ELSEVIER

Blood 142 (2023) 4683–4684

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

651.MULTIPLE MYELOMA AND PLASMA CELL DYSCRASIAS: BASIC AND TRANSLATIONAL

Impact of Gamma-Secretase Inhibition on the Multiple Myeloma Immune Microenvironment

David Coffey, MD[1], *Ola Landgren, MD*[2], *Andrew J. Cowan, MD*[3], *Pinar Ataca Atilla, MD*[4], *Sylvain Simon, PhD*[4], *Margot Pont*[5], *Melissa L Comstock*[4], *Geoffrey R Hill, MD*[4], *Stanley R. Riddell, MD*[4], *Damian J Green, MD*[4]

[1] Myeloma Division, Sylvester Comprehensive Cancer Center, University of Miami, Pinecrest, FL
[2] Sylvester Comprehensive Cancer Center, Myeloma Division, University of Miami, Miami, FL
[3] Clinical Research Division, Fred Hutchinson Cancer Center, Seattle, WA
[4] Translational Science and Therapeutics Division, Fred Hutchinson Cancer Center, Seattle, WA
[5] CellPoint BV, a Galapagos company, Oegstgeest, Netherlands

Background:
Therapy with monoclonal antibodies, chimeric antigen receptor (CAR) T-cells, and bispecific T-cell engagers (BiTE) has significantly changed the treatment landscape for multiple myeloma (MM). B-cell maturation antigen (BCMA), a cell surface protein highly expressed in malignant plasma cells, has been established as an effective MM cell target, however, achieving long-term responses in relapsed or refractory patients remains a challenge. Resistance to BCMA targeting may result from the enzymatic cleavage of BCMA by surface membrane gamma-secretase resulting in reduced target antigen density on MM cells, and from the soluble BCMA ectodomain that may hinder tumor cell recognition through binding to circulating therapeutic antibodies or to CAR T-cells.

Methods:
We have previously demonstrated that gamma-secretase inhibitors (GSIs) abrogate enzymatic function and increase BCMA surface density on plasma cells with a concomitant decrease in soluble BCMA concentrations [Pont, MJ. *et al.* Blood, 134(2019)]. In a phase I, first-in-human clinical trial (n=18; relapsed/refractory MM) combining the GSI, crenigacestat, with anti-BCMA CAR T-cell therapy (FCARH143), we recently demonstrated that plasma cell BCMA antibody-binding capacity increased a median of 12-fold among 17/18 (94%) of participants after they received a 5-day GSI "run-in" (25 mg orally administered QOD for 3 doses) [Cowan AJ, *et al.* Lancet Oncology. 24(7) 2023]. Overall, 78% of participants experienced a very good partial response or better to GSI with FCAR143, but the duration of response was significantly longer in patients without prior anti-BCMA exposure. Here, we report results from an analysis of the bone marrow aspirates collected at enrollment and again within 12 hours of the third "run-in" dose. We leveraged single-cell RNA sequencing (scRNAseq) coupled with the single-cell assay for transposase-accessible chromatin sequencing (scATACseq) to profile the transcriptome and chromatin accessibility of individual cells within the bone marrow microenvironment.

Results:
Single-cell multi-omic analysis was performed on 32 bone marrow mononuclear cell samples from 16 patients collected before and within 12 hours after the third oral dose of GSI. Six patients had previously been treated with BCMA-directed therapy, including antibody-drug conjugates, CAR T-cells, or BiTEs. After quality filtering, including compensation for ambient RNA, 142,498 cells were analyzed (median 6,373 cells/sample, range 613-17,150 cells/sample). Cells were automatically classified into 92 immune cell types using Celltypist and a reference dataset trained on immune sub-populations from 20 tissues in 18 studies. Comparing samples pre- and post-GSI exposure revealed a significant decrease in the abundance of plasmablasts, non-classical monocytes, germinal center B cells, mid-erythroid cells, and central memory/naïve cytotoxic T cells after GSI treatment. Additionally, gene expression analysis detected increased expression of Notch signaling genes, *NEURL1* and *HES1*, in non-classical monocytes following GSI treatment. Although RNA expression of *TNFRSF17* (*BCMA*) did not significantly change, chromatin accessibility was considerably higher in patients without a history of prior BCMA-directed therapy following GSI treatment. In non-plasma cells, we observed increased chromatin accessibility after GSI treatment involving genes encoding proteins known to be cleaved by gamma-secretase, such as *ERBB4*, *NOTCH1*, *NOTCH2*, and *TNFRSF17*. Accessibility of *CD38*, the target of daratumumab, was significantly increased in B cells, and *SLAMF7*, the target of elotuzumab, was significantly increased in plasma cells.

Conclusions:

BCMA cleavage from myeloma cells' surface is a putative resistance mechanism to BCMA-targeting immunotherapy. This study assessed the single-cell transcriptome and chromatin accessibility in the bone marrow environment of 16 patients given GSI monotherapy to ultimately enhance the efficacy of subsequent anti-BCMA CAR T-cell therapy. We found that prior BCMA-targeted therapy resulted in reduced chromatin accessibility within the BCMA epigenome. Surprisingly, GSI administration also modified the epigenome of other gamma-secretase sensitive genes. These data provide insight into the molecular consequences of prior BCMA-targeted therapy and GSI exposure that may inform future studies.

Disclosures Landgren: *Merck:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Membership on independent data monitoring committees; *Amgen:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Membership on independent data monitoring committees; *Takeda:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Membership on independent data monitoring committees; *Janssen:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Membership on independent data monitoring committees; *Celgene:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Membership on independent data monitoring committees; *Adaptive:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Membership on independent data monitoring committees; *Theradex:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Membership on independent data monitoring committees. **Cowan:** *EUSA:* Consultancy; *BMS:* Consultancy, Research Funding; *GSK:* Consultancy; *Harpoon:* Research Funding; *Janssen:* Consultancy, Research Funding; *Nektar:* Research Funding; *Sanofi:* Research Funding; *Secura Bio:* Consultancy; *Allogene:* Consultancy; *Adaptive Biotechnologies:* Membership on an entity's Board of Directors or advisory committees; *Abbvie:* Consultancy, Research Funding. **Pont:** *Lyell Immunopharma:* Current equity holder in publicly-traded company; *Springworks Therapeutics:* Consultancy; *Cellpoint BV, a Galapagos company:* Current Employment, Current equity holder in publicly-traded company. **Hill:** *Compass Therapeutics:* Research Funding; *iTeos Therapeutics:* Consultancy; *Serplus Technology:* Research Funding; *Genentech:* Research Funding; *Commonwealth Serum Laboratories:* Consultancy; *Cynata Therapeutics:* Consultancy; *Applied Molecular Transport:* Research Funding; *Heat Biologics:* Research Funding; *Syndax Pharmaceuticals:* Research Funding; *iTeos Therapeutics:* Research Funding; *Generon Corporation:* Consultancy; *NapaJen Pharma:* Consultancy; *Neoleukin Therapeutics:* Consultancy; *Laevoroc Oncology:* Research Funding. **Riddell:** *Adaptive Biotechnologies:* Consultancy; *Ozette Technologies:* Membership on an entity's Board of Directors or advisory committees; *Lyell Immunopharma:* Current equity holder in publicly-traded company, Current holder of *stock options* in a privately-held company, Other: Co-founder, Patents & Royalties, Research Funding; *Juno Therapeutics:* Consultancy, Current equity holder in publicly-traded company, Current holder of *stock options* in a privately-held company, Other: Co-founder, Research Funding. **Green:** *Celgene:* Consultancy; *Ensoma:* Consultancy; *Janssen Biotech:* Consultancy, Research Funding; *SpringWorks Therapeutics:* Research Funding; *GlaxoSmithKline:* Membership on an entity's Board of Directors or advisory committees; *Seattle Genetics:* Consultancy, Research Funding; *Juno Therapeutics A BMS Company:* Patents & Royalties, Research Funding; *Sanofi:* Research Funding; *Cellectar Biosciences:* Research Funding.

OffLabel Disclosure: Crenigacestat is a gamma-secretase inhibitor that is being investigated to enhance the efficacy of anti-BCMA CAR T-cell therapy and is not FDA approved.

https://doi.org/10.1182/blood-2023-186980