Abstract No. 117: Target Expression, Preclinical Activity and Mechanism of Action of EM801: A Novel First-in-Class Bcma T-Cell Bispecific Antibody for the Treatment of Multiple Myeloma

Myeloma: Pathophysiology and Pre-Clinical Studies, excluding Therapy

Program: Oral and Poster Abstracts

Type: Oral

Session: 652. Myeloma: Pathophysiology and Pre-Clinical Studies, excluding Therapy: Novel Immunotherapeutics and the Impact of the Microenvironment

Saturday, December 5, 2015: 2:30 PM

W414AB, Level 4 (Orange County Convention Center)

Anja Seckinger, MD*, Jose Antonio Delgado*, Laura Moreno*, Brigitte Neuber, PhD*, Anna Grab, PhD*, Susanne Lipp, MS*, Juana Merino, MD PhD*, Minh Diem Vu, PhD*, Klaus Strein, MD, PhD*, Felipe Prosper, MD PhD*, Michael Hundemer, MD*, Jesus San Miguel, MD PhD*, Dirk Hose, MD* and Bruno Paiva, PhD*

1Medizinische Klinik V, Universitätsklinikum Heidelberg, Heidelberg, Germany
2Department of Hematology and Immunology, Clínica Universidad de Navarra, Pamplona, Spain
3EngMab AG, Wilen, Switzerland
4Department of Hematology and Immunology, CIMA/UNAV/IDISNA, Pamplona, Spain
5Department of Internal Medicine V, University Hospital Heidelberg, Heidelberg, Germany

Background. T-cell bispecific antibodies (TCBs) simultaneously binding CD3 on T-cells and individual tumor antigens, activate T-cells and destroy tumor antigen carrying cells. B-cell maturation antigen (BCMA), a surface antigen reported to be expressed on normal and malignant plasma cells (PCs), could represent a potentially promising target for TCBs in multiple myeloma (MM).

The Aim of our study was to: i) assess expression of BCMA in normal and malignant PCs as well as cells of the bone marrow (BM) microenvironment by gene expression profiling and flow cytometry to validate it as potential clinical target for TCBs; ii) to evaluate activity of EM801 as member of a novel class of BCMA-TCBs in vitro on primary myeloma cells and in vivo in the H929-xenograft reconstituted NOG mouse model; and iii) to delineate its mechanism of action.

Results. Expression. We investigated the expression of BCMA in CD138-purified PCs from BM aspirates obtained from 726 patients including MGUS (n=62), asymptomatic (n=59) and symptomatic MM (605), as well as different BM cellular subsets from healthy donors (n=10 PCs; plasmablasts, memory B-cells, T-cells, CD34+, CD14+, CD15+, n=5 each; n=8 mesenchymal stromal cells) using Affymetrix DNA microarrays. BCMA expression was observed in malignant PC from 723/726 (99.5%) MGUS and MM patients, 10/10 normal PCs and 5/5 plasmablasts; gene expression of BCMA was undetectable in all other normal BM subsets. Using multiparameter flow cytometry, BCMA surface expression on malignant PCs was confirmed in 40/40 patients while being absent on normal BM cells. BCMA is thus a potential target in virtually all myeloma patients.

Activity. In vitro. EM801 induced concentration dependent significant cell death in malignant plasma cells in BM-samples of 21/28 (75%) previously untreated and 8/10 (80%) relapsed/refractory MM patients in concentrations ranging from 10pM to 30nM. No or only minor unspecific toxicity on cells of the BM microenvironment was observed. In vivo efficacy of EM801 was studied in a subcutaneous H929 myeloma cell line xenograft model in NOG (NOD/Shi-scid/IL-2RgammaCnull) mice reconstituted with human PBMCs. Three doses of EM801, i.e. 0.026, 0.26 and 2.6 nM/kg, the same doses of a BCMAxCD3-(scFv), and two control groups were investigated (n=9 mice/group). Three weekly intravenous doses were given, starting on day 19 after tumor cell injection when tumor volumes were 293±135 mm³. On day 47, all mice from control groups had their tumors grown beyond 2000 mm³ and were euthanized for ethical reasons. In contrast, at 2.6 nM/kg (0.5 mg/kg) EM801 tumor regression was already observed after the second i.v. injection in 6/9 animals and the tumor regressed to 16±3 mm³ on day 47. BCMAxCD3-(scFv), bispecific antibody without Fc did not show any efficacy at all doses studied.

Regarding the mechanism of action, we first demonstrated that EM801 effectively binds myeloma cells and T-cells with a strength of 1622±410 pN (5-10 fold of control) as measured by atomic force microscopy. Secondly, increasing concentrations (0.03-30nM) of EM801 led to progressive T-cell activation in primary BM samples, with significantly increased levels of CD69 (P<0.001), CD25 (P<0.001) and HLADR (P=0.001) expression in both CD4 and CD8 T-cells as compared to an unspecific TCB. Thirdly, EM801 induced
significant secretion of interferon-γ (19-3000 pg/ml), granzyme B (68-2986 pg/ml), and perforin (145-3712 pg/ml) as measured by ELISA, together explaining the strong in vitro and in vivo activity of EM801.

Conclusions. BCMA is selectively expressed at the RNA (723/726) and protein (40/40) levels on malignant PCs from virtually all MM patients, and thus represents a promising TCB-target. The novel BCMA-TCB EM801 was effective in vitro in 29/38 (76%) primary MM patients’ BM samples at picomolar to low nanomolar concentrations, easily achievable in vivo in patients, as well as in the H929-xenograft reconstituted NOG mouse model at 0.5 mg/kg once a week. Neither in vitro (the BM microenvironment) nor in vivo the compound shows significant toxicity or side effects. EM801 confers cytotoxicity by effectively coupling T-cells with malignant PCs, inducing T-cell activation, secretion of interferon-γ, granzyme B and perforin, and thereby effectively killing malignant PCs. EM801 is thus a promising new compound for the treatment of multiple myeloma to be investigated in clinical phase I/II trials.

Disclosures: Seckinger: EngMab AG: Research Funding ; Takeda: Other: Travel grant . Neuber: EngMab AG:Research Funding . Vu: EngMab AG: Employment , Equity Ownership , Membership on an entity’s Board of Directors or advisory committees . Strein: BB Biotech AG: Membership on an entity’s Board of Directors or advisory committees ; Novimmune SA: Membership on an entity’s Board of Directors or advisory committees ; EngMab AG: Employment , Equity Ownership , Membership on an entity’s Board of Directors or advisory committees . Hunderer: EngMab AG: Research Funding . San Miguel: Bristol-Myers Squibb: Honoraria ; Celgene:Honoraria ; Janssen-Cilag: Honoraria ; Millennium: Honoraria ; Novartis: Honoraria ; Sanofi-Aventis: Honoraria ;Onyx: Honoraria . Hose: Takeda: Other: Travel grant ; EngMab AG: Research Funding . Paiva: Celgene:Consultancy ; Janssen: Consultancy ; Binding Site: Consultancy ; BD Bioscience: Consultancy ; EngMab AG:Research Funding ; Onyx: Consultancy ; Millennium: Consultancy ; Sanofi: Consultancy .