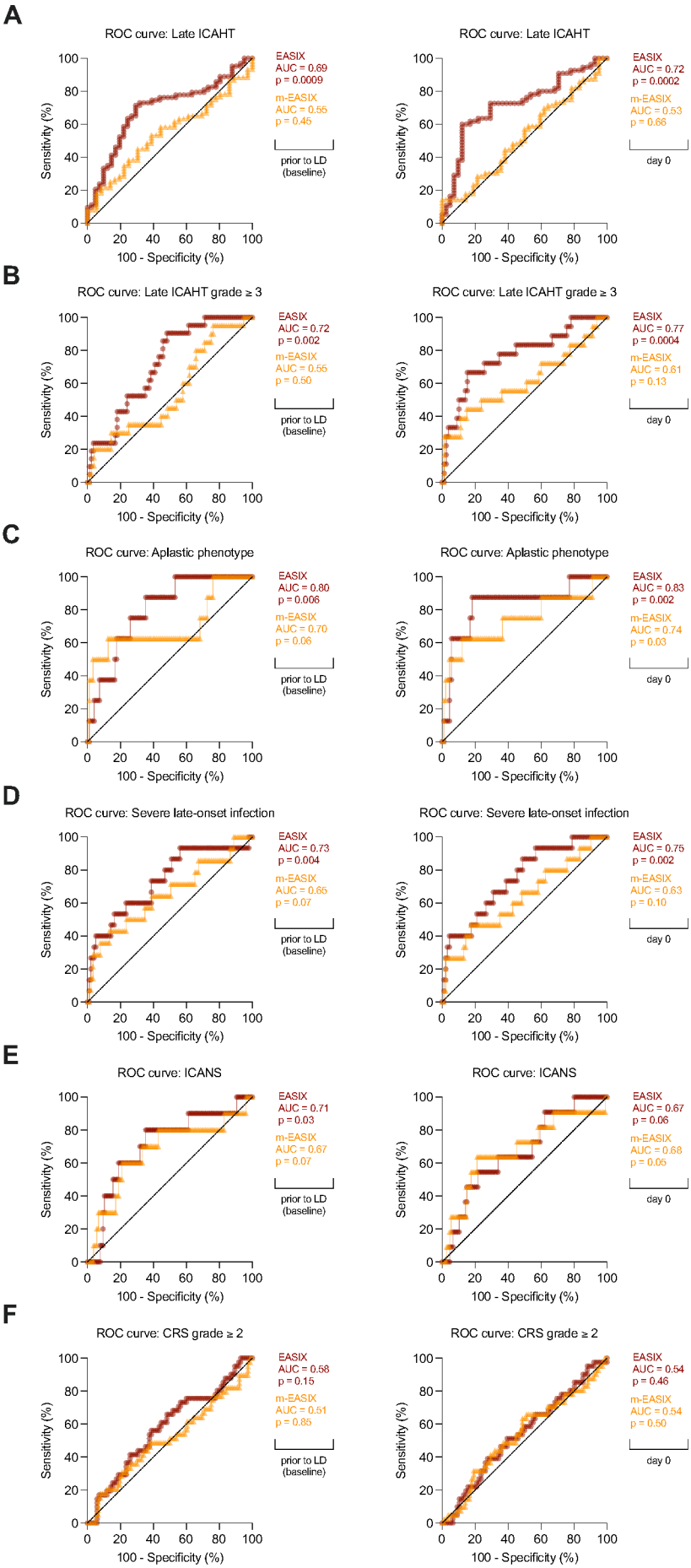


Supp. Figure S4 | Alluvial plots showing the individual patient distribution and associations between score-based risk groups prior to lymphodepletion (LD) and selected post-CAR-T complications. A. Associations between CAR-HEMATOTOX (CAR-HTX) groups, median-based EASIX groups and post-CAR-T complications in the German cohort (only patients with available CAR-HTX score shown). Left to right: CAR-HTX prior to LD (high [red] vs. low [green]), EASIX prior to LD > median (> 1.26) (yes vs. no), severe late immune effector cell-associated hematotoxicity (ICAHT) (yes vs. no vs. not available [NA]), aplastic phenotype of neutrophil recovery (yes vs. no vs. NA) and severe late-onset infection (yes vs. no vs. NA). **B.** Associations between CAR-HTX groups, upper quartile (Q_3)-based EASIX groups and post-CAR-T

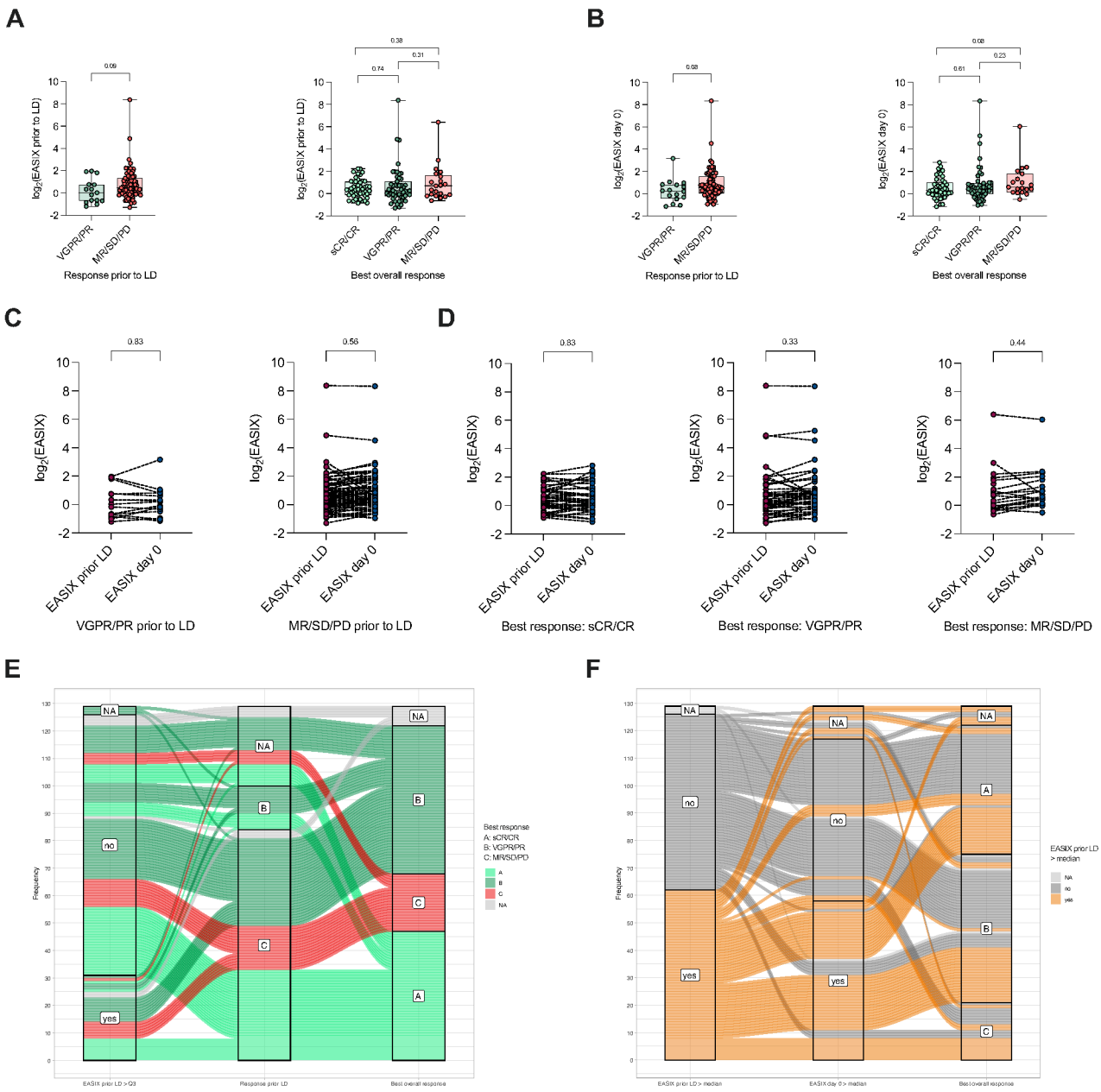
complications in the German cohort (only patients with available CAR-HTX score shown). Left to right: CAR-HTX prior to LD (high [red] vs. low [green]), EASIX prior to LD > Q_3 (> 2.15) (yes vs. no), severe late ICAHT (yes vs. no vs. NA), aplastic phenotype of neutrophil recovery (yes vs. no vs. NA) and severe late-onset infection (yes vs. no vs. NA).



Supp. Figure S5 | Receiver operating characteristic (ROC) curves to compare the potential of the Endothelial Activation and Stress Index (EASIX) at different time points to identify patients at risk for post-CAR-T complications. Curves refer to the baseline (bl) EASIX (prior to lymphodepletion [LD]) (red) and the EASIX at day 0 (day of CAR T-cell infusion) (blue). Area under the curve (AUC) values, p-values and sensitivity/specificity for selected baseline EASIX cut-off values (median, upper quartile [Q_3], optimal cut-off) are provided below. **A-F.** ROC curves for late immune effector cell-associated hematotoxicity (ICAHT; any grade) (**A**), severe late ICAHT (grade ≥ 3) (**B**), an aplastic phenotype of neutrophil recovery (**C**), severe late-onset infection (**D**), immune effector cell-associated neurotoxicity syndrome (ICANS) (**E**) and cytokine release syndrome (CRS) grade ≥ 2 (**F**) as endpoint.

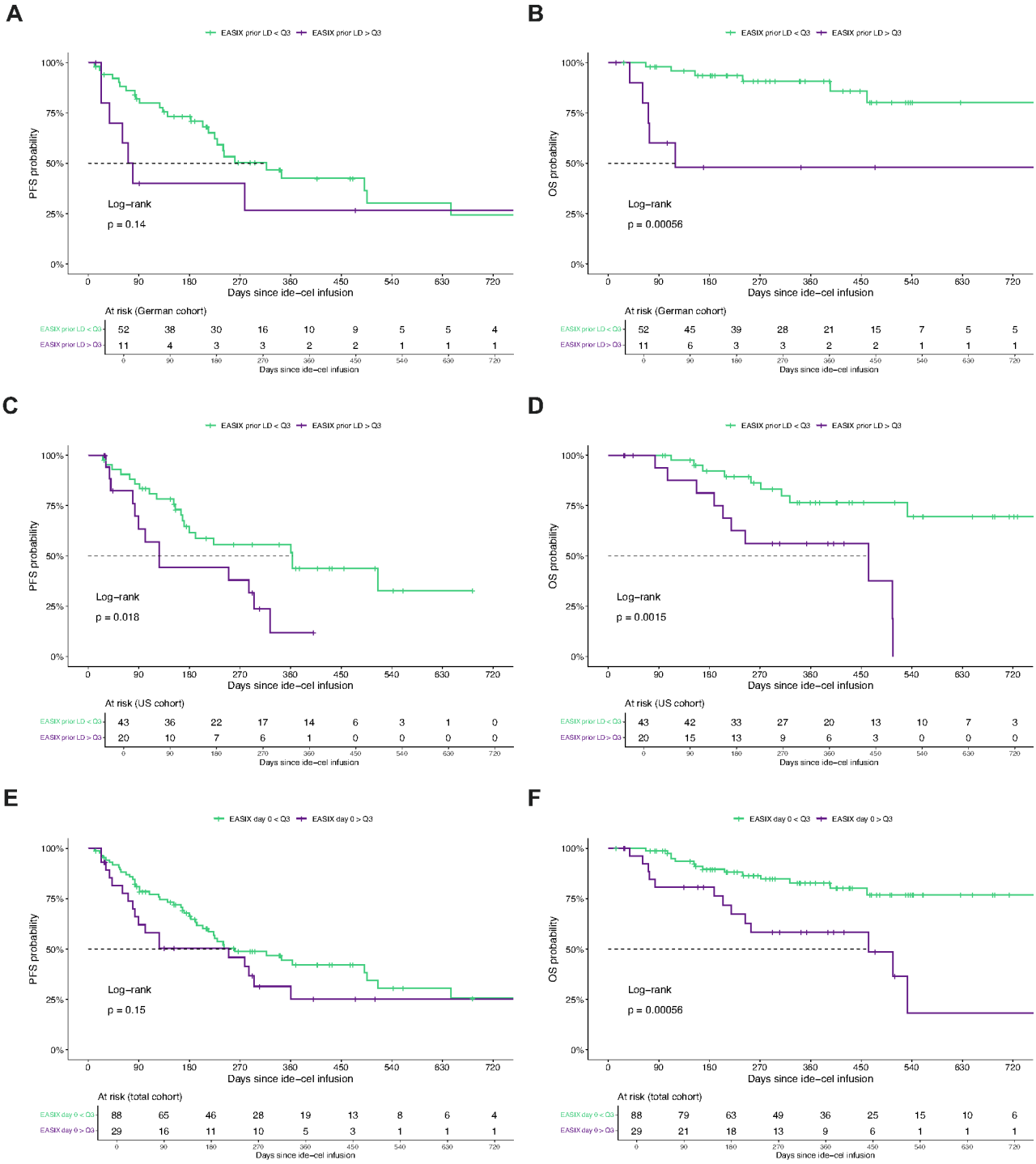

A
ROC curve: Late ICAHT
EASIX AUC = 0.69 p = 0.0009
m-EASIX AUC = 0.55 p = 0.45
prior to LD (baseline)
ROC curve: Late ICAHT
EASIX AUC = 0.72 p = 0.0002
m-EASIX AUC = 0.53 p = 0.66
day 0
B
ROC curve: Late ICAHT grade ≥ 3
EASIX AUC = 0.72 p = 0.002
m-EASIX AUC = 0.55 p = 0.50
prior to LD (baseline)
ROC curve: Late ICAHT grade ≥ 3
EASIX AUC = 0.77 p = 0.0004
m-EASIX AUC = 0.61 p = 0.13
day 0
C
ROC curve: Aplastic phenotype
EASIX AUC = 0.80 p = 0.006
m-EASIX AUC = 0.70 p = 0.06
prior to LD (baseline)
ROC curve: Aplastic phenotype
EASIX AUC = 0.83 p = 0.002
m-EASIX AUC = 0.74 p = 0.03
day 0
D
ROC curve: Severe late-onset infection
EASIX AUC = 0.73 p = 0.004
m-EASIX AUC = 0.65 p = 0.07
prior to LD (baseline)
ROC curve: Severe late-onset infection
EASIX AUC = 0.75 p = 0.002
m-EASIX AUC = 0.63 p = 0.10
day 0
E
ROC curve: ICANS
EASIX AUC = 0.71 p = 0.03
m-EASIX AUC = 0.67 p = 0.07
prior to LD (baseline)
ROC curve: ICANS
EASIX AUC = 0.67 p = 0.06
m-EASIX AUC = 0.68 p = 0.05
day 0
F
ROC curve: CRS grade ≥ 2
EASIX AUC = 0.58 p = 0.15
m-EASIX AUC = 0.61 p = 0.85
prior to LD (baseline)
ROC curve: CRS grade ≥ 2
EASIX AUC = 0.54 p = 0.46
m-EASIX AUC = 0.54 p = 0.50
day 0
Sensitivity (%)
100 - Specificity (%)
0 20 40 60 80 100

Supp. Figure S6 | Receiver operating characteristic (ROC) curves to compare the potential of the Endothelial Activation and Stress Index (EASIX) and the modified EASIX (m-EASIX) at different time points to identify patients at risk for post-CAR-T complications. Curves refer to the EASIX (red) and the m-EASIX (yellow) determined prior to lymphodepletion (LD; baseline) (left) and at day 0 (day of CAR T-cell infusion) (right). Area under the curve (AUC) values and p-values are provided next to the curves. **A-F.** ROC curves for late immune effector cell-associated hematotoxicity (ICAHT; any grade) (**A**), severe late ICAHT (grade ≥ 3) (**B**), an aplastic phenotype of neutrophil recovery (**C**), severe late-onset infection (**D**), immune effector cell-associated neurotoxicity syndrome (ICANS) (**E**) and cytokine release syndrome (CRS) grade ≥ 2 (**F**) as endpoint.



Supp. Figure S7 | Associations between Endothelial Activation and Stress Index (EASIX) prior to lymphodepletion (LD) and at day 0 (day of CAR T-cell infusion) and response status before and after CAR T-cell therapy. A. Baseline log_2(EASIX) values (prior to LD) depending on the response status prior to LD (left) (median [left to right]: 0.02 [n=15] vs. 0.46 [n=83]) and best overall response status after CAR T-cell therapy (right) (median [left to right]: 0.34 [n=47] vs. 0.26 [n=51] vs. 0.69 [n=21]). P-values of the group comparisons are shown at the top. CR, complete response. MR, minimal response. PD, progressive disease. PR, partial response. sCR, stringent complete response. SD, stable disease. VGPR, very good partial response. **B.** Log_2(EASIX) values at day 0 depending on the response status prior to LD (left) (median [left to right]: 0.23 [n=16] vs. 0.53 [n=75]) and best overall response status after CAR T-cell therapy (right) (median [left to right]: 0.32 [n=44] vs. 0.51 [n=49] vs. 0.61 [n=19]). P-values of the group comparisons are shown at the top. **C.** Individual changes of the log_2(EASIX) values between the time point prior to LD and at day 0 among patients with (left; n=15 and

n=16, respectively) and without (right; n=83 and n=75, respectively) treatment response prior to LD. P-values of the group comparisons are shown at the top. **D.** Individual changes of the log_2(EASIX) values between the time point prior to LD and at day 0 depending on best overall response after CAR T-cell therapy. Left to right: Patients with a CR or better (n=47 and n=44, respectively), patients with a PR or better (n=51 and n=49, respectively) and patients without treatment response (n=21 and n=19, respectively). P-values of the group comparisons are shown at the top. **E.** Alluvial plot showing the individual patient distribution and associations between the upper quartile (Q_3)-based EASIX groups prior to LD and response groups before and after CAR T-cell therapy in the total cohort. Left to right: EASIX prior to LD > Q_3 (> 2.15) (yes vs. no vs. not available [NA]), response group prior to LD (B vs. C vs. NA) and best overall response group after CAR T-cell therapy (A [light green] vs. B [dark green] vs. C [red] vs. NA [light grey]). Response groups: A (sCR/CR), B (VGPR/PR), C (MR/SD/PD) and NA (not available/applicable). **F.** Alluvial plot showing the individual patient distribution and associations between the median-based EASIX groups prior to LD, at day 0 and response groups after CAR T-cell therapy in the total cohort. Left to right: EASIX prior to LD > median (> 1.26) (yes [orange] vs. no [dark grey] vs. NA [light grey]), EASIX at day 0 > median (>1.36) (yes vs. no vs. NA) and best overall response group after CAR T-cell therapy (A vs. B vs. C vs. NA). Response groups: A (sCR/CR), B (VGPR/PR), C (MR/SD/PD) and NA (not available/applicable).



Supp. Figure S8 | Associations between Endothelial Activation and Stress Index (EASIX) and outcomes after CAR T-cell therapy. A. Kaplan-Meier estimates of the probability of progression-free survival (PFS) in days since ide-cel infusion for the EASIX prior to lymphodepletion [LD] ≤ upper quartile (Q_3) (≤ 2.15) group (green) (median PFS 317 days; 95% CI 225-not reached [NR]) and the EASIX prior to LD > Q_3 (> 2.15) group (violet) (median PFS 75 days; 95% CI 38-NR) in the German cohort. **B.** Kaplan-Meier estimates of the probability of overall survival (OS) in days since ide-cel infusion for the EASIX prior to LD ≤ Q_3 (≤ 2.15) group (green) (median OS NR) and the EASIX prior to LD > Q_3 (> 2.15) group (violet)

(median OS 119 days; 95% CI 71-NR) in the German cohort. **C.** Kaplan-Meier estimates of the probability of PFS in days since ide-cel infusion for the EASIX prior to LD ≤ Q_3 (≤ 2.15) group (green) (median PFS 363 days; 95% CI 180-NR) and the EASIX prior to LD > Q_3 (> 2.15) group (violet) (median PFS 126 days; 95% CI 89-NR) in the US cohort. **D.** Kaplan-Meier estimates of the probability of OS in days since ide-cel infusion for the EASIX prior to LD ≤ Q_3 (≤ 2.15) group (green) (median OS NR) and the EASIX prior to LD > Q_3 (> 2.15) group (violet) (median OS 463 days; 95% CI 204-NR) in the US cohort. **E.** Kaplan-Meier estimates of the probability of PFS in days since ide-cel infusion for the EASIX at day 0 (day of CAR T-cell infusion) ≤ Q_3 (≤ 2.06) group (green) (median PFS 261 days; 95% CI 214-515) and the EASIX at day 0 > Q_3 (> 2.06) group (violet) (median PFS 250 days; 95% CI 89-NR) in the total cohort. **F.** Kaplan-Meier estimates of the probability of OS in days since ide-cel infusion for the EASIX at day 0 ≤ Q_3 (≤ 2.06) group (green) (median OS NR) and the EASIX at day 0 > Q_3 (> 2.06) group (violet) (median OS 463 days; 95% CI 244-NR) in the total cohort.

Supp. Table S1 | Institutional standard operating procedures for prophylaxes and management of complications

	Heidelberg	Würzburg	Boston
CRS			
Tocilizumab	• CRS grade ≥ 2	• Consideration for CRS grade 1-2 • CRS grade ≥ 3	• Consideration for CRS grade 1 • CRS grade ≥ 2
Dexamethasone	• Consideration for CRS grade 2 • CRS grade 3	• Consideration for CRS grade 1-2 • CRS grade 3	• Consideration for CRS grade 1-2 • CRS grade 3
Methylprednisolone	• CRS grade 4	• CRS grade 4	• CRS grade 4
ICANS			
Dexamethasone	• ICANS grade 2 without improvement within 24 hours • ICANS grade 3	• Consideration for ICANS grade 1-2	• Consideration for ICANS grade 1-2
Methylprednisolone	• ICANS grade 3 without improvement within 24 hours • ICANS grade 4	• ICANS grade ≥ 3	• Consideration for ICANS grade ≥ 3
Cytopenias			
G-CSF	• Individual decision • Consideration in case of protracted neutropenia (> 10 days after infusion)	• Leukocytopenia CTC grade ≥ 3	• Individual decision • Consideration in case of protracted or severe neutropenia
TPO agonists			• Individual decision • Consideration in case of long-lasting or severe thrombocytopenia
Red blood cell transfusion	• Individual decision • Therapy-associated anemia with hemoglobin < 8 g/dl and without expected spontaneous reconstitution • Anemia with clinical symptoms	• Hemoglobin < 8 g/dl	• Hemoglobin < 8 g/dl
Platelet transfusion	• Relevant bleeding signs • Platelets < 20/nl (outpatient) / < 10/nl (inpatient)	• Bleeding • Platelets < 10/nl	• Bleeding • Platelets < 10/nl
Infection prophylaxis			
Antibacterial	• Rifaximin 200 mg p.o. 2x/day until neutrophil recovery		
Antiviral	• Aciclovir 400 mg p.o. 2x/day until $CD4^+$ T cell regeneration	• Aciclovir 400 mg p.o. 2x/day	• Aciclovir 400 mg p.o. 2x/day
Antifungal	• Fluconazole 200 mg p.o. 1x/day until neutrophil recovery *or* • Posaconazole 300 mg p.o. 1x/day (after loading dose) according to risk (e.g. steroid administration) • PCP prophylaxis: Cotrimoxazole 960 mg p.o. 1x/day three times per week until $CD4^+$ T cell regeneration	• PCP prophylaxis: Cotrimoxazole 960 mg p.o. 1x/day three times per week	• PCP prophylaxis: Trimethoprim/Sulfametho-xazole ss 1x/day

IVIG substitution	• Infection tendency, IgG < 4 g/l	• Infection tendency, IgG < 4 g/l	• Infection tendency, IgG < 4 g/l

CRS, cytokine release syndrome. CTC, Common Terminology Criteria for Adverse Events. G-CSF, granulocyte-colony stimulating factor. ICANS, immune effector cell-associated neurotoxicity syndrome. IVIG, intravenous immunoglobulin. PCP, pneumocystis pneumonia. TPO, thrombopoietin receptor.

Supp. Table S2 | Efficacy of CAR T-cell therapy with ide-cel

	Total cohort *n = 129*	German cohort *n = 63*	US cohort *n = 66*	*p*
Best overall response				
≥ PR (ORR)	101 (78)	48 (76)	53 (80)	0.81
≥ CR	47 (36)	23 (37)	24 (36)	0.16
VGPR	22 (17)	14 (22)	8 (12)	
PR	32 (25)	11 (17)	21 (32)	
MR	1 (1)	0 (0)	1 (2)	
SD	12 (9)	7 (11)	5 (8)	
PD	8 (6)	2 (3)	6 (9)	
Not applicable	7 (5)	6 (10)	1 (2)	
Time to first response, months, median (range)	0.9 (0.1-3.8)	0.6 (0.1-3.8)	1.0 (0.5-3.0)	**< 0.0001**
Time to best response, months, median (range)	1.0 (0.2-15.7)	0.9 (0.2-15.7)	1.1 (0.5-12.1)	**0.04**
Progression-free survival, months, median (95% CI)	8.6 (6.7-11.9)	8.6 (7.0-21.2)	8.2 (5.6-NR)	0.89
Overall survival, months, median (95% CI)	NR	NR	NR	0.29
Follow-up, months, median (95% CI)	9.6 (7.9-11.6)	8.8 (6.1-11.5)	10.8 (8.2-12.9)	0.38

CI, confidence interval. CR, complete response. MR, minimal response. NR, not reached. ORR, overall response rate. PD, progressive disease. PR, partial response. SD, stable disease. VGPR, very good partial response.

Supp. Table S3 | Safety of CAR T-cell therapy with ide-cel

	Total cohort *n = 129*	German cohort *n = 63*	US cohort *n = 66*	*p*
CRS, No. (%)				
Yes	109 (84)	57 (90)	52 (79)	
Grade 1	67 (52)	30 (48)	37 (56)	**0.04**
Grade 2	41 (32)	26 (41)	15 (23)	
Grade 3	1 (1)	1 (2)	0 (0)	
No	20 (16)	6 (10)	14 (21)	
ICANS, No. (%)				
Yes	11 (9)	4 (6)	7 (11)	
Grade 1	4 (3)	2 (3)	2 (3)	> 0.99
Grade 2	3 (2)	1 (2)	2 (3)	
Grade 3	3 (2)	1 (2)	2 (3)	
Grade 4	1 (1)	0 (0)	1 (2)	
No	118 (91)	59 (94)	59 (89)	
Supportive measures, No. (%)				
Tocilizumab	66 (51)	32 (51)	34 (52)	> 0.99
Dexamethasone	57 (44)	28 (44)	29 (44)	> 0.99
Late ICAHT, No. (%)				
Yes	64 (60)	35 (64)	29 (56)	
Grade 1	22 (21)	13 (24)	9 (17)	0.19
Grade 2	20 (19)	7 (13)	13 (25)	
Grade 3	16 (15)	10 (18)	6 (12)	
Grade 4	6 (6)	5 (9)	1 (2)	
Severe (Grade ≥ 3)	22 (21)	15 (27)	7 (13)	0.10
No	43 (40)	20 (36)	23 (44)	
Unknown	22	8[a]	14[b]	
Neutrophil recovery phenotype, No. (%)				
Quick	52 (49)	22 (40)	30 (58)	0.13
Intermittent	47 (44)	27 (49)	20 (38)	
Aplastic	8 (7)	6 (11)	2 (4)	0.27
Unknown	22	8[c]	14[c]	
Supportive measures, No. (%)				
Red blood cell transfusion				
≤ day 30	30 (31), n = 96	8 (27), n = 30[d]	22 (33)	0.64
> day 30	7 (8), n = 92	5 (17), n = 30	2 (3), n = 62[e]	**0.04**
Platelet transfusion				
≤ day 30	16 (17), n = 96	1 (3), n = 30[d]	15 (23)	**0.02**
> day 30	8 (9), n = 92	4 (13), n = 30	4 (6), n = 62[e]	0.43
G-CSF				
≤ day 30	47 (49), n = 96	7 (23), n = 30[d]	40 (61)	**0.0009**
> day 30	21 (23), n = 92	5 (17), n = 30	16 (26), n = 62[e]	0.43
as prophylaxis	52 (40)	0 (0)	52 (79)[f]	**< 0.0001**
TPO agonist				
≤ day 30	6 (5)	0 (0)	6 (9)	**0.03**
> day 30	5 (4), n = 122	0 (0), n = 60[g]	5 (8), n = 62[e]	0.06
Autologous SC boost	2 (2)	2 (3)[h]	0 (0)	0.24

Severe late-onset infection, No. (%)				
Yes	15 (13)	11 (20)	4 (7)	0.05
No	101 (87)	44 (80)	57 (93)	
Unknown	13	8[i]	5[j]	
Supportive measures, No. (%)				
IVIG substitution, day 0-90	34 (26)	13 (21)	21 (32)	0.17
CAR T-associated parkinsonism, No. (%)	1 (1)	1 (2)	0 (0)	0.49
Cause of death, No. (%)				
MM-dependent	23 (77)	9 (82)	14 (74)	
MM progression-related	19 (63)	5 (45)	14 (74)	**0.03**
Therapy-related	4 (13)	4 (36)	0 (0)	
Not attributable	0 (0)	0 (0)	0 (0)	
MM-independent	0 (0)	0 (0)	0 (0)	
Not attributable	1 (3)	0 (0)	1 (5)	
Unknown	6 (20)	2 (18)	4 (21)	
Non-relapse mortality, No. (%)	3[k] (10)	3 (27)	0 (0)	**0.02**
Others	25 (83)	7 (64)	18 (95)	
Unknown	2 (7)	1 (9)	1 (5)	

a. n=3 patients with a follow-up ≤ 30 days, n=1 patient without available absolute neutrophil count (ANC) values during the late post-CAR-T period and n=4 patients with only one available ANC value during the late post-CAR-T period (evaluable hemoglobin and platelet values were available for two of the four patients). b. n =4 patients with a follow-up ≤ 30 days, n=9 patients without available ANC values during the late post-CAR-T period and n=1 patient with only one available ANC value during the late post-CAR-T period. c. Patients without available data on ANC recovery during the late post-CAR-T period (see above). d. Data available as part of the medical documentation for n=30 patients. e. n=4 patients with a follow-up ≤ 30 days. f. As prophylaxis prior to CAR T-cell infusion (days before CAR T-cell infusion, median [range]: 3 [0-6]). g. n=3 patients with a follow-up ≤ 30 days. h. n=2 patients received an autologous stem cell boost. Both patients had regular need for red blood cell and platelet transfusions and growth factor stimulation during the late post-CAR-T period, without any signs of a spontaneous stabilization around day 60. Patient 1 received $3{,}2 \times 10^6$ $CD34^+$/kg body weight on day 72 after CAR T-cell infusion. Patient 2 received $2{,}37 \times 10^6$ $CD34^+$/kg body weight on day 63. Both patients showed adequate hematopoietic reconstitution after the stem cell boost. i. n=8 patients with a follow-up < 90 days. j. n=5 patients with a follow-up < 90 days. k. In all three cases, death was due to a severe infection.
ANC, absolute neutrophil count. CRS, cytokine release syndrome. G-CSF, granulocyte-colony stimulating factor. ICAHT, immune effector cell-associated hematotoxicity. ICANS, immune effector cell-associated neurotoxicity syndrome. IVIG, intravenous immunoglobulin. MM, multiple myeloma. SC, stem cell. TPO, thrombopoietin receptor.

Supp. Table S4 | Cytopenias prior to lymphodepletion

	Total cohort ***n = 129***			**German cohort** ***n = 63***			**US cohort** ***n = 66***			***p***
	No./Total No. (%)			No./Total No. (%)			No./Total No. (%)			
CTC grade	**Any**	**1-2**	**3-4**	**Any**	**1-2**	**3-4**	**Any**	**1-2**	**3-4**	
Anemia	113/128 (88)	107/128 (84)	6/128 (5)	56/63 (89)	55/63 (87)	1/63 (2)	57/65 (88)	52/65 (80)	5/65 (8)	0.28
Neutropenia	35/126 (28)	28/126 (22)	7/126 (6)	12/60 (20)	9/60 (15)	3/60 (5)	23/66 (35)	19/66 (29)	4/66 (6)	0.16
Thrombocytopenia	55/129 (43)	47/129 (36)	8/129 (6)	24/63 (38)	21/63 (33)	3/63 (5)	31/66 (47)	26/66 (39)	5/66 (8)	0.58

CTC, Common Terminology Criteria for Adverse Events.

Supp. Table S5 | Cytopenias during the early and late post-CAR-T period

	Total cohort ***n = 129***			**German cohort** ***n = 63***			**US cohort** ***n = 66***			***p***
	No./Total No. (%)			No./Total No. (%)			No./Total No. (%)			
CTC grade	**Any**	**1-2**	**3-4**	**Any**	**1-2**	**3-4**	**Any**	**1-2**	**3-4**	
Anemia										
Day 0-30	129/129 (100)	76/129 (59)	53/129 (41)	63/63 (100)	42/63 (67)	21/63 (33)	66/66 (100)	34/66 (52)	32/66 (48)	0.11
Day 31-90	102/109 (94)	87/109 (80)	15/109 (14)	55/57 (96)	42/57 (74)	13/57 (23)	47/52 (90)	45/52 (87)	2/52 (4)	**0.007**
Neutropenia										
Day 0-30	120/128 (94)	20/128 (16)	100/128 (78)	61/62 (98)	4/62 (6)	57/62 (92)	59/66 (89)	16/66 (24)	43/66 (65)	**0.0006**
Day 31-90	76/107 (71)	34/107 (32)	42/107 (39)	41/55 (75)	19/55 (35)	22/55 (40)	35/52 (67)	15/52 (29)	20/52 (38)	0.71
Thrombocytopenia										
Day 0-30	126/129 (98)	61/129 (47)	65/129 (50)	62/63 (98)	34/63 (54)	28/63 (44)	64/66 (97)	27/66 (41)	37/66 (56)	0.38
Day 31-90	83/109 (76)	46/109 (42)	37/109 (34)	45/57 (79)	25/57 (44)	20/57 (35)	38/52 (73)	21/52 (40)	17/52 (33)	0.78

CTC, Common Terminology Criteria for Adverse Events.

Supp. Table S6 | Comparison of longitudinal neutrophil, platelet and hemoglobin levels between late ICAHT groups

Global comparison of groups across time points			
	Neutrophils	**Platelets**	**Hemoglobin**
Contrast	***adj. P***	***adj. P***	***adj. P***
none – (Grade 1-2)	<0.001	<0.001	0.004
none – (Grade 3-4)	<0.001	<0.001	<0.001
(Grade 1-2) – (Grade 3-4)	<0.001	0.004	0.045

Comparison of groups at individual time points				
		Neutrophils	**Platelets**	**Hemoglobin**
Time point	**Contrast**	***adj. P***	***adj. P***	***adj. P***
Baseline	none – (Grade 1-2)	0.519	0.085	0.060
Baseline	none – (Grade 3-4)	0.078	0.061	0.003
Baseline	(Grade 1-2) – (Grade 3-4)	1.000	1.000	1.000
Day.0	none – (Grade 1-2)	0.138	0.119	0.885
Day.0	none – (Grade 3-4)	0.002	0.043	0.025
Day.0	(Grade 1-2) – (Grade 3-4)	1.000	1.000	1.000
Day..7	none – (Grade 1-2)	0.138	0.002	0.885
Day..7	none – (Grade 3-4)	<0.001	<0.001	0.178
Day..7	(Grade 1-2) – (Grade 3-4)	0.045	1.000	1.000
Day..14	none – (Grade 1-2)	0.737	<0.001	0.204
Day..14	none – (Grade 3-4)	0.054	<0.001	0.178
Day..14	(Grade 1-2) – (Grade 3-4)	1.000	1.000	1.000
Day..21	none – (Grade 1-2)	0.042	0.002	0.017
Day..21	none – (Grade 3-4)	0.001	<0.001	<0.001
Day..21	(Grade 1-2) – (Grade 3-4)	1.000	0.502	1.000
Day..28	none – (Grade 1-2)	0.204	<0.001	0.204
Day..28	none – (Grade 3-4)	<0.001	<0.001	<0.001
Day..28	(Grade 1-2) – (Grade 3-4)	0.003	0.044	0.516
Day..35	none – (Grade 1-2)	0.138	0.046	0.107
Day..35	none – (Grade 3-4)	<0.001	<0.001	<0.001
Day..35	(Grade 1-2) – (Grade 3-4)	0.005	<0.001	0.516
Day..42	none – (Grade 1-2)	0.189	0.011	0.595
Day..42	none – (Grade 3-4)	<0.001	<0.001	<0.001
Day..42	(Grade 1-2) – (Grade 3-4)	0.001	0.001	0.026
Day..50	none – (Grade 1-2)	0.737	0.299	0.885
Day..50	none – (Grade 3-4)	<0.001	<0.001	0.007
Day..50	(Grade 1-2) – (Grade 3-4)	<0.001	0.003	0.375
Day..63	none – (Grade 1-2)	0.097	0.050	0.041
Day..63	none – (Grade 3-4)	<0.001	<0.001	<0.001
Day..63	(Grade 1-2) – (Grade 3-4)	0.547	0.027	0.049
Day..90	none – (Grade 1-2)	0.138	0.050	0.041
Day..90	none – (Grade 3-4)	0.001	0.060	<0.001

Day..90	(Grade 1-2) – (Grade 3-4)	0.929	1.000	1.000

Analysis of interaction between group and time points

	Neutrophils	Platelets	Hemoglobin
Group	***adj. P***	***adj. P***	***adj. P***
all	0.007	<0.001	<0.001
none/Grade 1-2	0.858	0.2	0.198
none/Grade 3-4	<0.001	<0.001	<0.001
Grade 1-2/Grade 3-4	0.009	<0.001	0.005

The analyses shown refer to Fig. 1D-F. ICAHT groups: none vs. grade 1-2 vs. grade 3-4. ICAHT, immune effector cell-associated hematotoxicity.

Supp. Table S7 | Comparison of patient and disease characteristics between baseline EASIX groups (total cohort)

	EASIX ≤ median (≤ 1.26) *n = 64*	**EASIX > median (> 1.26) *n = 62***	***p***	**EASIX ≤ Q_3 (≤ 2.15) *n = 95***	**EASIX > Q_3 (> 2.15) *n = 31***	***p***
Age, years						
Median (range)	65 (35-83)	64 (34-79)	0.83	65 (34-83)	63 (48-74)	0.66
< 70, No. (%)	45 (70)	45 (73)	0.84	67 (71)	23 (74)	0.82
≥ 70, No. (%)	19 (30)	17 (27)		28 (29)	8 (26)	
Sex, No. (%)						
Male	36 (56)	49 (79)	**0.008**	62 (65)	23 (74)	0.39
Female	28 (44)	13 (21)		33 (35)	8 (26)	
ECOG[a], No. (%)						
0-1	55 (96)	55 (95)	> 0.99	83 (97)	27 (93)	0.60
2-3	2 (4)	3 (5)		3 (3)	2 (7)	
Unknown	7	4		9	2	
Cytogenetics, No. (%)						
Standard risk	34 (57)	39 (65)	0.45	53 (59)	20 (67)	0.52
High risk	26 (43)	21 (35)		37 (41)	10 (33)	
Unknown	4	2		5	1	
ISS stage[a], No. (%)						
I	35 (65)	28 (54)	**0.02**	54 (68)	9 (35)	**0.003**
II	18 (33)	15 (29)		22 (28)	11 (42)	
III	1 (2)	9 (17)		4 (5)	6 (23)	
Unknown	10	10		15	5	
R-ISS stage[a], No. (%)						
I	13 (25)	11 (22)	**0.04**	21 (27)	3 (12)	**0.003**
II	39 (75)	34 (67)		55 (71)	18 (69)	
III	0 (0)	6 (12)		1 (1)	5 (19)	
Unknown	12	11		18	5	
Extramedullary disease[a], No. (%)						
Yes	24 (38)	22 (37)	> 0.99	35 (37)	11 (38)	> 0.99
No	39 (62)	38 (63)		59 (63)	18 (62)	
Unknown	1	2		1	2	
Extraosseous disease[a], No. (%)						
Yes	14 (22)	16 (27)	0.68	21 (22)	9 (31)	0.34
No	49 (78)	44 (73)		73 (78)	20 (69)	
Unknown	1	2		1	2	
Bone marrow burden[b] **≥ 50%**, No. (%)						
Yes	6 (18)	8 (23)	0.77	11 (22)	3 (16)	0.74
No	28 (82)	27 (77)		39 (78)	16 (84)	
Unknown	30	27		45	12	
Disease status prior to LD, No. (%)						
≥ CR	0 (0)	0 (0)	0.16	0 (0)	0 (0)	0.54
VGPR/PR	10 (21)	5 (10)		12 (17)	3 (11)	
MR/SD/PD	37 (79)	46 (90)		58 (83)	25 (89)	
Not applicable	17	11		25	3	

Cytopenia CTC grade ≥ 3 prior to LD, No. (%)						
Yes	3 (5)	13 (22)	**0.006**	7 (8)	9 (30)	**0.003**
No	61 (95)	46 (78)		86 (92)	21 (70)	
Unknown	0	3		2	1	
eGFR[a], ml/min, No. (%)						
> 60	52 (81)	41 (66)	0.06	76 (80)	17 (55)	**0.002**
30-60	12 (19)	18 (29)		19 (20)	11 (35)	
< 30	0	3 (5)		0	3 (10)	
Triple-class refractory disease[c], No. (%)						
Yes	52 (81)	52 (84)	0.82	75 (79)	29 (94)	0.10
No	12 (19)	10 (16)		20 (21)	2 (6)	
Penta-drug refractory disease[d], No. (%)						
Yes	18 (28)	22 (35)	0.45	27 (28)	13 (42)	0.19
No	46 (72)	40 (65)		68 (72)	18 (58)	
Bridging therapy[e], No. (%)						
Yes	49 (77)	60 (97)	**0.001**	78 (82)	31 (100)	**0.01**
No	15 (23)	2 (3)		17 (18)	0 (0)	
Cytotoxic bridging therapy[e], No. (%)						
Yes	26 (41)	34 (55)	0.15	45 (47)	15 (48)	> 0.99
No	38 (59)	28 (45)		50 (53)	16 (51)	
Prior BCMA-targeted therapy, No. (%)						
Yes	8 (13)	13 (21)	0.24	13 (14)	8 (26)	0.16
No	56 (88)	49 (79)		82 (86)	23 (74)	
Prior therapy lines, median (95% CI)	5 (5-6)	6 (5-6)	0.15	5 (5-6)	6 (5-7)	0.19
Time from initial diagnosis to CAR T-cell therapy, years, median (range)	6.1 (1.6-14.4)	6.4 (0.6-17.6)	0.94	6.2 (1.6-17.6)	6.4 (0.6-17.2)	0.92
EASIX-F prior to LD, No. (%) [German cohort]						
Low	17 (63)	13 (46)	0.13	27 (60)	3 (30)	**0.0005**
Intermediate	10 (37)	11 (39)		18 (40)	3 (30)	
High	0 (0)	4 (14)		0 (0)	4 (40)	
Unknown	5	3		7	1	
EASIX-FC prior to LD, No. (%) [German cohort]						
Low	25 (93)	15 (54)	**0.003**	40 (89)	0 (0)	**<0.0001**
Intermediate	2 (7)	8 (29)		4 (9)	6 (60)	
High	0 (0)	5 (18)		1 (2)	4 (40)	
Unknown	5	3		7	1	
CAR-HEMATOTOX prior to LD, No. (%) [German cohort]						
Low	26 (93)	17 (61)	**0.01**	39 (85)	4 (40)	**0.007**
High	2 (7)	11 (39)		7 (15)	6 (60)	
Unknown	4	3		6	1	

a. Determined prior to lymphodepletion (baseline). b. Last bone marrow status determined within 90 days prior to CAR T-cell therapy. c. Refractory to an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 monoclonal antibody. d. Refractory to lenalidomide, pomalidomide, bortezomib, carfilzomib and daratumumab. e. Systemic treatment administered between leukapheresis and lymphodepletion (at least one drug).
BCMA, B-cell maturation antigen. CI, confidence interval. CR, complete response. CTC, Common Terminology Criteria for Adverse Events. EASIX, Endothelial Activation and Stress Index. ECOG, Eastern Cooperative Oncology Group performance status. eGFR, estimated glomerular filtration rate. ISS, International Staging System. LD, lymphodepletion. MR, minimal response. PD, progressive disease. PR, partial response. Q_3, third/upper quartile (75th percentile). R-ISS, Revised International Staging System. SD, stable disease. VGPR, very good partial response.

Supp. Table S8 | Comparison of outcomes, complications and supportive measures between baseline EASIX groups (total cohort)

	EASIX ≤ median (≤ 1.26) ***n = 64***	**EASIX > median (> 1.26)** ***n = 62***	***p***	**EASIX ≤ Q_3 (≤ 2.15)** ***n = 95***	**EASIX > Q_3 (> 2.15)** ***n = 31***	***p***
Best overall response, No. (%)						
≥ CR	24 (39)	23 (40)	0.89	37 (41)	10 (34)	0.57
VGPR/PR	28 (45)	23 (40)		39 (43)	12 (41)	
MR/SD/PD	10 (16)	11 (19)		14 (16)	7 (24)	
Not applicable	2	5		5	2	
CRS, No. (%)						
No	11 (17)	9 (15)	0.42	15 (16)	5 (16)	0.71
Grade 1	36 (56)	29 (47)		51 (54)	14 (45)	
Grade 2	17 (27)	23 (37)		28 (29)	12 (39)	
Grade 3	0 (0)	1 (2)		1 (1)	0 (0)	
ICANS, No. (%)						
No	62 (97)	54 (87)	0.08	91 (96)	25 (81)	**0.02**
Grade 1	0 (0)	4 (6)		1 (1)	3 (10)	
Grade 2	0 (0)	2 (3)		1 (1)	1 (3)	
Grade ≥ 3	2 (3)	2 (3)		2 (2)	2 (6)	
Tocilizumab, No. (%)						
No	39 (61)	24 (39)	**0.02**	51 (54)	12 (39)	0.21
Yes	25 (39)	38 (61)		44 (46)	19 (61)	
Dexamethasone, No. (%)						
No	43 (67)	29 (47)	**0.03**	57 (60)	15 (48)	0.30
Yes	21 (33)	33 (53)		38 (40)	16 (52)	
Late ICAHT, No. (%)						
No	31 (57)	10 (20)	**0.0008**	37 (46)	4 (17)	**0.02**
Grade 1	8 (15)	14 (28)		17 (21)	5 (21)	
Grade 2	9 (17)	11 (22)		14 (18)	6 (25)	
Grade ≥ 3 (severe)	6 (11)	15 (30)	**0.03**	12 (15)	9 (38)	**0.02**
Unknown	10	12		15	7	
Neutrophil recovery phenotype, No. (%)						
Quick	34 (63)	16 (32)	**0.002**	43 (54)	7 (29)	**0.01**
Intermittent	19 (35)	27 (54)		34 (43)	12 (50)	
Aplastic	1 (2)	7 (14)	**0.03**	3 (4)	5 (21)	**0.02**
Unknown	10	12		15	7	
Severe anemia, > day 30, No. (%)						
No	51 (94)	40 (77)	**0.01**	75 (91)	16 (67)	**0.005**
Yes	3 (6)	12 (23)		7 (9)	8 (33)	
Unknown	10	10		13	7	
Severe thrombocytopenia, > day 30, No. (%)						
No	45 (83)	26 (50)	**0.0004**	63 (77)	8 (33)	**0.0001**
Yes	9 (17)	26 (50)		19 (23)	16 (67)	
Unknown	10	10		13	7	
Red blood cell transfusion, > day 30, No. (%)						
No	47 (96)	35 (88)	0.24	63 (94)	19 (86)	0.36

Yes	2 (4)	5 (13)		4 (6)	3 (14)	
Unknown	15	22		28	9	
Platelet transfusion, > day 30, No. (%)						
No	47 (96)	34 (85)	0.13	63 (94)	18 (82)	0.10
Yes	2 (4)	6 (15)		4 (6)	4 (18)	
Unknown	15	22		28	9	
G-CSF, > day 30, No. (%)						
No	42 (86)	27 (68)	**0.05**	56 (84)	13 (59)	**0.04**
Yes	7 (14)	13 (33)		11 (16)	9 (41)	
Unknown	15	22		28	9	
G-CSF as prophylaxis, No. (%)						
No	37 (58)	40 (65)	0.47	59 (62)	18 (58)	0.83
Yes	27 (42)	22 (35)		36 (38)	13 (42)	
Severe late-onset infection, No. (%)						
No	54 (93)	44 (80)	0.05	81 (92)	17 (68)	**0.005**
Yes	4 (7)	11 (20)		7 (8)	8 (32)	
Unknown	6	7		7	6	
IVIG substitution, day 0-90, No. (%)						
No	50 (78)	42 (68)	0.23	69 (73)	23 (74)	> 0.99
Yes	14 (22)	20 (32)		26 (27)	8 (26)	
Cause of death, No. (%)						
MM-dependent	7 (70)	16 (80)		11 (73)	12 (80)	
MM progression-related	7 (70)	12 (60)	0.31	9 (60)	10 (67)	> 0.99
Therapy-related	0 (0)	4 (20)		2 (13)	2 (13)	
MM-independent	0 (0)	0 (0)		0 (0)	0 (0)	
Not attributable	1 (10)	0 (0)		1 (7)	0 (0)	
Unknown	2 (20)	4 (20)		3 (20)	3 (20)	
Non-relapse mortality, No. (%)	0 (0)	3 (15)	0.44	1 (7)	2 (13)	0.40
Others	10 (10)	15 (75)		14 (93)	11 (73)	
Unknown	0 (0)	2 (10)		0 (0)	2 (13)	

CR, complete response. CRS, cytokine release syndrome. EASIX, Endothelial Activation and Stress Index. G-CSF, granulocyte-colony stimulating factor. ICAHT, immune effector cell-associated hematotoxicity. ICANS, immune effector cell-associated neurotoxicity syndrome. IVIG, intravenous immunoglobulin. MM, multiple myeloma. MR, minimal response. PD, progressive disease. PR, partial response. Q_3, third/upper quartile (75^{th} percentile). SD, stable disease. VGPR, very good partial response.

Supp. Table S9 | Laboratory parameters and scores at day 0 (day of CAR T-cell infusion)

	Total cohort *n = 129*	German cohort *n = 63*	US cohort *n = 66*	*p*
Laboratory parameters at day 0 (day of CAR T-cell infusion), median (range)				
LDH, U/l	193 (108-1436), n = 119	191 (108-770), n = 60	202 (118-1436), n = 59	0.39
Creatinine, mg/dl	0.84 (0.45-4.82), n = 127	0.91 (0.45-1.68)	0.79 (0.47-4.82), n = 64	**0.003**
Platelet count, cells/nl	130 (7-369)	142 (14-369)	107 (7-253)	**0.001**
Absolute neutrophil count, cells/nl	1.83 (0.14-17.06), n = 112	1.11 (0.18-3.37), n = 46	3.29 (0.14-17.06)	**< 0.0001**
Hemoglobin, g/dl	9.8 (7.2-14.0)	10.2 (7.4-14.0)	9.2 (7.2-12.6)	**0.0003**
CRP, mg/dl	0.7 (0.1-29.49), n = 127	0.43 (0.1-29.49), n = 62	0.89 (0.1-12.55), n = 65	**0.007**
Ferritin, ng/ml	287 (18-4752), n = 105	261 (18-4752), n = 43	293 (68-3655), n = 62	0.61
Scores at day 0 (day of CAR T-cell infusion)				
EASIX, median (Q_1-Q_3)	1.36 (1.00-2.06), n = 117	1.33 (0.98-1.72), n = 60	1.43 (1.05-3.16), n = 57	0.17
> median (> 1.36), No. (%)	58 (50)	27 (45)	31 (54)	0.36
> Q_3 (> 2.06), No. (%)	29 (25)	10 (17)	19 (33)	0.05
Modified EASIX, median (Q_1-Q_3)	1.19 (0.43-3.96), n = 119	0.55 (0.33-2.11), n = 60	1.87 (0.65-7.87), n = 59	**0.0002**
> 6.2, No. (%)	24 (20)	8 (13)	16 (27)	0.07
EASIX-F, No. (%)				
Low	50 (51)	23 (52)	27 (50)	0.92
Intermediate	35 (36)	16 (36)	19 (35)	
High	13 (13)	5 (11)	8 (15)	
Unknown	31	19	12	
EASIX-FC, No. (%)				
Low	59 (60)	32 (74)	27 (48)	**0.002**
Intermediate	32 (32)	6 (14)	26 (46)	
High	8 (8)	5 (12)	3 (5)	
Unknown	30	20	10	
CAR-HEMATOTOX, No. (%)				
Low	38 (34)	17 (35)	21 (33)	0.84
High	73 (66)	31 (65)	42 (67)	
Unknown	18	15	3	

CRP, C-reactive protein. EASIX, Endothelial Activation and Stress Index. LDH, lactate dehydrogenase. Q_1, first/lower quartile (25th percentile). Q_3, third/upper quartile (75th percentile).

Supp. Table S10 | Logistic regression analysis of late ICAHT

	Univariate analysis: Late ICAHT				
Characteristic	**N**	**Event N**	**OR**	**95% CI**	**p-value**
Age [cont.]	107	64	1	0.96, 1.04	0,96
Age ≥ 70 years					
No	76	44	—	—	
Yes	31	20	1,32	0.56, 3.22	0,53
Sex					
M	76	42	—	—	
W	31	22	1,98	0.83, 5.05	0,14
High risk cytogenetics					
No	63	39	—	—	
Yes	39	24	0,98	0.43, 2.26	0,97
ISS 3[a]					
No	87	54	—	—	
Yes	8	5	1,02	0.23, 5.23	0,98
R-ISS 3[a]					
No	91	57	—	—	
Yes	4	2	0,6	0.07, 5.16	0,61
Extramedullary disease[a]					
No	63	36	—	—	
Yes	41	25	1,17	0.53, 2.64	0,7
Extraosseous disease[a]					
No	77	42	—	—	
Yes	27	19	1,98	0.79, 5.30	0,15
BM burden ≥ 50%[b]					
No	47	31	—	—	
Yes	11	8	1,38	0.34, 6.94	0,67
PD prior to LD					
No	45	23	—	—	
Yes	42	29	2,13	0.90, 5.23	0,09
Gr. 3-4 cytopenia prior to LD					
No	90	49	—	—	
Yes	14	13	10,9	2.03, 202	**0,024**
eGFR < 60 ml/min[a]					
No	80	47	—	—	
Yes	27	17	1,19	0.49, 3.01	0,7
Triple-class refractory[c]					
No	18	13	—	—	
Yes	89	51	0,52	0.15, 1.50	0,24
Penta-drug refractory[d]					
No	74	44	—	—	
Yes	33	20	1,05	0.46, 2.46	0,91
Prior BCMA-TT					
No	90	54	—	—	
Yes	17	10	0,95	0.33, 2.84	0,93
Bridging therapy[e]					
No	17	7	—	—	
Yes	90	57	2,47	0.87, 7.39	0,094
CRS ≥ °2					
No	73	40	—	—	
Yes	34	24	1,98	0.85, 4.88	0,12
Tocilizumab					
No	54	27	—	—	
Yes	53	37	2,31	1.06, 5.19	**0,038**
Dexamethasone					
No	63	33	—	—	
Yes	44	31	2,17	0.97, 5.00	0,063
log2(LDH) [bl]	104	63	2,12	1.00, 5.31	0,075
LDH > ULN [bl]					
No	78	44	—	—	
Yes	26	19	2,1	0.82, 5.89	0,14
log2(PLT) [bl]	107	64	0,31	0.14, 0.60	**0,001**
PLT < LLN [bl]					
No	63	28	—	—	
Yes	44	36	5,63	2.34, 14.8	**<0.001**
log2(creatinine) [bl]	107	64	0,95	0.40, 2.26	0,9

creatinine > ULN [bl]					
No	84	46	—	—	
Yes	23	18	2,97	1.07, 9.68	**0,048**
log2(CRP) [bl]	97	60	0,82	0.64, 1.03	0,093
CRP > ULN [bl]					
No	60	41	—	—	
Yes	37	19	0,49	0.21, 1.13	0,1
log2(ferritin) [bl][f]	47	32	1,15	0.88, 1.56	0,32
Ferritin > ULN [bl][f]					
No	29	20	—	—	
Yes	18	12	0,9	0.26, 3.27	0,87
log2(ANC) [bl]	104	62	0,34	0.17, 0.64	**0,001**
ANC < LLN [bl]					
No	74	38	—	—	
Yes	30	24	3,79	1.46, 11.2	**0,009**
log2(HGB) [bl]	106	63	0,03	0.00, 0.19	**<0.001**
HGB < LLN [bl]					
No	13	7	—	—	
Yes	93	56	1,3	0.39, 4.21	0,66
log2(B2-MG) [bl]	95	59	1,66	0.82, 3.54	0,17
log2(LDH x creatinine) [bl]	104	63	1,53	0.90, 2.90	0,15
log2(EASIX) [bl]	104	63	2,11	1.33, 3.65	**0,004**
EASIX > median (> 1.26) [bl]					
No	54	23	—	—	
Yes	50	40	5,39	2.30, 13.5	**<0.001**
EASIX > Q3 (> 2.15) [bl]					
No	80	43	—	—	
Yes	24	20	4,3	1.47, 15.8	**0,014**
log2(m-EASIX) [bl]	96	60	1	0.84, 1.20	>0.99
m-EASIX > 6.2 [bl]					
No	87	53	—	—	
Yes	9	7	2,25	0.51, 15.7	0,33
EASIX-F high [bl][f]					
No	52	32	—	—	
Yes	3	3	—	—	—
EASIX-F inter/high [bl][f]					
No	26	17	—	—	
Yes	21	15	1,32	0.38, 4.78	0,66
EASIX-FC high [bl][f]					
No	42	27	—	—	
Yes	5	5	—	—	—
EASIX-FC inter/high [bl][f]					
No	35	22	—	—	
Yes	14	11	2,17	0.55, 10.9	0,3
CAR-HTX high [bl][f]					
No	36	22	—	—	
Yes	12	12	—	—	—
log2(EASIX) [d0]	96	55	2,22	1.37, 3.99	**0,003**
EASIX > median (> 1.36) [d0]					
No	49	20	—	—	
Yes	47	35	4,23	1.81, 10.4	**0,001**
EASIX > Q3 (> 2.06) [d0]					
No	74	37	—	—	
Yes	22	18	4,5	1.51, 16.7	**0,012**
log2(m-EASIX) [d0]	98	56	1,09	0.92, 1.30	0,35
m-EASIX > 6.2 [d0]					
No	78	44	—	—	
Yes	20	12	1,16	0.43, 3.26	0,77
EASIX-F high [d0]					
No	86	47	—	—	
Yes	10	8	3,32	0.78, 22.9	0,14
EASIX-F inter/high [d0]					
No	41	23	—	—	
Yes	40	28	1,83	0.74, 4.65	0,2
EASIX-FC high [d0]					
No	77	47	—	—	
Yes	7	7	—	—	—
EASIX-FC inter/high [d0]					
No	47	30	—	—	
Yes	38	23	0,87	0.36, 2.11	0,75

CAR-HTX high [d0]					
No	30	15	—	—	
Yes	61	44	2,59	1.05, 6.51	**0,04**
			Multivariate analysis: Late ICAHT		
Characteristic			**OR**	**95% CI**	**p-value**
PD prior to LD			1,66	0.60, 4.66	0,33
Gr. 3-4 cytopenia prior to LD			8,36	1.28, 168	0,061
Bridging therapy			0,79	0.12, 5.45	0,8
Tocilizumab			1,36	0.37, 5.08	0,64
Dexamethasone			1,52	0.38, 6.07	0,55
EASIX > median (> 1.26) [bl]			3,59	1.30, 10.5	**0,016**
Age ≥ 70 years			1,77	0.54, 6.26	0,35
Sex [W]			6,01	1.64, 26.4	**0,011**
PD prior to LD			2,16	0.70, 6.92	0,18
Gr. 3-4 cytopenia prior to LD			8,7	1.16, 191	0,072
Bridging therapy			0,41	0.05, 3.23	0,39
Tocilizumab			1,52	0.51, 4.56	0,45
EASIX > median (> 1.26) [bl]			6,18	1.96, 22.2	**0,003**
log2(LDH) [bl]			2,15	0.81, 6.53	0,15
log2(PLT) [bl]			0,34	0.15, 0.66	**0,004**
log2(creatinine) [bl]			1,02	0.38, 2.70	0,97
log2(LDH) [bl]			3,63	1.06, 15.0	0,052
log2(PLT) [bl]			0,58	0.23, 1.35	0,23
log2(creatinine) [bl]			1,17	0.38, 3.62	0,78
log2(ANC) [bl]			0,57	0.23, 1.29	0,19
log2(HGB) [bl]			0,03	0.00, 0.45	**0,015**
log2(CRP) [bl]			0,68	0.48, 0.93	**0,019**
LDH > ULN [bl]			2,16	0.66, 7.80	0,21
PLT < LLN [bl]			4,55	1.61, 14.5	**0,006**
creatinine > ULN [bl]			4,93	1.32, 22.9	**0,026**
ANC < LLN [bl]			2,77	0.92, 9.36	0,081
HGB < LLN [bl]			0,76	0.16, 3.41	0,72
CRP > ULN [bl]			0,29	0.09, 0.83	**0,026**
CAR-HTX high [d0]			1,63	0.56, 4.68	0,37
EASIX > median (> 1.36) [d0]			3,82	1.37, 11.3	**0,012**

a. Determined prior to lymphodepletion (baseline). b. Last bone marrow status determined within 90 days prior to CAR T-cell therapy. c. Refractory to an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 monoclonal antibody. d. Refractory to lenalidomide, pomalidomide, bortezomib, carfilzomib and daratumumab. e. Systemic treatment administered between leukapheresis and lymphodepletion (at least one drug). f. Due to missing data for the US cohort, analyses of ferritin and ferritin-based scores prior to lymphodepletion were only performed for the German cohort.
ANC, absolute neutrophil count. B2-MG, beta-2-microglobulin. BCMA, B-cell maturation antigen. bl, baseline. BM, bone marrow. CAR-HTX, CAR-HEMATOTOX score. CI, confidence interval. CRP, C-reactive protein. CRS, cytokine release syndrome. d0, day 0 (day of CAR T-cell infusion). EASIX, Endothelial Activation and Stress Index. eGFR, estimated glomerular filtration rate. HGB, hemoglobin. ICAHT, immune effector cell-associated hematotoxicity. ICANS, immune effector cell-associated neurotoxicity syndrome. ISS, International Staging System. LD, lymphodepletion. LDH, lactate dehydrogenase. LLN, lower limit of normal. m-EASIX, modified EASIX. OR, odds ratio. PD, progressive disease. PLT, platelet count. Q_3, third/upper quartile (75th percentile). R-ISS, Revised International Staging System. ULN, upper limit of normal.

Supp. Table S11 | Logistic regression analysis of severe late ICAHT

	Univariate analysis: Severe late ICAHT				
Characteristic	**N**	**Event N**	**OR**	**95% CI**	**p-value**
Age [cont.]	107	22	0,98	0.93, 1.03	0,38
Age ≥ 70 years					
No	76	17	—	—	
Yes	31	5	0,67	0.20, 1.90	0,47
Sex					
M	76	13	—	—	
W	31	9	1,98	0.73, 5.26	0,17
High risk cytogenetics					
No	63	11	—	—	
Yes	39	11	1,86	0.71, 4.87	0,2
ISS 3[a]					
No	87	18	—	—	
Yes	8	2	1,28	0.18, 6.10	0,78
R-ISS 3[a]					
No	91	19	—	—	
Yes	4	1	1,26	0.06, 10.5	0,84
Extramedullary disease[a]					
No	63	14	—	—	
Yes	41	7	0,72	0.25, 1.93	0,52
Extraosseous disease[a]					
No	77	16	—	—	
Yes	27	5	0,87	0.26, 2.52	0,8
BM burden ≥ 50%[b]					
No	47	13	—	—	
Yes	11	1	0,26	0.01, 1.58	0,22
PD prior to LD					
No	45	8	—	—	
Yes	42	10	1,45	0.51, 4.21	0,49
Gr. 3-4 cytopenia prior to LD					
No	90	15	—	—	
Yes	14	6	3,75	1.10, 12.4	**0,03**
eGFR < 60 ml/min[a]					
No	80	15	—	—	
Yes	27	7	1,52	0.52, 4.15	0,43
Triple-class refractory[c]					
No	18	6	—	—	
Yes	89	16	0,44	0.15, 1.41	0,15
Penta-drug refractory[d]					
No	74	17	—	—	
Yes	33	5	0,6	0.18, 1.69	0,36
Prior BCMA-TT					
No	90	18	—	—	
Yes	17	4	1,23	0.32, 3.97	0,74
Bridging therapy[e]					
No	17	1	—	—	
Yes	90	21	4,87	0.91, 90.4	0,14
CRS ≥ °2					
No	73	14	—	—	
Yes	34	8	1,3	0.47, 3.42	0,6
Tocilizumab					
No	54	10	—	—	
Yes	53	12	1,29	0.50, 3.36	0,6
Dexamethasone					
No	63	12	—	—	
Yes	44	10	1,25	0.48, 3.22	0,64
log2(LDH) [bl]	104	21	3,5	1.60, 9.14	**0,004**
LDH > ULN [bl]					
No	78	11	—	—	
Yes	26	10	3,81	1.37, 10.6	**0,01**
log2(PLT) [bl]	107	22	0,76	0.47, 1.25	0,25
PLT < LLN [bl]					
No	63	9	—	—	
Yes	44	13	2,52	0.98, 6.75	0,059
log2(creatinine) [bl]	107	22	2,02	0.73, 5.93	0,18

creatinine > ULN [bl]					
No	84	11	—	—	
Yes	23	11	6,08	2.18, 17.5	**<0.001**
log2(CRP) [bl]	97	20	0,98	0.73, 1.29	0,89
CRP > ULN [bl]					
No	60	14	—	—	
Yes	37	6	0,64	0.21, 1.77	0,4
log2(ferritin) [bl][f]	47	14	1,19	0.90, 1.59	0,23
Ferritin > ULN [bl][f]					
No	29	9	—	—	
Yes	18	5	0,85	0.22, 3.07	0,81
log2(ANC) [bl]	104	20	0,5	0.25, 0.97	**0,045**
ANC < LLN [bl]					
No	74	12	—	—	
Yes	30	8	1,88	0.66, 5.17	0,22
log2(HGB) [bl]	106	22	0,08	0.01, 0.63	**0,02**
HGB < LLN [bl]					
No	13	0	—	—	
Yes	93	22	—	—	—
log2(B2-MG) [bl]	95	20	1,6	0.71, 3.64	0,25
log2(LDH x creatinine) [bl]	104	21	2,69	1.48, 5.57	**0,003**
log2(EASIX) [bl]	104	21	1,51	1.09, 2.26	**0,022**
EASIX > median (> 1.26) [bl]					
No	54	6	—	—	
Yes	50	15	3,43	1.26, 10.4	**0,02**
EASIX > Q3 (> 2.15) [bl]					
No	80	12	—	—	
Yes	24	9	3,4	1.20, 9.58	**0,02**
log2(m-EASIX) [bl]	96	20	1,09	0.89, 1.33	0,37
m-EASIX > 6.2 [bl]					
No	87	16	—	—	
Yes	9	4	3,55	0.80, 14.9	0,081
EASIX-F high [bl][f]					
No	52	12	—	—	
Yes	3	3	—	—	—
EASIX-F inter/high [bl][f]					
No	26	7	—	—	
Yes	21	7	1,36	0.38, 4.85	0,63
EASIX-FC high [bl][f]					
No	42	11	—	—	
Yes	5	3	4,23	0.62, 35.5	0,14
EASIX-FC inter/high [bl][f]					
No	35	8	—	—	
Yes	14	7	3,38	0.91, 13.0	0,069
CAR-HTX high [bl][f]					
No	36	10	—	—	
Yes	12	4	1,3	0.29, 5.18	0,71
log2(EASIX) [d0]	96	18	1,79	1.24, 2.87	**0,006**
EASIX > median (> 1.36) [d0]					
No	49	4	—	—	
Yes	47	14	4,77	1.55, 18.0	**0,011**
EASIX > Q3 (> 2.06) [d0]					
No	74	8	—	—	
Yes	22	10	6,87	2.28, 21.7	**<0.001**
log2(m-EASIX) [d0]	98	18	1,25	1.02, 1.55	**0,031**
m-EASIX > 6.2 [d0]					
No	78	10	—	—	
Yes	20	8	4,53	1.47, 14.0	**0,008**
EASIX-F high [d0]					
No	86	12	—	—	
Yes	10	6	9,25	2.32, 41.1	**0,002**
EASIX-F inter/high [d0]					
No	41	6	—	—	
Yes	40	10	1,94	0.64, 6.31	0,25
EASIX-FC high [d0]					
No	77	13	—	—	
Yes	7	4	6,56	1.30, 36.8	**0,022**

EASIX-FC inter/high [d0]					
No	47	8	—	—	
Yes	38	11	1,99	0.71, 5.76	0,19
CAR-HTX high [d0]					
No	30	6	—	—	
Yes	61	15	1,3	0.46, 4.05	0,63

Multivariate analysis: Severe late ICAHT			
Characteristic	**OR**	**95% CI**	**p-value**
Bridging therapy	2,78	0.46, 53.5	0,35
EASIX > median (> 1.26) [bl]	2,91	1.04, 9.14	0,051
Gr. 3-4 cytopenia prior to LD	2,86	0.79, 10.0	0,1
EASIX > median (> 1.26) [bl]	2,79	0.96, 8.83	0,066
Age ≥ 70 years	0,88	0.25, 2.76	0,83
Sex [W]	2,42	0.75, 8.09	0,14
Bridging therapy	2,96	0.44, 60.9	0,34
Gr. 3-4 cytopenia prior to LD	2,39	0.63, 8.60	0,18
EASIX > median (> 1.26) [bl]	3,16	0.99, 11.3	0,06
log2(LDH) [bl]	3,78	1.55, 10.3	**0,005**
log2(PLT) [bl]	1,26	0.65, 2.58	0,51
log2(creatinine) [bl]	1,97	0.66, 6.38	0,23
log2(LDH) [bl]	4,14	1.55, 12.8	**0,007**
log2(PLT) [bl]	2,25	0.99, 5.55	0,064
log2(creatinine) [bl]	2,01	0.62, 6.68	0,23
log2(ANC) [bl]	0,49	0.20, 1.09	0,093
log2(HGB) [bl]	0,21	0.01, 4.24	0,31
LDH > ULN [bl]	2,84	0.88, 8.98	0,075
PLT < LLN [bl]	1,96	0.62, 6.48	0,25
creatinine > ULN [bl]	5,56	1.71, 18.6	**0,004**
ANC < LLN [bl]	1,14	0.31, 3.84	0,83
CAR-HTX high [bl]	0,66	0.13, 3.04	0,6
EASIX > median (> 1.26) [bl]	4,69	1.14, 22.5	**0,039**
CAR-HTX high [d0]	0,66	0.16, 2.66	0,55
EASIX > median (> 1.36) [d0]	5,22	1.44, 23.9	**0,019**

a. Determined prior to lymphodepletion (baseline). b. Last bone marrow status determined within 90 days prior to CAR T-cell therapy. c. Refractory to an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 monoclonal antibody. d. Refractory to lenalidomide, pomalidomide, bortezomib, carfilzomib and daratumumab. e. Systemic treatment administered between leukapheresis and lymphodepletion (at least one drug). f. Due to missing data for the US cohort, analyses of ferritin and ferritin-based scores prior to lymphodepletion were only performed for the German cohort.
ANC, absolute neutrophil count. B2-MG, beta-2-microglobulin. BCMA, B-cell maturation antigen. bl, baseline. BM, bone marrow. CAR-HTX, CAR-HEMATOTOX score. CI, confidence interval. CRP, C-reactive protein. CRS, cytokine release syndrome. d0, day 0 (day of CAR T-cell infusion). EASIX, Endothelial Activation and Stress Index. eGFR, estimated glomerular filtration rate. HGB, hemoglobin. ICAHT, immune effector cell-associated hematotoxicity. ICANS, immune effector cell-associated neurotoxicity syndrome. ISS, International Staging System. LD, lymphodepletion. LDH, lactate dehydrogenase. LLN, lower limit of normal. m-EASIX, modified EASIX. OR, odds ratio. PD, progressive disease. PLT, platelet count. Q_3, third/upper quartile (75th percentile). R-ISS, Revised International Staging System. ULN, upper limit of normal.

Supp. Table S12 | Logistic regression analysis of an aplastic phenotype of neutrophil recovery

	Univariate analysis: Aplastic phenotype				
Characteristic	**N**	**Event N**	**OR**	**95% CI**	**p-value**
Age [cont.]	107	8	0,98	0.91, 1.06	0,64
Age ≥ 70 years					
No	76	6	—	—	
Yes	31	2	0,8	0.11, 3.73	0,8
Sex					
M	76	5	—	—	
W	31	3	1,52	0.30, 6.63	0,58
High risk cytogenetics					
No	63	3	—	—	
Yes	39	5	2,94	0.68, 15.1	0,16
ISS 3[a]					
No	87	7	—	—	
Yes	8	1	1,63	0.08, 11.3	0,67
R-ISS 3[a]					
No	91	7	—	—	
Yes	4	1	4	0.18, 36.4	0,26
Extramedullary disease[a]					
No	63	4	—	—	
Yes	41	3	1,16	0.22, 5.56	0,85
Extraosseous disease[a]					
No	77	4	—	—	
Yes	27	3	2,28	0.42, 11.1	0,3
BM burden ≥ 50%[b]					
No	47	5	—	—	
Yes	11	0	—	—	—
PD prior to LD					
No	45	1	—	—	
Yes	42	5	5,95	0.91, 117	0,11
Gr. 3-4 cytopenia prior to LD					
No	90	4	—	—	
Yes	14	3	5,86	1.04, 30.2	**0,033**
eGFR < 60 ml/min[a]					
No	80	6	—	—	
Yes	27	2	0,99	0.14, 4.61	0,99
Triple-class refractory[c]					
No	18	2	—	—	
Yes	89	6	0,58	0.12, 4.19	0,52
Penta-drug refractory[d]					
No	74	6	—	—	
Yes	33	2	0,73	0.10, 3.38	0,71
Prior BCMA-TT					
No	90	5	—	—	
Yes	17	3	3,64	0.69, 16.6	0,1
Bridging therapy[e]					
No	17	1	—	—	
Yes	90	7	1,35	0.22, 26.1	0,79
CRS ≥ °2					
No	73	4	—	—	
Yes	34	4	2,3	0.51, 10.3	0,26
Tocilizumab					
No	54	1	—	—	
Yes	53	7	8,07	1.36, 154	0,055
Dexamethasone					
No	63	2	—	—	
Yes	44	6	4,82	1.05, 34.0	0,062
log2(LDH) [bl]	104	8	3,36	1.39, 9.00	**0,008**
LDH > ULN [bl]					
No	78	3	—	—	
Yes	26	5	5,95	1.35, 31.0	**0,021**
log2(PLT) [bl]	107	8	0,63	0.35, 1.26	0,15
PLT < LLN [bl]					
No	63	3	—	—	
Yes	44	5	2,56	0.60, 13.1	0,21
log2(creatinine) [bl]	107	8	1,98	0.42, 8.33	0,35

creatinine > ULN [bl]					
No	84	3	—	—	
Yes	23	5	7,5	1.69, 39.4	**0,009**
log2(CRP) [bl]	97	8	1,53	1.04, 2.29	**0,031**
CRP > ULN [bl]					
No	60	3	—	—	
Yes	37	5	2,97	0.68, 15.2	0,15
log2(ferritin) [bl][f]	47	6	1,44	0.97, 2.27	0,084
Ferritin > ULN [bl][f]					
No	29	3	—	—	
Yes	18	3	1,73	0.29, 10.4	0,53
log2(ANC) [bl]	104	6	1,01	0.34, 3.34	0,99
ANC < LLN [bl]					
No	74	5	—	—	
Yes	30	1	0,48	0.02, 3.12	0,51
log2(HGB) [bl]	106	8	0,17	0.01, 3.88	0,26
HGB < LLN [bl]					
No	13	0	—	—	
Yes	93	8	—	—	—
log2(B2-MG) [bl]	95	8	1,58	0.48, 4.90	0,43
log2(LDH x creatinine) [bl]	104	8	2,44	1.23, 5.04	**0,01**
log2(EASIX) [bl]	104	8	1,53	1.05, 2.30	**0,026**
EASIX > median (> 1.26) [bl]					
No	54	1	—	—	
Yes	50	7	8,63	1.46, 165	**0,048**
EASIX > Q3 (> 2.15) [bl]					
No	80	3	—	—	
Yes	24	5	6,75	1.53, 35.3	**0,014**
log2(m-EASIX) [bl]	96	8	1,42	1.11, 1.90	**0,008**
m-EASIX > 6.2 [bl]					
No	87	4	—	—	
Yes	9	4	16,6	3.15, 93.4	**<0.001**
EASIX-F high [bl][f]					
No	52	4	—	—	
Yes	3	2	24	1.92, 591	**0,017**
EASIX-F inter/high [bl][f]					
No	26	3	—	—	
Yes	21	3	1,28	0.21, 7.64	0,78
EASIX-FC high [bl][f]					
No	42	3	—	—	
Yes	5	3	19,5	2.42, 206	**0,007**
EASIX-FC inter/high [bl][f]					
No	35	2	—	—	
Yes	14	4	6,6	1.12, 53.0	**0,044**
CAR-HTX high [bl][f]					
No	36	3	—	—	
Yes	12	3	3,67	0.59, 23.0	0,15
log2(EASIX) [d0]	96	8	1,67	1.14, 2.63	**0,011**
EASIX > median (> 1.36) [d0]					
No	49	1	—	—	
Yes	47	7	8,4	1.41, 160	0,051
EASIX > Q3 (> 2.06) [d0]					
No	74	2	—	—	
Yes	22	6	13,5	2.82, 98.2	**0,003**
log2(m-EASIX) [d0]	98	8	1,47	1.12, 1.99	**0,007**
m-EASIX > 6.2 [d0]					
No	78	3	—	—	
Yes	20	5	8,33	1.85, 44.3	**0,007**
EASIX-F high [d0]					
No	86	3	—	—	
Yes	10	5	27,7	5.38, 173	**<0.001**
EASIX-F inter/high [d0]					
No	41	3	—	—	
Yes	40	5	1,81	0.41, 9.35	0,44
EASIX-FC high [d0]					
No	77	5	—	—	
Yes	7	3	10,8	1.75, 64.8	**0,008**
EASIX-FC inter/high [d0]					
No	47	2	—	—	
Yes	38	6	4,22	0.91, 30.1	0,09

CAR-HTX high [d0]					
No	30	2	—	—	
Yes	61	6	1,53	0.33, 10.9	0,62

a. Determined prior to lymphodepletion (baseline). b. Last bone marrow status determined within 90 days prior to CAR T-cell therapy. c. Refractory to an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 monoclonal antibody. d. Refractory to lenalidomide, pomalidomide, bortezomib, carfilzomib and daratumumab. e. Systemic treatment administered between leukapheresis and lymphodepletion (at least one drug). f. Due to missing data for the US cohort, analyses of ferritin and ferritin-based scores prior to lymphodepletion were only performed for the German cohort.
ANC, absolute neutrophil count. B2-MG, beta-2-microglobulin. BCMA, B-cell maturation antigen. bl, baseline. BM, bone marrow. CAR-HTX, CAR-HEMATOTOX score. CI, confidence interval. CRP, C-reactive protein. CRS, cytokine release syndrome. d0, day 0 (day of CAR T-cell infusion). EASIX, Endothelial Activation and Stress Index. eGFR, estimated glomerular filtration rate. HGB, hemoglobin. ICANS, immune effector cell-associated neurotoxicity syndrome. ISS, International Staging System. LD, lymphodepletion. LDH, lactate dehydrogenase. LLN, lower limit of normal. m-EASIX, modified EASIX. OR, odds ratio. PD, progressive disease. PLT, platelet count. Q_3, third/upper quartile (75^{th} percentile). R-ISS, Revised International Staging System. ULN, upper limit of normal.

Supp. Table S13 | Logistic regression analysis of severe late-onset infections

	Univariate analysis: Severe late-onset infection				
Characteristic	**N**	**Event N**	**OR**	**95% CI**	**p-value**
Age [cont.]	116	15	0,97	0.91, 1.02	0,23
Age ≥ 70 years					
No	84	13	—	—	
Yes	32	2	0,36	0.05, 1.43	0,2
Sex					
No	80	12	—	—	
Yes	36	3	0,52	0.11, 1.76	0,33
High risk cytogenetics					
No	71	7	—	—	
Yes	41	8	2,22	0.73, 6.84	0,16
ISS 3[a]					
No	97	13	—	—	
Yes	8	2	2,15	0.29, 10.6	0,38
R-ISS 3[a]					
No	101	14	—	—	
Yes	4	1	2,07	0.10, 17.5	0,54
Extramedullary disease[a]					
No	70	6	—	—	
Yes	44	8	2,37	0.77, 7.72	0,14
Extraosseous disease[a]					
No	85	9	—	—	
Yes	29	5	1,76	0.50, 5.62	0,35
BM burden ≥ 50%[b]					
No	54	5	—	—	
Yes	13	2	1,78	0.23, 9.55	0,52
PD prior to LD					
No	50	4	—	—	
Yes	44	7	2,18	0.61, 8.84	0,24
Gr. 3-4 cytopenia prior to LD					
No	99	11	—	—	
Yes	14	3	2,18	0.44, 8.37	0,28
eGFR < 60 ml/min[a]					
No	85	8	—	—	
Yes	31	7	2,81	0.90, 8.63	0,069
Triple-class refractory[c]					
No	16	3	—	—	
Yes	100	12	0,59	0.16, 2.84	0,46
Penta-drug refractory[d]					
No	79	9	—	—	
Yes	37	6	1,51	0.47, 4.55	0,47
Prior BCMA-TT					
No	97	13	—	—	
Yes	19	2	0,76	0.11, 3.10	0,73
Bridging therapy[e]					
No	16	0	—	—	
Yes	100	15	—	—	—
CRS ≥ °2					
No	78	8	—	—	
Yes	38	7	1,98	0.64, 5.98	0,22
Tocilizumab					
No	57	6	—	—	
Yes	59	9	1,53	0.51, 4.86	0,45
Dexamethasone					
No	66	6	—	—	
Yes	50	9	2,2	0.74, 6.99	0,16
log2(LDH) [bl]	113	15	2,32	1.09, 5.11	**0,027**
LDH > ULN [bl]					
No	79	9	—	—	
Yes	34	6	1,67	0.52, 5.07	0,37
log2(PLT) [bl]	116	15	0,58	0.34, 0.99	**0,04**
PLT < LLN [bl]					
No	67	5	—	—	
Yes	49	10	3,18	1.05, 10.9	**0,048**
log2(creatinine) [bl]	116	15	3,1	1.00, 10.7	0,054

creatinine > ULN [bl]					
No	90	7	—	—	
Yes	26	8	5,27	1.69, 16.9	**0,004**
log2(CRP) [bl]	104	14	1,22	0.91, 1.65	0,18
CRP > ULN [bl]					
No	63	7	—	—	
Yes	41	7	1,65	0.52, 5.21	0,39
log2(ferritin) [bl][f]	48	11	1,1	0.80, 1.51	0,55
Ferritin > ULN [bl][f]					
No	30	8	—	—	
Yes	18	3	0,55	0.11, 2.26	0,43
log2(ANC) [bl]	113	13	1,02	0.47, 2.33	0,97
ANC < LLN [bl]					
No	81	10	—	—	
Yes	32	3	0,73	0.16, 2.61	0,66
log2(HGB) [bl]	115	15	0,05	0.00, 0.59	**0,021**
HGB < LLN [bl]					
No	13	0	—	—	
Yes	102	15	—	—	—
log2(B2-MG) [bl]	105	15	2,59	1.09, 6.56	**0,035**
log2(LDH x creatinine) [bl]	113	15	2,3	1.28, 4.40	**0,007**
log2(EASIX) [bl]	113	15	1,63	1.15, 2.51	**0,011**
EASIX > median (> 1.26) [bl]					
No	58	4	—	—	
Yes	55	11	3,38	1.07, 12.9	**0,049**
EASIX > Q3 (> 2.15) [bl]					
No	88	7	—	—	
Yes	25	8	5,45	1.74, 17.6	**0,004**
log2(m-EASIX) [bl]	103	14	1,24	1.00, 1.54	**0,043**
m-EASIX > 6.2 [bl]					
No	94	10	—	—	
Yes	9	4	6,72	1.46, 29.8	**0,011**
EASIX-F high [bl][f]					
No	51	8	—	—	
Yes	4	3	16,1	1.82, 350	**0,022**
EASIX-F inter/high [bl][f]					
No	26	6	—	—	
Yes	22	5	0,98	0.24, 3.82	0,98
EASIX-FC high [bl][f]					
No	43	8	—	—	
Yes	5	3	6,56	0.94, 56.6	0,058
EASIX-FC inter/high [bl][f]					
No	34	4	—	—	
Yes	15	7	6,56	1.60, 30.9	**0,011**
CAR-HTX high [bl][f]					
No	38	8	—	—	
Yes	11	3	1,41	0.26, 6.26	0,66
log2(EASIX) [d0]	105	15	1,67	1.18, 2.58	**0,008**
EASIX > median (> 1.36) [d0]					
No	54	4	—	—	
Yes	51	11	3,44	1.08, 13.2	**0,047**
EASIX > Q3 (> 2.06) [d0]					
No	80	8	—	—	
Yes	25	7	3,5	1.10, 11.1	**0,031**
log2(m-EASIX) [d0]	106	15	1,25	1.01, 1.56	**0,038**
m-EASIX > 6.2 [d0]					
No	85	9	—	—	
Yes	21	6	3,38	1.01, 10.9	**0,042**
EASIX-F high [d0]					
No	93	9	—	—	
Yes	12	6	9,33	2.47, 36.4	**<0.001**
EASIX-F inter/high [d0]					
No	45	6	—	—	
Yes	44	8	1,44	0.46, 4.77	0,53
EASIX-FC high [d0]					
No	86	9	—	—	
Yes	7	4	11,4	2.20, 66.4	**0,004**
EASIX-FC inter/high [d0]					
No	51	7	—	—	
Yes	43	8	1,44	0.47, 4.47	0,52

CAR-HTX high [d0]					
No	34	1	—	—	
Yes	64	14	9,24	1.73, 171	**0,036**
Multivariate analysis: Severe late-onset infection					
Characteristic			**OR**	**95% CI**	**p-value**
Age ≥ 70 years			0,3	0.04, 1.28	0,15
Sex [W]			0,52	0.10, 1.94	0,36
EASIX > Q3 (> 2.15) [bl]			5,7	1.77, 19.1	**0,004**
log2(LDH) [bl]			1,44	0.58, 3.63	0,43
log2(creatinine) [bl]			2,94	0.92, 9.75	0,066
log2(PLT) [bl]			0,87	0.43, 1.79	0,7
log2(HGB) [bl]			0,07	0.00, 1.43	0,088
LDH > ULN [bl]			1,36	0.38, 4.54	0,62
PLT < LLN [bl]			3,79	1.15, 14.3	**0,035**
creatinine > ULN [bl]			5,93	1.79, 20.9	**0,004**

a. Determined prior to lymphodepletion (baseline). b. Last bone marrow status determined within 90 days prior to CAR T-cell therapy. c. Refractory to an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 monoclonal antibody. d. Refractory to lenalidomide, pomalidomide, bortezomib, carfilzomib and daratumumab. e. Systemic treatment administered between leukapheresis and lymphodepletion (at least one drug). f. Due to missing data for the US cohort, analyses of ferritin and ferritin-based scores prior to lymphodepletion were only performed for the German cohort.
ANC, absolute neutrophil count. B2-MG, beta-2-microglobulin. BCMA, B-cell maturation antigen. bl, baseline. BM, bone marrow. CAR-HTX, CAR-HEMATOTOX score. CI, confidence interval. CRP, C-reactive protein. CRS, cytokine release syndrome. d0, day 0 (day of CAR T-cell infusion). EASIX, Endothelial Activation and Stress Index. eGFR, estimated glomerular filtration rate. HGB, hemoglobin. ICANS, immune effector cell-associated neurotoxicity syndrome. ISS, International Staging System. LD, lymphodepletion. LDH, lactate dehydrogenase. LLN, lower limit of normal. m-EASIX, modified EASIX. OR, odds ratio. PD, progressive disease. PLT, platelet count. Q_3, third/upper quartile (75^{th} percentile). R-ISS, Revised International Staging System. ULN, upper limit of normal.

Supp. Table S14 | Logistic regression analysis of CRS grade ≥ 2

	Univariate analysis: CRS grade ≥ 2				
Characteristic	**N**	**Event N**	**OR**	**95% CI**	**p-value**
Age [cont.]	129	42	1,02	0.98, 1.06	0,39
Age ≥ 70 years					
No	93	27	—	—	
Yes	36	15	1,75	0.78, 3.88	0,17
Sex					
M	87	28	—	—	
W	42	14	1,05	0.47, 2.29	0,9
High risk cytogenetics					
No	74	23	—	—	
Yes	49	16	1,08	0.49, 2.32	0,85
ISS 3[a]					
No	107	37	—	—	
Yes	10	4	1,26	0.31, 4.70	0,73
R-ISS 3[a]					
No	111	39	—	—	
Yes	6	2	0,92	0.12, 4.95	0,93
Extramedullary disease[a]					
No	78	22	—	—	
Yes	48	18	1,53	0.71, 3.29	0,28
Extraosseous disease[a]					
No	94	30	—	—	
Yes	32	10	0,97	0.40, 2.26	0,94
BM burden ≥ 50%[b]					
No	57	13	—	—	
Yes	14	6	2,54	0.72, 8.70	0,14
PD prior to LD					
No	51	16	—	—	
Yes	53	20	1,33	0.59, 3.01	0,5
Gr. 3-4 cytopenia prior to LD					
No	110	37	—	—	
Yes	16	3	0,46	0.10, 1.52	0,24
eGFR < 60 ml/min[a]					
No	95	26	—	—	
Yes	34	16	2,36	1.05, 5.34	**0,038**
Triple-class refractory[c]					
No	22	9	—	—	
Yes	107	33	0,64	0.25, 1.70	0,36
Penta-drug refractory[d]					
No	88	34	—	—	
Yes	41	8	0,39	0.15, 0.90	**0,034**
Prior BCMA-TT					
No	107	35	—	—	
Yes	22	7	0,96	0.34, 2.50	0,94
Bridging therapy[e]					
No	18	1	—	—	
Yes	111	41	9,96	1.93, 183	**0,028**
CRS ≥ °2					
No	87	0	—	—	
Yes	42	42	—	—	—
Tocilizumab					
No	63	3	—	—	
Yes	66	39	28,9	9.43, 127	**<0.001**
Dexamethasone					
No	72	6	—	—	
Yes	57	36	18,9	7.42, 55.6	**<0.001**
log2(LDH) [bl]	126	41	0,88	0.43, 1.65	0,69
LDH > ULN [bl]					
No	87	31	—	—	
Yes	39	10	0,62	0.26, 1.41	0,27
log2(PLT) [bl]	129	42	0,98	0.65, 1.51	0,91

PLT < LLN [bl]					
No	73	22	—	—	
Yes	56	20	1,29	0.61, 2.71	0,5
log2(creatinine) [bl]	129	42	1,6	0.75, 3.53	0,23
creatinine > ULN [bl]					
No	100	26	—	—	
Yes	29	16	3,5	1.49, 8.40	**0,004**
log2(CRP) [bl]	116	39	1	0.81, 1.22	0,98
CRP > ULN [bl]					
No	73	25	—	—	
Yes	43	14	0,93	0.41, 2.05	0,85
log2(ferritin) [bl][f]	55	26	1,1	0.86, 1.42	0,45
Ferritin > ULN [bl][f]					
No	34	14	—	—	
Yes	21	12	1,9	0.64, 5.87	0,25
log2(ANC) [bl]	126	40	0,98	0.58, 1.68	0,95
ANC < LLN [bl]					
No	91	30	—	—	
Yes	35	10	0,81	0.34, 1.87	0,64
log2(HGB) [bl]	128	42	0,55	0.11, 2.75	0,46
HGB < LLN [bl]					
No	15	6	—	—	
Yes	113	36	0,7	0.23, 2.23	0,53
log2(B2-MG) [bl]	117	41	1,25	0.71, 2.21	0,44
log2(LDH x creatinine) [bl]	126	41	1,1	0.67, 1.76	0,71
log2(EASIX) [bl]	126	41	1,05	0.79, 1.38	0,72
EASIX > median (> 1.26) [bl]					
No	64	17	—	—	
Yes	62	24	1,75	0.83, 3.76	0,15
EASIX > Q3 (> 2.15) [bl]					
No	95	29	—	—	
Yes	31	12	1,44	0.61, 3.33	0,4
log2(m-EASIX) [bl]	115	39	1,01	0.86, 1.18	0,87
m-EASIX > 6.2 [bl]					
No	104	33	—	—	
Yes	11	6	2,58	0.73, 9.55	0,14
EASIX-F high [bl][f]					
No	59	24	—	—	
Yes	4	3	4,38	0.52, 91.4	0,21
EASIX-F inter/high [bl][f]					
No	30	13	—	—	
Yes	25	13	1,42	0.49, 4.17	0,52
EASIX-FC high [bl][f]					
No	50	23	—	—	
Yes	5	3	1,76	0.27, 14.3	0,55
EASIX-FC inter/high [bl][f]					
No	40	16	—	—	
Yes	17	10	2,14	0.68, 7.05	0,2
CAR-HTX high [bl][f]					
No	43	18	—	—	
Yes	13	7	1,62	0.46, 5.83	0,45
log2(EASIX) [d0]	117	41	0,98	0.72, 1.28	0,86
EASIX > median (> 1.36) [d0]					
No	59	19	—	—	
Yes	58	22	1,29	0.60, 2.77	0,52
EASIX > Q3 (> 2.06) [d0]					
No	88	30	—	—	
Yes	29	11	1,18	0.48, 2.80	0,71
log2(m-EASIX) [d0]	119	41	0,97	0.82, 1.14	0,73
m-EASIX > 6.2 [d0]					
No	95	33	—	—	
Yes	24	8	0,94	0.35, 2.37	0,9
EASIX-F high [d0]					
No	104	36	—	—	
Yes	13	5	1,18	0.34, 3.81	0,78

EASIX-F inter/high [d0]					
No	50	19	—	—	
Yes	51	20	1,05	0.47, 2.36	0,9
EASIX-FC high [d0]					
No	97	35	—	—	
Yes	8	3	1,06	0.21, 4.60	0,94
EASIX-FC inter/high [d0]					
No	59	25	—	—	
Yes	47	14	0,58	0.25, 1.29	0,18
CAR-HTX high [d0]					
No	38	12	—	—	
Yes	73	27	1,27	0.56, 2.99	0,57

Multivariate analysis: CRS grade ≥ 2			
Characteristic	**OR**	**95% CI**	**p-value**
Age ≥ 70 years	1,94	0.65, 5.84	0,23
Sex [W]	1,86	0.67, 5.28	0,23
Extramedullary disease	1,32	0.51, 3.47	0,57
ISS 3	0,34	0.06, 1.72	0,21
PD prior to LD	1,69	0.64, 4.64	0,3
eGFR < 60 ml/min	5,53	1.59, 22.3	**0,01**
Pentra-drug refractory	0,39	0.12, 1.15	0,1

a. Determined prior to lymphodepletion (baseline). b. Last bone marrow status determined within 90 days prior to CAR T-cell therapy. c. Refractory to an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 monoclonal antibody. d. Refractory to lenalidomide, pomalidomide, bortezomib, carfilzomib and daratumumab. e. Systemic treatment administered between leukapheresis and lymphodepletion (at least one drug). f. Due to missing data for the US cohort, analyses of ferritin and ferritin-based scores prior to lymphodepletion were only performed for the German cohort.
ANC, absolute neutrophil count. B2-MG, beta-2-microglobulin. BCMA, B-cell maturation antigen. bl, baseline. BM, bone marrow. CAR-HTX, CAR-HEMATOTOX score. CI, confidence interval. CRP, C-reactive protein. CRS, cytokine release syndrome. d0, day 0 (day of CAR T-cell infusion). EASIX, Endothelial Activation and Stress Index. eGFR, estimated glomerular filtration rate. HGB, hemoglobin. ICANS, immune effector cell-associated neurotoxicity syndrome. ISS, International Staging System. LD, lymphodepletion. LDH, lactate dehydrogenase. LLN, lower limit of normal. m-EASIX, modified EASIX. OR, odds ratio. PD, progressive disease. PLT, platelet count. Q_3, third/upper quartile (75^{th} percentile). R-ISS, Revised International Staging System. ULN, upper limit of normal.

Supp. Table S15 | Logistic regression analysis of ICANS

	Univariate analysis: ICANS				
Characteristic	**N**	**Event N**	**OR**	**95% CI**	**p-value**
Age [cont.]	129	11	1,03	0.96, 1.10	0,44
Age ≥ 70 years					
No	93	8	—	—	
Yes	36	3	0,97	0.20, 3.57	0,96
Sex					
M	87	8	—	—	
W	42	3	0,76	0.16, 2.79	0,7
High risk cytogenetics					
No	74	6	—	—	
Yes	49	5	1,29	0.35, 4.53	0,69
ISS 3[a]					
No	107	9	—	—	
Yes	10	1	1,21	0.06, 7.62	0,86
R-ISS 3[a]					
No	111	10	—	—	
Yes	6	0	—	—	—
Extramedullary disease[a]					
No	78	7	—	—	
Yes	48	4	0,92	0.23, 3.24	0,9
Extraosseous disease[a]					
No	94	9	—	—	
Yes	32	2	0,63	0.09, 2.62	0,57
BM burden ≥ 50%[a]					
No	57	3	—	—	
Yes	14	3	4,91	0.82, 29.8	0,071
PD prior to LD					
No	51	3	—	—	
Yes	53	6	2,04	0.51, 10.1	0,33
Gr. 3-4 cytopenia prior to LD					
No	110	10	—	—	
Yes	16	1	0,67	0.04, 3.87	0,71
eGFR < 60 ml/min[a]					
No	95	8	—	—	
Yes	34	3	1,05	0.22, 3.90	0,94
Triple-class refractory[c]					
No	22	1	—	—	
Yes	107	10	2,16	0.38, 40.8	0,47
Penta-drug refractory[d]					
No	88	7	—	—	
Yes	41	4	1,25	0.31, 4.41	0,73
Prior BCMA-TT					
No	107	9	—	—	
Yes	22	2	1,09	0.16, 4.64	0,92
Bridging therapy[e]					
No	18	1	—	—	
Yes	111	10	1,68	0.29, 31.9	0,63
CRS ≥ °2					
No	87	4	—	—	
Yes	42	7	4,15	1.18, 16.7	**0,031**
Tocilizumab					
No	63	3	—	—	
Yes	66	8	2,76	0.76, 13.1	0,15
Dexamethasone					
No	72	0	—	—	
Yes	57	11	—	—	—
log2(LDH) [bl]	126	10	1,02	0.28, 2.63	0,97
LDH > ULN [bl]					
No	87	8	—	—	
Yes	39	2	0,53	0.08, 2.26	0,44
log2(PLT) [bl]	129	11	0,65	0.38, 1.19	0,13
PLT < LLN [bl]					
No	73	5	—	—	
Yes	56	6	1,63	0.47, 5.95	0,44
log2(creatinine) [bl]	129	11	1,13	0.29, 3.65	0,85

creatinine > ULN [bl]					
No	100	9	—	—	
Yes	29	2	0,75	0.11, 3.13	0,72
log2(CRP) [bl]	116	11	1,25	0.91, 1.70	0,16
CRP > ULN [bl]					
No	73	5	—	—	
Yes	43	6	2,21	0.62, 8.12	0,22
log2(ferritin) [bl][f]	55	4	0,77	0.42, 1.25	0,33
Ferritin > ULN [bl][f]					
No	34	4	—	—	
Yes	21	0	—	—	—
log2(ANC) [bl]	126	11	1,22	0.52, 3.13	0,66
ANC < LLN [bl]					
No	91	8	—	—	
Yes	35	3	0,97	0.20, 3.60	0,97
log2(HGB) [bl]	128	11	0,22	0.02, 2.98	0,24
HGB < LLN [bl]					
No	15	0	—	—	
Yes	113	11	—	—	—
log2(B2-MG) [bl]	117	10	0,89	0.30, 2.20	0,82
log2(LDH x creatinine) [bl]	126	10	1,02	0.39, 2.11	0,96
log2(EASIX) [bl]	126	10	1,25	0.82, 1.77	0,22
EASIX > median (> 1.26) [bl]					
No	64	2	—	—	
Yes	62	8	4,59	1.09, 31.3	0,061
EASIX > Q3 (> 2.15) [bl]					
No	95	4	—	—	
Yes	31	6	5,46	1.45, 22.8	**0,013**
log2(m-EASIX) [bl]	115	10	1,2	0.95, 1.49	0,1
m-EASIX > 6.2 [bl]					
No	104	7	—	—	
Yes	11	3	5,2	0.98, 23.2	**0,035**
EASIX-F high [bl][f]					
No	59	4	—	—	
Yes	4	0	—	—	—
EASIX-F inter/high [bl][f]					
No	30	4	—	—	
Yes	25	0	—	—	—
EASIX-FC high [bl][f]					
No	50	4	—	—	
Yes	5	0	—	—	—
EASIX-FC inter/high [bl][f]					
No	40	2	—	—	
Yes	17	2	2,53	0.28, 22.7	0,37
CAR-HTX high [bl][f]					
No	43	3	—	—	
Yes	13	1	1,11	0.05, 9.63	0,93
log2(EASIX) [d0]	117	11	1,24	0.82, 1.75	0,24
EASIX > median (> 1.36) [d0]					
No	59	4	—	—	
Yes	58	7	1,89	0.54, 7.56	0,33
EASIX > Q3 (> 2.06) [d0]					
No	88	5	—	—	
Yes	29	6	4,33	1.20, 16.3	**0,024**
log2(m-EASIX) [d0]	119	11	1,25	0.99, 1.59	0,053
m-EASIX > 6.2 [d0]					
No	95	6	—	—	
Yes	24	5	3,9	1.03, 14.3	**0,038**
EASIX-F high [d0]					
No	104	9	—	—	
Yes	13	2	1,92	0.27, 8.73	0,44
EASIX-F inter/high [d0]					
No	50	4	—	—	
Yes	51	5	1,25	0.31, 5.33	0,75
EASIX-FC high [d0]					
No	97	8	—	—	
Yes	8	0	—	—	—
EASIX-FC inter/high [d0]					
No	59	3	—	—	
Yes	47	7	3,27	0.85, 15.9	0,1

CAR-HTX high [d0]					
No	38	1	—	—	
Yes	73	9	5,2	0.92, 97.9	0,12
		Multivariate analysis: ICANS			
Characteristic			**OR**	**95% CI**	**p-value**
CRS ≥ °2			5,42	1.36, 27.2	**0,022**
EASIX > Q3 (> 2.15) [bl]			5,24	1.33, 22.9	**0,019**

a. Determined prior to lymphodepletion (baseline). b. Last bone marrow status determined within 90 days prior to CAR T-cell therapy. c. Refractory to an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 monoclonal antibody. d. Refractory to lenalidomide, pomalidomide, bortezomib, carfilzomib and daratumumab. e. Systemic treatment administered between leukapheresis and lymphodepletion (at least one drug). f. Due to missing data for the US cohort, analyses of ferritin and ferritin-based scores prior to lymphodepletion were only performed for the German cohort.
ANC, absolute neutrophil count. B2-MG, beta-2-microglobulin. BCMA, B-cell maturation antigen. bl, baseline. BM, bone marrow. CAR-HTX, CAR-HEMATOTOX score. CI, confidence interval. CRP, C-reactive protein. CRS, cytokine release syndrome. d0, day 0 (day of CAR T-cell infusion). EASIX, Endothelial Activation and Stress Index. eGFR, estimated glomerular filtration rate. HGB, hemoglobin. ICANS, immune effector cell-associated neurotoxicity syndrome. ISS, International Staging System. LD, lymphodepletion. LDH, lactate dehydrogenase. LLN, lower limit of normal. m-EASIX, modified EASIX. OR, odds ratio. PD, progressive disease. PLT, platelet count. Q_3, third/upper quartile (75^{th} percentile). R-ISS, Revised International Staging System. ULN, upper limit of normal.

Supp. Table S16 | Logistic regression analysis of treatment response

	Univariate analysis: Treatment response (≥ PR)				
Characteristic	**N**	**Event N**	**OR**	**95% CI**	**p-value**
Age [cont.]	122	101	1,01	0.96, 1.06	0,65
Age ≥ 70 years					
No	89	74	—	—	
Yes	33	27	0,91	0.33, 2.77	0,86
Sex					
No	83	67	—	—	
Yes	39	34	1,62	0.58, 5.30	0,38
High risk cytogenetics					
No	68	54	—	—	
Yes	48	43	2,23	0.78, 7.34	0,15
High risk cytogenetics with 1q					
No	46	34	—	—	
Yes	70	63	3,18	1.17, 9.25	**0,027**
ISS 3[a]					
No	103	88	—	—	
Yes	9	6	0,34	0.08, 1.75	0,16
R-ISS 3[a]					
No	106	90	—	—	
Yes	6	4	0,36	0.06, 2.72	0,25
Extramedullary disease[a]					
No	77	63	—	—	
Yes	42	36	1,33	0.49, 4.04	0,59
Extraosseous disease[a]					
No	92	78	—	—	
Yes	27	21	0,63	0.22, 1.95	0,39
BM burden ≥ 50%[b]					
No	53	41	—	—	
Yes	14	14	—	—	—
PD prior to LD					
No	46	37	—	—	
Yes	51	44	1,53	0.52, 4.66	0,44
Gr. 3-4 cytopenia prior to LD					
No	104	86	—	—	
Yes	15	12	0,84	0.24, 3.94	0,8
eGFR < 60 ml/min[a]					
No	89	73	—	—	
Yes	33	28	1,23	0.43, 4.03	0,71
Triple-class refractory[c]					
No	20	15	—	—	
Yes	102	86	1,79	0.52, 5.40	0,32
Penta-drug refractory[d]					
No	84	71	—	—	
Yes	38	30	0,69	0.26, 1.89	0,45
Prior BCMA-TT					
No	101	86	—	—	
Yes	21	15	0,44	0.15, 1.38	0,14
Bridging therapy[e]					
No	18	15	—	—	
Yes	104	86	0,96	0.21, 3.28	0,95
CRS ≥ °2					
No	81	66	—	—	
Yes	41	35	1,33	0.49, 3.99	0,59
Tocilizumab					
No	57	43	—	—	
Yes	65	58	2,7	1.03, 7.65	**0,049**
Dexamethasone					
No	67	52	—	—	
Yes	55	49	2,36	0.88, 7.05	0,1
log2(LDH) [bl]	119	98	0,85	0.42, 1.94	0,66
LDH > ULN [bl]					
No	83	69	—	—	
Yes	36	29	0,84	0.31, 2.41	0,74
log2(PLT) [bl]	122	101	1,39	0.85, 2.21	0,17
PLT < LLN [bl]					
No	68	59	—	—	
Yes	54	42	0,53	0.20, 1.37	0,2

log2(creatinine) [bl]	122	101	0,88	0.35, 2.39	0,8
creatinine > ULN [bl]					
No	94	79	—	—	
Yes	28	22	0,7	0.25, 2.14	0,5
log2(CRP) [bl]	110	91	0,95	0.74, 1.23	0,68
CRP > ULN [bl]					
No	68	56	—	—	
Yes	42	35	1,07	0.39, 3.12	0,89
log2(ferritin) [bl][f]	50	42	0,89	0.62, 1.27	0,52
Ferritin > ULN [bl][f]					
No	31	27	—	—	
Yes	19	15	0,56	0.12, 2.65	0,45
log2(ANC) [bl]	119	99	1,98	1.03, 3.94	**0,044**
ANC < LLN [bl]					
No	86	73	—	—	
Yes	33	26	0,66	0.24, 1.92	0,43
log2(HGB) [bl]	121	100	0,64	0.07, 4.73	0,67
HGB < LLN [bl]					
No	15	12	—	—	
Yes	106	88	1,22	0.26, 4.34	0,77
log2(B2-MG) [bl]	112	94	1,05	0.51, 2.39	0,91
log2(LDH x creatinine) [bl]	119	98	0,86	0.50, 1.60	0,61
log2(EASIX) [bl]	119	98	0,84	0.62, 1.16	0,25
EASIX > median (> 1.26) [bl]					
No	62	52	—	—	
Yes	57	46	0,8	0.31, 2.08	0,65
EASIX > Q3 (> 2.15) [bl]					
No	90	76	—	—	
Yes	29	22	0,58	0.21, 1.69	0,3
log2(m-EASIX) [bl]	109	90	0,94	0.78, 1.14	0,49
m-EASIX > 6.2 [bl]					
No	99	83	—	—	
Yes	10	7	0,45	0.11, 2.25	0,28
EASIX-F high [bl][f]					
No	53	45	—	—	
Yes	4	3	0,53	0.06, 11.5	0,61
EASIX-F inter/high [bl][f]					
No	27	23	—	—	
Yes	23	19	0,83	0.17, 3.92	0,8
EASIX-FC high [bl][f]					
No	45	38	—	—	
Yes	5	4	0,74	0.09, 15.6	0,8
EASIX-FC inter/high [bl][f]					
No	36	29	—	—	
Yes	16	14	1,69	0.35, 12.3	0,54
CAR-HTX high [bl][f]					
No	39	32	—	—	
Yes	11	10	2,19	0.33, 43.5	0,49
log2(EASIX) [d0]	112	93	0,83	0.60, 1.15	0,23
EASIX > median (> 1.36) [d0]					
No	57	49	—	—	
Yes	55	44	0,65	0.23, 1.76	0,4
EASIX > Q3 (> 2.06) [d0]					
No	85	72	—	—	
Yes	27	21	0,63	0.22, 1.98	0,41
log2(m-EASIX) [d0]	114	94	0,94	0.77, 1.15	0,52
m-EASIX > 6.2 [d0]					
No	91	77	—	—	
Yes	23	17	0,52	0.18, 1.63	0,23
EASIX-F high [d0]					
No	100	84	—	—	
Yes	12	9	0,57	0.15, 2.78	0,44
EASIX-F inter/high [d0]					
No	48	42	—	—	
Yes	50	41	0,65	0.20, 1.97	0,45
EASIX-FC high [d0]					
No	95	81	—	—	
Yes	8	7	1,21	0.19, 23.5	0,86

EASIX-FC inter/high [d0]					
No	58	50	—	—	
Yes	45	36	0,64	0.22, 1.83	0,4
CAR-HTX high [d0]					
No	36	31	—	—	
Yes	71	59	0,79	0.23, 2.35	0,69

a. Determined prior to lymphodepletion (baseline). b. Last bone marrow status determined within 90 days prior to CAR T-cell therapy. c. Refractory to an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 monoclonal antibody. d. Refractory to lenalidomide, pomalidomide, bortezomib, carfilzomib and daratumumab. e. Systemic treatment administered between leukapheresis and lymphodepletion (at least one drug). f. Baseline ferritin and ferritin-based scores were only analyzed in the German cohort.

ANC, absolute neutrophil count. B2-MG, beta-2-microglobulin. BCMA, B-cell maturation antigen. bl, baseline. BM, bone marrow. CAR-HTX, CAR-HEMATOTOX score. CI, confidence interval. CRP, C-reactive protein. CRS, cytokine release syndrome. d0, day 0 (day of CAR T-cell infusion). EASIX, Endothelial Activation and Stress Index. eGFR, estimated glomerular filtration rate. HGB, hemoglobin. ICANS, immune effector cell-associated neurotoxicity syndrome. ISS, International Staging System. LD, lymphodepletion. LDH, lactate dehydrogenase. LLN, lower limit of normal. m-EASIX, modified EASIX. OR, odds ratio. PD, progressive disease. PLT, platelet count. Q_3, third/upper quartile (75^{th} percentile). R-ISS, Revised International Staging System. ULN, upper limit of normal.

Supp. Table S17 | Cox regression analysis of progression-free survival (PFS)

	Univariate analysis: PFS				
Characteristic	**N**	**Event N**	**HR**	**95% CI**	**p-value**
Age [cont.]	129	70	0,98	0.96, 1.00	0,11
Age ≥ 70 years					
No	93	53	—	—	
Yes	36	17	0,69	0.40, 1.19	0,18
Sex					
M	87	53	—	—	
W	42	17	0,71	0.41, 1.23	0,23
High risk cytogenetics					
No	74	43	—	—	
Yes	49	25	0,97	0.59, 1.60	0,92
High risk cytogenetics with 1q					
No	49	27	—	—	
Yes	74	41	1,13	0.69, 1.85	0,63
ISS 3[a]					
No	107	52	—	—	
Yes	10	9	2,56	1.25, 5.23	**0,01**
R-ISS 3[a]					
No	111	56	—	—	
Yes	6	5	4,22	1.65, 10.8	**0,003**
Extramedullary disease[a]					
No	78	36	—	—	
Yes	48	33	1,91	1.18, 3.08	**0,008**
Extraosseous disease[a]					
No	94	45	—	—	
Yes	32	24	2,46	1.48, 4.09	**<0.001**
BM burden ≥ 50%[b]					
No	57	35	—	—	
Yes	14	6	0,65	0.27, 1.54	0,33
PD prior to LD					
No	51	31	—	—	
Yes	53	26	0,99	0.58, 1.67	0,96
Gr. 3-4 cytopenia prior to LD					
No	110	57	—	—	
Yes	16	10	1,35	0.69, 2.65	0,39
eGFR < 60 ml/min[a]					
No	95	51	—	—	
Yes	34	19	1	0.59, 1.69	0,99
Triple-class refractory[c]					
No	22	9	—	—	
Yes	107	61	1,12	0.55, 2.25	0,76
Penta-drug refractory[d]					
No	88	47	—	—	
Yes	41	23	1,01	0.61, 1.67	0,97
Prior BCMA-TT					
No	107	56	—	—	
Yes	22	14	1,27	0.71, 2.30	0,42
Bridging therapy[e]					
No	18	7	—	—	
Yes	111	63	2,14	0.97, 4.70	0,059
CRS ≥ °2					
No	87	45	—	—	
Yes	42	25	1,26	0.77, 2.06	0,36
Tocilizumab					
No	63	37	—	—	
Yes	66	33	0,83	0.52, 1.34	0,45
Dexamethasone					
No	72	41	—	—	
Yes	57	29	0,89	0.55, 1.44	0,64
log2(LDH) [bl]	126	68	1,52	1.04, 2.22	**0,032**
LDH > ULN [bl]					
No	87	46	—	—	
Yes	39	22	1,53	0.91, 2.55	0,11
log2(PLT) [bl]	129	70	0,77	0.60, 0.98	**0,037**
PLT < LLN [bl]					
No	73	35	—	—	
Yes	56	35	1,77	1.10, 2.85	**0,018**

log2(creatinine) [bl]	129	70	1,31	0.79, 2.19	0,3
creatinine > ULN [bl]					
No	100	52	—	—	
Yes	29	18	1,28	0.74, 2.18	0,38
log2(CRP) [bl]	116	64	1,2	1.06, 1.37	**0,005**
CRP > ULN [bl]					
No	73	31	—	—	
Yes	43	33	2,19	1.33, 3.60	**0,002**
log2(ferritin) [bl][f]	55	27	1,2	1.02, 1.41	**0,032**
Ferritin > ULN [bl][f]					
No	34	14	—	—	
Yes	21	13	1,75	0.82, 3.76	0,15
log2(ANC) [bl]	126	67	0,87	0.63, 1.20	0,38
ANC < LLN [bl]					
No	91	47	—	—	
Yes	35	20	1,1	0.65, 1.85	0,73
log2(HGB) [bl]	128	69	0,46	0.15, 1.37	0,16
HGB < LLN [bl]					
No	15	8	—	—	
Yes	113	61	0,87	0.42, 1.83	0,72
log2(B2-MG) [bl]	117	61	1,31	0.91, 1.89	0,15
log2(LDH x creatinine) [bl]	126	68	1,38	1.03, 1.85	**0,032**
log2(EASIX) [bl]	126	68	1,24	1.07, 1.43	**0,004**
EASIX > median (> 1.26) [bl]					
No	64	30	—	—	
Yes	62	38	1,73	1.07, 2.82	**0,026**
EASIX > Q3 (> 2.15) [bl]					
No	95	48	—	—	
Yes	31	20	2,05	1.21, 3.48	**0,008**
log2(m-EASIX) [bl]	115	63	1,18	1.07, 1.29	**<0.001**
m-EASIX > 6.2 [bl]					
No	104	55	—	—	
Yes	11	8	2,51	1.19, 5.30	**0,016**
EASIX-F high [bl][f]					
No	59	32	—	—	
Yes	4	2	0,98	0.23, 4.13	0,98
EASIX-F inter/high [bl][f]					
No	30	13	—	—	
Yes	25	14	1,47	0.69, 3.14	0,32
EASIX-FC high [bl][f]					
No	50	22	—	—	
Yes	5	5	3,35	1.24, 9.00	**0,017**
EASIX-FC inter/high [bl][f]					
No	40	19	—	—	
Yes	17	10	1,67	0.77, 3.62	0,2
CAR-HTX high [bl][f]					
No	43	20	—	—	
Yes	13	8	1,68	0.73, 3.85	0,22
log2(EASIX) [d0]	117	64	1,23	1.06, 1.42	**0,005**
EASIX > median (> 1.36) [d0]					
No	59	30	—	—	
Yes	58	34	1,61	0.97, 2.65	0,063
EASIX > Q3 (> 2.06) [d0]					
No	88	46	—	—	
Yes	29	18	1,5	0.87, 2.60	0,15
log2(m-EASIX) [d0]	119	65	1,09	0.99, 1.20	0,069
m-EASIX > 6.2 [d0]					
No	95	51	—	—	
Yes	24	14	1,61	0.89, 2.93	0,12
EASIX-F high [d0]					
No	104	54	—	—	
Yes	13	10	2,15	1.09, 4.25	**0,027**
EASIX-F inter/high [d0]					
No	50	19	—	—	
Yes	51	33	2,51	1.41, 4.45	**0,002**
EASIX-FC high [d0]					
No	97	45	—	—	
Yes	8	8	3,49	1.62, 7.54	**0,001**

EASIX-FC inter/high [d0]					
No	59	26	—	—	
Yes	47	28	1,64	0.95, 2.83	0,075
CAR-HTX high [d0]					
No	38	20	—	—	
Yes	73	37	1,22	0.70, 2.11	0,48

Multivariate analysis: PFS			
Characteristic	**HR**	**95% CI**	**p-value**
ISS 3	2,76	1.32, 5.77	**0,007**
Extraosseous disease	2,34	1.31, 4.19	**0,004**
EASIX > Q3 (> 2.15) [bl]	2,03	1.13, 3.64	**0,017**
ISS 3	2,56	1.21, 5.41	**0,014**
Extraosseous disease	2,27	1.27, 4.06	**0,006**
Bridging therapy	1,61	0.66, 3.91	0,29
EASIX > Q3 (> 2.15) [bl]	1,89	1.05, 3.41	**0,035**
ISS 3	2,86	1.24, 6.57	**0,013**
Extraosseous disease	2,1	1.15, 3.85	**0,016**
Bridging therapy	1,64	0.67, 3.99	0,28
Gr. 3-4 cytopenia prior to LD	1,06	0.50, 2.26	0,87
EASIX > Q3 (> 2.15) [bl]	1,73	0.93, 3.24	0,086
Age ≥ 70 years	0,8	0.44, 1.45	0,45
Sex [W]	0,67	0.36, 1.24	0,2
ISS 3	3,09	1.43, 6.68	**0,004**
Extraosseous disease	2,32	1.29, 4.16	**0,005**
EASIX > Q3 (> 2.15) [bl]	1,89	1.04, 3.43	**0,037**
log2(LDH) [bl]	1,34	0.84, 2.15	0,22
log2(PLT) [bl]	1,01	0.71, 1.45	0,94
log2(creatinine) [bl]	1,21	0.69, 2.14	0,51
log2(ANC) [bl]	0,72	0.48, 1.08	0,11
log2(HGB) [bl]	1,59	0.36, 7.02	0,54
log2(CRP) [bl]	1,21	1.04, 1.41	**0,013**
LDH > ULN [bl]	1,35	0.75, 2.42	0,31
PLT < LLN [bl]	1,53	0.89, 2.63	0,13
creatinine > ULN [bl]	1	0.54, 1.85	>0.99
ANC < LLN [bl]	1,02	0.56, 1.85	0,95
HGB < LLN [bl]	0,52	0.24, 1.14	0,1
CRP > ULN [bl]	2,11	1.22, 3.66	**0,008**
log2(EASIX) [bl]	1,17	0.99, 1.38	0,059
log2(CRP) [bl]	1,17	1.02, 1.33	**0,025**
EASIX > Q3 (> 2.15) [bl]	1,74	0.98, 3.09	0,058
CRP > ULN [bl]	2,02	1.21, 3.35	**0,007**
EASIX > Q3 (> 2.15) [bl]	1,4	0.50, 3.89	0,52
CAR-HTX high [bl]	1,48	0.58, 3.73	0,41
EASIX > Q3 (> 2.06) [d0]	1,7	0.92, 3.11	0,088
CAR-HTX high [d0]	0,98	0.54, 1.78	0,94

a. Determined prior to lymphodepletion (baseline). b. Last bone marrow status determined within 90 days prior to CAR T-cell therapy. c. Refractory to an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 monoclonal antibody. d. Refractory to lenalidomide, pomalidomide, bortezomib, carfilzomib and daratumumab. e. Systemic treatment administered between leukapheresis and lymphodepletion (at least one drug). f. Due to missing data for the US cohort, analyses of ferritin and ferritin-based scores prior to lymphodepletion were only performed for the German cohort.
ANC, absolute neutrophil count. B2-MG, beta-2-microglobulin. BCMA, B-cell maturation antigen. bl, baseline. BM, bone marrow. CAR-HTX, CAR-HEMATOTOX score. CI, confidence interval. CRP, C-reactive protein. CRS, cytokine release syndrome. d0, day 0 (day of CAR T-cell infusion). EASIX, Endothelial Activation and Stress Index. eGFR, estimated glomerular filtration rate. HGB, hemoglobin. HR, hazard ratio. ICANS, immune effector cell-associated neurotoxicity syndrome. ISS, International Staging System. LD, lymphodepletion. LDH, lactate dehydrogenase. LLN, lower limit of normal. m-EASIX, modified EASIX. PD, progressive disease. PLT, platelet count. Q_3, third/upper quartile (75^{th} percentile). R-ISS, Revised International Staging System. ULN, upper limit of normal.

Supp. Table S18 | Cox regression analysis of overall survival (OS)

	Univariate analysis: OS				
Characteristic	**N**	**Event N**	**HR**	**95% CI**	**p-value**
Age [cont.]	129	30	1	0.96, 1.04	0,93
Age ≥ 70 years					
No	93	24	—	—	
Yes	36	6	0,66	0.27, 1.63	0,37
Sex					
M	87	23	—	—	
W	42	7	0,8	0.34, 1.88	0,61
High risk cytogenetics					
No	74	18	—	—	
Yes	49	11	1,08	0.51, 2.30	0,83
High risk cytogenetics with 1q					
No	49	13	—	—	
Yes	74	16	0,88	0.43, 1.84	0,74
ISS 3[a]					
No	107	21	—	—	
Yes	10	6	3,51	1.41, 8.73	**0,007**
R-ISS 3[a]					
No	111	23	—	—	
Yes	6	4	5,75	1.96, 16.9	**0,001**
Extramedullary disease[a]					
No	78	16	—	—	
Yes	48	13	1,41	0.68, 2.92	0,36
Extraosseous disease[a]					
No	94	17	—	—	
Yes	32	12	2,3	1.10, 4.83	**0,027**
BM burden ≥ 50%[b]					
No	57	16	—	—	
Yes	14	1	0,26	0.03, 1.94	0,19
PD prior to LD					
No	51	14	—	—	
Yes	53	14	1,29	0.61, 2.71	0,5
Gr. 3-4 cytopenia prior to LD					
No	110	23	—	—	
Yes	16	6	2,24	0.91, 5.53	0,08
eGFR < 60 ml/min[a]					
No	95	21	—	—	
Yes	34	9	1,11	0.51, 2.44	0,79
Triple-class refractory[c]					
No	22	5	—	—	
Yes	107	25	0,75	0.29, 1.98	0,56
Penta-drug refractory[d]					
No	88	18	—	—	
Yes	41	12	1,43	0.69, 2.97	0,34
Prior BCMA-TT					
No	107	25	—	—	
Yes	22	5	0,9	0.34, 2.34	0,82
Bridging therapy[e]					
No	18	1	—	—	
Yes	111	29	6,44	0.87, 47.4	0,068
CRS ≥ °2					
No	87	19	—	—	
Yes	42	11	1,31	0.62, 2.75	0,48
Tocilizumab					
No	63	17	—	—	
Yes	66	13	0,77	0.37, 1.58	0,47
Dexamethasone					
No	72	17	—	—	
Yes	57	13	1,08	0.52, 2.22	0,84
log2(LDH) [bl]	126	30	1,65	0.99, 2.77	0,055
LDH > ULN [bl]					
No	87	18	—	—	
Yes	39	12	1,98	0.95, 4.15	0,068
log2(PLT) [bl]	129	30	0,62	0.45, 0.85	**0,003**
PLT < LLN [bl]					
No	73	12	—	—	
Yes	56	18	2,25	1.08, 4.68	**0,029**

log2(creatinine) [bl]	129	30	1,6	0.82, 3.14	0,17
creatinine > ULN [bl]					
No	100	22	—	—	
Yes	29	8	1,4	0.62, 3.14	0,42
log2(CRP) [bl]	116	29	1,38	1.15, 1.66	**<0.001**
CRP > ULN [bl]					
No	73	10	—	—	
Yes	43	19	3,25	1.51, 7.00	**0,003**
log2(ferritin) [bl][f]	55	9	1,2	0.88, 1.62	0,25
Ferritin > ULN [bl][f]					
No	34	6	—	—	
Yes	21	3	0,98	0.24, 3.96	0,97
log2(ANC) [bl]	126	29	0,85	0.52, 1.39	0,52
ANC < LLN [bl]					
No	91	22	—	—	
Yes	35	7	0,76	0.32, 1.77	0,52
log2(HGB) [bl]	128	30	0,05	0.01, 0.23	**<0.001**
HGB < LLN [bl]					
No	15	0	—	—	
Yes	113	30	—	—	—
log2(B2-MG) [bl]	117	27	2,03	1.27, 3.24	**0,003**
log2(LDH x creatinine) [bl]	126	30	1,55	1.07, 2.26	**0,02**
log2(EASIX) [bl]	126	30	1,34	1.12, 1.60	**0,001**
EASIX > median (> 1.26) [bl]					
No	64	10	—	—	
Yes	62	20	2,27	1.06, 4.86	**0,034**
EASIX > Q3 (> 2.15) [bl]					
No	95	15	—	—	
Yes	31	15	4,85	2.35, 10.0	**<0.001**
log2(m-EASIX) [bl]	115	29	1,28	1.13, 1.44	**<0.001**
m-EASIX > 6.2 [bl]					
No	104	23	—	—	
Yes	11	6	4,23	1.70, 10.5	**0,002**
EASIX-F high [bl][f]					
No	59	11	—	—	
Yes	4	0	—	—	—
EASIX-F inter/high [bl][f]					
No	30	5	—	—	
Yes	25	4	1,02	0.27, 3.80	0,98
EASIX-FC high [bl][f]					
No	50	7	—	—	
Yes	5	2	3,91	0.79, 19.5	0,1
EASIX-FC inter/high [bl][f]					
No	40	5	—	—	
Yes	17	5	3,29	0.94, 11.5	0,062
CAR-HTX high [bl][f]					
No	43	7	—	—	
Yes	13	3	1,83	0.47, 7.16	0,39
log2(EASIX) [d0]	117	27	1,35	1.13, 1.62	**<0.001**
EASIX > median (> 1.36) [d0]					
No	59	9	—	—	
Yes	58	18	2,47	1.11, 5.50	**0,027**
EASIX > Q3 (> 2.06) [d0]					
No	88	14	—	—	
Yes	29	13	3,49	1.64, 7.44	**0,001**
log2(m-EASIX) [d0]	119	28	1,18	1.04, 1.35	**0,013**
m-EASIX > 6.2 [d0]					
No	95	19	—	—	
Yes	24	9	2,61	1.16, 5.84	**0,02**
EASIX-F high [d0]					
No	104	20	—	—	
Yes	13	7	3,61	1.51, 8.60	**0,004**
EASIX-F inter/high [d0]					
No	50	6	—	—	
Yes	51	17	3,6	1.40, 9.24	**0,008**
EASIX-FC high [d0]					
No	97	18	—	—	
Yes	8	4	4,57	1.50, 14.0	**0,008**

EASIX-FC inter/high [d0]					
No	59	8	—	—	
Yes	47	16	2,84	1.21, 6.67	**0,017**
CAR-HTX high [d0]					
No	38	5	—	—	
Yes	73	20	2,88	1.07, 7.72	**0,036**

Multivariate analysis: OS			
Characteristic	**HR**	**95% CI**	**p-value**
ISS 3	4,42	1.62, 12.1	**0,004**
Extraosseous disease	3,42	1.44, 8.17	**0,006**
EASIX > Q3 (> 2.15) [bl]	3,89	1.71, 8.83	**0,001**
ISS 3	3,94	1.43, 10.8	**0,008**
Extraosseous disease	3,31	1.38, 7.91	**0,007**
Bridging therapy	3,13	0.40, 24.7	0,28
EASIX > Q3 (> 2.15) [bl]	3,44	1.51, 7.84	**0,003**
ISS 3	4,06	1.38, 11.9	**0,011**
Extraosseous disease	3,13	1.28, 7.63	**0,012**
Bridging therapy	3,57	0.45, 28.1	0,23
Gr. 3-4 cytopenia prior to LD	1,39	0.51, 3.83	0,52
EASIX > Q3 (> 2.15) [bl]	2,82	1.20, 6.61	**0,017**
Age ≥ 70 years	0,71	0.28, 1.81	0,48
Sex [W]	0,68	0.25, 1.85	0,45
ISS 3	4,69	1.67, 13.2	**0,003**
Extraosseous disease	3,41	1.42, 8.18	**0,006**
EASIX > Q3 (> 2.15) [bl]	3,52	1.51, 8.19	**0,004**
log2(LDH) [bl]	1,3	0.72, 2.34	0,38
log2(PLT) [bl]	1,03	0.63, 1.69	0,9
log2(creatinine) [bl]	1,38	0.64, 2.97	0,41
log2(ANC) [bl]	0,89	0.51, 1.56	0,69
log2(HGB) [bl]	0,17	0.02, 1.39	0,1
log2(CRP) [bl]	1,22	0.99, 1.51	0,062
LDH > ULN [bl]	1,75	0.79, 3.89	0,17
PLT < LLN [bl]	2,05	0.95, 4.43	0,067
creatinine > ULN [bl]	1,13	0.47, 2.71	0,79
ANC < LLN [bl]	0,8	0.33, 1.96	0,63
CRP > ULN [bl]	2,79	1.23, 6.32	**0,014**
log2(EASIX) [bl]	1,22	1.00, 1.48	0,053
log2(CRP) [bl]	1,32	1.09, 1.60	**0,005**
EASIX > Q3 (> 2.15) [bl]	3,74	1.73, 8.08	**<0.001**
CRP > ULN [bl]	2,46	1.11, 5.47	**0,027**
EASIX > Q3 (> 2.15) [bl]	4,9	1.12, 21.3	**0,034**
CAR-HTX high [bl]	0,86	0.18, 4.17	0,86
EASIX > Q3 (> 2.06) [d0]	3,95	1.62, 9.64	**0,003**
CAR-HTX high [d0]	1,59	0.55, 4.56	0,39

a. Determined prior to lymphodepletion (baseline). b. Last bone marrow status determined within 90 days prior to CAR T-cell therapy. c. Refractory to an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 monoclonal antibody. d. Refractory to lenalidomide, pomalidomide, bortezomib, carfilzomib and daratumumab. e. Systemic treatment administered between leukapheresis and lymphodepletion (at least one drug). f. Due to missing data for the US cohort, analyses of ferritin and ferritin-based scores prior to lymphodepletion were only performed for the German cohort.
ANC, absolute neutrophil count. B2-MG, beta-2-microglobulin. BCMA, B-cell maturation antigen. bl, baseline. BM, bone marrow. CAR-HTX, CAR-HEMATOTOX score. CI, confidence interval. CRP, C-reactive protein. CRS, cytokine release syndrome. d0, day 0 (day of CAR T-cell infusion). EASIX, Endothelial Activation and Stress Index. eGFR, estimated glomerular filtration rate. HGB, hemoglobin. HR, hazard ratio. ICANS, immune effector cell-associated neurotoxicity syndrome. ISS, International Staging System. LD, lymphodepletion. LDH, lactate dehydrogenase. LLN, lower limit of normal. m-EASIX, modified EASIX. PD, progressive disease. PLT, platelet count. Q_3, third/upper quartile (75th percentile). R-ISS, Revised International Staging System. ULN, upper limit of normal.

EASIX-guided risk stratification for complications and outcome after CAR T-cell therapy with ide-cel in relapsed/refractory multiple myeloma

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