LETTER TO THE EDITOR

TE-1146, a novel anti-CD38-antibody-lenalidomide conjugate, demonstrates potent *ex vivo* anti-myeloma activity

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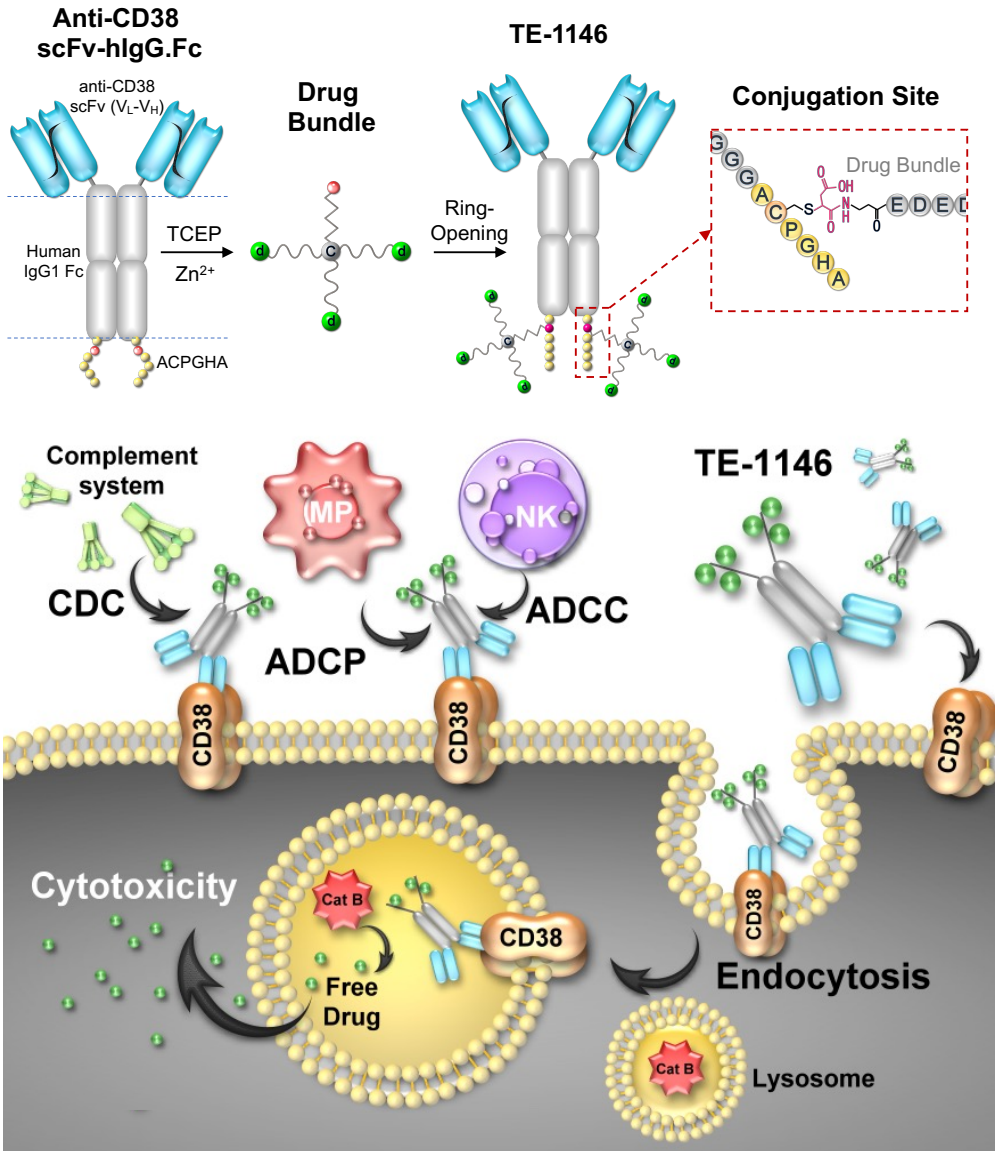

Supplementary Figure S1. TE-1146 preparation and proposed mechanism of action. (Top) Two drug bundles, each containing 3 lenalidomide molecules (green spheres), were prepared using a multi-arm linker and site-specifically conjugated to the engineered cysteines (pink) at the C-termini of a 2-chain α-CD38 single-chain variable fragment (scFv, blue)–human IgG1.Fc (gray)–A**C**PGHA (beads) fusion protein via S^{-}-maleimide reaction, followed by irreversible hydrolysis of the maleimide group to prevent premature drug release. (Bottom) The dual mechanisms of action of TE-1146: (i) direct cytotoxicity via internalization of the CD38/TE-1146 complex, cleavage by lysosomal cathepsin B, releasing cytotoxic lenalidomide, and (ii) Fc-mediated immune effector functions (complement-dependent cytotoxicity, CDC; antibody-dependent cellular phagocytosis, ADCP; and antibody-dependent cell-mediated cytotoxicity, ADCC). MP denotes macrophage and NK, natural killer cells.

Supplementary Table S1. Summary of patient cohort characteristics

Parameter	NDMM	RRMM1	RRMM2
# of patients[a]	5	5	5
Median age at diagnosis (range)	64 (45-90)	65 (42-77)	63 (54-63)
Gender (Male/Female)	(2/3)	(4/1)	(1/4)
Prior Therapy[b] (mAb, PI, IMiD, Others)	(0, 0, 0, 0)	(0, 4, 4, 2)	(4, 5, 5, 3)
ISS stage (I, II, III)[c]	(0, 3, 2)	(2, 2, 1)	(0, 2, 3)
M-Protein Subtype (IgA, IgG, IgM, LCD)	(2, 2, 0, 1)	(1, 1, 2, 1)	(0, 5, 0, 0)
MNCs[d] ($\times 10^6$, mean ± SD)	3.4 ± 3.1	4.1 ± 2.1	16.0 ± 13.2
$CD138^+$ cells[e] ($\times 10^6$, mean ± SD)	1.8 ± 2.6	2.5 ± 1.4	2.1 ± 0.9
$CD38^+$ cells[f] (mean ± SD)	2324 ± 991	4445 ± 542	5045 ± 4730
CD38 MFI[g] mean ± SD (range)	2853±1236 (976–4159)	3610±1256 (2351–5347)	3896±3398 (1472–9544)
CD56 MFI[g] mean ± SD (range)	2303±3914 (280–9298)	926±364 (462–1324)	6291±6986 (709–18403)
CD138 MFI[g] mean ± SD (range)	2923±5705 (81–13108)	2214±682 (1330–2971)	8419±5991 (3893–18330)

[a]15 MM patients were recruited between September 2023 and May 2024 after obtaining informed consent and approval by the Research Ethics Review Committee (IRB No. 112088-F) of Far Eastern Memorial Hospital, New Taipei City, Taiwan. However, only 14 MM patients were analyzed as 1 RRMM1 patient was $CD138^-$. [b]mAb: monoclonal antibodies, PI: proteasome inhibitors, IMiD: immunomodulatory drugs. [c]ISS: International Staging System classifying MM patients into 3 stages, with stage I denoting the best prognosis and stage III the worst, which was present in all three patient groups. [d]The mean number of mononuclear cells (MNCs) isolated via density gradient centrifugation using Ficoll-Paque 1.077 (GE Healthcare, Munich, Germany) from bone marrow aspirates (8–10 mL) obtained from each patient in the group. The mean counts of MNC cells did not differ significantly among the groups ($p > 0.05$), but RRMM2 patients showed a wider range of MNC counts. [e]The mean number of $CD138^+$ cells isolated from freshly

obtained MNCs using magnetic-activated cell sorting (Miltenyi Biotec), except for one $CD138^-$ RRMM1 patient. [f]The mean number of $CD38^+$ cells among total MNCs in MM patients, evaluated by flow cytometry using homemade anti-CD38-APC. RRMM2 patients showed significant variability with one patient exhibiting lower $CD38^+$ cell percentage (2%), and two patients higher proportions (21 and 54%), compared to the $CD38^+$ cell percentage in NDMM (5–13%) or RRMM1 (5–17%) patients. [g]MFI: mean fluorescence intensity of CD38, CD56, or CD138 marker on $CD138^+$ cells in patient samples prior to drug exposure, characterized by flow cytometry using fluorophore-conjugated antibodies: anti-CD38-APC (homemade), anti-CD138-PE (Biolegend), and anti-CD56-SB436 (eBioscience). Flow cytometry was conducted using an LSR Fortessa™ Cell Analyzer (BD Biosciences, San Jose, CA). Immunophenotypic data were analyzed using FlowJo v10 software (FlowJo LLC).