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POSTER ABSTRACTS

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

Co-Expression of GPRC5D, FcRH5 and BCMA Suggests That Targeting More Than One Cell Surface Marker May be a Viable Strategy in Relapsed/Refractory Multiple Myeloma (RRMM): Biomarker Results from the Phase I Study of Forimtamig, a GPRC5DxCD3 Bispecific Antibody

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Background: Forimtamig is a GPRC5DxCD3 T-cell engaging bispecific antibody that induces T-cell mediated multiple myeloma (MM) cell killing and has shown promising clinical activity in a Phase I study (NCT04557150) in patients with RRMM (Carlo-Stella et al. ASH 2022). GPRC5D is known to be overexpressed in MM plasma cells (MMPCs), but little is known about its prevalence in relation to risk status and other identified MM targets like FcRH5 and BCMA. We developed a unique exploratory multiparameter flow cytometry panel to characterize GPRC5D, FcRH5 and BCMA expression on MMPCs (Lelios et al. Cyto 2023). We present data on the prevalence and co-expression of these targets, and their association with baseline patient characteristics and response to forimtamig.

Methods: Baseline bone marrow aspirate samples were collected from patients who received intravenous or subcutaneous forimtamig during dose-escalation, and were analyzed with flow cytometry. Target expression was depicted as frequency of positive MMPCs and as receptor density (molecules of equivalent soluble fluorochrome). Patients were grouped by number of prior lines of therapy, ISS score, cytogenetic risk (high risk defined as presence of one or more of the following abnormalities: del(17p), t(4;14), t(14;16), and response to forimtamig (responder [≥PR] or non-responder [<PR]). All patients provided informed consent.

Results: At data cut-off (June 15, 2023), 48/163 patients were biomarker evaluable (samples passing pre-defined quality standards and containing ≥100 acquired MMPCs). GPRC5D was detected at baseline in 46/48 (96%) patients, with most MMPCs expressing the target (median 95.6%; min-max: 0-100%). GPRC5D expression was more prevalent on MMPCs than FcRH5 (median 78.6%; min-max: 3.7-100%) and BCMA (median 40.3%; min-max: 0-100%; **Figure**). Interestingly, GPRC5D receptor density (median 20,612; min-max: 6495-208,072) was 47-100-fold higher and more homogenous than FcRH5 (median 436; min-max: 8-3921) and BCMA (median 206; min-max: 14-6657).

Clinical response to forimtamig was not correlated with GPRC5D+ MMPC frequency or GPRC5D receptor density measured by flow cytometry (**Table**).

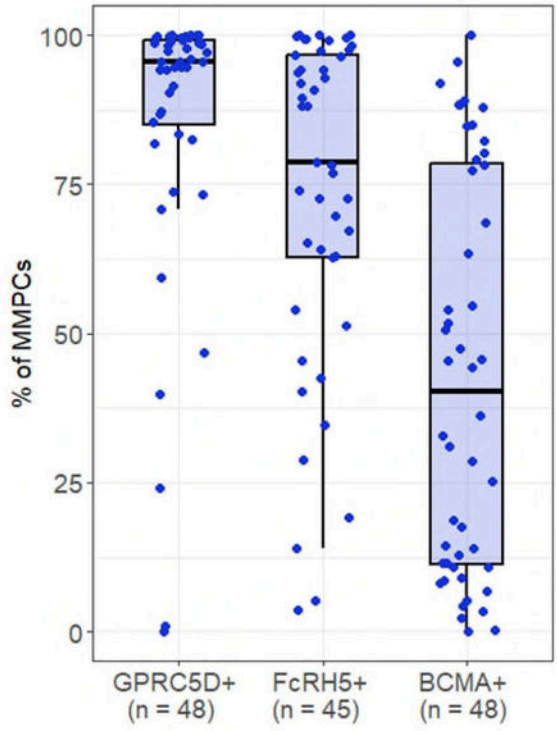
Percentages of GPRC5D+, FcRH5+ and BCMA+ MMPCs and receptor densities did not significantly differ between patient groups defined by ISS score, cytogenetic risk and number of prior lines of therapy. Patients previously exposed to BCMA-targeted agents (n=7) tended to have lower BCMA expression levels. GPRC5D and FcRH5 were co-expressed on 75.4% of MMPCs (min-max: 0-100%) followed by MMPCs co-expressing GPRC5D and BCMA (median 31.9%; min-max: 0-100%) or BCMA and FcRH5 (median 25.3%; min- max: 0-94.3%). In the majority of patients, double and triple negative MMPCs were rarely observed (0.5-6% of MMPCs expressed only one or none of the three targets across all analyzed patients).

Conclusions: GPRC5D, FcRH5 and BCMA are highly prevalent across MM patient subgroups, including high-risk patients who may warrant targeted therapy approaches. Based on our data and previously published work for FcRH5- and BCMA-targeted

T-cell bispecifics (Sumiyoshi et al. EHA 2021; Cortes-Selva et al. ASH 2022), target expression on MMPCs, as measured by flow cytometry, has not been associated with clinical response to the corresponding CD3 bispecifics, likely due to the high efficacy of T-cell mediated tumor cell killing. Co-expression of MM targets suggests that targeting more than one MM surface marker may result in double/triple hits on individual tumor cells. Our data support further testing of dual/triple MMPC targeting as a promising concept to promote fast and deep tumor clearance, and to achieve durable responses, while potentially avoiding clonal selection, in patients with RRMM. Further investigation is needed to understand the relevance of target expression differences measured by flow cytometry compared to other methods like immunohistochemistry, as well as to understand T-cell bispecific resistance mechanisms beyond target expression. Updated data will be presented.

Disclosures Dekhtiarenko: *F. Hoffmann La Roche Ltd:* Current Employment. **Lelios:** *F. Hoffmann La Roche Ltd:* Current Employment, Current equity holder in publicly-traded company. **Jacob:** *F. Hoffmann La Roche Ltd:* Current holder of *stock options* in a privately-held company; *Sponsor employee (Roche Diagnostics GmbH, Germany):* Current Employment. **Schneider:** *F. Hoffmann La Roche Ltd:* Current Employment, Current equity holder in private company, Current equity holder in publicly-traded company. **Weisser:** *F. Hoffmann La Roche Ltd:* Current equity holder in publicly-traded company, Current holder of *stock options* in a privately-held company, Patents & Royalties; *F. Hoffmann La Roche Ltd - Roche Pharma Research and Early Development:* Current Employment. **Carlo-Stella:** *Janssen Oncology:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Takeda:* Honoraria; *Novartis:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Gilead:* Honoraria; *Incyte:* Honoraria; *Celgene/BMS:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *AstraZeneca:* Honoraria; *Roche:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *ADC Therapeutics:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Sanofi:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Research Funding; *SOBI:* Honoraria, Membership on an entity's Board of Directors or advisory committees. **Manier:** *Abbvie, Amgen, Celgene/BMS, GlaxoSmithKline, Janssen, Novartis, Pfizer, Regeneron, Roche, Sanofi, Takeda:* Membership on an entity's Board of Directors or advisory committees; *Amgen:* Honoraria; *Janssen:* Honoraria; *BMS:* Honoraria. **Harrison:** *Abbvie, Amgen, Celgene/BMS, GSK, Janssen Cilag, Novartis, F. Hoffmann-La Roche Ltd / Genentech, Inc., Haemalogix, Eusa, Terumo BCT:* Honoraria; *Celgene/BMS, GSK, Janssen Cilag, Haemalogix:* Research Funding; *Haemalogix:* Membership on an entity's Board of Directors or advisory committees; *Abbvie, Amgen, Celgene/BMS, GSK, Janssen Cilag, Novartis, F. Hoffmann-La Roche Ltd / Genentech, Inc., Eusa:* Speakers Bureau; *Abbvie, Amgen, Celgene/BMS, GSK, Janssen Cilag, Novartis, F. Hoffmann-La Roche Ltd / Genentech, Inc., Haemalogix, Eusa, Terumo BCT*: Consultancy. **Popat:** *GSK:* Consultancy, Honoraria, Research Funding; *Abbvie:* Honoraria; *BMS:* Honoraria; *Janssen:* Honoraria; *Roche:* Honoraria. **Bröske:** *F. Hoffmann La Roche Ltd:* Current Employment.

Figure: GPRC5D, FcRH5 and BCMA expression on multiple myeloma plasma cells (MMPCs) in patients with relapsed/refractory multiple myeloma



Box plots depicting percentage of MMPCs positive for the selected targets (indicated on the x axis). Each dot represents one patient.

Table. Response correlative analysis of baseline target expression (pooled data from dose escalation)

	Responder, median (n; min–max)	Non-responder, median (n; min–max)
GPRC5D, %	94.1 (31; 0–100)	97.9 (15; 0.9–100)
GPRC5D, receptor density	20990 (28; 6485–208,072)	17704 (15; 6825–64,575)

Associations with response to forimtamig were not significant based on logistic regression analysis

Figure 1

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