(LB4001) PHASE 2 STUDY OF TALQUETAMAB + TECLISTAMAB IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA AND EXTRAMEDULLARY DISEASE: REDIRECTT-1

Topic: 14. Myeloma and other monoclonal gammopathies - Clinical

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Background

Patients (pts) with soft tissue plasmacytomas noncontiguous with bone (extramedullary disease [EMD]) have poor outcomes with standard therapies due to low overall response rates (ORRs) and rapid relapses. Talquetamab (Tal; anti-GPRC5D) and teclistamab (Tec; anti-BCMA) are first-in-class bispecific antibodies (BsAbs) approved as monotherapies for triple-class exposed (TCE) relapsed/refractory multiple myeloma (RRMM). In pts with RRMM with EMD, ORR was 41–48% with Tal and 36% with Tec monotherapies.

Aims

To report the efficacy and safety of Tal + Tec in pts with EMD in the phase 2 RedirecTT-1 EMD cohort (NCT04586426).

Methods

Pts had TCE RRMM and EMD defined as ≥1 nonradiated soft tissue plasmacytoma noncontiguous with bone ≥2 cm in 1 dimension (with or without paraskeletal plasmacytomas). Nonsecretory/oligosecretory disease was permitted. Prior CAR-T (≤20% of pts) and non-BCMA/-GPRC5D BsAb therapy was permitted. Pts received Tal 0.8 mg/kg Q2W + Tec 3.0 mg/kg Q2W, with step-up doses; pts could switch to Q4W dosing at investigator's discretion after cycle 6 or after cycle 4 with confirmed ≥VGPR. Response was assessed by IRC per IMWG criteria; EMD response was assessed by whole body PET-CT

scans.

Results

As of March 2025, 90 pts received Tal + Tec (median follow-up 12.6 mo [range 0.5–19.5]). Median age was 65 yrs; 22% had high-risk cytogenetics, 39% had nonsecretory/oligosecretory disease, and median number of plasmacytomas noncontiguous with bone was 2 (range 1–14). Median prior LOT was 4; 84% were triple-class refractory, 36% were penta-drug refractory, 20% had prior anti-BCMA CAR-T therapy, and 9% had prior BsAbs. ORR (95% CI) was 79% (69.0–86.8), with ≥CR of 52%; ORR was 83% (58.6–96.4; n=15/18) in pts with prior anti-BCMA CAR-T therapy and 75% (34.9–96.8; n=6/8) in pts with prior BsAb therapy. Overall, 9-mo DOR, PFS, and OS were 75%, 64%, and 80%, respectively. Most responders (>90%) deepened or maintained response after switching to Tal 0.8 mg/kg Q4W + Tec 3.0 mg/kg Q4W. Grade (gr) 3/4 AEs occurred in 78 (87%) pts. CRS occurred in 70 (78%) pts (all gr 1/2). ICANS occurred in 11 (12%) pts (gr 3, 1%; gr 4, 1%; gr 5, 0%). Neutropenia was the most common gr 3/4 AE (n=56, 62%). Taste changes (n=71, 79%), skin (n=62, 69%), and nail (n=50, 56%) were all gr 1/2, and rash (n=26, 29%) was mostly gr 1/2. Infections occurred in 71 (79%) pts (gr 3/4, 37%); 88% of gr 3/4 infections occurred within the first 6 mo. Sixty-three (70%) pts had posttreatment hypogammaglobulinemia. Overall, 78 (87%) pts received ≥1 dose of intravenous IgG. Eight (9%) pts discontinued Tal + Tec due to AEs; 5 due to gr 5 AEs (COVID-19 pneumonia, Klebsiella sepsis, aspiration, respiratory failure, euthanasia) and 3 due to non–gr 5 AEs. Two pts discontinued Tal only due to non–gr 5 AEs. No pts discontinued Tec only. Ten pts had gr 5 AEs (5 infections), 5 of which were drug related.

Summary/Conclusion

With 90 pts with confirmed EMD, the phase 2 cohort of RedirecTT-1 is the largest dedicated EMD study to date. Tal + Tec led to a high ORR and deep, durable responses; efficacy exceeded standard therapies, including BsAb monotherapies, and was comparable to CAR-T therapies in pts with RRMM with EMD. No new safety signals were identified, including no exacerbated Tal or Tec AEs. These data highlight the clinical benefit of dual-antigen targeting with the novel combination of Tal + Tec in pts with EMD, a population with high disease burden and significant unmet need.

(LB4002) INCA33989 IS A NOVEL, FIRST IN CLASS, MUTANT CALRETICULIN-SPECIFIC MONOCLONAL ANTIBODY THAT DEMONSTRATES SAFETY AND EFFICACY IN PATIENTS WITH ESSENTIAL THROMBOCYTHEMIA (ET)

Topic: 16. Myeloproliferative neoplasms - Clinical

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Background

Mutations of calreticulin in exon 9 (mut*CALR*) are found in ~25% of patients with ET. INCA33989 is a novel, fully human, Fc-silenced, IgG1 monoclonal antibody that targets the C-terminus of mutCALR and suppresses oncogenic signaling. INCA33989-101 (NCT05936359) and -102 (NCT06034002) are phase 1, first-in-human, multicenter, open-label studies evaluating INCA33989 in patients with ET or myelofibrosis (monotherapy or in combination with ruxolitinib). Data from dose escalation in ET are presented.

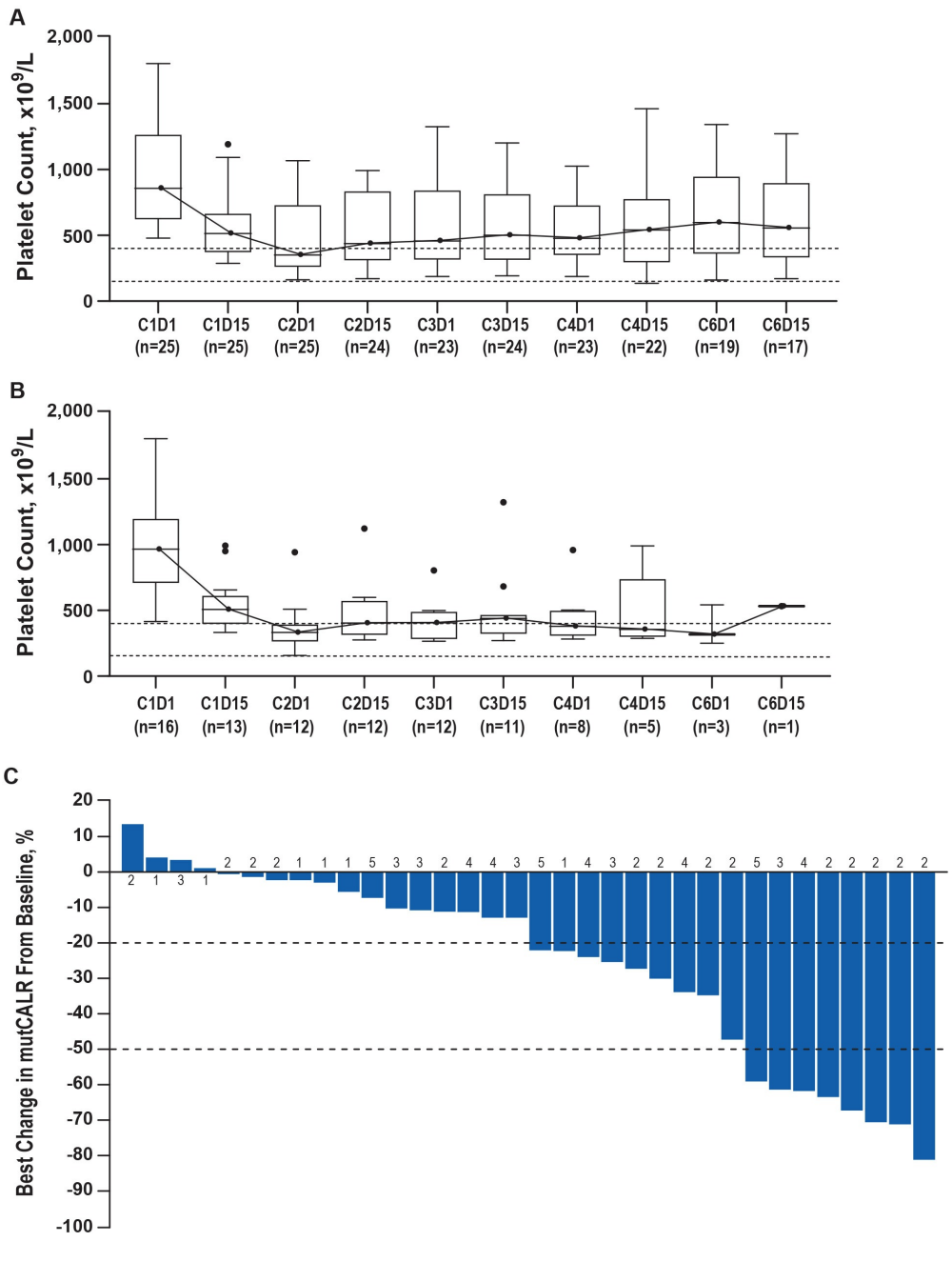
Methods

Patients had a pathogenic *CALR* mutation, resistance/intolerance to prior ET therapy, platelet count >450×10^9/L, and high-risk disease (age ≥60 years, history of thrombosis, major bleeding, or extreme thrombocytosis). Patients received INCA33989 intravenously every 2 weeks, and the primary endpoint was safety and tolerability. Efficacy was evaluated via hematologic response in patients that received >1 dose, defined as platelet count <400x10^9/L (complete response [CR]) or <600x10^9/L (partial response [PR]), together with leukocytes <10x10^9/L. Reduction in mutCALR variant allele frequency (VAF) was also assessed.

Results

As of the data cutoff (14Feb2025), 41 patients were enrolled and treated at doses ranging from 24 to 2500 mg; only 1 patient discontinued treatment and median exposure was 20 weeks (range, 0.4-62). Median age was 60 years (range, 23-82), 56% were female; 56%, 26% and 18% of patients had type-1, type-2 and type-other *CALR* mutations, respectively. The median baseline mutCALR VAF was 0.32 (range, 0.13-0.57) and the median platelet count was 933 $x10^9$/L (range, 447-1865). Across all dose cohorts, 33 patients (81%) had a treatment-emergent adverse event (TEAE), with the most common being fatigue (27%) and upper respiratory tract infection (17%), all grade ≤2. Nine patients (22%) had a grade ≥3 TEAE, with transient lipase increase without clinical findings of pancreatitis as the most common (5%). Anemia and neutropenia were reported in 6 (15%) and 5 (12%) patients, respectively, with only one grade 3 event (neutropenia at 100mg). No thrombocytopenia was reported in any patient. Two patients (both at 24 mg) had serious TEAEs: one had transient, asymptomatic lipase increase; the other had visceral venous thrombosis, followed by melena (after anticoagulant initiation) and treatment discontinuation. No dose reductions or infusion interruptions due to a TEAE were observed. No dose-limiting toxicities (DLTs) were observed, and a maximum tolerated dose was not reached. Rapid and durable reduction in platelets was observed across all dose levels; best overall response rate (CR+PR) was 79% (30/38), with most patients achieving a CR (66%, 25/38). Hematologic responses were achieved after 4 weeks (2 doses) and sustained for at least 8 weeks in 57% (CR) and 68% (CR+PR) of evaluable patients. A reduction in mutCALR VAF from baseline occurred in 30/34 (88%) evaluable patients, with 17/34 (50%) achieving > 20% reduction (**Figure**). A partial molecular response (PMR, >50% VAF reduction) was observed in 8 (25%) patients after 12 weeks of treatment.

Figure: Preliminary efficacy analyses in patients with ET receiving INCA33989 monotherapy. Platelet counts in patients receiving 24 to 250 mg (A) and ≥400 mg INCA33989 (B), and best percentage change in mutCALR VAF from baseline (C). For panels A and B, the dotted lines indicate upper and lower limit of normal. Boxes denote the first and third quartiles, lines represent the median. For panel C, the dotted lines represent 20% and 50% VAF thresholds; number of post-baseline VAF assessments is noted along the x-axis.



Summary/Conclusion

INCA33989 monotherapy in ET patients who were resistant/intolerant to prior therapy was well-tolerated with no DLTs, and 98% of patients remain on treatment. Rapid and durable normalization of blood counts and reduction of mutCALR VAF was observed in most patients, and the potential for disease modification was evidenced by 25% of patients achieving an early PMR.

(LB4003) TRANSCRIPTIONAL REPROGRAMMING AND SURVIVAL CO-DEPENDENCIES OF CHRONIC LYMPHOCYTIC LEUKEMIA RESISTANT TO VENETOCLAX

Topic: 05. Chronic lymphocytic leukemia and related disorders - Biology & translational research

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Background

High-risk chronic lymphocytic leukemia (CLL) that progresses on both Bruton's tyrosine kinase (BTK) inhibitors and venetoclax, particularly in the context of dysfunctional *TP53*, lacks effective treatment options. In a cohort of 15 dual-relapsed CLL, whole exome sequencing revealed that *BCL2* mutations emerge in minor subclones at relapse, while *TP53*, *BTK*, and *PLCG2* mutations dominate the relapsed population.

Results

Using single-cell RNA sequencing on paired pre-treatment and relapse samples, we observed significant transcriptional reprogramming impacting CLL survival. Among CLL cells (ROR1?/MS4A1?/CD19?/CD5?), we identified two minor relapse-specific subclusters (5 and 6) and three major clusters (0, 1, 2) present at both timepoints. Relapse-enriched clusters co-expressed *BCL2*, *MCL1*, and gained the MCL1-binding pro-apoptotic factor *PMAIP1*/NOXA, indicating a shift in apoptotic interactomes. We also noted expansion of a pre-existing *BCL2*-low cluster (cluster 1), which gained NF-κB signaling, upregulated *BCL2A1*/BFL-1 and *MCL1*, and expressed high levels of p53 targets *CDKN1A*/p21 and *GADD45A*. This cluster expanded in patients with mutant *TP53* at relapse (e.g., R282W, S215I), but not in wild-type or mutation-lost cases, suggesting mutant *TP53* may drive this phenotype. The most striking case involved R282W-mutant CLL expanding post-treatment cessation, suggesting intrinsic resistance features. Meanwhile, most relapsed cells fell into clusters 0 and 2, which downregulated *BCL2* and upregulated *BCL2L1*/BCL-XL. Drug sensitivity profiling showed primary CLL cells progressed on venetoclax failed to activate pore-forming proteins BAK/BAX (<30% activation), despite maintaining *BAK1* and *BAX* transcripts, and gaining *BCL2L11*/BIM, implying blockade of the apoptotic machinery. BH3 profiling confirmed functional co-dependence on BCL2 and alternative anti-apoptotic proteins, especially BCL-XL, as XXA1_Y4eK, a BCL-XL–specific BH3 peptide, triggered the strongest cytochrome C release. To target this vulnerability, we tested WH25244, a novel BCL2/BCL-XL-targeting PROTAC, in 8 venetoclax-relapsed CLL samples. WH25244 effectively induced cytochrome C release and BAK/BAX activation ($R^2 = 0.7035$, $P = 0.0007$). The highest sensitivity was observed in samples harboring BCL2 mutations (V156D, R107_110dup, G101V, F104S) and co-occurring TP53, BTK, and PLCG2 mutations. One highly sensitive sample had relapse-acquired *BCL2L1* and BCR pathway genes (*PLCG2*, *PRKCB*, *PRKCA*). WH25244 was validated in BCL-XL–dependent leukemia cell lines and in BCL2-mutant CRISPR knock-in CLL models (G101V, F104L, A113G, R107_110dup), where it degraded ~50% mutant BCL2 at 100 nM and 72 hr of treatment, and induced more cell death than venetoclax. Structural modeling showed WH25244 forms stable ternary complexes with mutant BCL2 and VHL. Inactivation of the VHL E3 ligase ligand on WH25244 hampered its anti-leukemic effect and abrogated BCL-XL/BCL2 degradation. Importantly, WH25244 avoids platelet toxicity linked to BCL-XL inhibition, as platelets express minimal

VHL.

Summary/Conclusion

These findings support WH25244 as a promising agent to overcome venetoclax resistance in dual BCL2/BTK inhibitor–relapsed CLL, by targeting resistant BCL2 variants and compensatory anti-apoptotic programs.

(LB4004) SAFETY AND EFFICACY OF CM313 IN ADULTS WITH IMMUNE THROMBOCYTOPENIA: A RANDOMIZED, PLACEBO-CONTROLLED TRIAL

Topic: 32. Platelet disorders

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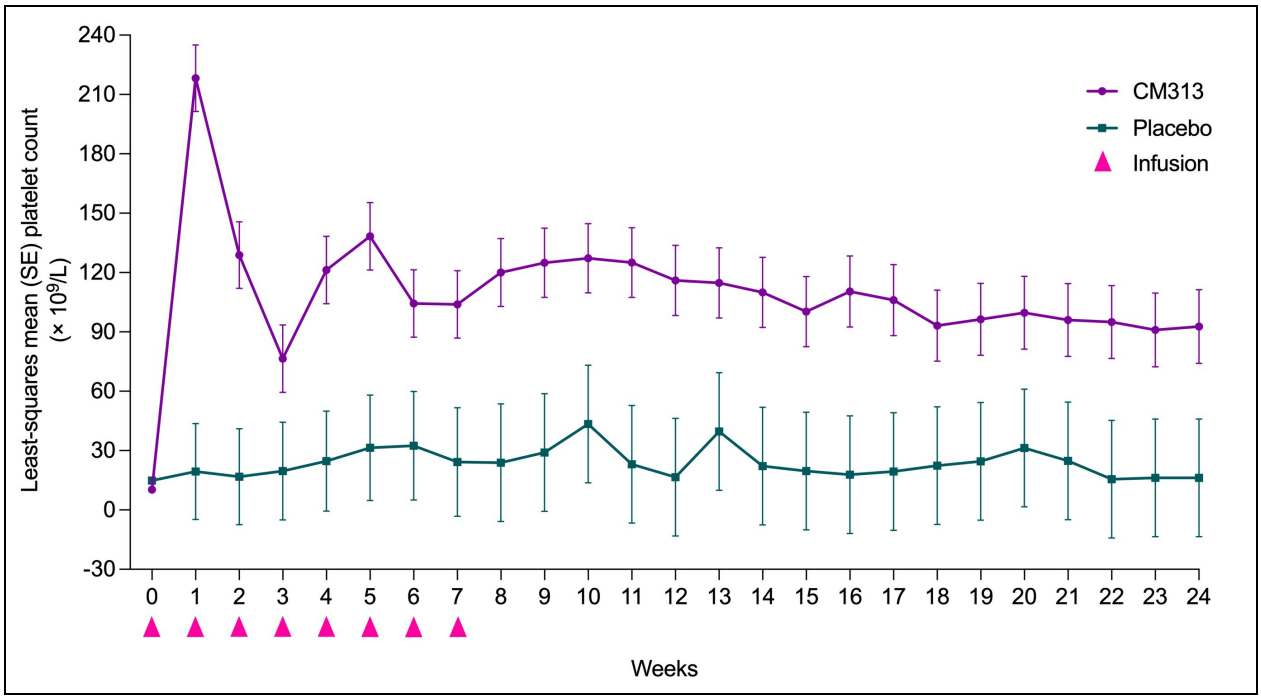
Background

Primary immune thrombocytopenia (ITP) is a relapsing autoimmune disorder that frequently requires multiple lines of therapy. CM313 is a novel anti-CD38 monoclonal antibody that selectively depletes CD38-expressing cells, including plasma cells.



Aims

This phase 2, multicenter, randomized, double-blind, placebo-controlled trial was conducted to evaluate the efficacy and safety of CM313 in adults with persistent or chronic ITP who had failed or relapsed after glucocorticoid therapy and had previously responded to standard first-line treatment.

Methods

Participants were randomized to receive intravenous CM313 (16 mg/kg) or placebo once weekly for eight weeks. The primary endpoint was the overall response rate at week 8, defined as at least two consecutive platelet counts ≥30 × 10?/L,

representing a doubling from baseline, in the absence of bleeding.

Results

Between January 16 and June 11, 2024, forty-five patients were enrolled and randomized in a 2:1 ratio to receive either CM313 (n = 30) or placebo (n = 15). By week 8, the proportion of patients achieving an overall response was significantly higher in the CM313 group (83%) compared to the placebo group (20%), yielding an absolute difference of 63 percentage points (95% confidence interval, 33.7 to 81.3; $p < 0.0001$). The median time to attain a platelet count ≥50 × 10?/L was one week in patients treated with CM313, whereas this threshold was not reached in the placebo group during the same period ($p < 0.0001$). Furthermore, the median cumulative duration of platelet counts maintained at ≥50 × 10?/L was 18 weeks in the CM313 arm, in contrast to 3 weeks among those receiving placebo ($p = 0.0035$). Treatment-emergent adverse events occurred in 83% of participants in the CM313 group and 80% in the placebo group. The most commonly reported events were infusion-related reactions and petechiae, with no unexpected safety signals observed.

Summary/Conclusion

CM313 was well tolerated and demonstrated clinically meaningful efficacy, characterized by rapid increases in platelet count, durable responses, and reduced bleeding risk. This trial is registered at ClinicalTrials.gov (NCT06199089).

(LB4005) HCT FRAILTY SCALE (HCT-FS) FOR ASSESSING FRAILTY IN ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANT PATIENTS. RESULTS FROM A MULTICENTER AND PROSPECTIVE CANADIAN AND SPANISH INITIATIVE

Topic: 22. Stem cell transplantation - Clinical

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Background

Frailty assessment has emerged as a key component of pre-transplant evaluation as its precence negatively impacts outcomes.

Aims

This prospective multicenter study aimed to validate the Hematopoietic Cell Transplantation Frailty Scale (HCT-FS) as a reliable tool for stratifying adult candidates for allogeneic hematopoietic cell transplantation (allo-HCT) into fit, pre-frail, and frail categories, and confirm frailty as predictor for transplant outcomes.

Methods

This observational, prospective and collaborative study included all consecutive adult patients evaluated for frailty using the HCT-FS at 16 allo-HCT programs (1 in Canada, 15 in Spain). Eligible participants were all adults who underwent allo-HCT between 2018–2024 at the Canadian institution and between 2022–2023 at the Spanish centers. Frailty was systematically assessed at the first allo-HCT consultation using the HCT-FS (https://hctfrailtyscale.com) and incorporated into routine clinical practice at each center without external funding. All patients included provided informed consent and prospective data was updated in February 2025.

Results

the median age was 56 years (range 8–76); 411 patients (38.2%) were over 60, and 640 (59.4%) were male. The most common underlying diagnoses were acute myeloid leukemia (46.2%), myelodysplastic syndromes (19.0%), and acute

lymphoblastic leukemia (10.5%). The median time from first consultation to HCT admission was 53 days (IQR: 43–63). At the first allo-HCT consultation, 360 patients (33.4%) were classified as fit, 579 (53.7%) as pre-frail, and 138 (12.8%) as frail. As shown in **Figure 1**, the proportion of patients classified as frail was nearly identical between PMCC and the Spanish centers (12.8% vs. 12.5%). However, the proportion of fit patients was higher at PMCC compared to the other institutions (36.4% vs. 27.1%, P=0.001). Frailty was associated with longer hospital stays during allo-HCT (28 days vs. 23 and 25; P=0.003) and higher ICU admission rates by day +180 (20.3% vs. 7.0% and 10.8%; P=0.002). Two-year OS decreased progressively with increasing frailty: 77.2% in fit, 65.7% in pre-frail, and 52.8% in frail patients (P<0.001). Corresponding non-relapse mortality (NRM) rates were 11.7%, 19.5%, and 32.2%, respectively (P=0.001). Multivariable analysis confirmed frailty as an independent predictor of inferior OS and increased NRM, even when adjusting for age, comorbidities, performance status, disease risk, and donor type. Taking advantage of a large sample size, this analysis also evaluated whether the frailty status of patients was equally informative of transplant outcomes across cuontries and subgroups of patients of different ages ranges (18-40, 41-59, and ≥60 years) and comorbidity burden (HCT-CI ≤2 vs. >2). As shown in **Figure 1,** the negative prognostic impact of frailty was consistent across geographic regions. Frail patients experienced significantly worse outcomes in both PMCC cohort and Spanish GETH-TC centers. In both settings, frailty was associated lower OS probability and elevated NRM. Similarly, frailty status was significantly associated with both inferior OS and NRM regardless of age or comorbidity burden.

HCT Frailty Scale				
Variables included	Normal Result		Abnormal Result	
Clinical Frailty Scale (CFS)	Score 1 or 2	0	Score ≥ 3	1.5
Instrumental Activities of Daily Living (IADL) Scale	No Limitations	0	≥ 1 Limitation	1
Timed Up and Go Test (TUGT)	≤ 10.0 seconds	0	> 10.0 seconds	1.5
Grip Strenght (GS) Test	Female ≥ 16.0 Kg , Male ≥ 26.0 Kg	0	Female < 16.0 Kg, Male < 26.0 Kg	1
Self-Rated Health Question (SRH-Q	Excellent, Very Good, Good	0	Fair, Poor	1
Fall in last 6 months	No	0	Yes	1
Albumin Serum Level	≥ 38 g/L	0	< 38 g/L	1.5
C-Reactive Protein (CRP)	< 11.0 mg/L	0	≥ 11.0 mg/L	2
Scoring System	Fit ≤ 1 Pre-Frail 1.5 – 5 Frail ≥ 5.5			

Summary/Conclusion

The HCT-FS provides reliable measures of the frailty status of allo-HCT candidates that are informative in anticipating transplant outcomes, particularly risk of OS. These results support the applicability of the scale in clinical practice regardless of patients' baseline characteristics.