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ICANS mitigation in high-risk elderly patients treated with CD28 co-stimulatory anti-CD19 CAR-T cells using a standardization protocol: a pilot study

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ABSTRACT

CAR-T has transformed relapsed/refractory LBCL treatment, with CD28-based products yielding rapid responses but higher ICANS rates. With Axicabtagene-ciloleucel and Brexucabtagene-autoleucel, overall and severe ICANS reach 78% and 35%, respectively. Older adults are vulnerable, yet mitigation strategies remain lacking. We aimed to develop and implement a standardized ICANS mitigation protocol for older adults receiving CD28-based anti-CD19 CAR-T, addressing this critical gap. We conducted a single-arm prospective pilot study in patients ≥75yr or ≥65 with additional risk factor receiving CD28-based CAR-T. The protocol included levetiracetam and thiamine prophylaxis, early grade-based corticosteroids and anakinra for grade ≥3 and refractory ICANS – defined as no improvement within 24hr. Endpoints were ICANS duration, refractoriness, response and toxicity. Forty-five patients met eligibility; median age 75 (65-86), 78% had ECOG ≥2 and 42% with neurologic comorbidity. Overall, grade ≥3, and refractory ICANS developed in 67%, 31%, and 20%, respectively. Median ICANS duration was 4 days, shorter than previous cohorts. Disease and patients' characteristics did not predict ICANS metrics, excluding LDH showing trend for severe ICANS (p=0.07). mEASIX and ICANS-PSS scores were not predictive; expansion was not compromised. Cumulative steroids associated with infections (p=.002) and NRM (p<.0001). Six-month PFS and OS were 46% and 59%, respectively. In this high-risk cohort, the ICANS mitigation protocol using anakinra in a graded approach (vs prophylaxis or salvage) and pragmatic refractory definition was associated with shorter ICANS duration despite severe event rates. Steroid-related toxicity remains a concern, and future efforts should focus on steroid-sparing mitigation to optimize outcomes in older adults undergoing CAR-T.

INTRODUCTION

Chimeric antigen receptor T cell (CAR-T) cell therapy has revolutionized the treatment landscape of large B-cell lymphoma (LBCL), offering a curative option for patients with relapsed or refractory LBCL with impressive overall and complete response rates[1-3]. A key distinction between available CAR-T products lies in the co-stimulatory domain: CD28 (e.g., axicabtagene-ciloleucel, axi-cel; brexucabtagene-autoleucel, brexu-cel) versus 4-1BB (e.g., tisagenlecleucel, tisa-cel; lisocabtagene-maraleucel, liso-cel)[1-6]. CD28-based CAR-T constructs are associated with a rapid T-cell expansion and earlier onset of clinical responses, but this comes at the cost of higher toxicity, particularly increased incidence and severity of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS)[4,7-9]. The early pivotal trials of axi-cel and brexu-cel reported any grade of ICANS in up to 64% and 78%, respectively, and grade ≥3 of 28% and 38%, respectively[1,5,6]. These high rates of ICANS were observed in both clinical trials and real-world setting[10-11], while parallel studies of non CD28-based anti-CD19 CAR constructs have demonstrated markedly lower rates and severity across indications and treatment settings[2,3], highlighting the impact of the co-stimulatory domain on ICANS development[7].

Incidence of ICANS is further increased among older patients[12]. In both the ZUMA-1 and ZUMA-7 trials, older age (≥65) was associated with increased incidence and severity of ICANS. Available data from ZUMA-7 suggested an age-dependent pattern, with patients aged ≥70 years experiencing higher ICANS rates than those aged ≥65 years[1,13]. Furthermore, several additional risk factors for ICANS are more prevalent in older age patients including advanced stage malignancy and high disease burden at lymphodepletion (LD) (potentially influenced by reduced tolerance to bridging therapy), as well as pre-existing neurologic comorbidities, and poor performance status[7,12,14-16]. While risk factors are typically assessed when considering candidates for CAR-T, formal eligibility criteria particularly regarding age and comorbidities still remains undefined, reflecting the complexity of using age and comorbidities as strict criteria for withholding an effective and life-saving treatment[17-18].

ICANS management is guided by consensus-based protocol and is mainly based on steroids administration[19], not specified for elderly patients who are prone to longer recovery periods in case severe ICANS develops. Similarly, management of prolonged and refractory ICANS is also not universally defined, and guided primarily by case series, some describing the off-label use of adjunctive agents such as thiamine, based on biological plausibility based on similar scenarios[20]. These case series are limited in the ability to evaluate efficacy and generalizability, particularly to elderly patients.

These factors expose older patients to both an unacceptable risk for ICANS and for treatment-associated deconditioning with potentially prolonged functional recovery and hospitalization, posing additional risk for complications, or in some cases limit patients access to CAR-T therapy due to toxicity concerns[18].

Considering the unmet-need for ICANS mitigation and the lack of standardized treatment, we aimed to develop and implement a prospectively predefined protocol for ICANS mitigation in elderly patients treated with CD28-based anti CD19 CAR-T.

METHODS

Patients and Investigational Protocol

We conducted a single arm prospective pilot study in the Tel Aviv Sourasky Medical Center. The study was performed in accordance with the Declaration of Helsinki, all patients gave

informed consent to the planned treatment schedule as well as for reporting of treatment outcomes and the study was approved by the local institutional review board (IRB).

Eligible patients were aged ≥75 or ≥65 with ≥1 additional risk factor: preexisting neurologic comorbidity, eastern cooperative oncology group (ECOG) performance status ≥ 2, high disease burden at LD (stable/progressive disease and/or LDH > upper normal limit) who received CD28-based CAR-T treatment.

The protocol comprised three components: prophylaxis, first-line treatment and second-line treatment for refractory ICANS (Table 1) –

1. *Prophylaxis* - All patients received PO levetiracetam and PO thiamine from day 0. For ICANS grade ≥2 both were converted to IV.

2. *First line treatment* - Corticosteroids administrated at grade-specific starting dose (Table 1), using higher initial once-daily doses to mitigate toxicity of prolonged courses. Anakinra was initiated for grade ≥3 ICANS. With concurrent CRS indicating tocilizumab, dexamethasone was co-administrated with each dose.

3. *Refractory ICANS* – Defined as no clinical improvement or worsening within 24 h of treatment initiation. Managed by escalating steroids to the next grade and adding anakinra if not already used.

4. *Additional Work up and Management* – Patients were evaluated by immune effector cell-associated encephalopathy (ICE) score once a day routinely, and in case of grade ≥2 ICANS, every 8 hours. All ICANS events were graded and evaluated for reversible causes (medications, electrolytes, etc.). CRS was defined and graded per ASTCT 2019 and ASCO 2021 guidelines, as the performance of imaging and EEG studies for grade >2 and refractory ICANS[19,21]. Lumbar puncture was performed when CNS involvement or infection was suspected.

Preparative Regimen and Supportive Care

All patients received ≥1 prior therapy before anti-CD19 CAR-T. Patients were admitted to the BMT ward in designated HEPA-filtered rooms (high efficiency particulate air filters). LD consisted of cyclophosphamide (500 mg/m^2) and fludarabine (30 mg/m^2) for 3 days (days –5 to –3). Prophylaxis included acyclovir from LD start, and ciprofloxacin and fluconazole during neutropenia (<500/μL). RBC and platelet transfusions were given for Hb <7 g/dL and platelets <10,000/μL, respectively. Premedication for infusion included IV promethazine 6.25 mg and PO paracetamol 1000 mg. Cells were thawed and infused per manufacturer recommendations[22,23].

Primary and Secondary End Points

Primary endpoints were ICANS duration and refractoriness. Secondary outcomes included hospitalization duration, cumulative corticosteroid dose (dexamethasone equivalents), disposition (home vs rehabilitation), CAR-T expansion, and 3-month CR rates. Safety endpoints included NRM and early/late toxicities (infections, immune effector cell-associated hematotoxicity (ICAHT) and immune effector cell-associated hemophagocytic syndrome (IEC-HS)).

Assessment

CAR-T expansion was measured by flow cytometry based on median time to peak expansion (day +7 for Axi-cel and day +14 for Brexu-cel) as reported in pivotal trials[1,5,6] and following additional in-house validation of expansion kinetics and was previously published by our group[24]. Disease was evaluated with PET-CT and bone marrow (if indicated) before LD, with response by Lugano criteria[25]. ECOG performance status[26] was recorded. Cytopenias were scored using ICAHT; IEC-HS was defined per ASTCT 2023[27-28]. Prediction models (day 3+ mEASIX[29] and ICANS-PSS[30]) were applied for severe ICANS risk.

Statistical Analyses

Mann–Whitney U test was used for two-group comparisons of continuous variables, ordinal logistic regression for ordered categorical outcomes, Kendall's tau for ordinal correlations, logistic regression and ROC analysis for predictive scores, and Kaplan–Meier with log-rank tests for time-to-event data. NRM was calculated using a competing risks approach with relapse as a time-dependent covariate in the Fine–Gray model. $p<0.05$ was considered significant. Analyses were performed in R v4.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patients

Between 04/2023 and 12/2024, 95 patients were referred for evaluation of anti CD19 CAR-T treatment. Four patients were not eligible or selected not to proceed to CAR-T. Two patients underwent lymphopheresis but had a rapid disease progression and did not receive the product. Eighty-seven (92%) patients received lymphodepletion, among those 45 (52%) patients met eligibility criteria. Median age in the cohort was 75 (range 65-86) years, 78% of patients had ECOG performance score of 2 and above, 42% of patients had a neurologic comorbidity and 22% had active CNS involvement. Twenty-four (53%) patients had progressive disease at lymphodepletion.

Other characteristics and population comparison to clinical trials and real-world data are outlined in Table 2. Overall, there was a high proportion of individuals with poor performance status (ECOG) and a significant percentage with progressive disease at the time of lymphodepletion. In 23 (82%) patients, CRS preceded ICANS (median time from CRS to ICANS 4 (range, 1-16) days), while in 5 (18%) patients CRS occurred concomitantly. Any grade CRS was observed in 98% of patients, of which 20% was grade ≥ 3. A median of 2 (range, 0-4) tocilizumab doses was given for CRS management.

ICANS Metrics and Management

Any grade ICANS developed in 67% of patients, median onset was 5 (range, 0-15) days post CAR-T, and median duration was 4 (range, 1-15) days. Grade ≥ 3 ICANS developed in 31% of patients. Among patients who developed any grade ICANS, writing abnormality was the presenting sign in 73%, inattention in 47%, naming in 33%, orientation in 30% and inability to follow commands in 17%. Two patients were not able to perform the full ICE score components and 1 patient presented with seizure. Refractory ICANS was observed in 9 (20%) patients and developed in a median of 6 (range, 4-16) days post CAR-T.

In a univariate analysis no significant association was found between age, disease status at LD, neurologic comorbidity, CRS grade, day of CRS onset, day 7+ expansion and tocilizumab use and the occurrence of refractory ICANS. Figure 1,2 and Figure 3 depict ICANS-related metrics and temporal trends. Median cumulative steroid dose was 160 (IQR, 20-530) mg,

Anakinra was used in 11 (24%) patients. Median hospitalization duration was 22 (range, 15-86) days and 7 (15%) patients required in-patient rehabilitation upon discharge.

EEG was performed in 13 patients. Abnormal activity was recorded in 85% of cases. In 7 patients, the findings were interpreted as generalized abnormal discharges. In 2 patients, the abnormal activity was restricted to the left temporal lobe, and in 1 patient each, it was localized to the right parietal and right frontal lobes. No epileptiform activity was recorded. Imaging was performed in 15 (33%) patients (MRI, n=10; CT scan, n=5). The most common finding in MRI was T2/ Fluid-Attenuated Inversion Recovery (FLAIR) hyperintensities found in 9 of 10 MRI scans. Most commonly located in the white matter (periventricular, subcortical), brainstem (pons, midbrain), thalami, and cerebellum. One patient had small microhemorrhage on Susceptibility-Weighted Imaging (SWI) sequence, located to the frontal lobe. Leptomeningeal enhancement, cerebral edema or restricted diffusion was not identified. Supplemental Table 1 summarizes the characteristics of MRI and EEG findings.

Predictors for Severity and Duration of ICANS

Early onset CRS (≤ Day 3+) was not associated with ICANS duration (p=0.57). Similarly, peak expansion of CAR-T cells was also not associated with ICANS duration (Spearman correlation (ρ): 0.01 p-value= 0.96) nor severity (121 cells/microL in patients who did not develop severe ICANS vs 48 cells/microL in patients who did, p=0.15).

Disease status at lymphodepletion was not associated with severe ICANS: 4/10 patients (40%) with low disease burden (CR/PR) developed severe ICANS, compared to 10/20 (50%) with high disease burden (p=0.89). Similarly, LDH levels at lymphodepletion showed no significant correlation with ICANS severity or duration, though a positive trend was noted. LDH levels correlated with ICANS duration (Spearman ρ=0.33, p=0.07), and patients who developed grade ≥3 ICANS had a higher median LDH (488 U/L) than those who did not (389 U/L, p=0.07). Baseline neurologic comorbidity was not associated with high grade CRS, however was associated with duration of ICANS (median 7 days vs 3 days in patients without, p=0.02). Nevertheless, no association was observed between baseline CNS involvement and severe ICANS (p=0.47) nor duration (p=0.36).

Poor performance status showed a statistically significant moderate positive correlation with ICANS severity (ρ = 0.38, p = 0.04), with a non-statistically significant trend toward ICANS duration (ρ = 0.33, p = 0.07). In contrast, no association was observed between age and ICANS duration or severity.

Higher mEASIX score was associated with a trend toward increased risk of ICANS ≥3, but did not reach statistical significance (p=0.11), the model discriminative performance was moderate (AUC=0.68). In contrary, the ICANS-PSS score was not associated with high grade ICANS (OR=0.99, CI 0.39-2.49, p=0.98), and demonstrated poor discriminative ability (AUC=0.50).

Non-ICANS CAR-T-associated toxicities

Twenty-one patients (47%) developed early ICAHT (≤30 days), of whom 12 (26%) had grade ≥3 events. Among patients who developed ICAHT, 71.4% experienced thrombocytopenia (T-ICAHT), 85.7% developed neutropenia (N-ICAHT) and 57.1% had both T-ICAHT and N-ICAHT. Steroid exposure was numerically higher in patients who developed ICAHT compared with those who did not (250 vs. 74mg, p=0.12). Granulocyte colony-stimulating factor was given to 37.8% of patients for early neutropenia and was not associated with cumulative steroid dose (OR = 1.001; 95% CI: 0.999–1.003; p = 0.19). Similarly, there was no associations between cumulative steroid exposure and patients who developed (n=10, 22%) or did not develop hypogammaglobulinemia (median 117.0 vs. 160.5 mg, respectively; p = 0.27). This

was also true between patients who developed (n=15, 34%) or did not develop IEC-HS (median 250 mg vs. 138 mg, respectively; p = 0.484). No post-CAR-T secondary malignancy was documented.

CMV reactivation requiring treatment occurred in 5 patients (11%). The median cumulative steroid dose was numerically higher among patients who developed CMV reactivation compared to those who did not (358.5 mg [IQR 320.0–380.0] vs. 138.0 mg [IQR 20.0–536.2], respectively, p=0.133).

Documented infections occurred in 19 of 45 patients (42%), including 14 bacterial infections, 4 invasive fungal infections, and 2 cases of COVID-19. In a univariate analysis patients who experienced infections had a significantly higher cumulative steroid dose compared to those who did not (median380 vs. 77.5 mg, respectively; p=0.002).

Anakinra use was not associated with infectious complications. Infections occurred in 10 out 18 patients (55.6%) who received anakinra compared with 13 out of 27 (48.1%) who did not (p=0.16). When analyzed by cumulative anakinra dose, we observed a non-significant trend toward higher infection rate with greater exposure (p=0.06). We did not observe any other adverse effect that can directly be attributed to anakinra use.

Incidences of NRM at 1- and 3-months post CAR-T were 8.7% (95%CI 0%-20.2%) and 26.1% (95% CI 8.1%-44%), respectively. The cause of NRMs were as follows: simultaneous ICAHT and infection (n=5), infection (n=2), ICAHT (n=1), and refractory ICANS (n=1). In two patients, the cause of death remained indeterminate. Higher steroid dose was significantly associated with higher NRM; the median cumulative steroids exposure was 850mg (IQR 532.5-1020.6) among NRM patients vs 77.5mg (IQR 20-239.4) among non-NRM patients. (p=0.02).

Efficacy of CAR-T

Median follow-up of surviving patients was 5.9 (range, 0.5-19.4) months. Nineteen (42%) patients were alive at data extraction. Median peak expansion of CAR-T was 72 (range, 0-1725) cells/microL. There was no association between the cumulative steroid dose and CAR-T expansion on day 7+ : τ (Kendall's tau)=0.0857, p=0.415. At 3 months post CAR-T, 20 (44%) patients achieved CR and 1 achieved PR. Cumulative incidences of PFS at 6 and 12 months were 46% (95% CI 30.0-59.7) and 42.9% (95% CI 26.9-56.8), respectively. Cumulative incidences overall survival at 6 and 12 months were 59% (95% CI 43.5-73.0) and 46.1% (95% CI 29.3-56.8), respectively, Figure 4.

DISCUSSION

To our knowledge, this is the first attempt to implement a specified ICANS treatment protocol for older patients treated with CAR-T, together with a pragmatic and short-interval definition of refractoriness, treatment escalation, and early integration of anakinra (rather than prophylactic or salvage). Taken together, our findings suggest that this protocol may mitigate ICANS duration in an extremely high-risk population of patients treated with a CD28-based co-stimulatory CAR-T, to levels comparable to those observed in standard-risk cohorts, with no signal for CAR-T expansion or efficacy compromise.

Treatment components and dosing were adapted from current consensus guidelines and case reports of refractory ICANS management[19-20] with adaptation to a high-risk population with steroids as the backbone of ICANS management. Previous attempts in safety cohorts of the ZUMA1 used prophylactic steroids and showed reduction in CRS incidence and severity in cohort 4[31], although with no benefit to ICANS development or grade in a matched analysis of cohort 6 of ZUMA1[32]. ICANS management in cohort 6 included steroid treatment from

grade 1, and long-term data showed no compromise of either expansion or outcomes[31,32]. Based on this, we decided to integrate steroids in early and intensive manner in the protocol, as outlined in study protocol in Table 1.

In cohort 3 of the ZUMA 1 prophylactic levetiracetam was given with tocilizumab and failed to reduce ICANS rates[33]. Considering scarcity of data, extremely high-risk patients and favorable toxicity profile of the drug we decided to give all patients seizure prophylaxis coverage with levetiracetam. The use of thiamine in the protocol is primarily supported by observational data, biological plausibility, and indirect evidence from analogous clinical scenarios including thiamine deficiency observed in patients with CRS and ICANS, imaging studies of ICANS patients mimicking Wernicke's encephalopathy and sepsis patients which are often thiamine depleted which is associated with damage to the blood brain barrier[34-36].

Anakinra use is based on several retrospective studies and case reports showing its potential as a rescue therapy for steroid refractory ICANS[20,37-39], and from early studies showing promising results of its effectiveness as a prophylactic agent[40-41]. Both scenarios showed good safety profile with the use in this setting. Considering timing and grade of CRS along with tocilizumab use are associated with ICANS development[12,31], each tocilizumab dose, was given together with dexamethasone.

Refractory ICANS lacks a uniform definition and has previously been described inconsistently across studies[20,37,39]. Our aim was to create a standardized treatment for this extremely high-risk population in whom high rates of ICANS were expected. Given the population's low physiological reserve and potentially consequential effects of prolonged and severe ICANS, we defined refractoriness as escalating or lack of improvement within 24 h of treatment initiation. We observed a different and more severe ICANS trajectory with patients who met the refractory definition in our cohort . Though clinically coherent and in some way expected, the lack of a uniform and time bound definition makes the observation that a 24 h time frame for lack of improvement might be sufficient for escalation of treatment, and perhaps beforehand when high risk features are present.

Key finding in our cohort was a markedly short median duration of ICANS of 4 days (range, 1-15), favorable compared with a median of 5-9 days observed in the ALYCANTE[42], real-word data[11,43], and ZUMA-7 trials[1,44], all with markedly less predisposed populations. This shorter duration was achieved despite a substantial incidence of ICANS (overall and severe in 67%, and 31% respectively). Interestingly, although more higher risk patients in our cohort, grade ≥3 ICANS incidence was comparable to that observed in the most elderly subgroups of the ZUMA-7 (27% for patients ≥65 and 33% for patients ≥70), underscoring the potential of the current protocol to mitigate neurologic further deterioration.

In order to examine effectiveness of the protocol with the caveat of a single arm design, we evaluated several surrogates that are known to be associated with ICANS severity. Several studies of both CD28 as well as 41-BB established association between CAR-T expansion and ICANS severity[4,7,9], which was not shown in our cohort of high-risk patients. Similarly, previously reported factors like disease status at lymphodepletion and CRS onset were also not associated with higher incidence of grade ≥3 ICANS, nor longer duration[7,12,14]. Interestingly, neurological comorbidities, which was widely defined, was associated with duration but not severity of ICANS, perhaps suggesting a distinct mechanism for ICANS pathogenesis and recovery and might further guide management of such patients. The lack of predictive value of both the mEASIX score[29] at day +3 and the ICANS-PSS[30] in our high-risk cohort may reflect either the prospective protocol effectively attenuated the clinical and biological factors captured by these models, or these models have limited applicability in

populations with an inherently elevated risk for ICANS, as they were not originally validated in such settings, and also the relatively small sample size.

Consistent with previous observation, our cohort demonstrated a distinct window period between CRS and ICANS. The findings that ICANS duration was short, and not associated with the timing of CRS onset support using this intervening period for pre-emptive mitigation strategy, and may be considered when designing future trials.

Considering this, anakinra has been utilized in ICANS management at both ends of the clinical spectrum - prophylactically and in refractory cases[20,39-41]. To our knowledge, we are the first to demonstrate that early integration of anakinra, initiated upon lack of rapid improvement or escalation within 24 h, may offer additional clinical benefit.

Non relapsed mortality and increased infectious complications (similar to other reports[45]) were notable in this protocol. Importantly, the majority of NRM cases in our cohort occurred in the context of concurrent cytopenia presumed to be ICAHT-related and the clinical vulnerability of our population. Nevertheless, risk might be minimized with a preventive approach stratified by steroid exposure, use of anakinra and meeting refractory ICANS definition.

We acknowledge several limitations to our study. First, a single arm pilot study design with a relatively small sample size (with ALL and MCL under represented). Nevertheless, comparing our extreme high risk population cohort and ICANS metrics to previous studies, although indirect, alongside several surrogates to assess efficacy and safety offers valuable information on ICANS management in this population with a novel standardized approach. Both axi-cel and liso-cel are available as second line, joining by tisa-cel for later lines - all with comparable efficacy in parallel studies but with higher toxicity profile for axi-cel[1-3]. This protocol may serve as a backbone in case 4-1BB based-anti CD-19 CAR-T is not available and axi-cel is chosen for these vulnerable population[46-47].

In summary, we demonstrate that since most risk factors for ICANS both pre- and post-infusion are unmodifiable, a mitigation-based approach may offer a compelling alternative to safely extend CAR-T therapy to high-risk elderly patients. Future studies should focus on decreasing steroid dose and incorporate steroid-sparing agents (i.e. anakinra, JAK inhibitors[48], siltuximab[49]) early in the course, to further mitigate ICANS and associated comorbidity burden.

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TABLES and FIGURES

Table 1 – Study Protocol

	Steroids	Anakinra	Seizure Prophylaxis	Supportive Care
No ICANS	NA	NA	PO Levetiracetam 750mg BID	PO Thiamine 1 Tab OD
Grade 1	IV Dexamethasone 20mg OD	NA	PO Levetiracetam 750mg BID	PO Thiamine 1 Tab OD
Grade 2	IV Dexamethasone 20mg QD	NA	IV Levetiracetam 1000mg BID	IV Thiamine 500mg TID
Grade 3	IV Methylprednisolone 1g OD	SC Anakinra 100mg BID	IV Levetiracetam 1000mg BID	IV Thiamine 500mg TID
Grade 4	IV Methylprednisolone 2g OD	SC Anakinra 100mg BID	IV Levetiracetam 1000mg BID	IV Thiamine 500mg TID
Refractory ICANS	Dose Escalation to subsequent grade	SC Anakinra 100mg BID	IV Levetiracetam 1000mg BID	IV Thiamine 500mg TID
Concurrent CRS	Dexamethasone 20mg with each dose of tocilizumab			
Refractory ICANS - No clinical improvement within 24 h of treatment initiation and/or worsening to a higher grade within 24 h under active treatment				
† Anakinra administration until ICANS grade reach ≤ 1				

Table 2 – Patients and Disease Characteristics

Characteristic	Study Protocol (N=45)	ZUMA 7 (N=180)	ZUMA 7 ≥ 65 (N=51)	ALYCANTE (N=62)	CIBMTR Registry (N=446)
Age (range) – median, yr	75 (65-86)	58 (21-80)	65 - 81	70 (49-81)	64 (19-86)
Age ≥ 65 – no. (%)	45 (100)	51 (28)	51 (100)	55 (88)	NR
Age ≥ 75 – no. (%)	23 (49)	NR	24 (47)	7 (11)	NR
Female sex no. (%)	20 (44)	70 (39)	NR	15 (24)	160 (36)
ECOG ≥ 2 – no. (%)	35 (78)	0 (0) *	0 (0) *	1 (2)	13 (3)
Neurologic comorbidity – no. (%)	19 (42)	0 (0)	0 (0)	NR	NR
Disease Characteristics					
DLBCL – no. (%)	36 (80)	110 (61)	51 (100)	52 (84)	347 (78)
MCL – no. (%)	8 (18)	0 (0)	0 (0)	0 (0)	0 (0)
ALL – no. (%)	1 (2%)	0 (0)	0 (0)	0 (0)	0 (0)
CNS involvement – no. (%)	10 (22)	0 (0)	0 (0)	0 (0)	NR
Primary Refractory \ Early relapse – no. (%)	19 (53) \ 13 (36)	133 (74) \ 47 (26)	36 (70) \ 15 (30)	NR	NR
Received bridging therapy – no. (%)	44 (98)	0 (0)	0 (0)	52 (84)	294 (66)
SD\PD at Lymphodepletion – no. (%)	27 (60)	NR	NR	7 (11)	NR
LDH > ULN Lymphodepletion – no. (%)	27 (62)	101 (56)	31 (61)	7 (11)	214 (48)
Non-ICANS Toxicities					
CRS Any grade – no. (%)	44 (98)	157 (92)	48 (98)	58 (93)	388 (87)
CRS Grade ≥3 – no. (%)	9 (20)	11 (6)	4 (8)	5 (8)	13 (3)
ICAHT† – no. (%)	21 (47)	43 (24)	NR	62 (27)	95 (21)
Infections – no. (%)	19 (42)	NR	NR	17 (27)	143 (32)
IEC-HS – no. (%)	15 (33)	0 (0)	0 (0)	NR	NR
Cumulative steroid‡ – Median (IQR)	160 (20-530)	NR	NR	NR	NR
Patients received Anakinra – no. (%)	11 (24)	0 (0)		0 (0)	80 (18)
Days in Hospital – Median (range)	22 (15-86)	NR	NR	NR	NR
Response					
ORR – no. (%)	21 (47)	149 (83)	25 (75)	47 (76)	353 (79)
CR – no. (%)	20 (44)	117 (65)	38 (75)	44 (71)	285 (64)
PFS§ – no. (%)	19 (43)	86 (48)	22 (42)	30 (49)	236 (53)
OS§ – no. (%)	21 (46)	135 (75)	33 (64)	49 (78)	317 (71)

ALL Acute lymphoblastic leukemia, CNS Central nervous system, CR Complete response, CRS Cytokine release syndrome, DLBCL Diffuse large B cell lymphoma, ECOG Eastern cooperative oncology group, ICAHT Immune effector cell-associated haematotoxicity, LDH Lactate dehydrogenase, MCL Mantle cell lymphoma, NR Not Reported, PD Progressive disease, PFS Progression free survival, SD Stable disease, ORR Overall response rate, OS Overall survival, ULN Upper limit of normal.
*Exlusion criteria, †Early (≤ 30 days), ‡Dexamthasone equivalent, §At 12 months

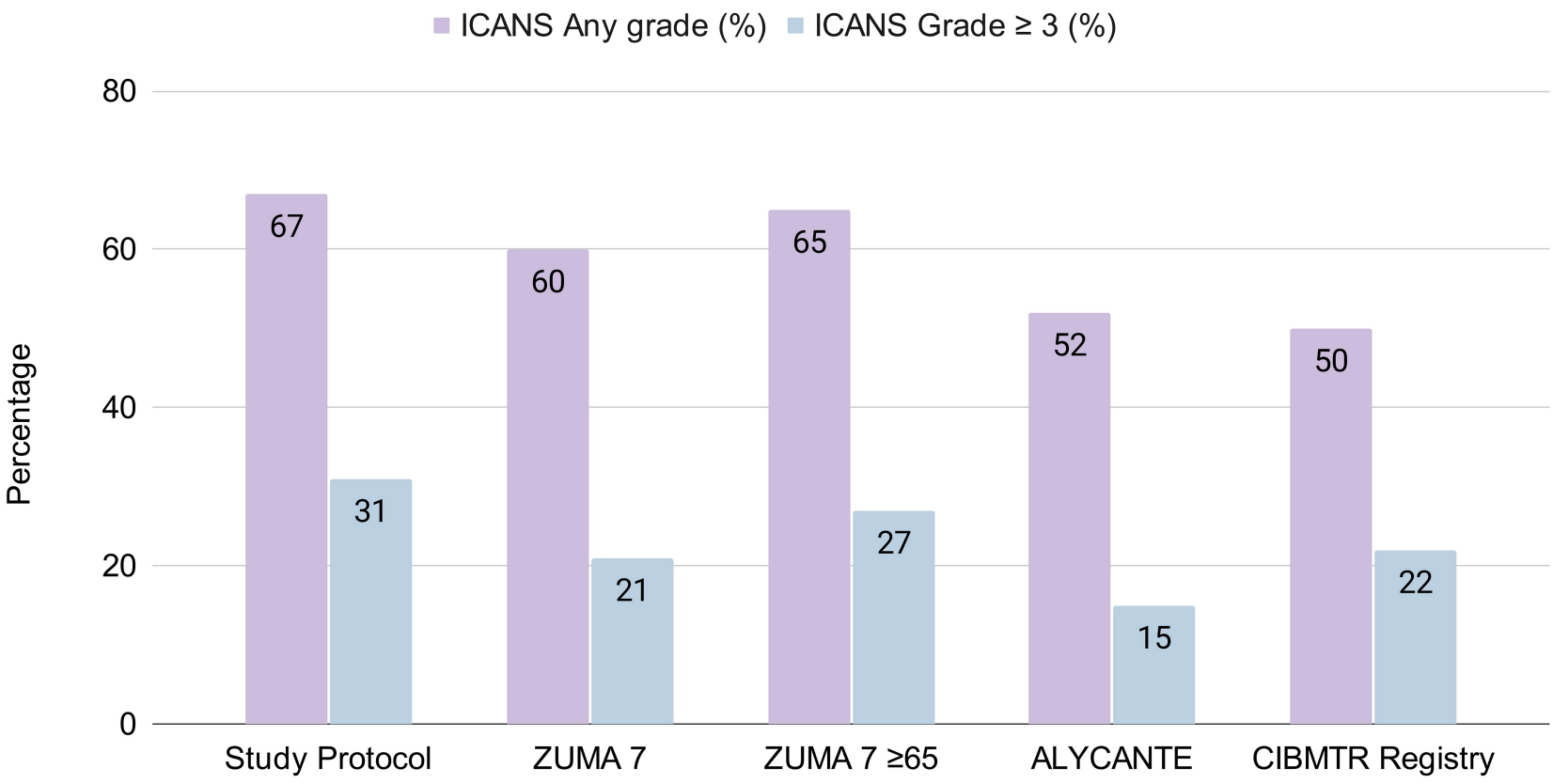
Figures Legends

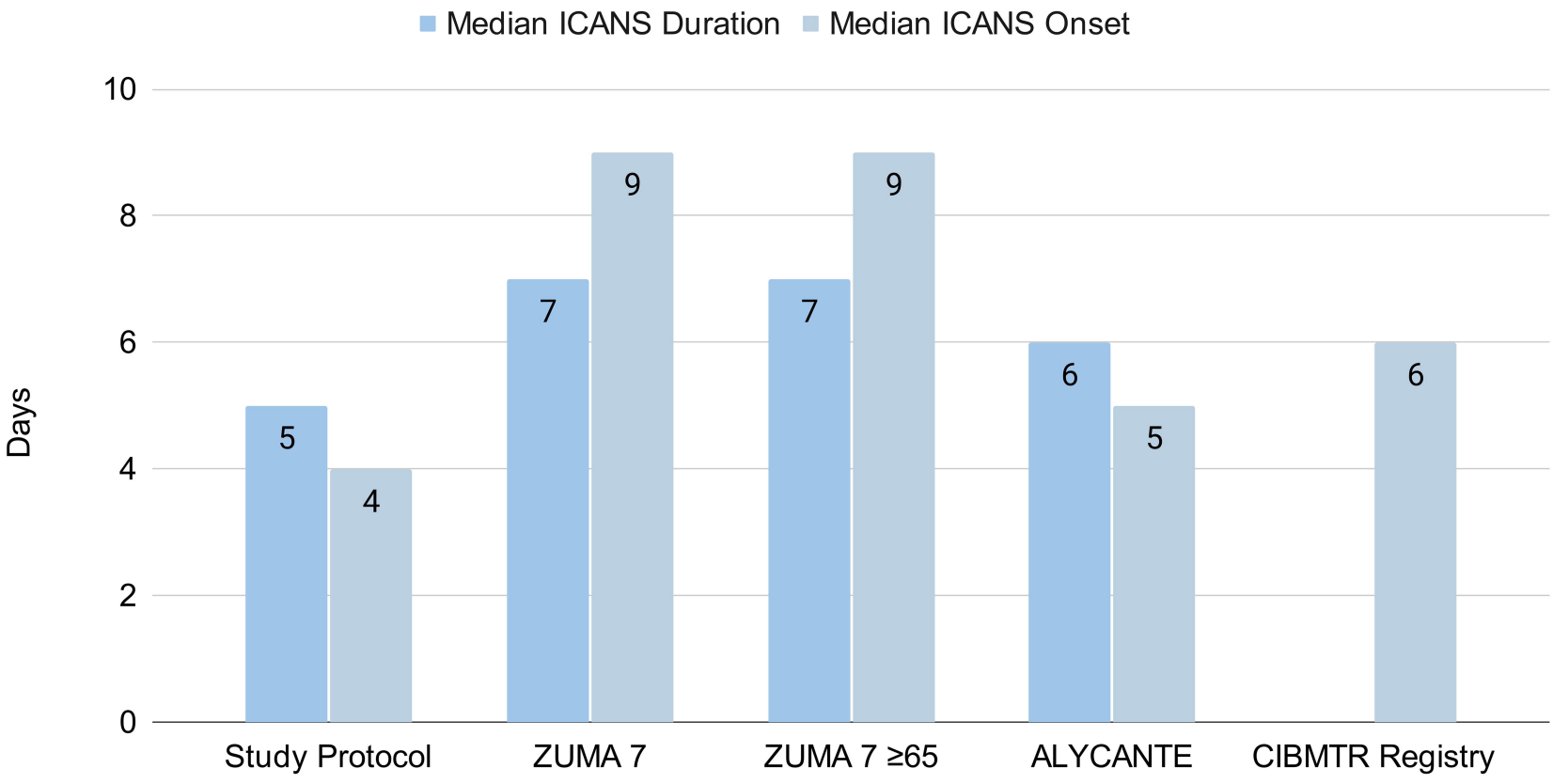
Figure 1 – ICANS Incidence

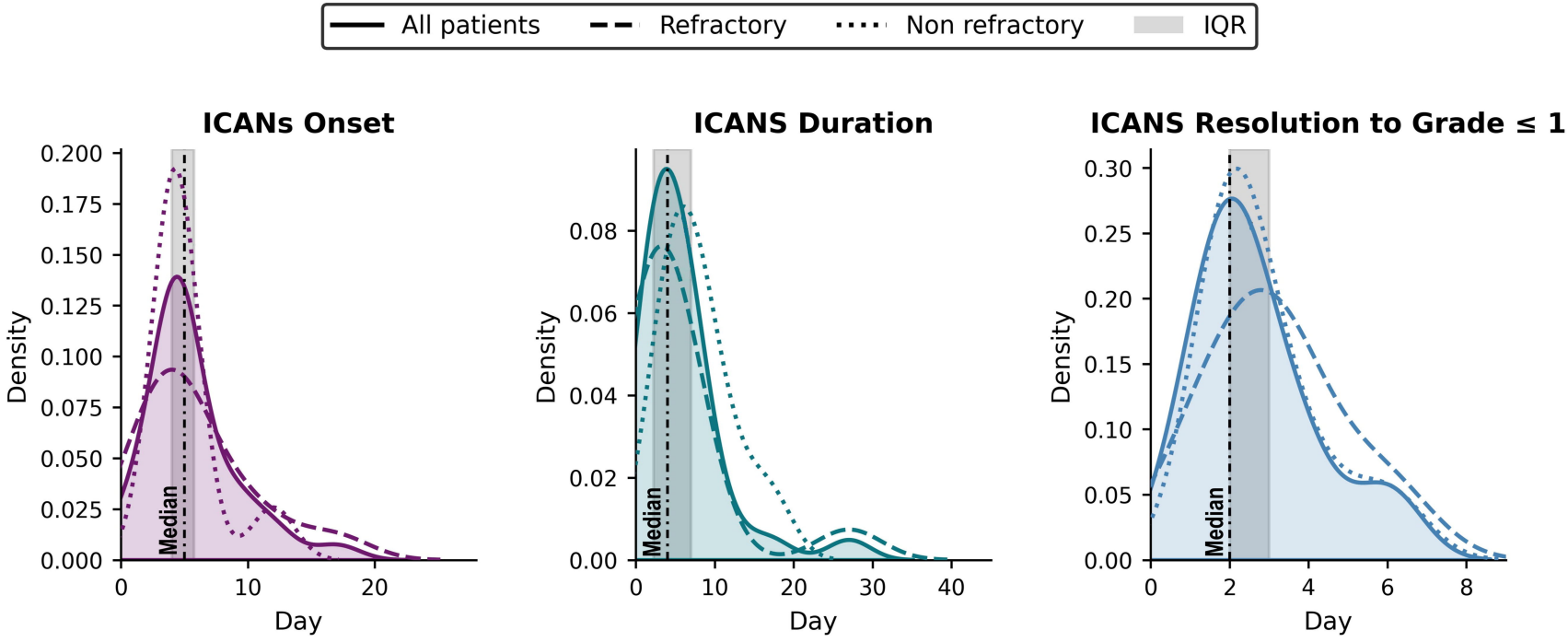
Figure 2 – ICANS Metrics Comparison
* ICANS onset was not specified in the publication of the CIBMTR registry

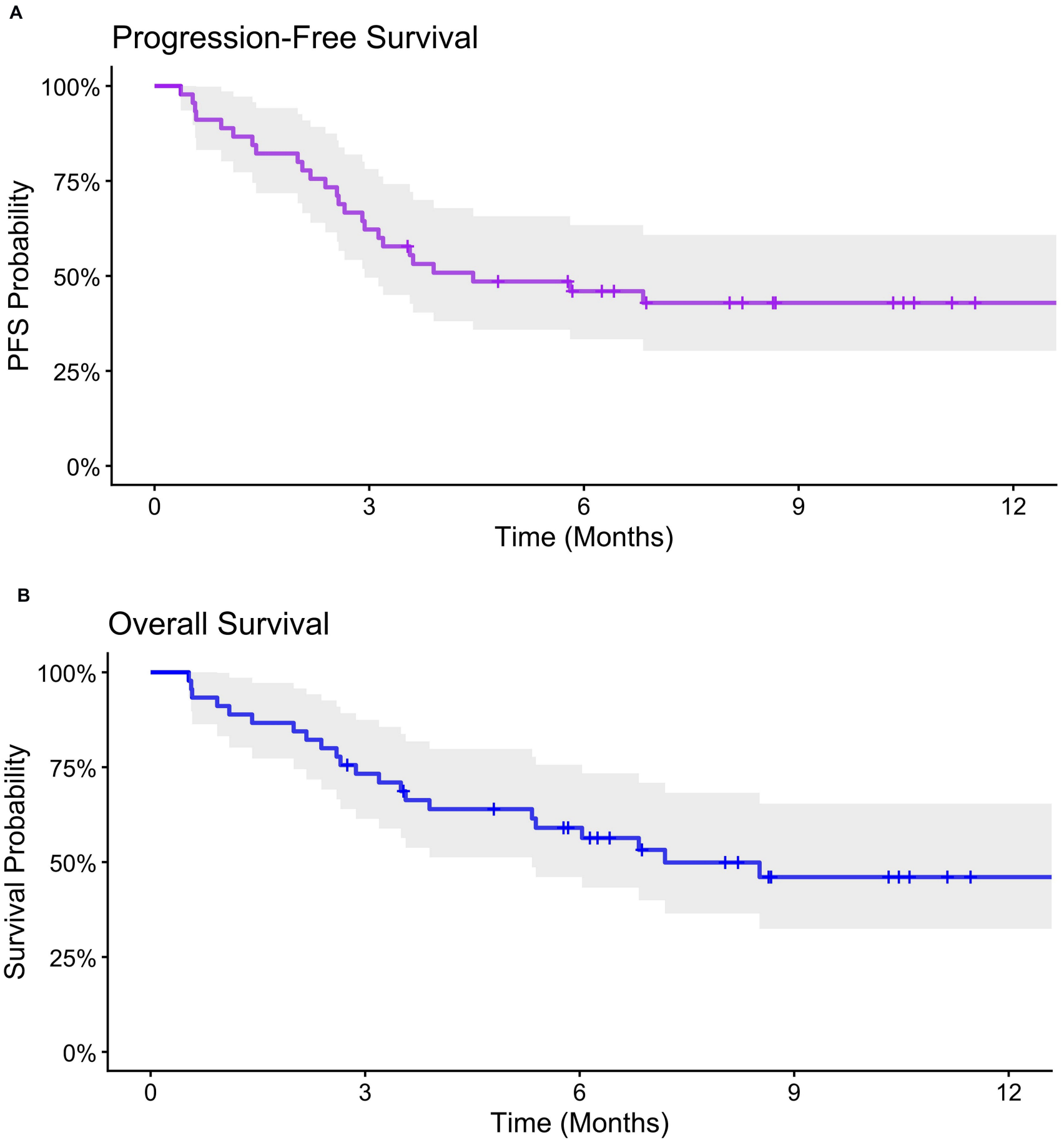
Figure 3 – ICANS Metrics Trends for Refractory and Non-Refractory ICANS

Figure 4 – Kaplan Meier Curves for Survival. Panel A - Progression Free Survival, Panel B - Overall Survival


ICANS Any grade (%)
ICANS Grade ≥ 3 (%)
Percentage
80
60
40
20
0
67
31
60
21
65
27
52
15
50
22
Study Protocol
ZUMA 7
ZUMA 7 ≥65
ALYCANTE
CIBMTR Registry


Median ICANS Duration
Median ICANS Onset
Days
10
8
6
4
2
0
5
4
7
9
7
9
6
5
6
Study Protocol
ZUMA 7
ZUMA 7 ≥65
ALYCANTE
CIBMTR Registry


All patients
Refractory
Non refractory
IQR
ICANs Onset
ICANS Duration
ICANS Resolution to Grade ≤ 1
Density
Day
Median
0.200
0.175
0.150
0.125
0.100
0.075
0.050
0.025
0.000
0.08
0.06
0.04
0.02
0.30
0.25
0.20
0.15
0.10
0.05
0
10
20
30
40
2
4
6
8


A
Progression-Free Survival
100%
75%
50%
25%
0%
PFS Probability
0
3
6
9
12
Time (Months)
B
Overall Survival
100%
75%
50%
25%
0%
Survival Probability
0
3
6
9
12
Time (Months)

Supplementary Table 1 – EEG and MRI Findings

Patient	ICANS Grade	EEG Dysfunction Territory	MRI Findings				
			T2/FLAIR Hyperintensities	Leptomeningeal Enhancement	Cerebral Edema	Microhemorrhages	Restricted Diffusion
2	3	NA	Periventricular + subcortical WM	None	None	None	None
10	3	NA	Bilateral WM, nonspecific	None	None	None	None
17	3	Right Parietal	WM + cerebellum, ischemic	None	None	Right frontal SWI	None
18	2	General	None	None	None	None	None
21	2	Left Temporal					
22	3	General	WM periventricular, stable	None	None	None	None
24	3	General	Cerebellar focus, m\p chronic	None	None	None	None
25	1*	General					
28	2	None					
29	3	General					
31	3	Frontal	Pons, midbrain, thalamus	None	None	None	None
36	3	General	Mild periventricular WM	None	None	None	None
38	3	NA	NA due to motion	None	None	None	None
39	1	Left Temporal					
40	3	None	Bilateral WM (leukoaraiosis)	None	None	None	None
44	3	General					

EEG Electroencephalogram, M\P Most probably, NA Not applicable, SWI Susceptibility Weighted Imaging, WM White matter
*EEG was performed pre-emptively based on early clinical concern for potential neurological deterioration and is a minor deviation from protocol