



## The 65th ASH Annual Meeting Abstracts

## POSTER ABSTRACTS

## 705.CELLULAR IMMUNOTHERAPIES: LATE PHASE AND COMMERCIALY AVAILABLE THERAPIES

**Fludarabine Lymphodepletion Exposure Is Associated with Idecabtagene Vicleucel Toxicity in Relapsed and Refractory Multiple Myeloma Patients: Real-World Experience from the US Myeloma Immunotherapy Consortium**

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**Background.** Idecabtagene vicleucel (ide-cel) is an anti-B-cell maturation antigen (BCMA) CAR-T associated with durable responses in relapsed/refractory multiple myeloma (RRMM) patients. Fludarabine (Flu), part of standard lymphodepleting chemotherapy (LDC), improves T-cell expansion and persistence, but BSA dosing results in significant pharmacokinetic (PK) variability. Flu exposure, defined by the area under the curve (AUC), has been shown to predict rates of relapse after anti-CD19 CAR-T in B-cell acute lymphoblastic leukemia (Fabrizio et al, *Blood Advances* 2022). We hypothesized Flu AUC may predict outcomes after ide-cel and, using a published population model (Langenhorst et al, *Clin Pharmacokinet* 2019 ) we assessed the impact of Flu AUC on standard-of-care (SOC) ide-cel outcomes.

**Methods.** RRMM patients receiving SOC ide-cel from 11 of the US Myeloma Immunotherapy Consortium centers were retrospectively analyzed. FluCy was given on days -5 to -3 before CAR-T infusion. Patients were excluded if they did not receive

FluCy LDC or ide-cel infusion, had ESRD on hemodialysis, or did not have creatinine values on LDC days. A population PK approach using cumulative Flu dose and PK covariates, eGFR and body weight (BW), was used to calculate  $C_{max}$  and AUC<sub>0-72h</sub>. PK parameters were first tested as continuous variables in univariable and multivariable (MV) analysis. ORs are expressed per 1 mg \* hr/L in the model.

**Results.** 285 patients were included with a median follow-up of 8.7 (4.3-14.2) months. eGFR distribution indicated large variability (mean=86.5 ml/min, CV 38.4%), with 151 (53%) having renal dysfunction (eGFR <90 ml/min/1.73). BW ranged from 42 to 147.2 kg. Wide PK variability was observed with a median Flu AUC of 19.01 (11.23-41.47) mg \* h/L (Fig 1). When adjusted for high-risk features including high risk cytogenetics, extramedullary disease, exposure to BCMA agents, and receipt of bridging therapy in a MV model, Flu AUC was not found to be associated with efficacy, including overall response and progression free survival. However, when adjusted for bridging therapy response and prior lines of therapy as an indicator of disease status/burden pre-CAR-T, each 1 mg \* h/L increment in Flu AUC was found to be associated with maximum grade  $\geq 2$  cytokine release syndrome (CRS) (OR 1.083; 95% CI 1.013-1.160;  $p=0.020$ ). While there was no difference in the occurrence of Grade 3/4 cytopenias, each 1 mg \* h/L increment in Flu AUC was significantly associated with use of stem cell boost (OR 1.130; 95% CI 1.038-1.235;  $p=0.005$ ).

**Discussion.** In this real-world dataset of ide-cel treated RRMM patients, Flu exposure was found to have a significant association with severe CRS and need for stem cell boost. This is consistent with prior studies (Hirayama et al, *Blood*, 2019) where a greater increase in cytokine levels and risk for CRS is seen with high intensity LDC. These data highlight how standard BSA-based Flu dosing results in significant PK variability and overestimates Flu AUC, increasing the risk of CAR-T toxicities. Prospective validation of our model-based findings through measurement of Flu blood levels, CAR-T PK, and clinical outcomes is warranted.

**Disclosures Wagner:** Abbvie Inc.: Other: Partner is employed as a medical science liaison. **Sweiss:** Sanofi: Consultancy. **Castaneda Puglianini:** Adaptive Biotechnologies: Speakers Bureau. **Freeman:** Celgene: Consultancy, Honoraria; ONK Therapeutics: Consultancy, Honoraria; Janssen: Consultancy, Honoraria, Research Funding; Bristol Myers Squibb: Consultancy, Honoraria, Research Funding. **Patel:** AbbVie; Allogene Therapeutics, Inc.; Arcellx; Bristol Myers Squibb/Celgene Corporation; Cellectis; Janssen Pharmaceuticals, Inc.; Nektar Therapeutic; Poseida Therapeutics; Precision BioSciences, Inc.; and Takeda Pharmaceuticals U.S.A., Inc.: Research Funding; Takeda: Consultancy; AbbVie; Arcellx, AstraZeneca; Bristol Myers Squibb/Celgene Corporation; Caribou Science; Cellectis; Curio Bioscience; Genentech; Janssen Pharmaceuticals, Inc.; Karyopharm; Legend Biotech; Merck & Co., Inc.; Oncopeptides; Pfizer; Precision BioSciences: Consultancy. **Gaballa:** Boxer Capital, LLC: Consultancy. **McGuirk:** Astellas Pharma: Research Funding; Fresenius Biotech: Research Funding; Novartis: Research Funding; EcoR1 Capital: Consultancy; Magenta Therapeutics: Consultancy; Allovir: Consultancy, Research Funding; Juno Therapeutics: Consultancy; Kite: Consultancy, Research Funding; Bellicum Pharmaceuticals: Research Funding; Gamida Cell: Research Funding; Pluristem Therapeutics: Research Funding. **Sidana:** Magenta Therapeutics, BMS, Janssen, Sanofi, Oncopeptides, Takeda, Pfizer: Consultancy; Magenta Therapeutics, BMS, Allogene, Janssen, Novartis: Research Funding. **Khouri:** Janssen: Consultancy, Membership on an entity's Board of Directors or advisory committees, Other: Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events; GPCR Therapeutics: Other: Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events. **Hashmi:** Janssen: Honoraria, Speakers Bureau; BMS: Honoraria; Karyopharm: Speakers Bureau; Sanofi: Honoraria, Speakers Bureau; GSK: Honoraria, Speakers Bureau. **Kaur:** BMS: Consultancy, Research Funding; Pfizer: Consultancy; Cellectar: Consultancy; Arcellx: Consultancy, Research Funding; Abbvie: Research Funding; Janssen: Consultancy, Research Funding; Sanofi: Consultancy; Kedrion: Consultancy. **Anderson:** Amgen: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; Bristol Myers Squibb: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; Janssen: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; Celgene: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; GlaxoSmithKline: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; AbbVie: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; Beigene: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; Cellectar: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; Sanofi: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; Prothena: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees. **Forsberg:** Karyopharm: Research Funding; Janssen: Consultancy; GlaxoSmithKline: Consultancy; Bristol-Myers Squibb: Consultancy. **Hansen:** Survivorship: Honoraria; Onc Live: Honoraria; Pentecost Family Myeloma Research Center: Research Funding; International Myeloma Society Young Investigator Award: Research Funding; Pfizer: Consultancy; Karyopharm: Consultancy, Research Funding; Janssen: Consultancy; BMS: Consultancy, Research Funding; BMS MM ASH Steering Committee: Membership on an entity's Board of Directors or advisory committees; BMS IMW Ide-Cel Academic Advisory Board: Membership on an entity's Board of Directors or advisory committees; MM Pfizer Advisory Board: Membership on an entity's Board of Directors or advisory committees. **Sborov:** Abbvie: Consultancy; Bioline: Consultancy; Arcellx: Consultancy; Sanofi: Consultancy, Honoraria; Pfizer: Consultancy; GlaxoSmithKline: Consultancy, Honoraria; Janssen: Consultancy.

Figure 1. Variability in Fludarabine AUC (mg\*h/L) Among RRMM patients undergoing ide-cel

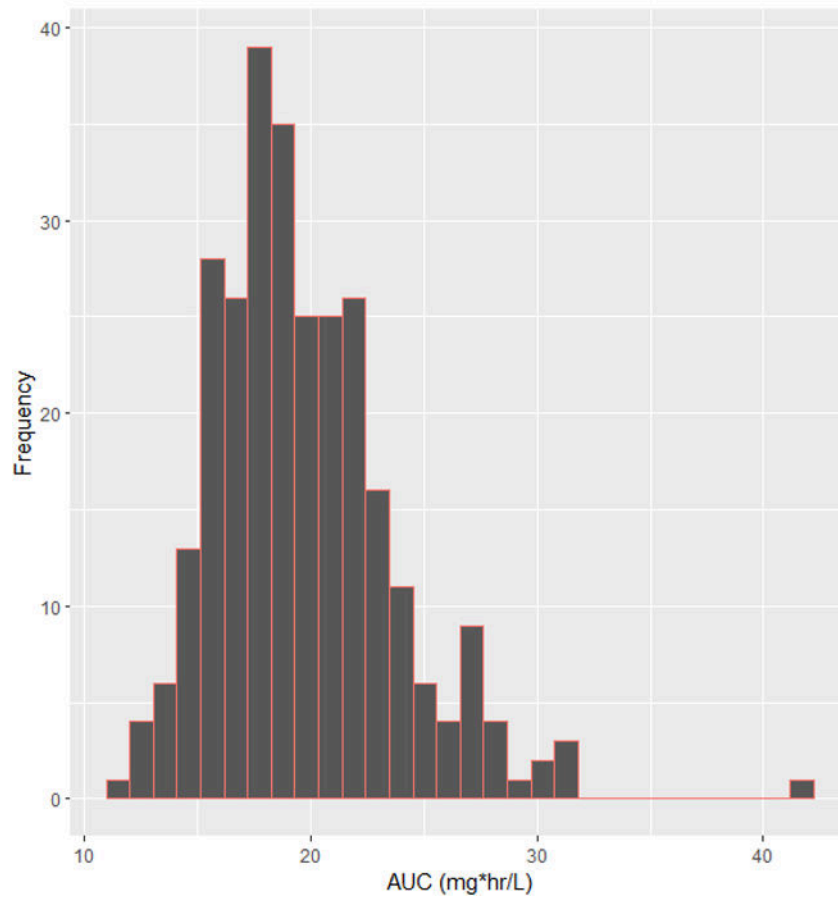


Figure 1

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