EHA EUROPEAN HEMATOLOGY ASSOCIATION

EHA2024
JUNE 13 - 16 | MADRID

CD200 IMMUNE CHECKPOINT EXPRESSION IS ASSOCIATED WITH TREATMENT RESISTANCE AND INFERIOR OUTCOME IN MULTIPLE MYELOMA PATIENTS TREATED BY ANTI-CD38 MoAb

D. Chemlal[1,2], C. Pochard[3], V. Jacquier[2], A. Bruyer[1], L. Gabellier[3], L. Fornero[3], C.Vempère[1], A. Machura[1], G. Requirand[3], N. Robert[3], C. Bret[2,3], G. Cartron[3], L. Vincent[3], H. De Boussac[1], J. Moreaux[2,3,4,5], C. Herbaux[2,3,4]

1. Diag2Tec, Montpellier, France; 2. UMR CNRS-UM 9002, Institute of Human Genetics, Montpellier, France; 3. CHU Montpellier, Montpellier, France; 4. Université de Montpellier, Montpellier, France; 5. Institut universitaire de France, Paris, France

INTRODUCTION

Multiple myeloma (MM) is the second most common hematological malignancy characterized by the accumulation of tumor plasma cells within the bone marrow, and a high molecular and clinical heterogeneity. In the last 10 years new therapeutic classes including targeted immunotherapies significantly improved the overall survival of MM patients. Thus, in newly diagnosed or relapsed/refractory MM, the anti-CD38 monoclonal antibody Daratumumab has became essential in the therapeutic arsenal. However, patients still relapse. Up to now, very few predictive factors of response to Daratumumab have been identified, as even the impact of low CD38 expression before treatment remains open to discussion.

AIM

Our study had two major objectives: **first** to identify predictive factors to Daratumumab response in patients, using clinical, phenotypic, karyotypic and gene expression profiling parameters, **and then** to functionally validate these predictive factors.

RESULTS

I. Characterization of a cohort of MM patients treated with Daratumumab

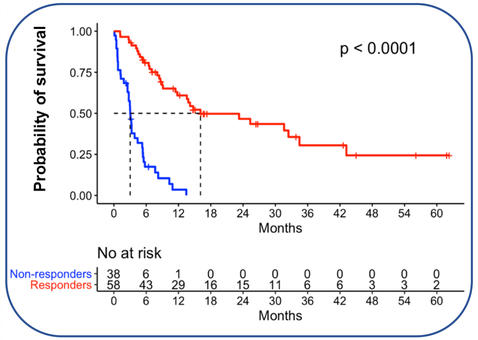


Figure 1: Progression free survival (PFS) of responders and non-responders to Daratumumab. *Median PFS was 3.0 months (95% CI 2.5-5.3) for "non-responders" and 16.1 months (95%CI 11.8-43.2) for "responders".* We included in the cohort 96 MM patients from Montpellier Hospital who had received at least one cycle of Daratumumab in first line or at relapse

II. CD200, CD45 and CD56 expression on tumor MM cells are predictive factors to Daratumumab response

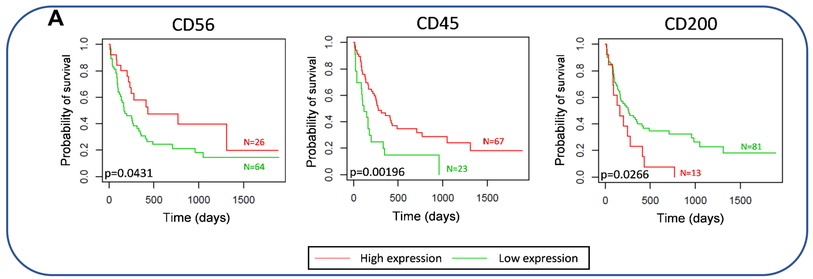


Figure 2: Identification of phenotypic predictive factor to Daratumumab response. **A)** We analyzed the expression of various flow Cytometry markers routinely used in clinic, for their potential link with patients' survival. Among the markers tested, CD56, CD45 and CD200 expression on tumor cells showed a correlation with PFS. **B)** Creation of a phenotypic based survival score for Daratumumab response based on the expression of 3 biomarkers (CD56, CD45 and CD200). A better outcome was observed for patients with low CD200 and high CD45 or CD56

III. MM Patients' NK cells subpopulations are influenced by CD200 expression on tumor cells

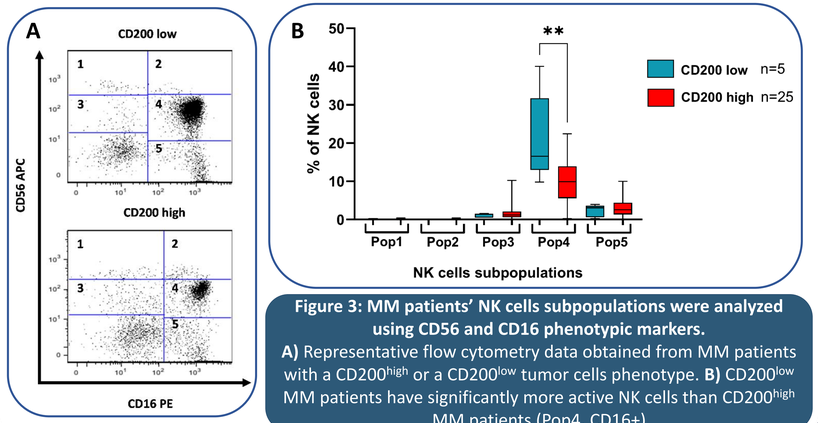
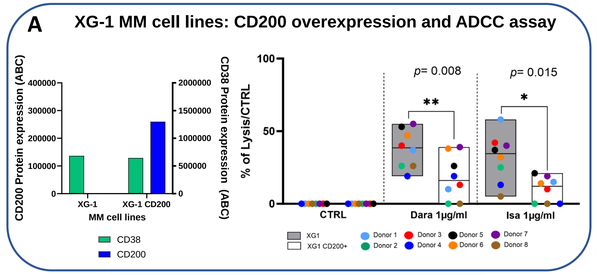


Figure 3: MM patients' NK cells subpopulations were analyzed using CD56 and CD16 phenotypic markers. **A)** Representative flow cytometry data obtained from MM patients with a CD200^{high} or a CD200^{low} tumor cells phenotype. **B)** CD200^{low} MM patients have significantly more active NK cells than CD200^{high} MM patients (Pop4, CD16+)

IV. CD200 expression reduces Anti-CD38 MoAb mediated ADCC of MM cell line



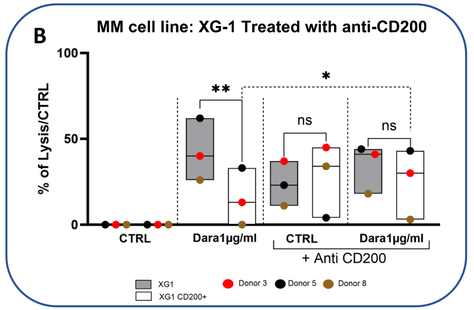


Figure 4. A) XG-1 MM cell line was transfected to overexpress CD200. Then *in vitro* ADCC assays were performed on XG1 or XG1CD200 cell lines co-cultured with purified healthy donors NK cells. The presence of CD200 significantly reduces ADCC mediated by anti-CD38 Daratumumab or Isatuximab. **B)** Here we performed ADCC assay in presence of Anti-CD200 to block the CD200-CD200R axis. Inhibition of the CD200 axis rescue the activity of Daratumumab on XG-1 CD200+.

V. The inhibition of CD200 improves CD200^{high} MM patient samples response to Daratumumab

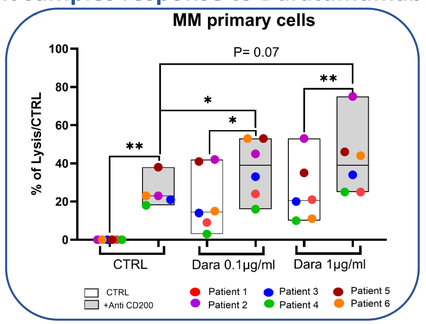
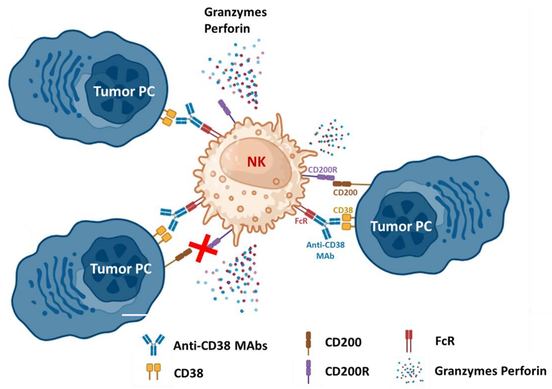


Figure 5: ***Ex vivo*** cytotoxic assays were performed on primary MM samples from patients (N=6), in presence or absence of Anti-CD200 to block the CD200-CD200R axis. CD200 axis inhibition significantly improves CD200high MM patients' samples response to 48h of Daratumumab treatment (P<0.01).

CONCLUSIONS



- **We characterized a new cohort of MM patients that received Daratumumab treatment.**
- **We identified CD200 expression on tumor MM cells as a predictive biomarker of Daratumumab response in MM.**
- **We showed that CD200-CD200R axis reduces sensitivity to Anti-CD38 MoAb treatment in MM cells.**
- **Thus, the inhibition of CD200-CD200R axis could be a new therapeutic avenues to overcome anti-CD38 immunotherapies resistance in MM.**

ACKNOWLEDGEMENT

The authors thank the patients whose data were collected in Montpellier University Hospital and their families.

DISCLOSURES

DC, AB, AM, HDB and JM have a relevant financial relationship with Diag2Tec. LV has Honoraria or Research Funding from Janssen, Takeda and Celgene. CH has Honoraria or Research Funding from Janssen, Takeda, AbbVie and Roche.

CONTACT INFORMATION

d.Chemlal@diag2tec.com
a.bruyer@diag2tec.com
c-herbaux@chu-montpellier.fr

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