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ORAL ABSTRACTS

705.CELLULAR IMMUNOTHERAPIES: LATE PHASE AND COMMERCIALLY AVAILABLE THERAPIES

A Phase II Trial of Prophylactic Anakinra to Prevent Neurotoxicity in Patients Receiving Anti-CD19 CAR T-Cell Therapy for Relapsed or Refractory Lymphoma: Final Results from Cohort 2

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Background: Whilst tocilizumab is effective in the management of chimeric antigen receptor T-cell (CAR-T) associated cytokine release syndrome (CRS), there are no targeted therapies for immune effector cell-associated neurotoxicity syndrome (ICANS). Rates of severe (≥ grade 3) ICANS remain high with axicabtagene (axi-cel) and brexucabtagene (brexu-cel) at > 30%. Preclinical models have shown that anakinra, an IL-1 receptor antagonist, reduced CAR-mediated immune toxicities without affecting efficacy. Based on these data, we conducted a phase 2 trial of prophylactic anakinra in patients receiving commercial anti-CD19 CAR-T for r/r B-cell lymphoma (NCT04148430). The study had sequential enrollment in 2 independent cohorts. We recently reported results from cohort 1 in which patients received subcutaneous (SC) anakinra from day 2 until at least day 10 post-CAR infusion and showed that prophylactic anakinra reduced the rate of severe ICANS to 9.7% (Park, Nat Med, 2023). Herein, we report results from cohort 2 of the study where we utilized anakinra as a complete prophylactic strategy.
Methods: Adult patients with a diagnosis of r/r large B-cell lymphoma (LBCL), high-grade B-cell lymphoma (HGBCL), follicular lymphoma (FL) or mantle cell lymphoma (MCL) receiving commercial anti-CD19 CAR-T were enrolled. Patients received SC anakinra 100 mg daily from day 0 for at least 7 d. The frequency of anakinra could be increased up to 100 mg every 6 h, and the duration beyond 7 d for persistent or progressive CRS and ICANS. Tocilizumab and steroid use were allowed for the management of persistent or progressive CRS and ICANS. A baseline and day 5 lumbar puncture were performed for CSF

analysis. The primary endpoint was the rate of severe ICANS, graded per the ASTCT criteria. Secondary endpoints included rates of severe CRS, all grade CRS and ICANS, overall response rate (ORR), survival outcomes, and serum and CSF biomarker levels.

Results: 37 patients were screened, 31 enrolled, and 30 treated (LBCL=13, HGBCL=6, FL=6, MCL=5). 1 enrolled patient did not proceed with treatment due to COVID-19 infection. The median age of the cohort was 65yrs (range: 24 - 81yrs) and patients received axi-cel (19 pts; 63%), brexu-cel (5 pts; 17%), lisocabtagene (4 pts; 13%) and tisagenlecleucel (2 pts; 7%). Patients received a median 3 prior lines of therapy (range: 1 - 7); 22 (73%) were refractory to their immediate prior therapy; 17 (57%) received bridging therapy and 3 (10%) had active CNS disease at CAR infusion. Pretherapy tumor burden as measured by the median sum of the products of diameters was 1638mm ^{2} (range: 0 - 21,570mm ^{2}).

All patients started anakinra on day 0. Anakinra administration was increased in 24 patients (80%) during CRS; it was increased to a maximum of 100mg q12h in 1 patient and 100mg q6h in 23 patients. The median duration of anakinra administration was 9.5 d (IQR 8 - 13). No patient stopped anakinra due to an adverse event.

A total of 3 patients (10%) experienced severe ICANS, all of which were grade 3 only. 9 patients (30%) experienced any grade ICANS (Fig 1A). The median time to ICANS onset was 6.5 d (range: 4 - 10 d). All-grade CRS occurred in 24 patients (80%). Most CRS events were grade 1 or 2 except for 3 grade 3 events (10%) (Fig 1A). Of the 24 patients who received CD28-containing CARs (axi-cel and brexu-cel), all-grade and severe ICANS rate was 29% and 12.5%, respectively (Fig 1B). In the 3 patients with active CNS disease, there was 1 grade 2, and 1 grade 3 ICANS event. 23 patients (77%) received tocilizumab and 18 (60%) received steroids for CRS and/or ICANS.

The median follow-up was 5.8mo. The best ORR by day 100 was 83% (95% CI 65-94%) with a CR rate of 73% (95% CI 54-89%). The estimated progression-free and overall survival at 6mo was 72% (95% CI 50-93%) and 81% (95% CI 66-86%), respectively.

Conclusion: Early use of prophylactic anakinra was safe, feasible and reduced the rate of severe ICANS without affecting efficacy in adult patients receiving anti-CD19 CAR-T for r/r B-cell lymphoma. Rates of severe ICANS were very similar between cohorts 1 and 2; at 9.7% and 10% in the entire cohorts, respectively, and 11% and 12.5% in patients treated with CD28-containing CARs, respectively. The risk-adapted dosing of anakinra likely contributed to the low rates of severe ICANS in this study. Detailed comparison of results from cohort 1, analysis of the anakinra dose-relationship on efficacy, and serum and CSF biomarkers will be presented at the meeting.

Disclosures Sauter: *Juno Therapeutics, Celgene/BMS, Bristol-Myers Squibb, Precision Biosciences, Actinium Pharmaceuticals, Sanofi-Genzyme and NKARTA.:* Research Funding; *Kite/a Gilead Company, Celgene/BMS, Gamida Cell, Karyopharm Therapeutics, Ono Pharmaceuticals, MorphoSys, CSL Behring, Syncopation Life Sciences, CRISPR Therapeutics and GSK.:* Consultancy. **Palomba:** *BMS:* Honoraria; *GarudaTherapeutics:* Honoraria; *Novartis:* Honoraria; *Pluto Immunotherapeutics:* Honoraria; *Rheos:* Honoraria; *MustangBio:* Honoraria; *Kite:* Honoraria; *Juno:* Honoraria, Patents & Royalties; *Ceramedix:* Honoraria; *Seres Therapeutics:* Honoraria, Patents & Royalties; *Smart Immune:* Honoraria; *Thymofox:* Honoraria; *Synthekine:* Honoraria; *Cellectar:* Honoraria. **Shah:** *Janssen:* Research Funding; *Beyond Spring:* Research Funding; *BMS:* Research Funding; *ArcellX:* Other: DSMB; *Amgen:* Research Funding. **Scordo:** *Medscape, LLC:* Honoraria; *Angiocrine Bioscience, Inc.:* Research Funding; *CancertNetwork (Intellisphere LLC):* Honoraria; *Amgen, Inc.:* Research Funding; *Omeros Corporation:* Consultancy, Research Funding. **Perales:** *Astellas:* Consultancy, Honoraria; *Caribou:* Consultancy, Honoraria; *Medigene:* Consultancy, Other; *Incyte:* Consultancy, Honoraria, Research Funding; *MorphoSys:* Consultancy, Honoraria; *Cidara Therapeutics:* Consultancy, Other; *Allogene:* Research Funding; *Servier:* Other; *Syncopation:* Honoraria; *Merck:* Consultancy, Honoraria; *Novartis:* Consultancy, Honoraria, Research Funding; *AbbVie:* Consultancy, Honoraria; *Exevir:* Consultancy, Honoraria; *Karyopharm:* Consultancy, Honoraria; *Nektar Therapeutics:* Consultancy, Honoraria, Research Funding; *Omeros:* Consultancy, Current equity holder in publicly-traded company, Honoraria; *Miltenyi Biotec:* Consultancy, Honoraria, Research Funding; *Miltenyi Biotec:* Honoraria; *BMS:* Consultancy, Honoraria; *Celgene:* Honoraria; *DSMB:* Other; *Orcabio:* Consultancy, Current equity holder in publicly-traded company, Honoraria; *Equillium:* Consultancy, Honoraria; *VectivBio AG:* Consultancy, Honoraria; *Vor Biopharma:* Consultancy, Honoraria; *Adicet:* Honoraria; *Allovir:* Consultancy; *Takeda:* Consultancy, Honoraria; *Sellas Life Sciences:* Consultancy; *Kite:* Consultancy, Honoraria, Research Funding; *NexImmune:* Consultancy, Current equity holder in publicly-traded company. **Leslie:** *BeiGene:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *ADC Therapeutics:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Pharmacyclics:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Other: Travel support, Speakers Bureau; *LLS:* Other: Educational role/ Leadership role in LLS light the night events (unpaid); *TG Therapeutics:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Other: Travel support, Speakers Bureau; *SeaGen:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Other: Travel support, Speakers Bureau; *Kite, a Gilead Company:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Other: Travel support, Speakers Bureau; *Janssen/PCYC:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Other: Travel support, Speakers Bureau; *Astrazeneca:* Consultancy, Other: Travel support, Speakers Bureau; *Beigene:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Other: Travel support, Speakers Bureau; *Eli Lilly:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Other: Travel support, Speakers Bureau; *Janssen/ J&J:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Epizyme:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Other: Travel support, Speakers Bureau; *LRF:* Other: Educational role; *Abbvie:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Other: Travel support, Speakers Bureau; *Merck:* Consultancy, Membership on an entity's Board of Directors or

advisory committees; *Genmab:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *CLL:* Other: Educational role; *Celgene/ Bristol Myers Squibb:* Other: Travel support, Speakers Bureau. **Santomasso:** *for Celgene, Janssen, Legend Biotech, Incyte, Kite/Gilead and In8bio:* Other: Consulting or Advisory Role; *MSKCC:* Patents & Royalties: Provisional Patent: Diagnosis and treatment of immunotherapy-induced neurotoxicity. **Holodny:** *fMRI Consultants:* Other: Owner/president of fMRI Consultants, LLC. **Brentjens:** *R.J.B. has licensed intellectual property to and collect royalties from BMS, Caribou and Sanofi. R.J.B. received research funding from BMS. R.J.B. is a consultant to BMS, Atara Biotherapeutics Inc, Coimmune, Triumvira and was a consultant for Gracell Bi:* Consultancy, Current equity holder in publicly-traded company, Current holder of *stock options* in a privately-held company, Membership on an entity's Board of Directors or advisory committees, Patents & Royalties: BMS, Caribou and Sanofi, Research Funding. **Riviere:** *Takeda Development Center Americas, Inc.:* Current Employment, Current equity holder in publicly-traded company. **Sadelain:** *Atara:* Research Funding; *Minerva:* Current equity holder in private company; *Mnemo:* Current equity holder in private company, Research Funding; *Takeda:* Research Funding; *Fate:* Research Funding. **Park:** *Minerva Bio:* Consultancy; *Genentech, Inc.:* Research Funding; *Kite:* Consultancy; *Amgen:* Consultancy; *Takeda:* Consultancy, Research Funding; *Incyte:* Research Funding; *Autolus Therapeutics:* Research Funding; *Fate Therapeutics:* Research Funding; *Bright Pharmacetuicals:* Consultancy; *Allogene:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *BeiGene:* Consultancy; *Curocell:* Consultancy; *Be Biopharma:* Consultancy; *GC Cell:* Membership on an entity's Board of Directors or advisory committees; *Servier:* Consultancy, Research Funding; *Intella:* Consultancy; *Artiva Biotherapeutics:* Consultancy, Current holder of *stock options* in a privately-held company, Membership on an entity's Board of Directors or advisory committees; *Pfizer:* Consultancy; *Affyimmune:* Consultancy; *Sobi:* Consultancy, Research Funding.

OffLabel Disclosure: Anakinra for management of ICANS

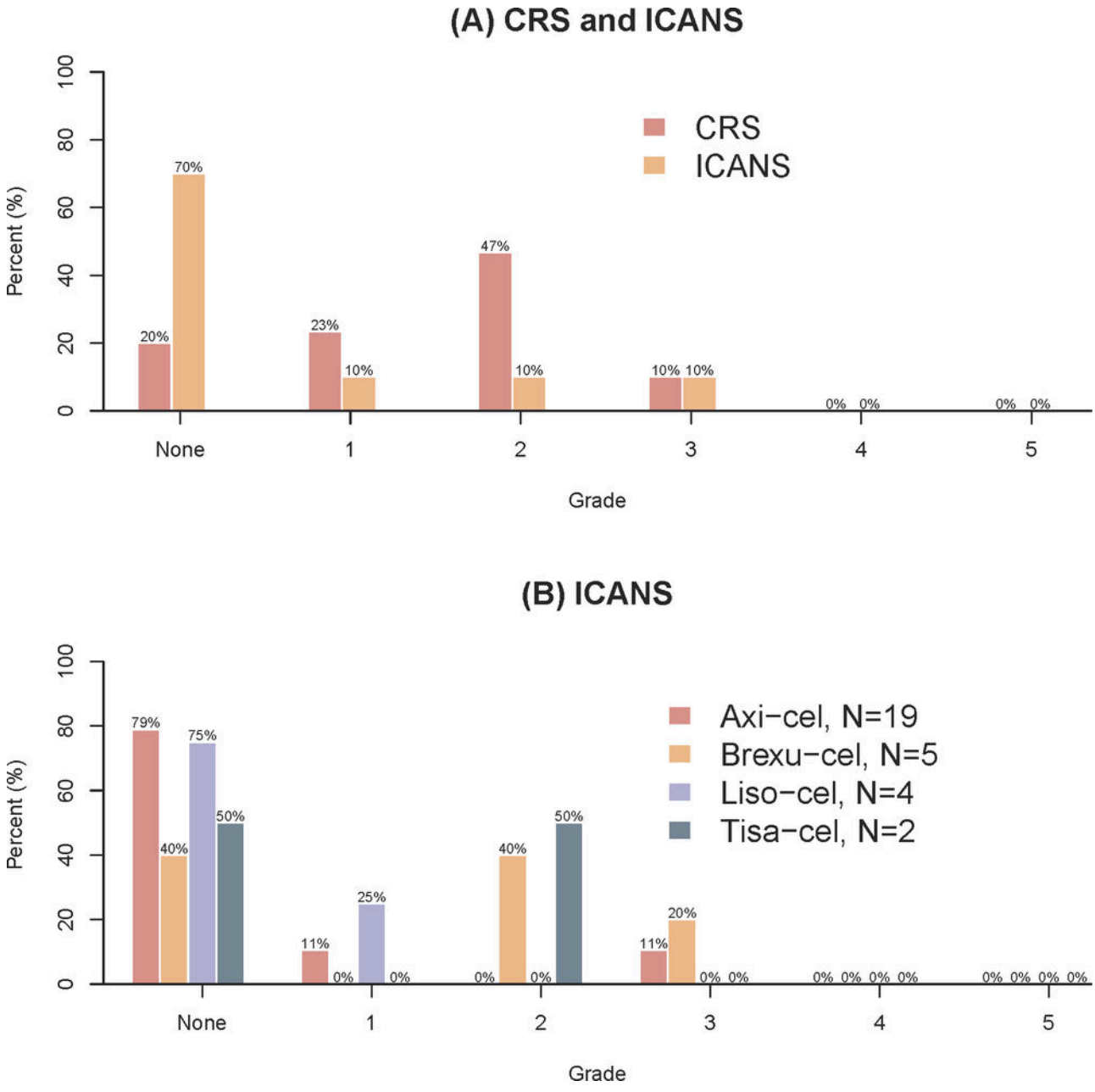

Figure 1

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