Relapsed/refractory patients

EHA 2018 | Preclinical data for BCMAxCD3 bi-specific antibody JNJ-957

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The 23rd Congress of the European Hematology Association (EHA) took place in Stockholm from 14–17 June 2018. On Sunday 17 June, an oral session took place in which, Kristine A. Frerichs from the VU University Medical Center, Amsterdam, the Netherlands, presented data from a pre-clinical evaluation of JNJ-957, a BCMAxCD3 bi-specific antibody, for the treatment of multiple myeloma (MM). This so-called ‘DuoBody’ is designed to engage B cell maturation antigen (BCMA) on plasma cells and CD3 on T cells, in order to bring both cells in close proximity to enable T-cell killing of myeloma cells.

BCMA has been identified as a key target in multiple myeloma (MM), as it has restricted expression on plasma B cells, and promising data has emerged from clinical trials using BCMA CAR T-cells and from BCMA-directed antibody-drug conjugates. The rationale for this study is that there is an ongoing need for new agents for patients (pts) with relapsed and refractory (RR) MM, in particular, for patients that are refractory to immunomodulatory agents (IMiDs), proteasome inhibitors (PIs) and CD38-targeting antibodies, and for those with high-risk cytogenetics.

Key Data:

- MM cell lines (RPMI-8226, UM9, U266, and MM1.S) expressed high levels of BCMA
- These were incubated with peripheral blood mononuclear cells (PBMCs) from healthy donors (HDs) for 48 hrs with varying doses of JNJ-957 (titrated from 0.0064–4 µg/ml)
- Dose-dependent lysis of CD138\(^{\text{high}}\)/CD38\(^{+}\) MM cells was assessed by flow cytometry
- JNJ-957 led to effective lysis of BCMA\(^{+}\) MM cell lines in a dose-dependent manner by HD PBMCs
- JNJ-957-mediated lysis was accompanied by activation and degranulation of double positive CD4\(^{+}\) and CD8\(^{+}\) T-cells, as assessed by CD25 and CD107 positivity
- PBMCs were then taken from the following MM patient subtypes:
  - Newly diagnosed (ND) MM = 11 pts
  - RRMM (daratumumab [dara]-naïve) = 19 pts
  - RRMM (dara-refractory) = 15 pts
- All pts were exposed to immunomodulatory drugs (IMiDs) and proteasome inhibitors (PIs)
- Median age of NDMM and RRMM pts (years) = 66; median age dara-naïve = 68
- Mean lysis of MM cells by JNJ-957 at 4.0µg/ml:
  - NDMM = 79% (range: 66–92%)
- RRMM pts refractory to lenalidomide (n = 16 pts): mean lysis = 69% (range: 24–98%); these pts were also refractory to bortezomib (73%), pomalidomide (82%), and carfilzomib (9%)

- RRMM pts refractory to dara (n = 15 pts) = 83% (range: 52–99%)

- Determinants of JNJ-957 efficacy:
  - No association between the expression of BCMA or PD-L1
  - Not affected by high-risk cytogenetics
  - No association with the effector: target ratios or T-cell composition
  - High levels of baseline regulatory T-cells (T-regs) negatively influenced the efficacy of MM cell lysis (in RRMM but not in ND samples)
  - Higher doses of JNJ-957 could overcome this negative influence
  - It was postulated that dara could enhance the efficacy of JNJ-957 by the elimination of CD38+ T-regs, B cells and myeloid-derived suppressor cells (MDSCs), leading to proliferation and activation of T cells and improved tumor response
  - A dose-response of dara-refractory pt cells was significantly better compared to dara-naïve pt cells

- In-vivo pre-treatment with dara also improved in-vitro efficacy:

- BM samples from RRMM pts (n = 8) exposed to dara (median treatment duration = 3 months (range, 1–7)), showed significantly improved lysis compared to samples from dara-naïve pts

- Mean MM cell lysis in samples obtained after disease progression during dara treatment, compared to samples taken before dara treatment = 93% vs 74%

**Conclusion**

The JNJ-957 DuoBody is effective in samples from both newly diagnosed patients and heavily pre-treated patients. A high percentage of T-regs negatively influences the JNJ-958 efficacy at low doses, but higher doses were able to overcome this. Pre-treatment with dara was found to enhance the efficacy of JNJ-957 by driving immunomodulatory effects, such as decreasing the number of T-regs and increasing the number of effector cells. Overall, these data strengthen the rationale for the ongoing phase I/II clinical trials for use of JNJ-957 as either a monotherapy or in combination with daratumumab.

**References**


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