

Clinics Review Articles
Hematology/Oncology Clinics

New Developments in Myeloma
骨髓瘤临床新进展

参 考 文 献

原著主审 [美] George P. Canellos
[美] Edward J. Benz Jr

主 编 [美] Peter Leif Bergsagel

主 审 侯 健

主 译 陈君敏 郭冬梅 吴晓勇

目 录

献 辞.....	1
1 多发性骨髓瘤的分子发病机制及临床意义.....	2
2 骨髓瘤的免疫发生机制.....	7
3 冒烟型多发性骨髓瘤：观察、控制与根治.....	13
4 靶向 cereblon 连接酶降解剂治疗骨髓瘤：作用及耐药机制.....	16
5 蛋白酶体抑制剂治疗多发性骨髓瘤：基于功能基因组学作用或耐药机制的生物学见解.....	21
6 多发性骨髓瘤中的单克隆抗体治疗.....	29
7 双特异性抗体在多发性骨髓瘤治疗中的应用.....	39
8 嵌合抗原受体 T 细胞在多发性骨髓瘤治疗中的应用	47
9 造血干细胞移植在多发性骨髓瘤治疗中是否仍有重要地位.....	54
10 巩固治疗和维持治疗的作用.....	59
11 新诊断多发性骨髓瘤管理的现状及未来.....	63
12 克隆异质性对多发性骨髓瘤的影响.....	68
13 多发性骨髓瘤可测量残留病和决策制订.....	76
14 高危多发性骨髓瘤的治疗方法.....	83
15 复发难治性多发性骨髓瘤的新疗法涌现.....	90
16 多发性骨髓瘤免疫活性小鼠模型：治疗意义.....	94

献 辞

- [1] Kuehl WM, Kaplan BA, Scharff MD. Characterization of light chain and light chain constant region fragment mRNAs in MPC 11 mouse myeloma cells and variants. *Cell* 1975;5(2):139–47.
- [2] Margulies DH, Kuehl WM, Scharff MD. Somatic cell hybridization of mouse myeloma cells. *Cell* 1976;8(3):405–15.
- [3] Riley SC, Brock EJ, Kuehl WM. Induction of light chain expression in a pre-B cell line by fusion to myeloma cells. *Nature* 1981;289(5800):804–6.
- [4] Emorine L, Kuehl M, Weir L, et al. A conserved sequence in the immunoglobulin J kappa-C kappa intron: possible enhancer element. *Nature* 1983;304(5925): 447–9.
- [5] Bender TP, Kuehl WM. Murine myb protooncogene mRNA: cDNA sequence and evidence for 5' heterogeneity. *Proc Natl Acad Sci U S A* 1986;83(10):3204–8.
- [6] Timblin C, Bergsagel PL, Kuehl WM. Identification of consensus genes expressed in plasmacytomas but not B lymphomas. *Curr Top Microbiol Immunol* 1990;166:141–7.
- [7] Bergsagel PL, Victor-Kobrin C, Brents LA, et al. Genes expressed selectively in plasmacytomas: markers of differentiation and transformation. *Curr Top Microbiol Immunol* 1992;182:223–8.
- [8] Bergsagel PL, Brents LA, Trepel JB, et al. Genes expressed selectively in murine and human plasma cell neoplasms. *Curr Top Microbiol Immunol* 1995;194:57–61.
- [9] Bergsagel PL, Chesi M, Nardini E, et al. Promiscuous translocations into immunoglobulin heavy chain switch regions in multiple myeloma. *Proc Natl Acad Sci U S A* 1996;93(24):13931–6.
- [10] Kuehl WM, Brents LA, Chesi M, et al. Selective expression of one c-myc allele in two human myeloma cell lines. *Cancer Res* 1996;56(19):4370–3.
- [11] Misund K, Keane N, Stein CK, et al. MYC dysregulation in the progression of multiple myeloma. *Leukemia* 2020;34(1):322–6.

1 多发性骨髓瘤的分子发病机制及临床意义

- [1] Kuehl WM, Bergsagel PL. Molecular pathogenesis of multiple myeloma and its premalignant precursor. *J Clin Invest* 2012;122(10):3456–63.
- [2] Bergsagel PL, Chesi M, Nardini E, et al. Promiscuous translocations into immunoglobulin heavy chain switch regions in multiple myeloma. *Proc Natl Acad Sci U S A* 1996;93(24):13931–6.
- [3] Fonseca R, Barlogie B, Bataille R, et al. Genetics and cytogenetics of multiple myeloma: a workshop report. *Cancer Res* 2004;64(4):1546–58.
- [4] Keats JJ, Chesi M, Egan JB, et al. Clonal competition with alternating dominance in multiple myeloma. *Blood* 2012;120(5):1067–76.
- [5] Kyle RA, Larson DR, Therneau TM, et al. Long-Term Follow-up of Monoclonal Gammopathy of Undetermined Significance. *N Engl J Med* 2018;378(3):241–9.
- [6] Kyle RA, Remstein ED, Therneau TM, et al. Clinical course and prognosis of smoldering (asymptomatic) multiple myeloma. *N Engl J Med* 2007;356(25):2582–90.
- [7] ACS. Cancer Statistics Center. 2023; Available at: <https://cancerstatisticscenter.cancer.org/#!/cancer-site/Myeloma>. Accessed June 19, 2023.
- [8] Greenberg AJ, Vachon CM, Rajkumar SV. Disparities in the prevalence, pathogenesis and progression of monoclonal gammopathy of undetermined significance and multiple myeloma between blacks and whites. *Leukemia* 2012;26(4):609–14.
- [9] Landgren O, Graubard BI, Katzmann JA, et al. Racial disparities in the prevalence of monoclonal gammopathies: a population-based study of 12,482 persons from the National Health and Nutritional Examination Survey. *Leukemia* 2014; 28(7):1537–42.
- [10] Landgren O, Kyle RA, Pfeiffer RM, et al. Monoclonal gammopathy of undetermined significance (MGUS) consistently precedes multiple myeloma: a prospective study. *Blood* 2009;113(22):5412–7.
- [11] Weiss BM, Abadie J, Verma P, et al. A monoclonal gammopathy precedes multiple myeloma in most patients. *Blood* 2009;113(22):5418–22.
- [12] Murray DL, Puig N, Kristinsson S, et al. Mass spectrometry for the evaluation of monoclonal proteins in multiple myeloma and related disorders: an International Myeloma Working Group Mass Spectrometry Committee Report. *Blood Cancer J* 2021;11(2):24.
- [13] Rustad EH, Yellapantula V, Leongamornlert D, et al. Timing the initiation of multiple myeloma. *Nat Commun* 2020;11(1):1917.
- [14] Chesi M, Bergsagel PL, Brents LA, et al. Dysregulation of cyclin D1 by translocation into an IgH gamma switch region in two multiple myeloma cell lines. *Blood* 1996;88(2):674–81.
- [15] Shaughnessy J Jr, Gabrea A, Qi Y, et al. Cyclin D3 at 6p21 is dysregulated by recurrent chromosomal translocations to

- immunoglobulin loci in multiple myeloma. *Blood* 2001;98(1):217–23.
- [16] de Leval L, Alizadeh AA, Bergsagel PL, et al. Genomic profiling for clinical decision making in lymphoid neoplasms. *Blood* 2022;140(21):2193–227.
- [17] Baughn LB, Li Z, Pearce K, et al. The CCND1 c.870G risk allele is enriched in individuals of African ancestry with plasma cell dyscrasias. *Blood Cancer J* 2020; 10(3):39.
- [18] Chesi M, Stein CK, Garbitt VM, et al. Monosomic loss of MIR15A/MIR16-1 is a driver of multiple myeloma proliferation and disease progression. *Blood Cancer Discov* 2020;1(1):68–81.
- [19] Bryce AH, Ketterling RP, Gertz MA, et al. Translocation t(11;14) and survival of patients with light chain (AL) amyloidosis. *Haematologica* 2009;94(3):380–6.
- [20] Fonseca R, Blood EA, Oken MM, et al. Myeloma and the t(11;14)(q13;q32); evidence for a biologically defined unique subset of patients. *Blood* 2002;99(10): 3735–41.
- [21] Zhan F, Huang Y, Colla S, et al. The molecular classification of multiple myeloma. *Blood* 2006;108(6):2020–8.
- [22] Nair B, van Rhee F, Shaughnessy JD Jr, et al. Superior results of Total Therapy 3 (2003-33) in gene expression profiling-defined low-risk multiple myeloma confirmed in subsequent trial 2006-66 with VRD maintenance. *Blood* 2010; 115(21):4168–73.
- [23] van Rhee F, Zangari M, Schinke CD, et al. Long-term outcome of total therapy regimens: impact of molecular subgroups. *Blood* 2019;134:3309.
- [24] Touzeau C, Dousset C, Le Gouill S, et al. The Bcl-2 specific BH3 mimetic ABT-199: a promising targeted therapy for t(11;14) multiple myeloma. *Leukemia* 2014;28(1):210–2.
- [25] Kumar S, Kaufman JL, Gasparetto C, et al. Efficacy of venetoclax as targeted therapy for relapsed/refractory t(11;14) multiple myeloma. *Blood* 2017;130(22): 2401–9.
- [26] Chesi M, Bergsagel PL, Shonukan OO, et al. Frequent dysregulation of the c-maf proto-oncogene at 16q23 by translocation to an Ig locus in multiple myeloma. *Blood* 1998;91(12):4457–63.
- [27] Avet-Loiseau H, Malard F, Campion L, et al. Translocation t(14;16) and multiple myeloma: is it really an independent prognostic factor? *Blood* 2011;117(6): 2009–11.
- [28] Walker BA, Wardell CP, Murison A, et al. APOBEC family mutational signatures are associated with poor prognosis translocations in multiple myeloma. *Nat Commun* 2015;6:6997.
- [29] Maura F, Petljak M, Lionetti M, et al. Biological and prognostic impact of APOBEC-induced mutations in the spectrum of plasma cell dyscrasias and multiple myeloma cell lines. *Leukemia* 2018;32(4):1044–8.
- [30] Weinhold N, Heuck CJ, Rosenthal A, et al. Clinical value of molecular subtyping multiple myeloma using gene expression profiling. *Leukemia* 2016;30(2):423–30.
- [31] Qiang YW, Ye S, Chen Y, et al. MAF protein mediates innate resistance to proteasome inhibition therapy in multiple myeloma. *Blood* 2016;128(25):2919–30.
- [32] Hurt EM, Wiestner A, Rosenwald A, et al. Overexpression of c-maf is a frequent

- oncogenic event in multiple myeloma that promotes proliferation and pathological interactions with bone marrow stroma. *Cancer Cell* 2004;5(2):191–9.
- [33] Chesi M, Nardini E, Brents LA, et al. Frequent translocation t(4;14)(p16.3;q32.3) in multiple myeloma is associated with increased expression and activating mutations of fibroblast growth factor receptor 3. *Nat Genet* 1997;16(3):260–4.
- [34] Chesi M, Nardini E, Lim RS, et al. The t(4;14) translocation in myeloma dysregulates both FGFR3 and a novel gene, MMSET, resulting in IgH/MMSET hybrid transcripts. *Blood* 1998;92(9):3025–34.
- [35] Kuo AJ, Cheung P, Chen K, et al. NSD2 links dimethylation of histone H3 at lysine 36 to oncogenic programming. *Mol Cell* 2011;44(4):609–20.
- [36] Martinez-Garcia E, Popovic R, Min DJ, et al. The MMSET histone methyl transferase switches global histone methylation and alters gene expression in t(4;14) multiple myeloma cells. *Blood* 2011;117(1):211–20.
- [37] Li F, Zhai YP, Lai T, et al. MB4-2/MB4-3 transcripts of IGH-MMSET fusion gene in t(4;14)(pos) multiple myeloma indicate poor prognosis. *Oncotarget* 2017;8(31): 51608–20.
- [38] Stong N, Ortiz-Estevéz M, Towfic F, et al. The location of the t(4;14) translocation breakpoint within the NSD2 gene identifies a subset of patients with high-risk NDMM. *Blood* 2023;141(13):1574–83.
- [39] Benard B, Christofferson A, Legendre C, et al. FGFR3 mutations are an adverse prognostic factor in patients with t (4; 14) (p16; q32) multiple myeloma: an MmrF compass analysis. *Blood* 2017;130:3027.
- [40] Scheid C, Reece D, Beksac M, et al. Phase 2 study of dovitinib in patients with relapsed or refractory multiple myeloma with or without t(4;14) translocation. *Eur J Haematol* 2015;95(4):316–24.
- [41] Croucher DC, Devasia AJ, Abelman DD, et al. Single-cell profiling of multiple myeloma reveals molecular response to FGFR3 inhibitor despite clinical progression. *Cold Spring Harb Mol Case Stud* 2023;9(2).
- [42] Fonseca R, Bergsagel PL, Drach J, et al. International Myeloma Working Group molecular classification of multiple myeloma: spotlight review. *Leukemia* 2009;23(12):2210–21.
- [43] Misund K, Keane N, Stein CK, et al. MYC dysregulation in the progression of multiple myeloma. *Leukemia* 2020;34(1):322–6.
- [44] Barwick BG, Neri P, Bahlis NJ, et al. Multiple myeloma immunoglobulin lambda translocations portend poor prognosis. *Nat Commun* 2019;10(1):1911.
- [45] Kalkat M, De Melo J, Hickman KA, et al. MYC Deregulation in Primary Human Cancers. *Genes* 2017;8(6).
- [46] Boyle EM, Deshpande S, Tytarenko R, et al. The molecular make up of smoldering myeloma highlights the evolutionary pathways leading to multiple myeloma. *Nat Commun* 2021;12(1):293.
- [47] Subbiah V, Kreitman RJ, Wainberg ZA, et al. Dabrafenib plus trametinib in BRAFV600E-mutated rare cancers: the phase 2 ROAR trial. *Nat Med* 2023; 29(5):1103–12.
- [48] Le Calvez B, Le Bris Y, Herbreteau G, et al. RAS mutation leading to acquired resistance to dabrafenib and trametinib therapy in a multiple myeloma patient harboring BRAF mutation. *EJHaem* 2020;1(1):318–22.

- [49] Yang Y, Bolonsky A, Oellerich T, et al. Oncogenic RAS commandeers amino acid sensing machinery to aberrantly activate mTORC1 in multiple myeloma. *Nat Commun* 2022;13(1):5469.
- [50] Keats JJ, Fonseca R, Chesi M, et al. Promiscuous mutations activate the noncanonical NF-kappaB pathway in multiple myeloma. *Cancer Cell* 2007;12(2): 131–44.
- [51] De Bosscher K, Vanden Berghe W, Vermeulen L, et al. Glucocorticoids repress NF-kappaB-driven genes by disturbing the interaction of p65 with the basal transcription machinery, irrespective of coactivator levels in the cell. *Proc Natl Acad Sci U S A* 2000;97(8):3919–24.
- [52] Uhlenhaut NH, Barish GD, Yu RT, et al. Insights into negative regulation by the glucocorticoid receptor from genome-wide profiling of inflammatory cistromes. *Mol Cell* 2013;49(1):158–71.
- [53] Palombella VJ, Conner EM, Fuseler JW, et al. Role of the proteasome and NF-kappaB in streptococcal cell wall-induced polyarthritis. *Proc Natl Acad Sci U S A* 1998;95(26):15671–6.
- [54] Richardson PG, Kumar SK, Masszi T, et al. Final Overall Survival Analysis of the TOURMALINE-MM1 Phase III Trial of Ixazomib, Lenalidomide, and Dexamethasone in Patients With Relapsed or Refractory Multiple Myeloma. *J Clin Oncol* 2021;39(22):2430–42.
- [55] Dash AB, Zhang J, Shen L, et al. Clinical benefit of ixazomib plus lenalidomide-dexamethasone in myeloma patients with non-canonical NF-kappaB pathway activation. *Eur J Haematol* 2020;105(3):274–85.
- [56] Morgan D, Garg M, Tergaonkar V, et al. Pharmacological significance of the non- canonical NF-kappaB pathway in tumorigenesis. *Biochim Biophys Acta Rev Cancer* 2020;1874(2):188449.
- [57] Lee H, Ahn S, Maity R, et al. Mechanisms of antigen escape from BCMA- or GPRC5D-targeted immunotherapies in multiple myeloma. *Nat Med* 2023;29(9): 2295–306.
- [58] Dib A, Peterson TR, Raducha-Grace L, et al. Paradoxical expression of INK4c in proliferative multiple myeloma tumors: bi-allelic deletion vs increased expression. *Cell Div* 2006;1:23.
- [59] Walker BA, Leone PE, Chiecchio L, et al. A compendium of myeloma-associated chromosomal copy number abnormalities and their prognostic value. *Blood* 2010;116(15):e56–65.
- [60] Chesi M, Robbiani DF, Sebag M, et al. AID-dependent activation of a MYC trans- gene induces multiple myeloma in a conditional mouse model of post-germinal center malignancies. *Cancer Cell* 2008;13(2):167–80.
- [61] Linden M, Kirchhof N, Carlson C, et al. Targeted overexpression of Bcl-XL in B-lymphoid cells results in lymphoproliferative disease and plasma cell malignancies. *Blood* 2004;103(7):2779–86.
- [62] Zhan F, Colla S, Wu X, et al. CKS1B, overexpressed in aggressive disease, regulates multiple myeloma growth and survival through SKP2- and p27Kip1- dependent and -independent mechanisms. *Blood* 2007;109(11):4995–5001.
- [63] Wu D, Dean J. RNA exosome ribonuclease DIS3 degrades Pou6f1 to promote mouse pre-implantation cell differentiation. *Cell*

- Rep 2023;42(2):112047.
- [64] Corre J, Perrot A, Caillot D, et al. del(17p) without TP53 mutation confers a poor prognosis in intensively treated newly diagnosed patients with multiple myeloma. Blood 2021;137(9):1192–5.

2 骨髓瘤的免疫发生机制

- [1] Kumar SK, Rajkumar V, Kyle RA, et al. Multiple myeloma. *Nat Rev Dis Primers* 2017;3:17046.
- [2] Landgren O, Kyle RA, Pfeiffer RM, et al. Monoclonal gammopathy of undetermined significance (MGUS) consistently precedes multiple myeloma: a prospective study. *Blood* 2009;113(22):5412–7.
- [3] Dhodapkar MV. MGUS to myeloma: a mysterious gammopathy of underexplored significance. *Blood* 2016;128(23):2599–606.
- [4] El-Khoury H, Lee DJ, Alberge JB, et al. Prevalence of monoclonal gammopathies and clinical outcomes in a high-risk US population screened by mass spectrometry: a multicentre cohort study. *Lancet Haematol* 2022;9(5):e340–9.
- [5] Rognvaldsson S, Love TJ, Thorsteinsdottir S, et al. Iceland screens, treats, or prevents multiple myeloma (iStopMM): a population-based screening study for monoclonal gammopathy of undetermined significance and randomized controlled trial of follow-up strategies. *Blood Cancer J* 2021;11(5):94.
- [6] Vesely MD, Kershaw MH, Schreiber RD, et al. Natural innate and adaptive immunity to cancer. *Annu Rev Immunol* 2011;29:235–71.
- [7] Dhodapkar MV. The immune system in multiple myeloma and precursor states: lessons and implications for immunotherapy and interception. *Am J Hematol* 2023;98 Suppl 2(Suppl 2):S4–12.
- [8] Cohen AD, Raje N, Fowler JA, et al. How to Train Your T Cells: Overcoming Immune Dysfunction in Multiple Myeloma. *Clin Cancer Res* 2020;26(7):1541–54.
- [9] Shah N, Aiello J, Avigan DE, et al. The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of multiple myeloma. *Journal for immunotherapy of cancer* 2020;8(2):e000734.
- [10] Dhodapkar MV, Krasovsky J, Osman K, et al. Vigorous premalignancy specific effector T cell response in the bone marrow of patients with preneoplastic gammopathy. *J Exp Med* 2003;198:1753–7.
- [11] Finn OJ. Premalignant lesions as targets for cancer vaccines. *J Exp Med* 2003;198(11):1623–6.
- [12] Smyth MJ, Dunn GP, Schreiber RD. Cancer immunosurveillance and immunoediting: the roles of immunity in suppressing tumor development and shaping tumor immunogenicity. *Adv Immunol* 2006;90:1–50.
- [13] Dhodapkar MV, Krasovsky J, Osman K, et al. Vigorous premalignancy-specific effector T cell response in the bone marrow of patients with monoclonal gammopathy. *J Exp Med* 2003;198(11):1753–7.
- [14] Spisek R, Kukreja A, Chen LC, et al. Frequent and specific immunity to the embryonal stem cell-associated antigen SOX2 in patients with monoclonal gammopathy. *J Exp Med* 2007;204(4):831–40.
- [15] Maura F, Landgren O, Morgan GJ. Designing

- Evolutionary Based Interception Strategies to Block the Transition from Precursor Phases to Multiple Myeloma. *Clin Cancer Res* 2021;27(1):15–23.
- [16] Kini Bailur J, Mehta S, Zhang L, et al. Changes in bone marrow innate lymphoid cell subsets in monoclonal gammopathy: target for IMiD therapy. *Blood Adv* 2017;1(25):2343–7.
- [17] Bailur JK, McCachren SS, Doxie DB, et al. Early alterations in stem-like/resident T cells, innate and myeloid cells in the bone marrow in preneoplastic gammopathy. *JCI Insight* 2019;5(11):e127807.
- [18] Boiarsky R, Haradhvala NJ, Alberge JB, et al. Single cell characterization of myeloma and its precursor conditions reveals transcriptional signatures of early tumorigenesis. *Nat Commun* 2022;13(1):7040.
- [19] Zavidij O, Haradhvala NJ, Mouhieddine TH, et al. Single-cell RNA sequencing reveals compromised immune microenvironment in precursor stages of multiple myeloma. *Nature Cancer* 2020;1(5):493–506.
- [20] De Jong MME, Kellermayer Z, Papazian N, et al. The multiple myeloma microenvironment is defined by an inflammatory stromal cell landscape. *Nat Immunol* 2021;22(6):769–80.
- [21] Dhodapkar MV, Sexton R, Das R, et al. Prospective analysis of antigen-specific immunity, stem-cell antigens, and immune checkpoints in monoclonal gammopathy. *Blood* 2015;126(22):2475–8.
- [22] Guillerey C, Ferrari de Andrade L, Vuckovic S, et al. Immunosurveillance and therapy of multiple myeloma are CD226 dependent. *J Clin Invest* 2015;125(7):2904.
- [23] Guillerey C, Ferrari de Andrade L, Vuckovic S, et al. Immunosurveillance and therapy of multiple myeloma are CD226 dependent. *J Clin Invest* 2015;125(5): 2077–89.
- [24] Nakamura K, Kassem S, Cleynen A, et al. Dysregulated IL-18 Is a Key Driver of Immunosuppression and a Possible Therapeutic Target in the Multiple Myeloma Microenvironment. *Cancer Cell* 2018;33(4):634–648 e5.
- [25] Larrayoz M, Garcia-Barchino MJ, Celay J, et al. Preclinical models for prediction of immunotherapy outcomes and immune evasion mechanisms in genetically heterogeneous multiple myeloma. *Nat Med* 2023;29(3):632–45.
- [26] Das R, Strowig T, Verma R, et al. Microenvironment-dependent growth of preneoplastic and malignant plasma cells in humanized mice. *Nat Med* 2016;22(11): 1351–7.
- [27] Khoo WH, Ledergor G, Weiner A, et al. A niche-dependent myeloid transcriptome signature defines dormant myeloma cells. *Blood* 2019;134(1):30–43.
- [28] Mateos MV, Hernandez MT, Giraldo P, et al. Lenalidomide plus dexamethasone versus observation in patients with high-risk smouldering multiple myeloma (QuiRedex): long-term follow-up a randomised, controlled, phase 3 trial. *Lancet Oncol* 2016;17(8):1127–36.
- [29] Lonial S, Jacobus S, Fonseca R, et al. Randomized Trial of Lenalidomide Versus Observation in Smoldering Multiple Myeloma. *J Clin Oncol* 2020;38(11):1126–37.
- [30] Sklavenitis-Pistofidis R, Aranha MP, Redd RA, et al. Immune biomarkers of response

- to immunotherapy in patients with high-risk smoldering myeloma. *Cancer Cell* 2022;40(11):1358–13573 e8.
- [31] Paiva B, Mateos MV, Sanchez-Abarca LI, et al. Immune status of high-risk smoldering multiple myeloma patients and its therapeutic modulation under LenDex: a longitudinal analysis. *Blood* 2016;127(9):1151–62.
- [32] Sehgal K, Das R, Zhang L, et al. Clinical and pharmacodynamic analysis of pomalidomide dosing strategies in myeloma: impact of immune activation and cereblon targets. *Blood* 2015;125(26):4042–51.
- [33] Dhodapkar MV, Dhodapkar KM. Moving Immunoprevention Beyond Virally Mediated Malignancies: Do We Need to Link It to Early Detection? *Front Immunol* 2019;10:2385.
- [34] Robinson M, Villa NY, Jaye D, et al. Regulation of antigen-specific T-cell infiltration and spatial architecture in myeloma and premalignancy. *J Clin Invest* 2023; 133(15):e167629.
- [35] McShane CM, Murray LJ, Landgren O, et al. Prior autoimmune disease and risk of monoclonal gammopathy of undetermined significance and multiple myeloma: a systematic review. *Cancer Epidemiol Biomarkers Prev* 2014;23(2):332–42.
- [36] Rustad EH, Yellapantula V, Leongamornlert D, et al. Timing the initiation of multiple myeloma. *Nat Commun* 2020;11(1):1917.
- [37] Maura F, Rustad EH, Yellapantula V, et al. Role of AID in the temporal pattern of acquisition of driver mutations in multiple myeloma. *Leukemia* 2020;34(5): 1476–80.
- [38] Koduru S, Wong E, Strowig T, et al. Dendritic cell-mediated activation-induced cytidine deaminase (AID)-dependent induction of genomic instability in human myeloma. *Blood* 2012;119(10):2302–9.
- [39] Weinreb NJ, Mistry PK, Rosenbloom BE, et al. MGUS, lymphoplasmacytic malignancies, and Gaucher disease: the significance of the clinical association. *Blood* 2018;131(22):2500–1.
- [40] Nair S, Branagan AR, Liu J, et al. Clonal Immunoglobulin against Lysolipids in the Origin of Myeloma. *N Engl J Med* 2016;374(6):555–61.
- [41] Nair S, Sng J, Boddupalli CS, et al. Antigen-mediated regulation in monoclonal gammopathies and myeloma. *JCI Insight* 2018;3(8):e98259.
- [42] Claflin JL, Rudikoff S, Potter M, et al. Structural, functional, and idiotypic characteristics of a phosphorylcholine-binding IgA myeloma protein of C57BL/ka allo-type. *J Exp Med* 1975;141(3):608–19.
- [43] Chesi M, Robbiani DF, Sebag M, et al. AID-dependent activation of a MYC transgene induces multiple myeloma in a conditional mouse model of post-germinal center malignancies. *Cancer Cell* 2008;13(2):167–80.
- [44] Kumar S, Larson DR, Dispenzieri A, et al. Polyclonal serum free light chain elevation is associated with increased risk of monoclonal gammopathies. *Blood Cancer J* 2019;9(6):49.
- [45] Nair S, Bar N, Xu ML, et al. Glucosylsphingosine but not Saposin C, is the target antigen in Gaucher disease-associated gammopathy. *Mol Genet Metab* 2020; 129(4):286–91.
- [46] Pavlova EV, Archer J, S ZW, et al. Inhibition of UDP-glucosylceramide synthase in mice prevents Gaucher disease-associated B-cell malignancy. *J Pathol* 2015; 235(1):113–24.

- [47] Chen JW, Rice TA, Bannock JM, et al. Autoreactivity in naive human fetal B cells is associated with commensal bacteria recognition. *Science* 2020;369(6501): 320–5.
- [48] Myles A, Sanz I, Cancro MP. T-bet(+) B cells: A common denominator in protective and autoreactive antibody responses? *Curr Opin Immunol* 2019;57:40–5.
- [49] Azeem MI, Nooka AK, Shanmugasundaram U, et al. Impaired SARS-CoV-2 Variant Neutralization and CD8+ T-cell Responses Following 3 Doses of mRNA Vaccines in Myeloma: Correlation with Breakthrough Infections. *Blood Cancer Discov* 2023;4(2):106–17.
- [50] Calcinotto A, Brevi A, Chesi M, et al. Microbiota-driven interleukin-17-producing cells and eosinophils synergize to accelerate multiple myeloma progression. *Nat Commun* 2018;9(1):4832.
- [51] Dhodapkar MV, Sexton R, Hoering A, et al. Race-Dependent Differences in Risk, Genomics, and Epstein-Barr Virus Exposure in Monoclonal Gammopathies: Results of SWOG S0120. *Clin Cancer Res* 2020;26(22):5814–9.
- [52] Bosseboeuf A, Feron D, Tallet A, et al. Monoclonal IgG in MGUS and multiple myeloma targets infectious pathogens. *JCI Insight* 2017;2(19):e95367.
- [53] Kaushal A, Nooka AK, Carr AR, et al. Aberrant Extrafollicular B Cells, Immune Dysfunction, Myeloid Inflammation, and MyD88-Mutant Progenitors Precede Waldenstrom Macroglobulinemia. *Blood Cancer Discov* 2021;2(6):600–15.
- [54] Rodriguez S, Celay J, Goicoechea I, et al. Preneoplastic somatic mutations including MYD88(L265P) in lymphoplasmacytic lymphoma. *Sci Adv* 2022;8(3): eabl4644.
- [55] Nooka AK, Shanmugasundaram U, Cheedarla N, et al. Determinants of Neutralizing Antibody Response After SARS CoV-2 Vaccination in Patients With Myeloma. *J Clin Oncol* 2022;JCO2102257
- [56] Chung DJ, Pronschinske KB, Shyer JA, et al. T-cell Exhaustion in Multiple Myeloma Relapse after Autotransplant: Optimal Timing of Immunotherapy. *Cancer Immunol Res* 2016;4(1):61–71.
- [57] Joshua DE, Vuckovic S, Favaloro J, et al. Treg and Oligoclonal Expansion of Terminal Effector CD8(+) T Cell as Key Players in Multiple Myeloma. *Front Immunol* 2021;12:620596.
- [58] Dhodapkar KM, Barbuto S, Matthews P, et al. Dendritic cells mediate the induction of polyfunctional human IL17-producing cells (Th17-1 cells) enriched in the bone marrow of patients with myeloma. *Blood* 2008;112(7):2878–85.
- [59] Prabhala RH, Pelluru D, Fulciniti M, et al. Elevated IL-17 produced by TH17 cells promotes myeloma cell growth and inhibits immune function in multiple myeloma. *Blood* 2010;115(26):5385–92.
- [60] Perumal D, Imai N, Lagana A, et al. Mutation-derived Neoantigen-specific T-cell Responses in Multiple Myeloma. *Clin Cancer Res* 2020;26(2):450–64.
- [61] Bar N, Costa F, Das R, et al. Differential effects of PD-L1 versus PD-1 blockade on myeloid inflammation in human cancer. *JCI Insight* 2020;5(12):e129353.
- [62] Costa F, Das R, Kini Bailur J, et al. Checkpoint Inhibition in Myeloma: Opportunities and Challenges. *Front Immunol* 2018;9:2204.

- [63] Andrews LP, Yano H, Vignali DAA. Inhibitory receptors and ligands beyond PD-1, PD-L1 and CTLA-4: breakthroughs or backups. *Nat Immunol* 2019;20(11): 1425–34.
- [64] Guillerey C, Harjunpaa H, Carrie N, et al. TIGIT immune checkpoint blockade restores CD8(+) T cell immunity against multiple myeloma. *Blood* 2018;132(16): 1689–94.
- [65] Minnie SA, Kuns RD, Gartlan KH, et al. Myeloma escape after stem cell transplantation is a consequence of T cell exhaustion and is reversed by TIGIT inhibition. *Blood* 2018;132(16):1675–88.
- [66] Akhmetzyanova I, Aaron T, Galbo P, et al. Tissue-resident macrophages promote early dissemination of multiple myeloma via IL-6 and TNFalpha. *Blood Adv* 2021; 5(18):3592–608.
- [67] Hayashi T, Hideshima T, Nguyen AN, et al. Transforming growth factor beta receptor I kinase inhibitor down-regulates cytokine secretion and multiple myeloma cell growth in the bone marrow microenvironment. *Clin Cancer Res* 2004;10(22): 7540–6.
- [68] Wang S, Yang J, Qian J, et al. Tumor evasion of the immune system: inhibiting p38 MAPK signaling restores the function of dendritic cells in multiple myeloma. *Blood* 2006;107(6):2432–9.
- [69] Brimnes MK, Vangsted AJ, Knudsen LM, et al. Increased Level of both CD4+FOXP3+ Regulatory T Cells and CD14+HLA-DR-/low Myeloid-Derived Suppressor Cells and Decreased Level of Dendritic Cells in Patients with Multiple Myeloma 2010;72(6):540–7.
- [70] Guillerey C, Nakamura K, Vuckovic S, et al. Immune responses in multiple myeloma: role of the natural immune surveillance and potential of immunotherapies. *Cell Mol Life Sci* 2016;73(8):1569–89.
- [71] Alrasheed N, Lee L, Ghorani E, et al. Marrow-Infiltrating Regulatory T Cells Correlate with the Presence of Dysfunctional CD4(+)PD-1(+) Cells and Inferior Survival in Patients with Newly Diagnosed Multiple Myeloma. *Clin Cancer Res* 2020; 26(13):3443–54.
- [72] Prabhala RH, Neri P, Bae JE, et al. Dysfunctional T regulatory cells in multiple myeloma. *Blood* 2006;107(1):301–4.
- [73] Tai YT, Lin L, Xing L, et al. APRIL signaling via TACI mediates immunosuppression by T regulatory cells in multiple myeloma: therapeutic implications. *Leukemia* 2019;33(2):426–38.
- [74] Tai YT, Cho SF, Anderson KC. Osteoclast Immunosuppressive Effects in Multiple Myeloma: Role of Programmed Cell Death Ligand 1. *Front Immunol* 2018;9:1822.
- [75] Wu X, Wang Y, Xu J, et al. MM-BMSCs induce naive CD4+ T lymphocytes dysfunction through fibroblast activation protein alpha. *Oncotarget* 2017;8(32): 52614–28.
- [76] Ramachandran IR, Martner A, Pisklakova A, et al. Myeloid-Derived Suppressor Cells Regulate Growth of Multiple Myeloma by Inhibiting T Cells in Bone Marrow 2013;190(7):3815–23.
- [77] Gorgun GT, Whitehill G, Anderson JL, et al. Tumor-promoting immune-suppressive myeloid-derived suppressor cells in the multiple myeloma microenvironment in humans. *Blood* 2013;121(15):2975–87.
- [78] Serafini P, Meckel K, Kelso M, et al.

- Phosphodiesterase-5 inhibition augments endogenous antitumor immunity by reducing myeloid-derived suppressor cell function. *J Exp Med* 2006;203(12):2691–702.
- [79] Asimakopoulos F, Hope C, Johnson MG, et al. Extracellular matrix and the myeloid-in-myeloma compartment: balancing tolerogenic and immunogenic inflammation in the myeloma niche. *J Leukoc Biol* 2017;102(2):265–75.
- [80] Hope C, Foulcer S, Jagodinsky J, et al. Immunoregulatory roles of versican proteolysis in the myeloma microenvironment. *Blood* 2016;128(5):680–5.
- [81] Jinushi M, Vanneman M, Munshi NC, et al. MHC class I chain-related protein A antibodies and shedding are associated with the progression of multiple myeloma. *Proc Natl Acad Sci* 2008;105(4):1285–90.
- [82] Neparidze N, Dhodapkar MV. Harnessing CD1d-restricted T cells toward anti-tumor immunity in humans. *Ann N Y Acad Sci* 2009;1174:61–7.
- [83] Dhodapkar MV, Krasovsky J, Olson K. T cells from the tumor microenvironment of patients with progressive myeloma can generate strong tumor specific cytolytic responses to autologous tumor loaded dendritic cells. *Proc Natl Acad Sci USA* 2002;99:13009–13.
- [84] Dhodapkar MV, Geller MD, Chang DH, et al. A reversible defect in natural killer T cell function characterizes the progression of premalignant to malignant multiple myeloma. *J Exp Med* 2003;197(12):1667–76.
- [85] Noonan K, Matsui W, Serafini P, et al. Activated marrow-infiltrating lymphocytes effectively target plasma cells and their clonogenic precursors. *Cancer Res* 2005;65(5):2026–34.
- [86] Lancman G, Sastow DL, Cho HJ, et al. Bispecific Antibodies in Multiple Myeloma: Present and Future. *Blood Cancer Discov* 2021;2(5):423–33.
- [87] Kukreja A, Hutchinson A, Dhodapkar KM, et al. Enhancement of clonogenicity of human multiple myeloma by dendritic cells. *J Exp Med* 2006;203(8):1859–65.
- [88] Chauhan D, Singh AV, Brahmandam M, et al. Functional interaction of plasmacytoid dendritic cells with multiple myeloma cells: a therapeutic target. *Cancer Cell* 2009;16(4):309–23.
- [89] Dhodapkar KM, Cohen AD, Kaushal A, et al. Changes in Bone Marrow Tumor and Immune Cells Correlate with Durability of Remissions Following BCMA CAR T Therapy in Myeloma. *Blood Cancer Discov* 2022;3(6):490–501.
- [90] Kukreja A, Radfar S, Sun BH, et al. Dominant role of CD47-thrombospondin-1 interactions in myeloma-induced fusion of human dendritic cells: implications for bone disease. *Blood* 2009;114(16):3413–21.

3 冒烟型多发性骨髓瘤：观察、控制与根治

- [1] Rajkumar SV. Multiple myeloma: 2020 update on diagnosis, risk-stratification and management. *Am J Hematol* 2020;95:548–67.
- [2] Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol* 2014;15:e538–48.
- [3] Kyle RA, Therneau TM, Rajkumar SV, et al. Prevalence of monoclonal gammopathy of undetermined significance. *N Engl J Med* 2006;354:1362–9.
- [4] Dispenzieri A, Katzmann JA, Kyle RA, et al. Prevalence and risk of progression of light-chain monoclonal gammopathy of undetermined significance: a retrospective population-based cohort study. *Lancet* 2010;375:1721–8.
- [5] Murray D, Kumar SK, Kyle RA, et al. Detection and prevalence of monoclonal gammopathy of undetermined significance: a study utilizing mass spectrometry-based monoclonal immunoglobulin rapid accurate mass measurement. *Blood Cancer J* 2019;9:102.
- [6] Kyle RA, Therneau TM, Rajkumar SV, et al. A long-term study of prognosis of monoclonal gammopathy of undetermined significance. *N Engl J Med* 2002; 346:564–9.
- [7] Kyle RA, Larson DR, Therneau TM, et al. Long-term follow-up of monoclonal gammopathy of undetermined significance. *N Engl J Med* 2018;378:241–9.
- [8] Thorsteinsdottir S, Gislason GK, Aspelund T, et al. Prevalence of smoldering multiple myeloma: results from the Iceland screens, treats, or prevents multiple myeloma (iStopMM) study. *Blood* 2021;138:151.
- [9] Kyle RA, Remstein ED, Therneau TM, et al. Clinical course and prognosis of smoldering (asymptomatic) multiple myeloma. *N Engl J Med* 2007;356:2582–90.
- [10] Mateos MV, Kumar S, Dimopoulos MA, et al. International Myeloma Working Group risk stratification model for smoldering multiple myeloma (SMM). *Blood Cancer J* 2020;10:102.
- [11] Chaudhry HM, Mauermann ML, Rajkumar SV. Monoclonal gammopathy-associated peripheral neuropathy: diagnosis and management. *Mayo Clin Proc* 2017;92:838–50.
- [12] Sethi S, Rajkumar SV. Monoclonal gammopathy-associated proliferative glomerulonephritis. *Mayo Clin Proc* 2013;88:1284–93.
- [13] Kyle RA, Durie BGM, Rajkumar SV, et al, International Myeloma Working Group. Monoclonal gammopathy of undetermined significance (MGUS) and smoldering (asymptomatic) multiple myeloma: IMWG consensus perspectives risk factors for progression and guidelines for monitoring and management. *Leukemia* 2010;24: 1121–7.
- [14] Hillengass J, Usmani S, Rajkumar SV, et al. International Myeloma Working Group consensus recommendations on imaging in

- monoclonal plasma cell disorders. *Lancet Oncol* 2019;20:e302–12.
- [15] Perez-Persona E, Vidriales MB, Mateo G, et al. New criteria to identify risk of progression in monoclonal gammopathy of uncertain significance and smoldering multiple myeloma based on multiparameter flow cytometry analysis of bone marrow plasma cells. *Blood* 2007;110:2586–92.
- [16] Dispenzieri A, Kyle RA, Katzmann JA, et al. Immunoglobulin free light chain ratio is an independent risk factor for progression of smoldering (asymptomatic) multiple myeloma. *Blood* 2008;111:785–9.
- [17] Rosinol L, Blade J, Esteve J, et al. Smoldering multiple myeloma: natural history and recognition of an evolving type. *Br J Haematol* 2003;123:631–6.
- [18] Rajkumar SV, Gupta V, Fonseca R, et al. Impact of primary molecular cytogenetic abnormalities and risk of progression in smoldering multiple myeloma. *Leukemia* 2013;27:1738–44.
- [19] Neben K, Jauch A, Hielscher T, et al. Progression in smoldering myeloma is independently determined by the chromosomal abnormalities del(17p), t(4;14), gain 1q, hyperdiploidy, and tumor load. *J Clin Oncol* 2013;31:4325–32.
- [20] Dhodapkar MV, Sexton R, Waheed S, et al. Clinical, genomic, and imaging predictors of myeloma progression from asymptomatic monoclonal gammopathies (SWOG S0120). *Blood* 2014;123:78–85.
- [21] Bianchi G, Kyle RA, Larson DR, et al. High levels of peripheral blood circulating plasma cells as a specific risk factor for progression of smoldering multiple myeloma. *Leukemia* 2013;27:680–5.
- [22] Hillengass J, Fechtner K, Weber MA, et al. Prognostic significance of focal lesions in whole-body magnetic resonance imaging in patients with asymptomatic multiple myeloma. *J Clin Oncol* 2010;28:1606–10.
- [23] Merz M, Hielscher T, Wagner B, et al. Predictive value of longitudinal whole-body magnetic resonance imaging in patients with smoldering multiple myeloma. *Leukemia* 2014;28:1902–8.
- [24] Zamagni E, Nanni C, Gay F, et al. 18F-FDG PET/CT focal, but not osteolytic, lesions predict the progression of smoldering myeloma to active disease. *Leukemia* 2016;30:417–22.
- [25] Mateos M-V, Herná'ndez M-T, Giraldo P, et al. Lenalidomide plus Dexamethasone for High-Risk Smoldering Multiple Myeloma. *N Engl J Med* 2013;369:438–47.
- [26] Lakshman A, Paul S, Rajkumar SV, et al. Prognostic significance of interphase FISH in monoclonal gammopathy of undetermined significance. *Leukemia* 2018;32(8):1811–5.
- [27] Lakshman A, Rajkumar SV, Buadi FK, et al. Risk stratification of smoldering multiple myeloma incorporating revised IMWG diagnostic criteria. *Blood Cancer J* 2018;8:59.
- [28] Fernandez de Larrea C, Isola I, Pereira A, et al. Evolving M-protein pattern in patients with smoldering multiple myeloma: impact on early progression. *Leukemia* 2018;32:1427–34.
- [29] Ravi P, Kumar S, Larsen JT, et al. Evolving changes in disease biomarkers and risk of early progression in smoldering multiple myeloma. *Blood Cancer J* 2016;6:e454.
- [30] Rajkumar SV, Landgren O, Mateos MV. Smoldering multiple myeloma. *Blood*

- 2015;125:3069–75.
- [31] Mateos MV, Hernandez MT, Giraldo P, et al. Lenalidomide plus dexamethasone versus observation in patients with high-risk smouldering multiple myeloma (QuiRedex): long-term follow-up of a randomised, controlled, phase 3 trial. *Lancet Oncol* 2016;17:1127–36.
- [32] Lonial S, Jacobus S, Fonseca R, et al. Randomized Trial of Lenalidomide Versus Observation in Smoldering Multiple Myeloma. *J Clin Oncol* 2020;38:1126–37.
- [33] Lonial S, Jacobus SJ, Weiss M, et al. E3A06: Randomized phase III trial of lenalidomide versus observation alone in patients with asymptomatic high-risk smoldering multiple myeloma. *J Clin Oncol* 2019;37.
- [34] Tsuda K, Tanimoto T, Komatsu T. Treatment for high-risk smoldering myeloma. *N Engl J Med* 2013;369:1763.
- [35] Mateos MV, San Miguel JF. Treatment for high-risk smoldering myeloma. *N Engl J Med* 2013;369:1764–5.
- [36] D’Arena G, Gobbi PG, Broglia C, et al, Gimema Gruppo Italiano Malattie Ematologiche Dell’Adulto, Multiple Myeloma Working Party, Gisl Gruppo Italiano Studio Linfomi Cooperative Group. Pamidronate versus observation in asymptomatic myeloma: final results with long-term follow-up of a randomized study. *Leuk Lymphoma* 2011;52:771–5.
- [37] Musto P, Petrucci MT, Bringhen S, et al, GIMEMA Italian Group for Adult Hematologic Diseases/Multiple Myeloma Working Party and the Italian Myeloma Network. A multicenter, randomized clinical trial comparing zoledronic acid versus observation in patients with asymptomatic myeloma. *Cancer* 2008;113: 1588–95.
- [38] Mateos M-V, Martinez Lopez J, Rodriguez-Otero P, et al. Curative strategy for high-risk smoldering myeloma (GEM-CESAR): carfilzomib, lenalidomide and dexamethasone (KRd) as induction followed by HDT-ASCT, consolidation with KRd and maintenance with Rd. *Blood* 2017;130:402.

4 靶向 cereblon 连接酶降解剂治疗骨髓瘤：作用及耐药机制

- [1] Ito T, Ando H, Suzuki T, et al. Identification of a primary target of thalidomide teratogenicity. *Science* (New York, NY) 2010;327(5971):1345–50.
- [2] Chamberlain PP, Lopez-Girona A, Miller K, et al. Structure of the human Cereblon-DDB1-lenalidomide complex reveals basis for responsiveness to thalidomide analogs. *Nat Struct Mol Biol* 2014;21(9):803–9.
- [3] Lu G, Middleton RE, Sun H, et al. The myeloma drug lenalidomide promotes the cereblon-dependent destruction of Ikaros proteins. *Science* (New York, NY) 2014;343(6168):305–9.
- [4] Krönke J, Udeshi ND, Narla A, et al. Lenalidomide causes selective degradation of IKZF1 and IKZF3 in multiple myeloma cells. *Science* (New York, NY) 2014; 343(6168):301–5.
- [5] Georgopoulos K, Bigby M, Wang JH, et al. The Ikaros gene is required for the development of all lymphoid lineages. *Cell* 1994;79(1):143–56.
- [6] Cortes M, Wong E, Koipally J, et al. Control of lymphocyte development by the Ikaros gene family. *Curr Opin Immunol* 1999;11(2):167–71.
- [7] Zhu YX, Braggio E, Shi CX, et al. Cereblon expression is required for the antimyeloma activity of lenalidomide and pomalidomide. *Blood* 2011;118(18):4771–9.
- [8] Nückel H, Frey UH, Sellmann L, et al. The IKZF3 (Aiolos) transcription factor is highly upregulated and inversely correlated with clinical progression in chronic lymphocytic leukaemia. *Br J Haematol* 2009;144(2):268–70.
- [9] Morgan B, Sun L, Avitahl N, et al. Aiolos, a lymphoid restricted transcription factor that interacts with Ikaros to regulate lymphocyte differentiation. *Embo j* 1997; 16(8):2004–13.
- [10] Corte's M, Georgopoulos K. Aiolos is required for the generation of high affinity bone marrow plasma cells responsible for long-term immunity. *J Exp Med* 2004;199(2): 209–19.
- [11] Matyskiela ME, Zhang W, Man HW, et al. A Cereblon Modulator (CC-220) with Improved Degradation of Ikaros and Aiolos. *J Med Chem* 2018;61(2):535–42.
- [12] Hansen JD, Correa M, Nagy MA, et al. Discovery of CRBN E3 Ligase Modulator CC-92480 for the Treatment of Relapsed and Refractory Multiple Myeloma. *J Med Chem* 2020;63(13):6648–76.
- [13] Bjorklund CC, Kang J, Amatangelo M, et al. Iberdomide (CC-220) is a potent cereblon E3 ligase modulator with antitumor and immunostimulatory activities in lenalidomide- and pomalidomide-resistant multiple myeloma cells with dysregulated CRBN. *Leukemia* 2020;34(4):1197–201.
- [14] Watson ER, Novick S, Matyskiela ME, et al. Molecular glue CELMoD compounds are

- regulators of cereblon conformation. *Science* (New York, NY) 2022;378(6619):549–53.
- [15] Ichikawa S, Flaxman HA, Xu W, et al. The E3 ligase adapter cereblon targets the C-terminal cyclic imide degron. *Nature* 2022;610(7933):775–82.
- [16] Sievers QL, Petzold G, Bunker RD, et al. Defining the human C2H2 zinc finger degrome targeted by thalidomide analogs through CRBN. *Science* (New York, NY) 2018;362(6414).
- [17] An J, Ponthier CM, Sack R, et al. pSILAC mass spectrometry reveals ZFP91 as IMiD-dependent substrate of the CRL4(CRBN) ubiquitin ligase. *Nat Commun* 2017;8:15398.
- [18] Donovan KA, An J, Nowak RP, et al. Thalidomide promotes degradation of SALL4, a transcription factor implicated in Duane Radial Ray syndrome. *Elife* 2018;7:e38430.
- [19] Bird S, Pawlyn C. IMiD resistance in multiple myeloma: current understanding of the underpinning biology and clinical impact. *Blood* 2023;142(2):131–40.
- [20] Krönke J, Fink EC, Hollenbach PW, et al. Lenalidomide induces ubiquitination and degradation of CK1 α in del(5q) MDS. *Nature* 2015;523(7559):183–8.
- [21] Petzold G, Fischer ES, Thomä NH. Structural basis of lenalidomide-induced CK1 α degradation by the CRL4(CRBN) ubiquitin ligase. *Nature* 2016; 532(7597):127–30.
- [22] Matyskiela ME, Lu G, Ito T, et al. A novel cereblon modulator recruits GSPT1 to the CRL4(CRBN) ubiquitin ligase. *Nature* 2016;535(7611):252–7.
- [23] Lopez-Girona A, Mendy D, Ito T, et al. Cereblon is a direct protein target for immunomodulatory and antiproliferative activities of lenalidomide and pomalidomide. *Leukemia* 2012;26(11):2326–35.
- [24] Eichner R, Heider M, Ferná'ndez-Sa'iz V, et al. Immunomodulatory drugs disrupt the cereblon-CD147-MCT1 axis to exert antitumor activity and teratogenicity. *Nat Med* 2016;22(7):735–43.
- [25] Zhu YX, Shi C-X, Bruins LA, et al. Identification of lenalidomide resistance pathways in myeloma and targeted resensitization using cereblon replacement, inhibition of STAT3 or targeting of IRF4. *Blood Cancer J* 2019;9(2):19.
- [26] Sebastian S, Zhu YX, Braggio E, et al. Multiple myeloma cells' capacity to decompose H₂O₂ determines lenalidomide sensitivity. *Blood* 2017;129(8):991–1007.
- [27] LeBlanc R, Hideshima T, Catley LP, et al. Immunomodulatory drug costimulates T cells via the B7-CD28 pathway. *Blood* 2004;103(5):1787–90.
- [28] Haslett PA, Corral LG, Albert M, et al. Thalidomide costimulates primary human T lymphocytes, preferentially inducing proliferation, cytokine production, and cytotoxic responses in the CD8 α subset. *J Exp Med* 1998;187(11):1885–92.
- [29] Schafer PH, Gandhi AK, Loveland MA, et al. Enhancement of cytokine production and AP-1 transcriptional activity in T cells by thalidomide-related immunomodulatory drugs. *J Pharmacol Exp Therapeut* 2003;305(3):1222–32.
- [30] Payvandi F, Wu L, Naziruddin SD, et al. Immunomodulatory drugs (IMiDs) increase the production of IL-2 from stimulated T cells by increasing PKC- θ activation and enhancing the DNA-binding activity of

- AP-1 but not NF-kappaB, OCT-1, or NF-AT. *J Interferon Cytokine Res* 2005;25(10):604–16.
- [31] Thompson EC, Cobb BS, Sabbattini P, et al. Ikaros DNA-binding proteins as integral components of B cell developmental-stage-specific regulatory circuits. *Immunity* 2007;26(3):335–44.
- [32] Avitahl N, Winandy S, Friedrich C, et al. Ikaros sets thresholds for T cell activation and regulates chromosome propagation. *Immunity* 1999;10(3):333–43.
- [33] Quintana FJ, Jin H, Burns EJ, et al. Aiolos promotes TH17 differentiation by directly silencing Il2 expression. *Nat Immunol* 2012;13(8):770–7.
- [34] Gandhi AK, Kang J, Havens CG, et al. Immunomodulatory agents lenalidomide and pomalidomide co-stimulate T cells by inducing degradation of T cell repressors Ikaros and Aiolos via modulation of the E3 ubiquitin ligase complex CRL4(CRBN). *Br J Haematol* 2014;164(6):811–21.
- [35] Quach H, Ritchie D, Stewart AK, et al. Mechanism of action of immunomodulatory drugs (IMiDs) in multiple myeloma. *Leukemia* 2010;24(1):22–32.
- [36] Davies FE, Raje N, Hideshima T, et al. Thalidomide and immunomodulatory derivatives augment natural killer cell cytotoxicity in multiple myeloma. *Blood* 2001; 98(1):210–6.
- [37] Hayashi T, Hideshima T, Akiyama M, et al. Molecular mechanisms whereby immunomodulatory drugs activate natural killer cells: clinical application. *Br J Haematol* 2005;128(2):192–203.
- [38] Chang DH, Liu N, Klimek V, et al. Enhancement of ligand-dependent activation of human natural killer T cells by lenalidomide: therapeutic implications. *Blood* 2006; 108(2):618–21.
- [39] Zhu D, Corral LG, Fleming YW, et al. Immunomodulatory drugs Revlimid (lenalidomide) and CC-4047 induce apoptosis of both hematological and solid tumor cells through NK cell activation. *Cancer immunology, immunotherapy CII* 2008;57(12):1849–59.
- [40] Roda JM, Parihar R, Magro C, et al. Natural killer cells produce T cell-recruiting chemokines in response to antibody-coated tumor cells. *Cancer Res* 2006; 66(1):517–26.
- [41] Galustian C, Meyer B, Labarthe MC, et al. The anti-cancer agents lenalidomide and pomalidomide inhibit the proliferation and function of T regulatory cells. *Cancer immunology, immunotherapy CII* 2009;58(7):1033–45.
- [42] Dredge K, Marriott JB, Macdonald CD, et al. Novel thalidomide analogues display anti-angiogenic activity independently of immunomodulatory effects. *Br J Cancer* 2002;87(10):1166–72.
- [43] Dredge K, Horsfall R, Robinson SP, et al. Orally administered lenalidomide (CC-5013) is anti-angiogenic in vivo and inhibits endothelial cell migration and Akt phosphorylation in vitro. *Microvasc Res* 2005;69(1–2):56–63.
- [44] Gupta D, Treon SP, Shima Y, et al. Adherence of multiple myeloma cells to bone marrow stromal cells upregulates vascular endothelial growth factor secretion: therapeutic applications. *Leukemia* 2001;15(12):1950–61.
- [45] D’Amato RJ, Loughnan MS, Flynn E, et al. Thalidomide is an inhibitor of angiogenesis.

- Proc Natl Acad Sci USA 1994;91(9):4082–5.
- [46] Geitz H, Handt S, Zwingenberger K. Thalidomide selectively modulates the density of cell surface molecules involved in the adhesion cascade. *Immunopharmacology* 1996;31(2–3):213–21.
- [47] Breitkreutz I, Raab MS, Vallet S, et al. Lenalidomide inhibits osteoclastogenesis, survival factors and bone-remodeling markers in multiple myeloma. *Leukemia* 2008;22(10):1925–32.
- [48] Bolzoni M, Storti P, Bonomini S, et al. Immunomodulatory drugs lenalidomide and pomalidomide inhibit multiple myeloma-induced osteoclast formation and the RANKL/OPG ratio in the myeloma microenvironment targeting the expression of adhesion molecules. *Exp Hematol* 2013;41(4):387–97.e381.
- [49] Gooding S, Ansari-Pour N, Towfic F, et al. Multiple cereblon genetic changes are associated with acquired resistance to lenalidomide or pomalidomide in multiple myeloma. *Blood* 2021;137(2):232–7.
- [50] Kortüm KM, Mai EK, Hanafiah NH, et al. Targeted sequencing of refractory myeloma reveals a high incidence of mutations in CRBN and Ras pathway genes. *Blood* 2016;128(9):1226–33.
- [51] Neri P, Maity R, Keats JJ, et al. Cereblon Splicing of Exon 10 Mediates IMiDs Resistance in Multiple Myeloma: Clinical Validation in the CoMMpass Trial. *Blood* 2016;128(22):120.
- [52] Gupta VA, Barwick BG, Matulis SM, et al. Venetoclax sensitivity in multiple myeloma is associated with B-cell gene expression. *Blood* 2021;137(26):3604–15.
- [53] Karagoz K, Stokes M, Ortiz-Estevez M, et al. Multiple Myeloma Patient Tumors With High Levels of Cereblon Exon-10 Deletion Splice Variant Upregulate Clinically Targetable Pro-Inflammatory Cytokine Pathways. *Front Genet* 2022;13:831779.
- [54] Haertle L, Barrio S, Munawar U, et al. Cereblon enhancer methylation and IMiD resistance in multiple myeloma. *Blood* 2021;138(18):1721–6.
- [55] Zhou N, Gutierrez-Uzquiza A, Zheng XY, et al. RUNX proteins desensitize multiple myeloma to lenalidomide via protecting IKZFs from degradation. *Leukemia* 2019;33(8):2006–21.
- [56] Sperling AS, Burgess M, Keshishian H, et al. Patterns of substrate affinity, competition, and degradation kinetics underlie biological activity of thalidomide analogs. *Blood* 2019;134(2):160–70.
- [57] Barwick BG, Neri P, Bahlis NJ, et al. Multiple myeloma immunoglobulin lambda translocations portend poor prognosis. *Nat Commun* 2019;10(1):1911.
- [58] Neri P, Barwick BG, Jung D, et al. ETV4-Dependent Transcriptional Plasticity Maintains MYC Expression and Results in IMiD Resistance in Multiple Myeloma. *Blood Cancer Discov* 2024;5(1):56–73.
- [59] Welsh SJ, Barwick BG, Meermeier EW, et al. Transcriptional Heterogeneity Overcomes Super-Enhancer Disrupting Drug Combinations in Multiple Myeloma. *Blood Cancer Discov* 2024;5(1):34–55.
- [60] Nicosia L, Spencer GJ, Brooks N, et al. Therapeutic targeting of EP300/CBP by bromodomain inhibition in hematologic malignancies. *Cancer Cell* 2023;41(12):2136–53.e2113.

- [61] Sievers QL, Gasser JA, Cowley GS, et al. Genome-wide screen identifies cullin-RING ligase machinery required for lenalidomide-dependent CRL4CRBN activity. *Blood* 2018;132(12):1293–303.
- [62] Liu J, Song T, Zhou W, et al. A genome-scale CRISPR-Cas9 screening in myeloma cells identifies regulators of immunomodulatory drug sensitivity. *Leukemia* 2019;33(1):171–80.
- [63] Tateno S, Iida M, Fujii S, et al. Genome-wide screening reveals a role for subcellular localization of CRBN in the anti-myeloma activity of pomalidomide. *Sci Rep* 2020;10(1):4012.
- [64] Costacurta M, Vervoort SJ, Hogg SJ, et al. Whole genome CRISPR screening identifies TOP2B as a potential target for IMiD sensitization in multiple myeloma. *Haematologica* 2021;106(7):2013–7.
- [65] Cavadini S, Fischer ES, Bunker RD, et al. Cullin-RING ubiquitin E3 ligase regulation by the COP9 signalosome. *Nature* 2016;531(7596):598–603.
- [66] Lu G, Weng S, Matyskiela M, et al. UBE2G1 governs the destruction of cereblon neomorphic substrates. *Elife* 2018;7.
- [67] Gooding S, Ansari-Pour N, Kazeroun M, et al. Loss of COP9 signalosome gene at 2q37 is associated with IMiD resistance in multiple myeloma. *Blood* 2022;140(16):1816–21.
- [68] Liu J, Hideshima T, Xing L, et al. ERK signaling mediates resistance to immunomodulatory drugs in the bone marrow microenvironment. *Sci Adv* 2021;7(23).
- [69] Ocio EM, Fernández-La'zaro D, San-Segundo L, et al. In vivo murine model of acquired resistance in myeloma reveals differential mechanisms for lenalidomide Lee et al 318 and pomalidomide in combination with dexamethasone. *Leukemia* 2015;29(3):705–14.
- [70] Dimopoulos K, Søgaard Helbo A, Fibiger Munch-Petersen H, et al. Dual inhibition of DNMTs and EZH2 can overcome both intrinsic and acquired resistance of myeloma cells to IMiDs in a cereblon-independent manner. *Mol Oncol* 2018;12(2):180–95.

5 蛋白酶体抑制剂治疗多发性骨髓瘤：基于功能基因组学作用或耐药机制的生物学见解

- [1] Singhal S, Mehta J, Desikan R, et al. Antitumor activity of thalidomide in refractory multiple myeloma. *N Engl J Med* 1999;341:1565–71.
- [2] Orlowski RZ, Stinchcombe TE, Mitchell BS, et al. Phase I trial of the proteasome inhibitor PS-341 in patients with refractory hematologic malignancies. *J Clin Oncol* 2002;20:4420–7.
- [3] Richardson PG, Barlogie B, Berenson J, et al. A phase 2 study of bortezomib in relapsed, refractory myeloma. *N Engl J Med* 2003;348:2609–17.
- [4] Richardson PG, Sonneveld P, Schuster MW, et al. Assessment of Proteasome Inhibition for Extending Remissions I. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. *N Engl J Med* 2005;352:2487–98.
- [5] Hideshima T, Richardson P, Chauhan D, et al. The proteasome inhibitor PS-341 inhibits growth, induces apoptosis, and overcomes drug resistance in human multiple myeloma cells. *Cancer Res* 2001;61:3071–6.
- [6] Adams J. Proteasome inhibition: a novel approach to cancer therapy. *Trends Mol Med* 2002;8:S49–54.
- [7] Adams J. Development of the proteasome inhibitor PS-341. *Oncol* 2002;7:9–16.
- [8] Adams J, Kauffman M. Development of the proteasome inhibitor Velcade (Bortezomib). *Cancer Invest* 2004;22:304–11.
- [9] LeBlanc R, Catley LP, Hideshima T, et al. Proteasome inhibitor PS-341 inhibits human myeloma cell growth in vivo and prolongs survival in a murine model. *Cancer Res* 2002;62:4996–5000.
- [10] Mitsiades N, Mitsiades CS, Poulaki V, et al. Molecular sequelae of proteasome inhibition in human multiple myeloma cells. *Proc Natl Acad Sci U S A* 2002;99:14374–9.
- [11] Chesi M, Robbiani DF, Sebag M, et al. AID-dependent activation of a MYC transgene induces multiple myeloma in a conditional mouse model of post-germinal center malignancies. *Cancer Cell* 2008;13:167–80.
- [12] Chesi M, Matthews GM, Garbitt VM, et al. Drug response in a genetically engineered mouse model of multiple myeloma is predictive of clinical efficacy. *Blood* 2012;120:376–85.
- [13] Larrayoz M, Garcia-Barchino MJ, Celay J, et al. Preclinical models for prediction of immunotherapy outcomes and immune evasion mechanisms in genetically heterogeneous multiple myeloma. *Nat Med* 2023;29:632–45.
- [14] Mitsiades N, Mitsiades CS, Poulaki V, et al. Apoptotic signaling induced by immunomodulatory thalidomide analogs in human multiple myeloma cells: therapeutic implications. *Blood* 2002;99:4525–30.
- [15] Hideshima T, Chauhan D, Ishitsuka K, et al. Molecular characterization of PS-

- 341 (bortezomib) resistance: implications for overcoming resistance using lysophosphatidic acid acyltransferase (LPAAT)-beta inhibitors. *Oncogene* 2005;24:3121–9.
- [16] Sharma A, Nair R, Achreja A, et al. Therapeutic implications of mitochondrial stress-induced proteasome inhibitor resistance in multiple myeloma. *Sci Adv* 2022;8:eabq5575.
- [17] Gu Y, Barwick BG, Shanmugam M, et al. Downregulation of PA28alpha induces proteasome remodeling and results in resistance to proteasome inhibitors in multiple myeloma. *Blood Cancer J* 2020;10:125.
- [18] Catley L, Weisberg E, Tai YT, et al. NVP-LAQ824 is a potent novel histone deacetylase inhibitor with significant activity against multiple myeloma. *Blood* 2003;102:2615–22.
- [19] Chauhan D, Li G, Shringarpure R, et al. Blockade of Hsp27 overcomes Bortezomib/proteasome inhibitor PS-341 resistance in lymphoma cells. *Cancer Res* 2003;63:6174–7.
- [20] Hideshima T, Chauhan D, Hayashi T, et al. Proteasome inhibitor PS-341 abrogates IL-6 triggered signaling cascades via caspase-dependent downregulation of gp130 in multiple myeloma. *Oncogene* 2003;22:8386–93.
- [21] Mitsiades N, Mitsiades CS, Richardson PG, et al. The proteasome inhibitor PS-341 potentiates sensitivity of multiple myeloma cells to conventional chemotherapeutic agents: therapeutic applications. *Blood* 2003;101:2377–80.
- [22] Chauhan D, Li G, Podar K, et al. Targeting mitochondria to overcome conventional and bortezomib/proteasome inhibitor PS-341 resistance in multiple myeloma (MM) cells. *Blood* 2004;104:2458–66.
- [23] Chauhan D, Li G, Podar K, et al. The bortezomib/proteasome inhibitor PS-341 and triterpenoid CDDO-Im induce synergistic anti-multiple myeloma (MM) activity and overcome bortezomib resistance. *Blood* 2004;103:3158–66.
- [24] Catley L, Weisberg E, Kiziltepe T, et al. Aggresome induction by proteasome inhibitor bortezomib and alpha-tubulin hyperacetylation by tubulin deacetylase (TDAC) inhibitor LBH589 are synergistic in myeloma cells. *Blood* 2006;108:3441–9.
- [25] Garcia-Gomez A, Quwaider D, Canavese M, et al. Preclinical activity of the oral proteasome inhibitor MLN9708 in Myeloma bone disease. *Clin Cancer Res* 2014;20:1542–54.
- [26] Mulligan G, Lichter DI, Di Bacco A, et al. Mutation of NRAS but not KRAS significantly reduces myeloma sensitivity to single-agent bortezomib therapy. *Blood* 2014;123:632–9.
- [27] Mulligan G, Mitsiades C, Bryant B, et al. Gene expression profiling and correlation with outcome in clinical trials of the proteasome inhibitor bortezomib. *Blood* 2007;109:3177–88.
- [28] Chng WJ, Kumar S, Vanwier S, et al. Molecular dissection of hyperdiploid multiple myeloma by gene expression profiling. *Cancer Res* 2007;67:2982–9.
- [29] Jakubowiak A, Usmani SZ, Krishnan A, et al. Daratumumab Plus Carfilzomib, Lenalidomide, and Dexamethasone in Patients With Newly Diagnosed Multiple

- Myeloma. *Clin Lymphoma Myeloma Leuk* 2021;21:701–10.
- [30] Jakubowski AJ, Dytfeld D, Griffith KA, et al. A phase 1/2 study of carfilzomib in combination with lenalidomide and low-dose dexamethasone as a frontline treatment for multiple myeloma. *Blood* 2012;120:1801–9.
- [31] Jakubowski AJ, Jasielec JK, Rosenbaum CA, et al. Phase 1 study of selinexor plus carfilzomib and dexamethasone for the treatment of relapsed/refractory multiple myeloma. *Br J Haematol* 2019;186:549–60.
- [32] Jakubowski AJ, Siegel DS, Martin T, et al. Treatment outcomes in patients with relapsed and refractory multiple myeloma and high-risk cytogenetics receiving single-agent carfilzomib in the PX-171-003-A1 study. *Leukemia* 2013;27:2351–6.
- [33] Costa LJ, Davies FE, Monohan GP, et al. Phase 2 study of venetoclax plus carfilzomib and dexamethasone in patients with relapsed/refractory multiple myeloma. *Blood Adv* 2021;5:3748–59.
- [34] Derman BA, Zonder J, Reece D, et al. Phase 1/2 study of carfilzomib, pomalidomide, and dexamethasone with and without daratumumab in relapsed multiple myeloma. *Blood Adv* 2023;7:5703–12.
- [35] de Matos Simoes R, Shirasaki R, Downey-Kopyscinski SL, et al. Genome-scale functional genomics identify genes preferentially essential for multiple myeloma cells compared to other neoplasias. *Nat Cancer* 2023;4:754–73.
- [36] Boise LH, Kaufman JL, Bahlis NJ, et al. The Tao of myeloma. *Blood* 2014;124:1873–9.
- [37] Finley D. Recognition and processing of ubiquitin-protein conjugates by the proteasome. *Annu Rev Biochem* 2009;78:477–513.
- [38] Goldberg AL. Protein degradation and protection against misfolded or damaged proteins. *Nature* 2003;426:895–9.
- [39] Goldberg AL, Dice JF. Intracellular protein degradation in mammalian and bacterial cells. *Annu Rev Biochem* 1974;43:835–69.
- [40] Pohl C, Dikic I. Cellular quality control by the ubiquitin-proteasome system and autophagy. *Science* 2019;366:818–22.
- [41] Kannt A, Dikic I. Expanding the arsenal of E3 ubiquitin ligases for proximity-induced protein degradation. *Cell Chem Biol* 2021;28:1014–31.
- [42] Cable J, Weber-Ban E, Clausen T, et al. Targeted protein degradation: from small molecules to complex organelles—a Keystone Symposia report. *Ann N Y Acad Sci* 2022;1510:79–99.
- [43] Dikic I, Schulman BA. An expanded lexicon for the ubiquitin code. *Nat Rev Mol Cell Biol* 2023;24:273–87.
- [44] Berndsen CE, Wolberger C. New insights into ubiquitin E3 ligase mechanism. *Nat Struct Mol Biol* 2014;21:301–7.
- [45] Adams J. The proteasome: structure, function, and role in the cell. *Cancer Treat Rev* 2003;29(Suppl 1):3–9.
- [46] Dong Y, Zhang S, Wu Z, et al. Cryo-EM structures and dynamics of substrate-engaged human 26S proteasome. *Nature* 2019;565:49–55.
- [47] Murata S, Takahama Y, Kasahara M, et al. The immunoproteasome and thymoproteasome: functions, evolution and human disease. *Nat Immunol* 2018;19:923–31.
- [48] Herndon TM, Deisseroth A, Kaminskas E, et al. Food and Drug Administration approval:

- carfilzomib for the treatment of multiple myeloma. *Clin Cancer Res* 2013;19:4559–63.
- [49] Landgren O, Sonneveld P, Jakubowiak A, et al. Carfilzomib with immunomodulatory drugs for the treatment of newly diagnosed multiple myeloma. *Leukemia* 2019;33:2127–43.
- [50] Chim CS, Kumar SK, Orlowski RZ, et al. Management of relapsed and refractory multiple myeloma: novel agents, antibodies, immunotherapies and beyond. *Leukemia* 2018;32:252–62.
- [51] Wang J, Fang Y, Fan RA, et al. Proteasome Inhibitors and Their Pharmacokinetics, Pharmacodynamics, and Metabolism. *Int J Mol Sci* 2021;22.
- [52] Voorhees PM, Orlowski RZ. The proteasome and proteasome inhibitors in cancer therapy. *Annu Rev Pharmacol Toxicol* 2006;46:189–213.
- [53] Elliott PJ, Ross JS. The proteasome: a new target for novel drug therapies. *Am J Clin Pathol* 2001;116:637–46.
- [54] Kisselev AF. Site-Specific Proteasome Inhibitors. *Biomolecules* 2021;12.
- [55] Fogli S, Galimberti S, Gori V, et al. Pharmacology differences among proteasome inhibitors: Implications for their use in clinical practice. *Pharmacol Res* 2021;167:105537.
- [56] Fricker LD. Proteasome Inhibitor Drugs. *Annu Rev Pharmacol Toxicol* 2020;60:457–76.
- [57] Wang Z, Yang J, Kirk C, et al. Clinical pharmacokinetics, metabolism, and drugdrug interaction of carfilzomib. *Drug Metab Dispos* 2013;41:230–7.
- [58] Besse A, Besse L, Kraus M, et al. Proteasome Inhibition in Multiple Myeloma: Head-to-Head Comparison of Currently Available Proteasome Inhibitors. *Cell Chem Biol* 2019;26:340–351 e343.
- [59] Obeng EA, Carlson LM, Gutman DM, et al. Proteasome inhibitors induce a terminal unfolded protein response in multiple myeloma cells. *Blood* 2006;107:4907–16.
- [60] Hideshima T, Chauhan D, Richardson P, et al. NF-kappa B as a therapeutic target in multiple myeloma. *J Biol Chem* 2002;277:16639–47.
- [61] Bianchi G, Oliva L, Cascio P, et al. The proteasome load versus capacity balance determines apoptotic sensitivity of multiple myeloma cells to proteasome inhibition. *Blood* 2009;113:3040–9.
- [62] Cenci S, Mezghrani A, Cascio P, et al. Progressively impaired proteasomal capacity during terminal plasma cell differentiation. *EMBO J* 2006;25:1104–13.
- [63] Masciarelli S, Fra AM, Pengo N, et al. CHOP-independent apoptosis and pathway-selective induction of the UPR in developing plasma cells. *Mol Immunol* 2010;47:1356–65.
- [64] Cenci S. The proteasome in terminal plasma cell differentiation. *Semin Hematol* 2012;49:215–22.
- [65] Pengo N, Scolari M, Oliva L, et al. Plasma cells require autophagy for sustainable immunoglobulin production. *Nat Immunol* 2013;14:298–305.
- [66] Carpenter RO, Evbuomwan MO, Pittaluga S, et al. B-cell maturation antigen is a promising target for adoptive T-cell therapy of multiple myeloma. *Clin Cancer Res* 2013;19:2048–60.
- [67] Ali SA, Shi V, Maric I, et al. T cells

- p>expressing an anti-B-cell maturation antigen chimeric antigen receptor cause remissions of multiple myeloma.
- Blood*
- 2016;128:1688–700.
- [68] Brudno JN, Maric I, Hartman SD, et al. T Cells Genetically Modified to Express an Anti-B-Cell Maturation Antigen Chimeric Antigen Receptor Cause Remissions of Poor-Prognosis Relapsed Multiple Myeloma. *J Clin Oncol* 2018;36:2267–80.
- [69] Raje N, Berdeja J, Lin Y, et al. Anti-BCMA CAR T-Cell Therapy bb2121 in Relapsed or Refractory Multiple Myeloma. *N Engl J Med* 2019;380:1726–37.
- [70] Cappell KM, Kochenderfer JN. Long-term outcomes following CAR T cell therapy: what we know so far. *Nat Rev Clin Oncol* 2023;20:359–71.
- [71] Lin Y, Raje NS, Berdeja JG, et al. Idecabtagene vicleucel for relapsed and refractory multiple myeloma: post hoc 18-month follow-up of a phase 1 trial. *Nat Med* 2023;29:2286–94.
- [72] Ramadoss NS, Schulman AD, Choi SH, et al. An anti-B cell maturation antigen bispecific antibody for multiple myeloma. *J Am Chem Soc* 2015;137:5288–91.
- [73] Usmani SZ, Garfall AL, van de Donk N, et al. Teclistamab, a B-cell maturation antigen x CD3 bispecific antibody, in patients with relapsed or refractory multiple myeloma (MajesTEC-1): a multicentre, open-label, single-arm, phase 1 study. *Lancet* 2021;398:665–74.
- [74] Bahlis NJ, Costello CL, Raje NS, et al. Elranatamab in relapsed or refractory multiple myeloma: the MagnetisMM-1 phase 1 trial. *Nat Med* 2023;29:2570–6.
- [75] Lesokhin AM, Tomasson MH, Arnulf B, et al. Elranatamab in relapsed or refractory multiple myeloma: phase 2 MagnetisMM-3 trial results. *Nat Med* 2023;29:2259–67.
- [76] Atamaniuk J, Gleiss A, Porpaczy E, et al. Overexpression of G protein-coupled receptor 5D in the bone marrow is associated with poor prognosis in patients with multiple myeloma. *Eur J Clin Invest* 2012;42:953–60.
- [77] Kodama T, Kochi Y, Nakai W, et al. Anti-GPRC5D/CD3 Bispecific T-Cell-Redirecting Antibody for the Treatment of Multiple Myeloma. *Mol Cancer Ther* 2019;18:1555–64.
- [78] Smith EL, Harrington K, Staehr M, et al. GPRC5D is a target for the immunotherapy of multiple myeloma with rationally designed CAR T cells. *Sci Transl Med* 2019;11.
- [79] Leung-Hagesteijn C, Erdmann N, Cheung G, et al. Xbp1s-negative tumor B cells and pre-plasmablasts mediate therapeutic proteasome inhibitor resistance in multiple myeloma. *Cancer Cell* 2013;24:289–304.
- [80] Neubert K, Meister S, Moser K, et al. The proteasome inhibitor bortezomib depletes plasma cells and protects mice with lupus-like disease from nephritis. *Nat Med* 2008;14:748–55.
- [81] Walhelm T, Gunnarsson I, Heijke R, et al. Clinical Experience of Proteasome Inhibitor Bortezomib Regarding Efficacy and Safety in Severe Systemic Lupus Erythematosus: A Nationwide Study. *Front Immunol* 2021;12:756941.
- [82] Sjowall C, Hjorth M, Eriksson P. Successful treatment of refractory systemic lupus erythematosus using proteasome inhibitor bortezomib followed by belimumab: description of two cases. *Lupus* 2017;26:1333–8.

- [83] Alexander T, Sarfert R, Klotsche J, et al. The proteasome inhibitor bortezomib depletes plasma cells and ameliorates clinical manifestations of refractory systemic lupus erythematosus. *Ann Rheum Dis* 2015;74:1474–8.
- [84] Keats JJ, Fonseca R, Chesi M, et al. Promiscuous mutations activate the noncanonical NF-kappaB pathway in multiple myeloma. *Cancer Cell* 2007;12:131–44.
- [85] Annunziata CM, Davis RE, Demchenko Y, et al. Frequent engagement of the classical and alternative NF-kappaB pathways by diverse genetic abnormalities in multiple myeloma. *Cancer Cell* 2007;12:115–30.
- [86] Shabaneh TB, Downey SL, Goddard AL, et al. Molecular basis of differential sensitivity of myeloma cells to clinically relevant bolus treatment with bortezomib. *PLoS One* 2013;8:e56132.
- [87] Downey-Kopyscinski S, Daily EW, Gautier M, et al. An inhibitor of proteasome beta2 sites sensitizes myeloma cells to immunoproteasome inhibitors. *Blood Adv* 2018;2:2443–51.
- [88] Chen T, Ho M, Briere J, et al. Multiple myeloma cells depend on the DDI2/NRF1-mediated proteasome stress response for survival. *Blood Adv* 2022;6:429–40.
- [89] Downey-Kopyscinski SL, Srinivasa S, Kisselev AF. A clinically relevant pulse treatment generates a bortezomib-resistant myeloma cell line that lacks proteasome mutations and is sensitive to Bcl-2 inhibitor venetoclax. *Sci Rep* 2022;12:12788.
- [90] Barretina J, Caponigro G, Stransky N, et al. The Cancer Cell Line Encyclopedia enables predictive modelling of anticancer drug sensitivity. *Nature* 2012;483:603–7.
- [91] Richardson PG, Weller E, Jagannath S, et al. Multicenter, phase I, dose-escalation trial of lenalidomide plus bortezomib for relapsed and relapsed/refractory multiple myeloma. *J Clin Oncol* 2009;27:5713–9.
- [92] Richardson PG, Xie W, Jagannath S, et al. A phase 2 trial of lenalidomide, bortezomib, and dexamethasone in patients with relapsed and relapsed/refractory myeloma. *Blood* 2014;123:1461–9.
- [93] Franke NE, Niewerth D, Assaraf YG, et al. Impaired bortezomib binding to mutant beta5 subunit of the proteasome is the underlying basis for bortezomib resistance in leukemia cells. *Leukemia* 2012;26:757–68.
- [94] Meng L, Carpenter K, Mollard A, et al. Inhibition of Nek2 by small molecules affects proteasome activity. *BioMed Res Int* 2014;2014:273180.
- [95] Acosta-Alvear D, Cho MY, Wild T, et al. Paradoxical resistance of multiple myeloma to proteasome inhibitors by decreased levels of 19S proteasomal subunits. *Elife* 2015;4:e08153.
- [96] Tsvetkov P, Sokol E, Jin D, et al. Suppression of 19S proteasome subunits marks emergence of an altered cell state in diverse cancers. *Proc Natl Acad Sci U S A* 2017;114:382–7.
- [97] Tsvetkov P, Detappe A, Cai K, et al. Mitochondrial metabolism promotes adaptation to proteotoxic stress. *Nat Chem Biol* 2019;15:681–9.
- [98] Wallington-Beddoe CT, Sobieraj-Teague M, Kuss BJ, et al. Resistance to proteasome inhibitors and other targeted therapies in myeloma. *Br J Haematol* 2018;182:11–28.
- [99] Gonzalez-Santamarta M, Quinet G, Reyes-Garau D, et al. Resistance to the Proteasome

- Inhibitors: Lessons from Multiple Myeloma and Mantle Cell Lymphoma. *Adv Exp Med Biol* 2020;1233:153–74.
- [100] Besse L, Besse A, Mendez-Lopez M, et al. A metabolic switch in proteasome inhibitor-resistant multiple myeloma ensures higher mitochondrial metabolism, protein folding and sphingomyelin synthesis. *Haematologica* 2019;104:e415–9.
- [101] Besse A, Stolze SC, Rasche L, et al. Carfilzomib resistance due to ABCB1/MDR1 overexpression is overcome by nelfinavir and lopinavir in multiple myeloma. *Leukemia* 2018;32:391–401.
- [102] Farrell ML, Reagan MR. Soluble and Cell-Cell-Mediated Drivers of Proteasome Inhibitor Resistance in Multiple Myeloma. *Front Endocrinol* 2018;9:218.
- [103] Meul T, Berschneider K, Schmitt S, et al. Mitochondrial Regulation of the 26S Proteasome. *Cell Rep* 2020;32:108059.
- [104] Allmeroth K, Horn M, Kroef V, et al. Bortezomib resistance mutations in PSMB5 determine response to second-generation proteasome inhibitors in multiple myeloma. *Leukemia* 2021;35:887–92.
- [105] Leonardo-Sousa C, Carvalho AN, Guedes RA, et al. Revisiting Proteasome Inhibitors: Molecular Underpinnings of Their Development, Mechanisms of Resistance and Strategies to Overcome Anti-Cancer Drug Resistance. *Molecules* 2022;27.
- [106] Ferguson ID, Lin YT, Lam C, et al. Allosteric HSP70 inhibitors perturb mitochondrial proteostasis and overcome proteasome inhibitor resistance in multiple myeloma. *Cell Chem Biol* 2022;29:1288–302.e7.
- [107] Haertle L, Buenache N, Cuesta Hernandez HN, et al. Genetic Alterations in Members of the Proteasome 26S Subunit, AAA-ATPase (PSMC) Gene Family in the Light of Proteasome Inhibitor Resistance in Multiple Myeloma. *Cancers* 2023;15.
- [108] Haertle L, Barrio S, Munawar U, et al. Single-Nucleotide Variants and Epimutations Induce Proteasome Inhibitor Resistance in Multiple Myeloma. *Clin Cancer Res* 2023;29:279–88.
- [109] Wang Q, Zhao D, Xian M, et al. MIF as a biomarker and therapeutic target for overcoming resistance to proteasome inhibitors in human myeloma. *Blood* 2020;136:2557–73.
- [110] Wang Q, Shinkre BA, Lee JG, et al. The ERAD inhibitor Eeyarestatin I is a bifunctional compound with a membrane-binding domain and a p97/VCP inhibitory group. *PLoS One* 2010;5:e15479.
- [111] Wang Q, Mora-Jensen H, Weniger MA, et al. ERAD inhibitors integrate ER stress with an epigenetic mechanism to activate BH3-only protein NOXA in cancer cells. *Proc Natl Acad Sci U S A* 2009;106:2200–5.
- [112] Darawshi O, Muz B, Naamat SG, et al. An mTORC1 to HRI signaling axis promotes cytotoxicity of proteasome inhibitors in multiple myeloma. *Cell Death Dis* 2022;13:969.
- [113] Cohen YC, Zada M, Wang SY, et al. Identification of resistance pathways and therapeutic targets in relapsed multiple myeloma patients through single-cell sequencing. *Nat Med* 2021;27:491–503.
- [114] McConkey DJ, Zhu K. Mechanisms of proteasome inhibitor action and resistance in cancer. *Drug Resist Updat* 2008;11:164–79.
- [115] Niewerth D, Jansen G, Assaraf YG, et al. Molecular basis of resistance to proteasome

- p>inhibitors in hematological malignancies.
- Drug Resist Updat*
- 2015;18:18–35.
- [116] Bo Kim K. Proteasomal adaptations to FDA-approved proteasome inhibitors: a potential mechanism for drug resistance? *Cancer Drug Resist* 2021;4:634–45.
- [117] Patino-Escobar B, Talbot A, Wiita AP. Overcoming proteasome inhibitor resistance in the immunotherapy era. *Trends Pharmacol Sci* 2023;44:507–18.
- [118] Barrio S, Stuhmer T, Da-Via M, et al. Spectrum and functional validation of PSMB5 mutations in multiple myeloma. *Leukemia* 2019;33:447–56.
- [119] Cloos J, Roeten MS, Franke NE, et al. (Immuno)proteasomes as therapeutic target in acute leukemia. *Cancer Metastasis Rev* 2017;36:599–615.
- [120] Verbrugge SE, Assaraf YG, Dijkmans BA, et al. Inactivating PSMB5 mutations and P-glycoprotein (multidrug resistance-associated protein/ATP-binding cassette B1) mediate resistance to proteasome inhibitors: ex vivo efficacy of (immuno)proteasome inhibitors in mononuclear blood cells from patients with rheumatoid arthritis. *J Pharmacol Exp Ther* 2012;341:174–82.
- [121] Ri M, Iida S, Nakashima T, et al. Bortezomib-resistant myeloma cell lines: a role for mutated PSMB5 in preventing the accumulation of unfolded proteins and fatal ER stress. *Leukemia* 2010;24:1506–12.
- [122] Oerlemans R, Franke NE, Assaraf YG, et al. Molecular basis of bortezomib resistance: proteasome subunit beta5 (PSMB5) gene mutation and overexpression of PSMB5 protein. *Blood* 2008;112:2489–99.
- [123] Hideshima T, Bradner JE, Wong J, et al. Small-molecule inhibition of proteasome and aggresome function induces synergistic antitumor activity in multiple myeloma. *Proc Natl Acad Sci U S A* 2005;102:8567–72.
- [124] Nawrocki ST, Carew JS, Pino MS, et al. Aggresome disruption: a novel strategy to enhance bortezomib-induced apoptosis in pancreatic cancer cells. *Cancer Res* 2006;66:3773–81.

6 多发性骨髓瘤中的单克隆抗体治疗

- [1] Brink M, Visser O, Zweegman S, et al. First-line treatment and survival of newly diagnosed primary plasma cell leukemia patients in the Netherlands: a population-based study, 1989-2018. *Blood Cancer J* 2021;11(2):22.
- [2] van de Donk N, Richardson PG, Malavasi F. CD38 antibodies in multiple myeloma: back to the future. *Blood* 2018;131(1):13-29.
- [3] van de Donk NW, Moreau P, Plesner T, et al. Clinical efficacy and management of monoclonal antibodies targeting CD38 and SLAMF7 in multiple myeloma.
- [4] Zhu C, Song Z, Wang A, et al. Isatuximab Acts Through Fc-Dependent, Independent, and Direct Pathways to Kill Multiple Myeloma Cells. *Front Immunol* 2020;11:1771.
- [5] Deckert J, Wetzel MC, Bartle LM, et al. SAR650984, a novel humanized CD38-targeting antibody, demonstrates potent antitumor activity in models of multiple myeloma and other CD381 hematologic malignancies. *Clin Cancer Res* 2014;20(17):4574-83.
- [6] Jiang H, Acharya C, An G, et al. SAR650984 directly induces multiple myeloma cell death via lysosomal-associated and apoptotic pathways, which is further enhanced by pomalidomide. *Leukemia* 2016;30(2):399-408.
- [7] de WM, Tai YT, van d V, et al. Daratumumab, a novel therapeutic human CD38 monoclonal antibody, induces killing of multiple myeloma and other hematological tumors. *J Immunol* 2011;186(3):1840-8.
- [8] Krejcik J, Casneuf T, Nijhof IS, et al. Daratumumab depletes CD381 immune regulatory cells, promotes T-cell expansion, and skews T-cell repertoire in multiple myeloma. *Blood* 2016;128(3):384-94.
- [9] Adams HC 3rd, Stevenaert F, Krejcik J, et al. High-Parameter Mass Cytometry Evaluation of Relapsed/Refractory Multiple Myeloma Patients Treated with Daratumumab Demonstrates Immune Modulation as a Novel Mechanism of Action. *Cytometry Part A : The Journal of the International Society for Analytical Cytology* 2019;95(3):279-89.
- [10] Feng X, Zhang L, Acharya C, et al. Targeting CD38 Suppresses Induction and Function of T Regulatory Cells to Mitigate Immunosuppression in Multiple Myeloma. *Clin Cancer Res* 2017;23(15):4290-300.
- [11] Lammerts van Bueren J, Jakobs D, Kaldenhoven N, et al. Direct in Vitro Comparison of Daratumumab with Surrogate Analogs of CD38 Antibodies MOR03087, SAR650984 and Ab79. *Blood* 2014;124(21):3474.
- [12] Kinder M, Bahlis NJ, Malavasi F, et al. Comparison of CD38 antibodies in vitro and ex vivo mechanisms of action in multiple myeloma. *Haematologica* 2021;106(7):2004-8.
- [13] Quach H, Ritchie D, Stewart AK, et al. Mechanism of action of immunomodulatory drugs (IMiDS) in multiple myeloma.

- Leukemia 2010;24(1):22–32.
- [14] van de Donk NW, Görgün G, Groen RW, et al. Lenalidomide for the treatment of relapsed and refractory multiple myeloma. *Cancer Manag Res* 2012;4:253–68.
- [15] Nijhof IS, Groen RW, Noort WA, et al. Preclinical Evidence for the Therapeutic Potential of CD38-Targeted Immuno-Chemotherapy in Multiple Myeloma Patients Refractory to Lenalidomide and Bortezomib. *Clin Cancer Res* 2015;21(12):2802–10.
- [16] van der Veer MS, de WM, van KB, et al. The therapeutic human CD38 antibody daratumumab improves the anti-myeloma effect of newly emerging multi-drug therapies. *Blood Cancer J* 2011;1(10):e41.
- [17] Cai T, Wetzel M, Nicolazzi C, et al. Preclinical chracterization of SAR650984, a humanized anti-CD38 antibody for the treatment of multiple myeloma. *Clin Lymphoma Myeloma Leuk* 2013;288.
- [18] Krejcik J, Frerichs KA, Nijhof IS, et al. Monocytes and Granulocytes Reduce CD38 Expression Levels on Myeloma Cells in Patients Treated with Daratumumab. *Clin Cancer Res* 2017;23(24):7498–511.
- [19] Nijhof IS, Casneuf T, van VJ, et al. CD38 expression and complement inhibitors affect response and resistance to daratumumab therapy in myeloma. *Blood* 2016;128(7):959–70.
- [20] Verkleij CPM, Frerichs KA, Broekmans MEC, et al. NK Cell Phenotype Is Associated With Response and Resistance to Daratumumab in Relapsed/Refractory Multiple Myeloma. *Hemasphere* 2023;7(5):e881.
- [21] Casneuf T, Xu XS, Adams HC 3rd, et al. Effects of daratumumab on natural killer cells and impact on clinical outcomes in relapsed or refractory multiple myeloma. *Blood advances* 2017;1(23):2105–14.
- [22] de Haart SJ, Holthof L, Noort WA, et al. Sepantronium bromide (YM155) improves daratumumab-mediated cellular lysis of multiple myeloma cells by abrogation of bone marrow stromal cell-induced resistance. *Haematologica* 2016;101(8):e339–42.
- [23] Giri S, Grimshaw A, Bal S, et al. Evaluation of Daratumumab for the Treatment of Multiple Myeloma in Patients With High-risk Cytogenetic Factors: A Systematic Review and Meta-analysis. *JAMA Oncol* 2020;6(11):1759–65.
- [24] Mateos MV, Cavo M, Blade J, et al. Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): a randomised, open-label, phase 3 trial. *Lancet* 2020;395(10218):132–41.
- [25] Mateos MV, Dimopoulos MA, Cavo M, et al, ALCYONE Trial Investigators. Daratumumab plus Bortezomib, Melphalan, and Prednisone for Untreated Myeloma. *N Engl J Med* 2018;378(6):518–28.
- [26] Facon T, Kumar S, Plesner T, et al, MAIA Trial Investigators. Daratumumab plus Lenalidomide and Dexamethasone for Untreated Myeloma. *N Engl J Med* 2019;380(22):2104–15.
- [27] Moreau P, Attal M, Hulin C, et al. Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomised, openlabel, phase 3 study. *Lancet* 2019;394(10192):29–38.

- [28] Chari A, Kaufman JL, Laubach JP, et al. Daratumumab Plus Lenalidomide, Bortezomib, and Dexamethasone (D-RVd) in Transplant-Eligible Newly Diagnosed Multiple Myeloma (NDMM) Patients (Pts): Final Analysis of Griffin Among Clinically Relevant Subgroups. *Blood* 2022;140(Supplement 1):7278–81.
- [29] Moreau P, Facon T, Usmani S, et al. Daratumumab Plus Lenalidomide and Dexamethasone (D-Rd) Versus Lenalidomide and Dexamethasone (Rd) in Transplant-Ineligible Patients (Pts) with Newly Diagnosed Multiple Myeloma (NDMM): Clinical Assessment of Key Subgroups of the Phase 3 Maia Study. *Blood* 2022;140(Supplement 1):7297–300.
- [30] Costa LJ, Chhabra S, Medvedova E, et al. Daratumumab, Carfilzomib, Lenalidomide, and Dexamethasone With Minimal Residual Disease Response-Adapted Therapy in Newly Diagnosed Multiple Myeloma. *J Clin Oncol* 2022;40(25):2901–12.
- [31] Usmani SZ, Nahi H, Plesner T, et al. Daratumumab monotherapy in patients with heavily pretreated relapsed or refractory multiple myeloma: final results from the phase 2 GEN501 and SIRIUS trials. *Lancet Haematol* 2020;7(6):e447–55.
- [32] Lokhorst HM, Plesner T, Laubach JP, et al. Targeting CD38 with Daratumumab Monotherapy in Multiple Myeloma. *N Engl J Med* 2015;373(13):1207–19.
- [33] Lonial S, Weiss BM, Usmani SZ, et al. Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial. *Lancet* 2016;387(10027):1551–60.
- [34] Dimopoulos M, Bringhen S, Anttila P, et al. Isatuximab as monotherapy and combined with dexamethasone in patients with relapsed/refractory multiple myeloma. *Blood* 2021;137(9):1154–65.
- [35] Mateos MV, Nahi H, Legiec W, et al. Subcutaneous versus intravenous daratumumab in patients with relapsed or refractory multiple myeloma (COLUMBA): a multicentre, open-label, non-inferiority, randomised, phase 3 trial. *Lancet Haematol* 2020;7(5):e370–80.
- [36] Usmani SZ, Nahi H, Mateos MV, et al. Subcutaneous delivery of daratumumab in relapsed or refractory multiple myeloma. *Blood* 2019;134(8):668–77.
- [37] Oostendorp M, Lammerts van Bueren JJ, Doshi P, et al. When blood transfusion medicine becomes complicated due to interference by monoclonal antibody therapy. *Transfusion* 2015;55(6 Pt 2):1555–62.
- [38] van de Donk NW, Otten HG, El Haddad O, et al. Interference of daratumumab in monitoring multiple myeloma patients using serum immunofixation electrophoresis can be abrogated using the daratumumab IFE reflex assay (DIRA). *Clin Chem Lab Med* 2016;54(6):1105–9.
- [39] Martin T, Dimopoulos MA, Mikhael J, et al. Isatuximab, carfilzomib, and dexamethasone in patients with relapsed multiple myeloma: updated results from IKEMA, a randomized Phase 3 study. *Blood Cancer J* 2023;13(1):72.
- [40] Attal M, Richardson PG, Rajkumar SV, et al, ICARIA-MM study group. Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): a randomised, multicentre, open-label, phase

- 3 study. *Lancet* 2019;394(10214):2096–107.
- [41] Lonial S, Dimopoulos M, Palumbo A, et al. ELOQUENT-2 Investigators. Elotuzumab Therapy for Relapsed or Refractory Multiple Myeloma. *N Engl J Med* 2015;373(7):621–31.
- [42] Cavo M, San-Miguel J, Usmani SZ, et al. Prognostic value of minimal residual disease negativity in myeloma: combined analysis of POLLUX, CASTOR, ALCYONE, and MAIA. *Blood* 2022;139(6):835–44.
- [43] Facon T, Kumar SK, Plesner T, et al. Daratumumab, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone alone in newly diagnosed multiple myeloma (MAIA): overall survival results from a randomised, openlabel, phase 3 trial. *Lancet Oncol* 2021;22(11):1582–96.
- [44] Moreau P, Hulin C, Perrot A, et al. Maintenance with daratumumab or observation following treatment with bortezomib, thalidomide, and dexamethasone with or without daratumumab and autologous stem-cell transplant in patients with newly diagnosed multiple myeloma (CASSIOPEIA): an open-label, randomised, phase 3 trial. *Lancet Oncol* 2021;22(10):1378–90.
- [45] Voorhees PM, Kaufman JL, Laubach J, et al. Daratumumab, lenalidomide, bortezomib, and dexamethasone for transplant-eligible newly diagnosed multiple myeloma: the GRIFFIN trial. *Blood* 2020;136(8):936–45.
- [46] Mateos MV, Dimopoulos MA, Cavo M, et al. Daratumumab Plus Bortezomib, Melphalan, and Prednisone Versus Bortezomib, Melphalan, and Prednisone in Transplant-Ineligible Newly Diagnosed Multiple Myeloma: Frailty Subgroup Analysis of ALCYONE. *Clin Lymphoma, Myeloma & Leukemia* 2021;21(11):785–98.
- [47] Facon T, Cook G, Usmani SZ, et al. Daratumumab plus lenalidomide and dexamethasone in transplant-ineligible newly diagnosed multiple myeloma: frailty subgroup analysis of MAIA. *Leukemia* 2022;36(4):1066–77.
- [48] Palumbo A, Bringhen S, Mateos MV, et al. Geriatric assessment predicts survival and toxicities in elderly myeloma patients: an International Myeloma Working Group report. *Blood* 2015;125(13):2068–74.
- [49] Facon T, Dimopoulos MA, Meuleman N, et al. A simplified frailty scale predicts outcomes in transplant-ineligible patients with newly diagnosed multiple myeloma treated in the FIRST (MM-020) trial. *Leukemia* 2020;34(1):224–33.
- [50] Stege CAM, Nasserinejad K, van der Spek E, et al. Ixazomib, Daratumumab, and Low-Dose Dexamethasone in Frail Patients With Newly Diagnosed Multiple Myeloma: The Hovon 143 Study. *J Clin Oncol* 2021;39(25):2758–67.
- [51] Korst C, van de Donk N. Should all newly diagnosed MM patients receive CD38 antibody-based treatment? *Hematology American Society of Hematology Education Program* 2020;2020(1):259–63.
- [52] Krishnan A, Hoering A, Hari P, et al. Phase III Study of Daratumumab/rhuph20 (nsc-810307) 1 Lenalidomide or Lenalidomide As Post-Autologous Stem Cell Transplant Maintenance Therapy in Patients with Multiple Myeloma (mm) Using Minimal Residual Disease To Direct Therapy Duration (DRAMMATIC study): SWOG s1803. *Blood* 2020;136:21–2.

- [53] Goldschmidt H, Mai EK, Bertsch U, et al. German-Speaking Myeloma Multicenter Group GMMG HD7 investigators. Addition of isatuximab to lenalidomide, bortezomib, and dexamethasone as induction therapy for newly diagnosed, transplantation-eligible patients with multiple myeloma (GMMG-HD7): part 1 of an open-label, multicentre, randomised, active-controlled, phase 3 trial. *Lancet Haematol* 2022;9(11):e810–21.
- [54] Leypoldt LB, Besemer B, Asemissen AM, et al. Isatuximab, carfilzomib, lenalidomide, and dexamethasone (Isa-KRd) in front-line treatment of high-risk multiple myeloma: interim analysis of the GMMG-CONCEPT trial. *Leukemia* 2022;36(3): 885–8.
- [55] Royle KL, Coulson AB, Ramasamy K, et al. Risk and response adapted therapy following autologous stem cell transplant in patients with newly diagnosed multiple myeloma (RADAR (UK-MRA Myeloma XV Trial): study protocol for a phase II/III randomised controlled trial. *BMJ Open* 2022;12(11):e063037.
- [56] Plesner T, Arkenau T, Lokhorst H, et al. Preliminary Safety and Efficacy Data Of Daratumumab In Combination With Lenalidomide and Dexamethasone In Relapsed Or Refractory Multiple Myeloma. *Blood* 2013;122(21):1986.
- [57] Martin T, Baz R, Benson DM, et al. A phase 1b study of isatuximab plus lenalidomide and dexamethasone for relapsed/refractory multiple myeloma. *Blood* 2017;129(25):3294–303.
- [58] Dimopoulos MA, Oriol A, Nahi H, et al, POLLUX Investigators. Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma. *N Engl J Med* 2016; 375(14):1319–31.
- [59] Dimopoulos MA, San-Miguel J, Belch A, et al. Daratumumab plus lenalidomide and dexamethasone versus lenalidomide and dexamethasone in relapsed or refractory multiple myeloma: updated analysis of POLLUX. *Haematologica* 2018; 103(12):2088–96.
- [60] Dimopoulos MA, Oriol A, Nahi H, et al. Overall Survival With Daratumumab, Lenalidomide, and Dexamethasone in Previously Treated Multiple Myeloma (POLLUX): A Randomized, Open-Label, Phase III Trial. *J Clin Oncol* 2023;41(8):1590–9.
- [61] Chari A, Suvannasankha A, Fay JW, et al. Daratumumab plus pomalidomide and dexamethasone in relapsed and/or refractory multiple myeloma. *Blood* 2017;130(8):974–81.
- [62] Dimopoulos MA, Terpos E, Boccadoro M, et al, APOLLO Trial Investigators. Daratumumab plus pomalidomide and dexamethasone versus pomalidomide and dexamethasone alone in previously treated multiple myeloma (APOLLO): an open-label, randomised, phase 3 trial. *Lancet Oncol* 2021;22(6):801–12.
- [63] Richardson PG, Perrot A, San-Miguel J, et al. Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): follow-up analysis of a randomised, phase 3 study. *Lancet Oncol* 2022;23(3): 416–27.
- [64] Sonneveld P, Chanan-Khan A, Weisel K, et al. Overall Survival With Daratumumab, Bortezomib, and Dexamethasone in

- Previously Treated Multiple Myeloma (CASTOR): A Randomized, Open-Label, Phase III Trial. *J Clin Oncol* 2023;41(8):1600–9.
- [65] Palumbo A, Chanan-Khan A, Weisel K, et al, CASTOR Investigators. Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma. *N Engl J Med* 2016;375(8):754–66.
- [66] Dimopoulos M, Quach H, Mateos MV, et al. Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma (CANDOR): results from a randomised, multicentre, open-label, phase 3 study. *Lancet* 2020;396(10245):186–97.
- [67] Usmani SZ, Quach H, Mateos MV, et al. Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma (CANDOR): updated outcomes from a randomised, multicentre, open-label, phase 3 study. *Lancet Oncol* 2022;23(1):65–76.
- [68] Usmani SZ, Quach H, Mateos MV, et al. Final analysis of carfilzomib, dexamethasone, and daratumumab vs carfilzomib and dexamethasone in the CANDOR study. *Blood Advances* 2023;7(14):3739–48.
- [69] Brinchen S, Milan A, Ferri C, et al, European Hematology Association, the European Myeloma Network and the Italian Society of Arterial Hypertension. Cardiovascular adverse events in modern myeloma therapy - Incidence and risks. A review from the European Myeloma Network (EMN) and Italian Society of Arterial Hypertension (SIIA). *Haematologica* 2018;103(9):1422–32.
- [70] Dimopoulos MA, Goldschmidt H, Niesvizky R, et al. Carfilzomib or bortezomib in relapsed or refractory multiple myeloma (ENDEAVOR): an interim overall survival analysis of an open-label, randomised, phase 3 trial. *Lancet Oncol* 2017; 18(10):1327–37.
- [71] van de Donk NW. Carfilzomib versus bortezomib: no longer an ENDEAVOR. *Lancet Oncol* 2017;18(10):1288–90.
- [72] Nooka AK, Joseph NS, Kaufman JL, et al. Clinical efficacy of daratumumab, pomalidomide, and dexamethasone in patients with relapsed or refractory myeloma: Utility of re-treatment with daratumumab among refractory patients. *Cancer* 2019;125(17):2991–3000.
- [73] Hussain MJ, Robinson MM, Hamadeh I, et al. Daratumumab, pomalidomide and dexamethasone combination therapy in daratumumab and/or pomalidomide refractory multiple myeloma. *Br J Haematol* 2019;186(1):140–4.
- [74] Alici E, Chrobok M, Lund J, et al. Re-challenging with anti-CD38 monotherapy in triple-refractory multiple myeloma patients is a feasible and safe approach. *Br J Haematol* 2016;174(3):473–7.
- [75] Bahlis NJ, Zonder JA, Wroblewski S, et al. Subcutaneous daratumumab in patients with multiple myeloma who have been previously treated with intravenous daratumumab: A multicenter, randomized, phase II study (LYNX). *J Clin Oncol* 2020;38(15_suppl):TPS8553.
- [76] Hsi ED, Steinle R, Balasa B, et al. CS1, a potential new therapeutic antibody target for the treatment of multiple myeloma. *Clin Cancer Res* 2008;14(9):2775–84.

- [77] Kurdi AT, Glavey SV, Bezman NA, et al. Antibody-Dependent Cellular Phagocytosis by Macrophages is a Novel Mechanism of Action of Elotuzumab. *Mol Cancer Therapeut* 2018;17(7):1454–63.
- [78] Tai YT, Dillon M, Song W, et al. Anti-CS1 humanized monoclonal antibody HuLuc63 inhibits myeloma cell adhesion and induces antibody-dependent cellular cytotoxicity in the bone marrow milieu. *Blood* 2008;112(4):1329–37.
- [79] Collins SM, Bakan CE, Swartzel GD, et al. Elotuzumab directly enhances NK cell cytotoxicity against myeloma via CS1 ligation: evidence for augmented NK cell function complementing ADCC. *Cancer Immunol Immunother* 2013;62(12):1841–9.
- [80] Hoylman E, Brown A, Perissinotti AJ, et al. Optimal sequence of daratumumab and elotuzumab in relapsed and refractory multiple myeloma. *Leuk Lymphoma* 2020;61(3):691–8.
- [81] Becnel M, Rubin L, Nair R, et al. Effect of Timing of Monoclonal Antibody Therapy on the Time to Next Treatment and Response Rate in Heavily Pre-Treated Patients with Myeloma Who Separately Received Both Daratumumab and Elotuzumab-Based Regimens. *Blood* 2018;132:3258.
- [82] Dimopoulos MA, Richardson PG, Bahlis NJ, et al, ELOQUENT-1 investigators. Addition of elotuzumab to lenalidomide and dexamethasone for patients with newly diagnosed, transplantation ineligible multiple myeloma (ELOQUENT-1): an open-label, multicentre, randomised, phase 3 trial. *Lancet Haematol* 2022; 9(6):e403–14.
- [83] Goldschmidt H, Mai EK, Bertsch U, et al. Elotuzumab in Combination with Lenalidomide, Bortezomib, Dexamethasone and Autologous Transplantation for Newly-Diagnosed Multiple Myeloma: Results from the Randomized Phase III GMMG-HD6 Trial. *Blood* 2021;138:486.
- [84] Usmani SZ, Hoering A, Ailawadhi S, et al, SWOG1211 Trial Investigators. Bortezomib, lenalidomide, and dexamethasone with or without elotuzumab in patients with untreated, high-risk multiple myeloma (SWOG-1211): primary analysis of a randomised, phase 2 trial. *Lancet Haematol* 2021;8(1):e45–54.
- [85] Knop S, Stuebig T, Kull M, et al. Carfilzomib, lenalidomide, and dexamethasone (KRd) versus elotuzumab and KRd in transplant-eligible patients with newly diagnosed multiple myeloma: Post-induction response and MRD results from an open-label randomized phase 3 study. *J Clin Oncol* 2023;41(16_suppl):8000.
- [86] Zonder JA, Mohrbacher AF, Singhal S, et al. A phase 1, multicenter, open-label, dose escalation study of elotuzumab in patients with advanced multiple myeloma. *Blood* 2012;120(3):552–9 %19.
- [87] Dimopoulos MA, Lonial S, Betts KA, et al. Elotuzumab plus lenalidomide and dexamethasone in relapsed/refractory multiple myeloma: Extended 4-year follow-up and analysis of relative progression-free survival from the randomized ELOQUENT-2 trial. *Cancer* 2018;124(20):4032–43.
- [88] Dimopoulos MA, Lonial S, White D, et al. Elotuzumab, lenalidomide, and dexamethasone in RRMM: final overall survival results from the phase 3 randomized ELOQUENT-2 study. *Blood Cancer J* 2020;10(9):91.

- [89] Dimopoulos MA, Dytfield D, Grosicki S, et al. Elotuzumab plus Pomalidomide and Dexamethasone for Multiple Myeloma. *N Engl J Med* 2018;379(19):1811–22.
- [90] Dimopoulos MA, Dytfield D, Grosicki S, et al. Elotuzumab Plus Pomalidomide and Dexamethasone for Relapsed/Refractory Multiple Myeloma: Final Overall Survival Analysis From the Randomized Phase II ELOQUENT-3 Trial. *J Clin Oncol* 2023;41(3):568–78.
- [91] van RF, Szmania SM, Dillon M, et al. Combinatorial efficacy of anti-CS1 monoclonal antibody elotuzumab (HuLuc63) and bortezomib against multiple myeloma. *Mol Cancer Ther* 2009;8(9):2616–24.
- [92] Jakubowiak A, Offidani M, Pegourie B, et al. Randomized phase 2 study: elotuzumab plus bortezomib/dexamethasone vs bortezomib/dexamethasone for relapsed/refractory MM. *Blood* 2016;127(23):2833–40.
- [93] Moreau P, Garfall AL, van de Donk N, et al. Teclistamab in Relapsed or Refractory Multiple Myeloma. *N Engl J Med* 2022;387(6):495–505.
- [94] Martin T, Usmani SZ, Berdeja JG, et al. Ciltacabtagene Autoleucel, an Anti-B-cell Maturation Antigen Chimeric Antigen Receptor T-Cell Therapy, for Relapsed/Refractory Multiple Myeloma: CARTITUDE-1 2-Year Follow-Up. *J Clin Oncol* 2023;41(6):1265–74.
- [95] Lonial S, Lee HC, Badros A, et al. Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): a two-arm, randomised, open-label, phase 2 study. *Lancet Oncol* 2020;21(2):207–21.
- [96] van de Donk N, Usmani SZ, Yong K. CAR T-cell therapy for multiple myeloma: state of the art and prospects. *Lancet Haematol* 2021;8(6):e446–61.
- [97] O'Neill C, van de Donk N. T-cell redirecting bispecific antibodies in multiple myeloma: Current landscape and future directions. *EJHaem* 2023;4(3):811–22.
- [98] van de Donk N, Zweegman S. T-cell-engaging bispecific antibodies in cancer. *Lancet* 2023;402(10396):142–58.
- [99] Ryan MC, Hering M, Peckham D, et al. Antibody targeting of B-cell maturation antigen on malignant plasma cells. *Mol Cancer Therapeut* 2007;6(11):3009–18.
- [100] Hoffman JE, Lipe B, Melear J, et al. SEA-BCMA, an Investigational Nonfucosylated Monoclonal Antibody: Ongoing Results of a Phase 1 Study in Patients with Relapsed/Refractory Multiple Myeloma (SGNBCMA-001). *Blood* 2021;138:2740.
- [101] Hoffman JE, Lipe B, Melear J, et al. Sea-BCMA Mono- and Combination Therapy in Patients with Relapsed/Refractory Multiple Myeloma: Updated Results of a Phase 1 Study (SGNBCMA-001). *Blood* 2022;140(Supplement 1):10160–2.
- [102] Lonial S, Popat R, Hulin C, et al. Iberdomide plus dexamethasone in heavily pretreated late-line relapsed or refractory multiple myeloma (CC-220-MM-001): a multicentre, multicohort, open-label, phase 1/2 trial. *Lancet Haematol* 2022;9(11):e822–32.
- [103] Richardson PG, Trudel S, Quach H, et al. Mezigdomide (CC-92480), a Potent, Novel Cereblon E3 Ligase Modulator (CELMoD), Combined with Dexamethasone(DEX) in Patients (pts) with Relapsed/Refractory Multiple Myeloma (RRMM): Preliminary Results from the Dose-Expansion Phase of the CC-92480-MM-001 Trial. *Blood*

- 2022;140(Supplement 1):1366–8.
- [104] Lonial S, Amatangelo M, Popat R, et al. Preclinical, Translational, and Clinical Evidence of a Differentiated Profile for the Novel CELMoD, Iberdomide (CC220). *Blood* 2019;134:3119.
- [105] van de Donk NWCJ, Popat R, Larsen J, et al. First Results of Iberdomide (IBER;CC-220) in Combination with Dexamethasone (DEX) and Daratumumab (DARA) or Bortezomib (BORT) in Patients with Relapsed/Refractory Multiple Myeloma(RRMM). *Blood* 2020;136(Supplement 1):16–7.
- [106] Cortes-Selva D, Casneuf T, Vishwamitra D, et al. Teclistamab, a B-Cell Maturation Antigen (BCMA) x CD3 Bispecific Antibody, in Patients with Relapsed/Refractory Multiple Myeloma (RRMM): Correlative Analyses from MajesTEC-1. *Blood* 2022;140(Supplement 1):241–3.
- [107] Frerichs KA, Broekmans MEC, Marin Soto JA, et al. Preclinical Activity of JNJ7957, a Novel BCMACD3 Bispecific Antibody for the Treatment of Multiple Myeloma, Is Potentiated by Daratumumab. *Clin Cancer Res* 2020;26(9):2203–15.
- [108] Verkleij CPM, Broekmans MEC, van Duin M, et al. Preclinical activity and determinants of response of the GPRC5DxCD3 bispecific antibody talquetamab in multiple myeloma. *Blood Advances* 2021;5(8):2196–215.
- [109] Rodríguez-Otero P, D’Souza A, Reece DE, et al. A novel, immunotherapy-based approach for the treatment of relapsed/refractory multiple myeloma (RRMM): Updated phase 1b results for daratumumab in combination with teclistamab (a BCMA x CD3 bispecific antibody). *J Clin Oncol* 2022;40(16_suppl):8032.
- [110] Dholaria B, Weisel K, Mateos M-V, et al. Talquetamab (tal) 1 daratumumab(dara) in patients (pts) with relapsed/refractory multiple myeloma (RRMM): Updated TRIMM-2 results. *J Clin Oncol* 2023;41(16_suppl):8003.
- [111] Naeimi Kararoudi M, Nagai Y, Elmas E, et al. CD38 deletion of human primary NK cells eliminates daratumumab-induced fratricide and boosts their effector activity. *Blood* 2020;136(21):2416–27.
- [112] Frerichs KA, Minnema MC, Levin MD, et al. Efficacy and safety of daratumumab combined with all-trans retinoic acid in relapsed/refractory multiple myeloma. *Blood Advances* 2021;5(23):5128–39.
- [113] Kassem S, Diallo BK, El-Murr N, et al. SAR442085, a novel anti-CD38 antibody with enhanced antitumor activity against multiple myeloma. *Blood* 2022;139(8):1160–76.
- [114] Hiemstra IH, Santegoets KCM, Janmaat ML, et al. Preclinical anti-tumour activity of HexaBody-CD38, a next-generation CD38 antibody with superior complement dependent cytotoxic activity. *EBioMedicine* 2023;93:104663.
- [115] Spencer A, Iversen KF, Dhakal B, et al. Preliminary Dose-Escalation Results from a Phase 1/2 Study of GEN3014 (HexaBody-CD38) in Patients (pts) with Relapsed or Refractory Multiple Myeloma (RRMM). *Blood* 2022;140(Supplement 1):7320–1.
- [116] Spencer A, Lentzsch S, Weisel K, et al. Daratumumab plus bortezomib and dexamethasone versus bortezomib and dexamethasone in relapsed or refractory multiple myeloma: updated analysis of CASTOR. *Haematologica*

- 2018;103(12):2079–87.
- [117] Moreau P, Dimopoulos MA, Mikhael J, et al, IKEMA study group. Isatuximab, carfilzomib, and dexamethasone in relapsed multiple myeloma (IKEMA): a multicentre, open-label, randomised phase 3 trial. *Lancet* 2021;397(10292):2361–71.

7 双特异性抗体在多发性骨髓瘤治疗中的应用

- [1] Rajkumar SV. Multiple myeloma: 2022 update on diagnosis, risk stratification, and management. *Am J Hematol* 2022;97(8):1086–107.
- [2] Attal M, Lauwers-Cances V, Hulin C, et al. Lenalidomide, Bortezomib, and Dexamethasone with Transplantation for Myeloma. *N Engl J Med* 2017;376(14):1311–20.
- [3] Goldschmidt H, Lokhorst HM, Mai EK, et al. Bortezomib before and after high-dose therapy in myeloma: long-term results from the phase III HOVON-65/GMMG-HD4 trial. *Leukemia* 2018;32(2):383–90.
- [4] Chetter I, Arundel C, Bell K, et al. The epidemiology, management and impact of surgical wounds healing by secondary intention: a research programme including the SWHSI feasibility RCT. Southampton (UK): Programme Grants for Applied Research; 2020.
- [5] Durie BGM, Hoering A, Abidi MH, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. *Lancet* 2017;389(10068):519–27.
- [6] Facon T, Kumar SK, Plesner T, et al. Daratumumab, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone alone in newly diagnosed multiple myeloma (MAIA): overall survival results from a randomised, open-label, phase 3 trial. *Lancet Oncol* 2021;22(11):1582–96.
- [7] Zhou X, Einsele H, Danhof S. Bispecific Antibodies: A New Era of Treatment for Multiple Myeloma. *J Clin Med* 2020;9(7):2166.
- [8] Ho WY, Blattman JN, Dossett ML, et al. Adoptive immunotherapy: engineering T cell responses as biologic weapons for tumor mass destruction. *Cancer Cell* 2003;3(5):431–7.
- [9] Yang Q, Li X, Zhang F, et al. Efficacy and Safety of CAR-T Therapy for Relapse or Refractory Multiple Myeloma: A systematic review and meta-analysis. *Int J Med Sci* 2021;18(8):1786–97.
- [10] Cipkar C, Chen C, Trudel S. Antibodies and bispecifics for multiple myeloma: effective effector therapy. *Hematology Am Soc Hematol Educ Program* 2022; 2022(1):163–72.
- [11] Mullard A. FDA approves first BCMA-targeted CAR-T cell therapy. *Nat Rev Drug Discov* 2021;20(5):332.
- [12] Mullard A. FDA approves second BCMA-targeted CAR-T cell therapy. *Nat Rev Drug Discov* 2022;21(4):249.
- [13] Kang C. Teclistamab: First Approval. *Drugs* 2022;82(16):1613–9.
- [14] Rendo MJ, Joseph JJ, Phan LM, et al. CAR T-Cell Therapy for Patients with Multiple Myeloma: Current Evidence and Challenges. *Blood Lymphat Cancer* 2022;12:119–36.

- [15] Kazandjian D, Kowalski A, Landgren O. T cell redirecting bispecific antibodies for multiple myeloma: emerging therapeutic strategies in a changing treatment landscape. *Leuk Lymphoma* 2022;63(13):3032–43.
- [16] Granger K, Gaffney KJ, Davis JA. Newly approved and forthcoming T-cell-redirecting bispecific antibodies for the treatment of relapsed/refractory multiple myeloma. *J Oncol Pharm Pract* 2023;29(3):722–6.
- [17] Link BK, Kostelny SA, Cole MS, et al. Anti-CD3-based bispecific antibody designed for therapy of human B-cell malignancy can induce T-cell activation by antigen-dependent and antigen-independent mechanisms. *Int J Cancer* 1998;77(2):251–6.
- [18] Shah N, Chari A, Scott E, et al. B-cell maturation antigen (BCMA) in multiple myeloma: rationale for targeting and current therapeutic approaches. *Leukemia* 2020;34(4):985–1005.
- [19] Li J, Stagg NJ, Johnston J, et al. Membrane-Proximal Epitope Facilitates Efficient T Cell Synapse Formation by Anti-FcRH5/CD3 and Is a Requirement for Myeloma Cell Killing. *Cancer Cell* 2017;31(3):383–95.
- [20] Seckinger A, Delgado JA, Moser S, et al. Target Expression, Generation, Preclinical Activity, and Pharmacokinetics of the BCMA-T Cell Bispecific Antibody EM801 for Multiple Myeloma Treatment. *Cancer Cell* 2017;31(3):396–410.
- [21] Goldstein RL, Goyos A, Li CM, et al. AMG 701 induces cytotoxicity of multiple myeloma cells and depletes plasma cells in cynomolgus monkeys. *Blood Adv* 2020;4(17):4180–94.
- [22] Brinkmann U, Kontermann RE. The making of bispecific antibodies. *mAbs* 2017;9(2):182–212.
- [23] Madduri D, Dhodapkar MV, Lonial S, et al. SOHO State of the Art Updates and Next Questions: T-Cell-Directed Immune Therapies for Multiple Myeloma: Chimeric Antigen Receptor-Modified T Cells and Bispecific T-Cell-Engaging Agents. *Clin Lymphoma, Myeloma & Leukemia* 2019;19(9):537–44.
- [24] Kontermann RE, Brinkmann U. Bispecific antibodies. *Drug Discov Today* 2015;20(7):838–47.
- [25] Moreau P, Touzeau C. T-cell-redirecting bispecific antibodies in multiple myeloma: a revolution? *Blood* 2022;139(26):3681–7.
- [26] Zhou X, Rasche L, Kortum KM, et al. BCMA loss in the epoch of novel immunotherapy for multiple myeloma: from biology to clinical practice. *Haematologica* 2023;108(4):958–68.
- [27] Tai YT, Acharya C, An G, et al. APRIL and BCMA promote human multiple myeloma growth and immunosuppression in the bone marrow microenvironment. *Blood* 2016;127(25):3225–36.
- [28] Moreaux J, Legouffe E, Jourdan E, et al. BAFF and APRIL protect myeloma cells from apoptosis induced by interleukin 6 deprivation and dexamethasone. *Blood* 2004;103(8):3148–57.
- [29] Tai YT, Li XF, Breitkreutz I, et al. Role of B-cell-activating factor in adhesion and growth of human multiple myeloma cells in the bone marrow microenvironment. *Cancer Res* 2006;66(13):6675–82.
- [30] Cho SF, Anderson KC, Tai YT. Targeting B Cell Maturation Antigen (BCMA) in Multiple Myeloma: Potential Uses of BCMA-Based Immunotherapy. *Front*

- Immunol 2018;9:1821.
- [31] Demchenko YN, Glebov OK, Zingone A, et al. Classical and/or alternative NFkappaB pathway activation in multiple myeloma. *Blood* 2010;115(17):3541–52.
- [32] Pillarisetti K, Powers G, Luistro L, et al. Teclistamab is an active T cell-redirecting bispecific antibody against B-cell maturation antigen for multiple myeloma. *Blood Adv* 2020;4(18):4538–49.
- [33] Hipp S, Tai YT, Blanset D, et al. A novel BCMA/CD3 bispecific T-cell engager for the treatment of multiple myeloma induces selective lysis in vitro and in vivo. *Leukemia* 2017;31(8):1743–51.
- [34] Gao Y, Wang X, Yan H, et al. Comparative Transcriptome Analysis of Fetal Skin Reveals Key Genes Related to Hair Follicle Morphogenesis in Cashmere Goats. *PLoS One* 2016;11(3):e0151118.
- [35] Inoue S, Nambu T, Shimomura T. The RAIG family member, GPRC5D, is associated with hard-keratinized structures. *J Invest Dermatol* 2004;122(3):565–73.
- [36] Kim YJ, Yoon B, Han K, et al. Comprehensive Transcriptome Profiling of Balding and Non-Balding Scalps in Trichorhinophalangeal Syndrome Type I Patient. *Ann Dermatol* 2017;29(5):597–601.
- [37] Atamaniuk J, Gleiss A, Porpaczy E, et al. Overexpression of G protein-coupled receptor 5D in the bone marrow is associated with poor prognosis in patients with multiple myeloma. *Eur J Clin Invest* 2012;42(9):953–60.
- [38] Cohen Y, Gutwein O, Garach-Jehoshua O, et al. GPRC5D is a promising marker for monitoring the tumor load and to target multiple myeloma cells. *Hematology* 2013;18(6):348–51.
- [39] Smith EL, Harrington K, Staehr M, et al. GPRC5D is a target for the immunotherapy of multiple myeloma with rationally designed CAR T cells. *Sci Transl Med* 2019;11(485):eaau7746.
- [40] Pillarisetti K, Edavettal S, Mendonca M, et al. A T-cell-redirecting bispecific G-protein-coupled receptor class 5 member D x CD3 antibody to treat multiple myeloma. *Blood* 2020;135(15):1232–43.
- [41] Elkins K, Zheng B, Go M, et al. FcRL5 as a target of antibody-drug conjugates for the treatment of multiple myeloma. *Mol Cancer Therapeut* 2012;11(10):2222–32.
- [42] Polson AG, Zheng B, Elkins K, et al. Expression pattern of the human FcRH/IRTA receptors in normal tissue and in B-chronic lymphocytic leukemia. *Int Immunol* 2006;18(9):1363–73.
- [43] Stewart AK, Krishnan AY, Singhal S, et al. Phase I study of the anti-FcRH5 antibody-drug conjugate DFRF4539A in relapsed or refractory multiple myeloma. *Blood Cancer J* 2019;9(2):17.
- [44] Inoue J, Otsuki T, Hirasawa A, et al. Overexpression of PDZK1 within the 1q12-q22 amplicon is likely to be associated with drug-resistance phenotype in multiple myeloma. *Am J Pathol* 2004;165(1):71–81.
- [45] Funaro A, Malavasi F. Human CD38, a surface receptor, an enzyme, an adhesion molecule and not a simple marker. *J Biol Regul Homeost Agents* 1999;13(1):54–61.
- [46] Lin P, Owens R, Tricot G, et al. Flow cytometric immunophenotypic analysis of 306 cases of multiple myeloma. *Am J Clin Pathol* 2004;121(4):482–8.
- [47] de Weers M, Tai YT, van der Veer MS, et al.

- Daratumumab, a novel therapeutic human CD38 monoclonal antibody, induces killing of multiple myeloma and other hematological tumors. *J Immunol* 2011;186(3):1840–8.
- [48] Zhu C, Song Z, Wang A, et al. Isatuximab Acts Through Fc-Dependent, Independent, and Direct Pathways to Kill Multiple Myeloma Cells. *Front Immunol* 2020;11:1771.
- [49] Zuch de Zafra CL, Fajardo F, Zhong W, et al. Targeting Multiple Myeloma with AMG 424, a Novel Anti-CD38/CD3 Bispecific T-cell-recruiting Antibody Optimized for Cytotoxicity and Cytokine Release. *Clin Cancer Res* 2019;25(13): 3921–33.
- [50] Akhmetzyanova I, McCarron MJ, Parekh S, et al. Dynamic CD138 surface expression regulates switch between myeloma growth and dissemination. *Leukemia* 2020;34(1):245–56.
- [51] Gotte M. Syndecans in inflammation. *Faseb J* 2003;17(6):575–91.
- [52] Chen D, Zou J, Zong Y, et al. Anti-human CD138 monoclonal antibodies and their bispecific formats: generation and characterization. *Immunopharmacol Immunotoxicol* 2016;38(3):175–83.
- [53] Robillard N, Wullemme S, Moreau P, et al. Immunophenotype of normal and myelomatous plasma-cell subsets. *Front Immunol* 2014;5:137.
- [54] Tembhare PR, Yuan CM, Venzon D, et al. Flow cytometric differentiation of abnormal and normal plasma cells in the bone marrow in patients with multiple myeloma and its precursor diseases. *Leuk Res* 2014;38(3):371–6.
- [55] Nerretter T, Letschert S, Gotz R, et al. Super-resolution microscopy reveals ultralow CD19 expression on myeloma cells that triggers elimination by CD19 CAR-T. *Nat Commun* 2019;10(1):3137.
- [56] Ali S, Moreau A, Melchiorri D, et al. Blinatumomab for Acute Lymphoblastic Leukemia: The First Bispecific T-Cell Engager Antibody to Be Approved by the EMA for Minimal Residual Disease. *Oncol* 2020;25(4):e709–15.
- [57] Bargou R, Leo E, Zugmaier G, et al. Tumor regression in cancer patients by very low doses of a T cell-engaging antibody. *Science* 2008;321(5891):974–7.
- [58] Kantarjian H, Stein A, Gokbuget N, et al. Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia. *N Engl J Med* 2017;376(9):836–47.
- [59] Topp MS, Gokbuget N, Stein AS, et al. Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study. *Lancet Oncol* 2015;16(1):57–66.
- [60] Hsi ED, Steinle R, Balasa B, et al. CS1, a potential new therapeutic antibody target for the treatment of multiple myeloma. *Clin Cancer Res* 2008;14(9):2775–84.
- [61] Tai YT, Soydan E, Song W, et al. CS1 promotes multiple myeloma cell adhesion, clonogenic growth, and tumorigenicity via c-maf-mediated interactions with bone marrow stromal cells. *Blood* 2009;113(18):4309–18.
- [62] Tai YT, Dillon M, Song W, et al. Anti-CS1 humanized monoclonal antibody HuLuc63 inhibits myeloma cell adhesion and induces antibody-dependent cellular cytotoxicity in the bone marrow milieu. *Blood* 2008;112(4):1329–37.

- [63] Wang Y, Sanchez L, Siegel DS, et al. Elotuzumab for the treatment of multiple myeloma. *J Hematol Oncol* 2016;9(1):55.
- [64] Magen H, Muchtar E. Elotuzumab: the first approved monoclonal antibody for multiple myeloma treatment. *Ther Adv Hematol* 2016;7(4):187–95.
- [65] Ratner M. FDA approves three different multiple myeloma drugs in one month. *Nat Biotechnol* 2016;34(2):126.
- [66] Chan WK, Kang S, Youssef Y, et al. A CS1-NKG2D Bispecific Antibody Collectively Activates Cytolytic Immune Cells against Multiple Myeloma. *Cancer Immunol Res* 2018;6(7):776–87.
- [67] Topp MS, Duell J, Zugmaier G, et al. Anti-B-Cell Maturation Antigen BiTE Molecule AMG 420 Induces Responses in Multiple Myeloma. *J Clin Oncol* 2020;38(8):775–83.
- [68] Harrison SJ, Minnema MC, Lee HC, et al. A Phase 1 First in Human (FIH) Study of AMG 701, an Anti-B-Cell Maturation Antigen (BCMA) Half-Life Extended (HLE) BiTE (bispecific T-cell engager) Molecule, in Relapsed/Refractory(RR) Multiple Myeloma (MM). *Blood* 2020;136(Supplement 1):28–9.
- [69] Moreau P, Garfall AL, van de Donk N, et al. Teclistamab in Relapsed or Refractory Multiple Myeloma. *N Engl J Med* 2022;387(6):495–505.
- [70] Searle E, Quach H, Wong SW, et al. Teclistamab in Combination with Subcutaneous Daratumumab and Lenalidomide in Patients with Multiple Myeloma: Results from One Cohort of MajesTEC-2, a Phase1b, Multicohort Study. *Blood* 2022;140(Supplement 1):394–6.
- [71] Rodriguez-Otero P, D'Souza A, Reece DE, et al. A novel, immunotherapy-based approach for the treatment of relapsed/refractory multiple myeloma (RRMM): Updated phase 1b results for daratumumab in combination with teclistamab (a BCMA x CD3 bispecific antibody). *J Clin Oncol* 2022;40(16_suppl):8032.
- [72] Krejcik J, Casneuf T, Nijhof IS, et al. Daratumumab depletes CD381 immune regulatory cells, promotes T-cell expansion, and skews T-cell repertoire in multiple myeloma. *Blood* 2016;128(3):384–94.
- [73] Rodriguez-Otero P, Dholaria B, Askari E, et al. Subcutaneous Teclistamab in Combination with Daratumumab for the Treatment of Patients with Relapsed/Refractory Multiple Myeloma: Results from a Phase 1b Multicohort Study. *Blood* 2021;138(Supplement 1):1647.
- [74] Zamagni E, Boccadoro M, Spencer A, et al. MajesTEC-4 (EMN30): A Phase 3 Trial of Teclistamab 1 Lenalidomide Versus Lenalidomide Alone As Maintenance Therapy Following Autologous Stem Cell Transplantation in Patients with Newly Diagnosed Multiple Myeloma. *Blood* 2022;140(Supplement 1):7289–91.
- [75] Krishnan AY, Manier S, Terpos E, et al. MajesTEC-7: A Phase 3, Randomized Study of Teclistamab 1 Daratumumab 1 Lenalidomide (Tec-DR) Versus Daratumumab 1 Lenalidomide 1 Dexamethasone (DRd) in Patients with Newly Diagnosed Multiple Myeloma Who Are Either Ineligible or Not Intended for Autologous Stem Cell Transplant. *Blood* 2022;140(Supplement 1):10148–9.
- [76] Sebag M, Raje NS, Bahlis NJ, et al. Elranatamab (PF-06863135), a B-Cell Maturation Antigen (BCMA) Targeted

- CD3-Engaging Bispecific Molecule, for Patients with Relapsed or Refractory Multiple Myeloma: Results from MagnetisMM-1. *Blood* 2021;138(Supplement 1):895.
- [77] Lesokhin A, Iida S, Stevens D, et al. MagnetisMM-3: An Open-Label, Multicenter, Non-Randomized Phase 2 Study of Elranatamab (PF-06863135) in Patients with Relapsed or Refractory Multiple Myeloma. *Blood* 2021;138(Supplement 1):1674.
- [78] Tomasson MH, Arnulf B, Bahlis NJ, et al. Elranatamab, a B-cell maturation antigen (BCMA)-CD3 bispecific antibody, for patients (pts) with relapsed/refractory multiple myeloma (RRMM): Extended follow up and biweekly administration from the MagnetisMM-3 study. *J Clin Oncol* 2023;41(16_suppl):8039.
- [79] Costa LJ, Wong SW, Bermudez A, et al. First Clinical Study of the B-Cell Maturation Antigen (BCMA) 211 T Cell Engager (TCE) CC-93269 in Patients (Pts) with Relapsed/Refractory Multiple Myeloma (RRMM): Interim Results of a Phase 1 Multicenter Trial. *Blood* 2019;134(Supplement_1):143.
- [80] Wong SW, Bar N, Paris L, et al. Alnuctamab (ALNUC; BMS-986349; CC-93269), a B-Cell Maturation Antigen (BCMA) x CD3 T-Cell Engager (TCE), in Patients (pts) with Relapsed/Refractory Multiple Myeloma (RRMM): Results from a Phase 1 First-in-Human Clinical Study. *Blood* 2022;140(Supplement 1):400-2.
- [81] Buma N, Richter JR, Dhodapkar MV, et al. LINKER-MM1 study: Linvoseltamab (REGN5458) in patients with relapsed/refractory multiple myeloma. *J Clin Oncol* 2023;41(16_suppl):8006.
- [82] D'Souza A, Shah N, Rodriguez C, et al. A Phase I First-in-Human Study of ABBV-383, a B-Cell Maturation Antigen x CD3 Bispecific T-Cell Redirecting Antibody, in Patients With Relapsed/Refractory Multiple Myeloma. *J Clin Oncol* 2022;40(31):3576-86.
- [83] Verkleij CPM, Broekmans MEC, van Duin M, et al. Preclinical activity and determinants of response of the GPRC5D x CD3 bispecific antibody talquetamab in multiple myeloma. *Blood Adv* 2021;5(8):2196-215.
- [84] Chari A, Minnema MC, Berdeja JG, et al. Talquetamab, a T-Cell-Redirecting GPRC5D Bispecific Antibody for Multiple Myeloma. *N Engl J Med* 2022; 387(24):2232-44.
- [85] Krishnan AY, Minnema MC, Berdeja JG, et al. Updated Phase 1 Results from MonumenTAL-1: First-in-Human Study of Talquetamab, a G Protein-Coupled Receptor Family C Group 5 Member D x CD3 Bispecific Antibody, in Patients with Relapsed/Refractory Multiple Myeloma. *Blood* 2021;138(Supplement 1):158.
- [86] Cohn Y, Morillo D. First results from the RedirecTT-1 study with teclistamab (tec) 1 talquetamab (tal) simultaneously targeting BCMA and GPRC5D in patients (pts) with relapsed/refractory multiple myeloma (RRMM), *J Clin Oncol*, 41,(16_suppl), 2023, 8002.
- [87] Morillo D, Gatt ME, Sebag M, et al. First results from the RedirecTT-1 study with teclistamab (tec) 1 talquetamab (tal) simultaneously targeting BCMA and GPRC5D in patients (pts) with relapsed/refractory multiple myeloma (RRMM). *J Clin Oncol* 2023;41(16_suppl):8002.
- [88] Hasselbalch Riley C, Hutchings M,

- Yoon S-S, et al. S180: RG6234, A NOVELGPRC5D T-CELL ENGAGING BISPECIFIC ANTIBODY, INDUCES RAPID RESPONSES IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA: PRELIMINARY RESULTS FROM A FIRST-IN-HUMAN TRIAL. *HemaSphere* 2022;6:81–2.
- [89] Sim BZ, Longhitano A, Er J, et al. Infectious complications of bispecific antibody therapy in patients with multiple myeloma. *Blood Cancer J* 2023;13(1):34.
- [90] Mazahreh F, Mazahreh L, Schinke C, et al. Risk of infections associated with the use of bispecific antibodies in multiple myeloma: a pooled analysis. *Blood Adv* 2023;7(13):3069–74.
- [91] Cohen AD, Harrison SJ, Krishnan A, et al. Initial Clinical Activity and Safety of BFCR4350A, a FcRH5/CD3 T-Cell-Engaging Bispecific Antibody, in Relapsed/Refractory Multiple Myeloma. *Blood* 2020;136(Supplement 1):42–3.
- [92] Trudel S, Cohen AD, Krishnan AY, et al. Cevostamab Monotherapy Continues to Show Clinically Meaningful Activity and Manageable Safety in Patients with Heavily Pre-Treated Relapsed/Refractory Multiple Myeloma (RRMM): Updated Results from an Ongoing Phase I Study. *Blood* 2021;138(Supplement 1):157.
- [93] Lesokhin AM, Richter J, Trudel S, et al. Enduring Responses after 1-Year, FixedDuration Cevostamab Therapy in Patients with Relapsed/Refractory Multiple Myeloma: Early Experience from a Phase I Study. *Blood* 2022;140(Supplement 1):4415–7.
- [94] Mohan SR, Costa Chase C, Berdeja JG, et al. Initial Results of Dose Escalation of ISB 1342, a Novel CD3xCD38 Bispecific Antibody, in Patients with Relapsed/Refractory Multiple Myeloma (RRMM). *Blood* 2022;140(Supplement 1):7264–6.
- [95] Viardot A, Bargou R. Bispecific antibodies in haematological malignancies. *Cancer Treat Rev* 2018;65:87–95.
- [96] Ahn S, Leblay N, Neri P. Understanding the Mechanisms of Resistance to T Cellbased Immunotherapies to Develop More Favorable Strategies in Multiple Myeloma. *Hemasphere* 2021;5(6):e575.
- [97] Da Via MC, Dietrich O, Truger M, et al. Homozygous BCMA gene deletion in response to anti-BCMA CAR T cells in a patient with multiple myeloma. *NatMed* 2021;27(4):616–9.
- [98] Samur MK, Fulciniti M, Aktas Samur A, et al. Biallelic loss of BCMA as a resistance mechanism to CAR T cell therapy in a patient with multiple myeloma. *Nat Commun* 2021;12(1):868.
- [99] Bannerji R, Allan JN, Arnason JE, et al. Clinical Activity of REGN1979, a Bispecific Human, Anti-CD20 x Anti-CD3 Antibody, in Patients with Relapsed/Refractory (R/R) B-Cell Non-Hodgkin Lymphoma (B-NHL). *Blood* 2019;134(Supplement_1):762.
- [100] Bannerji R, Arnason JE, Advani R, et al. Emerging Clinical Activity of REGN1979, an Anti-CD20 x Anti-CD3 Bispecific Antibody, in Patients with Relapsed/Refractory Follicular Lymphoma (FL), Diffuse Large B-Cell Lymphoma (DLBCL), and Other B-Cell Non-Hodgkin Lymphoma (B-NHL) Subtypes. *Blood* 2018;132(Supplement1):1690.
- [101] Verkleij CPM, Broekmans M, Wong A, et al.

- Mechanisms of Resistance and Determinants of Response of the GPRC5D-Targeting T-Cell Redirecting Bispecific Antibody JNJ-7564 in Multiple Myeloma. *Blood* 2020;136(Supplement 1):8–9.
- [102] Truger MS, Duell J, Zhou X, et al. Single- and double-hit events in genes encoding immune targets before and after T cell-engaging antibody therapy in MM. *Blood Adv* 2021;5(19):3794–8.
- [103] Lee H, Neri P, Ahn S, et al. Role of TNFRSF17 and GPRC5D Structural and Point Mutations in Resistance to Targeted Immunotherapies in Multiple Myeloma (MM). *Blood* 2022;140(Supplement 1):252–3.
- [104] Bahlis N, Lee H, Ahn S, et al. Mechanisms of antigen escape from BCMA- or GPRC5D-targeted immunotherapies in multiple myeloma. *Nat Med* 2023;29(9):2295–306.
- [105] Leblay N, Maity R, Barakat E, et al. Cite-Seq Profiling of T Cells in Multiple Myeloma Patients Undergoing BCMA Targeting CAR-T or Bites Immunotherapy. *Blood* 2020;136(Supplement 1):11–2.
- [106] Philipp N, Kazerani M, Nicholls A, et al. T-cell exhaustion induced by continuous bispecific molecule exposure is ameliorated by treatment-free intervals. *Blood* 2022;140(10):1104–18.
- [107] Karlin L, Benboubker L, Nahi H, et al. Durability of responses with biweekly dosing of teclistamab in patients with relapsed/refractory multiple myeloma achieving a clinical response in the majesTEC-1 study. *J Clin Oncol* 2023; 41(16_suppl):8034.
- [108] Neri P, Ahn S, Lee H, et al. Dysfunctional Hyper-Expanded Clonotypes and Lack of TCR Clonal Replacement Predict Resistance to T Cell Engagers in Multiple Myeloma. *Blood* 2022;140(Supplement 1):2093–4.
- [109] Friedrich MJ, Neri P, Kehl N, et al. The pre-existing T cell landscape determines the response to bispecific T cell engagers in multiple myeloma patients. *Cancer Cell* 2023;41(4):711–725 e6.
- [110] Cho SF, Lin L, Xing L, et al. The immunomodulatory drugs lenalidomide and pomalidomide enhance the potency of AMG 701 in multiple myeloma preclinical models. *Blood Adv* 2020;4(17):4195–207.
- [111] Meermeier EW, Welsh SJ, Sharik ME, et al. Tumor burden limits bispecific antibody efficacy through T cell exhaustion averted by concurrent cytotoxic therapy. *Blood Cancer Discov* 2021;2(4):354–69.
- [112] Meermeier EW, Welsh SJ, Sharik M, et al. Abstract 5588: PD-1 blockade synergizes with IMiDs to enhance bispecific T cell engager immune responses to Vk*MYChCRBN multiple myeloma by preventing T cell exhaustion. *Cancer Res* 2022;82(12_Supplement):5588.
- [113] Ravi G, Costa LJ. Bispecific T-cell engagers for treatment of multiple myeloma. *Am J Hematol* 2023;98(Suppl 2):S13–21.

8 嵌合抗原受体 T 细胞在多发性骨髓瘤治疗中的应用

- [1] Eshhar Z, Waks T, Gross G, et al. Specific activation and targeting of cytotoxic lymphocytes through chimeric single chains consisting of antibody-binding domains and the gamma or zeta subunits of the immunoglobulin and T-cell receptors. *Proc Natl Acad Sci USA* 1993;90:720–4.
- [2] Milone MC, Fish JD, Carpenito C, et al. Chimeric receptors containing CD137 signal transduction domains mediate enhanced survival of T cells and increased antileukemic efficacy in vivo. *Mol Ther* 2009;17:1453–64.
- [3] Savoldo B, Ramos CA, Liu E, et al. CD28 costimulation improves expansion and persistence of chimeric antigen receptor-modified T cells in lymphoma patients. *J Clin Invest* 2011;121:1822–6.
- [4] Scholler J, Brady TL, Binder-Scholl G, et al. Decade-long safety and function of retroviral-modified chimeric antigen receptor T cells. *Sci Transl Med* 2012;4: 132ra53.
- [5] Levine BL, Humeau LM, Boyer J, et al. Gene transfer in humans using a conditionally replicating lentiviral vector. *Proc Natl Acad Sci USA* 2006;103:17372–7.
- [6] Turtle CJ, Hanafi LA, Berger C, et al. Immunotherapy of non-Hodgkin's lymphoma with a defined ratio of CD81 and CD41 CD19-specific chimeric antigen receptor-modified T cells. *Sci Transl Med* 2016;8:355ra116.
- [7] Porter DL, Hwang WT, Frey NV, et al. Chimeric antigen receptor T cells persist and induce sustained remissions in relapsed refractory chronic lymphocytic leukemia. *Sci Transl Med* 2015;7:303ra139.
- [8] Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. *N Engl J Med* 2018;378: 439–48.
- [9] Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. *N Engl J Med* 2017;377:2531–44.
- [10] Garfall AL, Maus MV, Hwang WT, et al. Chimeric Antigen Receptor T Cells against CD19 for Multiple Myeloma. *N Engl J Med* 2015;373:1040–7.
- [11] Matsui W, Wang Q, Barber JP, et al. Clonogenic multiple myeloma progenitors, stem cell properties, and drug resistance. *Cancer Res* 2008;68:190–7.
- [12] Garfall AL, Stadtmauer EA, Hwang WT, et al. Anti-CD19 CAR T cells with highdose melphalan and autologous stem cell transplantation for refractory multiple myeloma. *JCI insight* 2018;3:e120505.
- [13] Guo B, Chen M, Han Q, et al. CD138-directed adoptive immunotherapy of chimeric antigen receptor (CAR)-modified T cells for multiple myeloma. *J Cell Immunother* 2016;2:28–35.
- [14] Ramos CA, Savoldo B, Torrano V, et al. Clinical responses with T lymphocytes targeting malignancy-associated k light chains. *J Clin Invest* 2016;126:2588–96.
15. Salem DA, Maric I, Yuan CM, et al.

- Quantification of B-cell maturation antigen, a target for novel chimeric antigen receptor T-cell therapy in Myeloma. *Leuk Res* 2018;71:106–11.
- [16] Carpenter RO, Evbuomwan MO, Pittaluga S, et al. B-cell maturation antigen is a promising target for adoptive T-cell therapy of multiple myeloma. *Clin Cancer Res* 2013;19:2048–60.
- [17] Brudno JN, Maric I, Hartman SD, et al. T Cells Genetically Modified to Express an Anti-B-Cell Maturation Antigen Chimeric Antigen Receptor Cause Remissions of Poor-Prognosis Relapsed Multiple Myeloma. *J Clin Oncol* 2018;36:2267–80.
- [18] Cohen AD, Garfall AL, Stadtmauer EA, et al. B cell maturation antigen-specific CAR T cells are clinically active in multiple myeloma. *J Clin Invest* 2019;129:2210–21.
- [19] Raje N, Berdeja J, Lin Y, et al. Anti-BCMA CAR T-Cell Therapy bb2121 in Relapsed or Refractory Multiple Myeloma. *N Engl J Med* 2019;380:1726–37.
- [20] Zhao W-H, Liu J, Wang BY, et al. A phase 1, open-label study of LCAR-B38M, a chimeric antigen receptor T cell therapy directed against B cell maturation antigen, in patients with relapsed or refractory multiple myeloma. *J Hematol Oncol* 2018;11:141.
- [21] Munshi NC, Anderson LD Jr, Shah N, et al. Idecabtagene Vicleucel in Relapsed and Refractory Multiple Myeloma. *N Engl J Med* 2021;384:705–16.
- [22] Manier S, Kansagra AJ, Anderson, Jr LD, et al. Characteristics of neurotoxicity associated with idecabtagene vicleucel (ide-cel, bb2121) in patients with relapsed and refractory multiple myeloma (RRMM) in the pivotal phase II KarMMa study. *J Clin Oncol* 2021;39:8036.
- [23] Shah N, Mojebi A, Ayers D, et al. Indirect treatment comparison of idecabtagene vicleucel versus conventional care in triple-class exposed multiple myeloma. *J Comp Eff Res* 2022;11:737–49.
- [24] Rodriguez-Otero P, Ayers D, Cope S, et al. Matching adjusted indirect comparisons of efficacy outcomes for idecabtagene vicleucel (ide-cel, bb2121) versus selinexor 1 dexamethasone and belantamab mafodotin in relapsed and refractory multiple myeloma. *Leuk Lymphoma* 2021;62:2482–91.
- [25] Jagannath S, Lin Y, Goldschmidt H, et al. KarMMa-RW: comparison of idecabtagene vicleucel with real-world outcomes in relapsed and refractory multiple myeloma. *Blood Cancer J* 2021;11:116.
- [26] Sanoyan DA, Seipel K, Bacher U, et al. Real-life experiences with CAR T-cell therapy with idecabtagene vicleucel (ide-cel) for triple-class exposed relapsed/refractory multiple myeloma patients. *BMC Cancer* 2023;23:345.
- [27] Hansen DK, Sidana S, Peres LC, et al. Idecabtagene Vicleucel for Relapsed/Refractory Multiple Myeloma: Real-World Experience From the Myeloma CAR T Consortium. *J Clin Oncol* 2023;41:2087–97.
- [28] Ferreri CJ, Hildebrandt MA, Hashmi H, et al. Idecabtagene Vicleucel (Ide-cel) Chimeric Antigen Receptor (CAR) T-Cell Therapy in Patients with Relapsed/Refractory Multiple Myeloma (RRMM) Who Have Received a Prior BCMA-Targeted Therapy: Real World, Multi-Institutional Experience. *Blood* 2022;140:1856–8.
- [29] Rodriguez-Otero P, Ailawadhi S, Arnulf B, et al. Ide-cel or Standard Regimens in Relapsed

- and Refractory Multiple Myeloma. *N Engl J Med* 2023;388:1002–14.
- [30] Mi J-Q, Zhao WH, Chen LJ, et al. Long-term remission and survival in patients with relapsed or refractory multiple myeloma after treatment of LCAR-B38M CAR-T: At least 5-year follow-up in LEGEND-2. *J Clin Oncol* 2023;41:8010.
- [31] Martin T, Lin Y, Agha M, et al. Health-related quality of life in patients given ciltacabtagene autoleucel for relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b-2, open-label study. *Lancet Haematol* 2022;9:e897–905.
- [32] Berdeja JG, Madduri D, Usmani SZ, et al. Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study. *Lancet (London, England)* 2021;398:314–24.
- [33] Lin Y, Martin TG, Usmani SZ, et al. CARTITUDE-1 final results: Phase 1b/2 study of ciltacabtagene autoleucel in heavily pretreated patients with relapsed/refractory multiple myeloma. *J Clin Oncol* 2023;41:8009.
- [34] Martin T, Usmani SZ, Schechter JM, et al. Matching-adjusted indirect comparison of efficacy outcomes for ciltacabtagene autoleucel in CARTITUDE-1 versus idecabtagene vicleucel in KarMMa for the treatment of patients with relapsed or refractory multiple myeloma. *Curr Med Res Opin* 2021;37:1779–88.
- [35] Weisel K, Martin T, Krishnan A, et al. Comparative Efficacy of Ciltacabtagene Autoleucel in CARTITUDE-1 vs Physician's Choice of Therapy in the Long-Term Follow-Up of POLLUX, CASTOR, and EQUULEUS Clinical Trials for the Treatment of Patients with Relapsed or Refractory Multiple Myeloma. *Clin Drug Investig* 2022;42:29–41.
- [36] Hansen DK, Patel KK, Peres LC, et al. Safety and efficacy of standard of care (SOC) ciltacabtagene autoleucel (Cilta-cel) for relapsed/refractory multiple myeloma (RRMM). *J Clin Oncol* 2023;41:8012.
- [37] Cohen AD, Mateos MV, Cohen YC, et al. Efficacy and safety of cilta-cel in patients with progressive multiple myeloma after exposure to other BCMA-targeting agents. *Blood* 2023;141:219–30.
- [38] San-Miguel J, Dhakal B, Yong K, et al. Cilta-cel or Standard Care in Lenalidomide-Refractory Multiple Myeloma. *N Engl J Med* 2023. <https://doi.org/10.1056/NEJMoa2303379>.
- [39] Dhakal B, Yong K, Harrison SJ, et al. First phase 3 results from CARTITUDE-4: Cilta-cel versus standard of care (Pvd or DPd) in lenalidomide-refractory multiple myeloma. *J Clin Oncol* 2023;41:LBA106.
- [40] Garfall AL, Cohen AD, Susanibar-Adaniya SP, et al. Anti-BCMA/CD19 CAR T Cells with Early Immunomodulatory Maintenance for Multiple Myeloma Responding to Initial or Later-Line Therapy. *Blood cancer Discov* 2023;4:118–33.
- [41] Chen W, Fu C, Fang B, et al. Phase II Study of Fully Human BCMA-Targeting CAR-T Cells (Zevorcabtagene Autoleucel) in Patients with Relapsed/Refractory Multiple Myeloma. *Blood* 2022;140:4564–5.
- [42] Li C, Wang D, Song Y, et al. CT103A, a novel fully human BCMA-targeting CAR-

- Tcells, in patients with relapsed/refractory multiple myeloma: Updated results of phase 1b/2 study (FUMANBA-1). *J Clin Oncol* 2023;41:8025.
- [43] Frigault MJ, Bishop MR, Rosenblatt J, et al. Phase 1 study of CART-ddBCMA for the treatment of subjects with relapsed and refractory multiple myeloma. *Blood Adv* 2023;7:768–77.
- [44] Raje NS, Shah N, Jagannath S, et al. Updated Clinical and Correlative Results from the Phase I CRB-402 Study of the BCMA-Targeted CAR T Cell Therapy bb21217 in Patients with Relapsed and Refractory Multiple Myeloma. *Blood* 2021;138:548.
- [45] Costello CL, Cohen AD, Patel KK, et al. Phase 1/2 Study of the Safety and Response of P-BCMA-101 CAR-T Cells in Patients with Relapsed/Refractory (r/r) Multiple Myeloma (MM) (PRIME) with Novel Therapeutic Strategies. *Blood* 2020;136:29–30.
46. Mailankody S, Jakubowiak AJ, Htut M, et al. Orvacabtagene autoleucel (orvace), a B-cell maturation antigen (BCMA)-directed CAR T cell therapy for patients (pts) with relapsed/refractory multiple myeloma (RRMM): update of the phase 1/2 EVOLVE study (NCT03430011). *J Clin Oncol* 2020;38:8504.
- [47] Costa LJ, Kumar SK, Atrash S, et al. Results from the First Phase 1 Clinical Study of the B-Cell Maturation Antigen (BCMA) Nex T Chimeric Antigen Receptor (CAR) T Cell Therapy CC-98633/BMS-986354 in Patients (pts) with Relapsed/Refractory Multiple Myeloma (RRMM). *Blood* 2022;140:1360–2.
- [48] Sperling AS, Derman BA, Nikiforow S, et al. Updated phase I study results of PHE885, a T-Charge manufactured BCMA-directed CAR-T cell therapy, for patients (pts) with r/r multiple myeloma (RRMM). *J Clin Oncol* 2023;41:8004.
- [49] Du J, Fu WJ, Jiang H, et al. Updated results of a phase I, open-label study of BCMA/CD19 dual-targeting fast CAR-T GC012F for patients with relapsed/refractory multiple myeloma (RRMM). *J Clin Oncol* 2023;41:8005.
- [50] Mailankody S, Matous JV, Chhabra S, et al. Allogeneic BCMA-targeting CAR T cells in relapsed/refractory multiple myeloma: phase 1 UNIVERSAL trial interim results. *Nat Med* 2023;29:422–9.
- [51] Frey N, Porter D. Cytokine release syndrome with chimeric antigen receptor T cell therapy. *J Am Soc Blood Marrow Transplant* 2019;25:e123–7.
- [52] Hines MR, Knight TE, McNerney KO, et al. Immune Effector Cell-Associated Hemophagocytic Lymphohistiocytosis-Like Syndrome. *Transplant Cell Ther* 2023;29:438.e1–16.
- [53] Martin T, Usmani SZ, Berdeja JG, et al. Ciltacabtagene Autoleucel, an Anti-B-cell Maturation Antigen Chimeric Antigen Receptor T-Cell Therapy, for Relapsed/Refractory Multiple Myeloma: CARTITUDE-1 2-Year Follow-Up. *J Clin Oncol* 2023;41:1265–74.
- [54] Cohen AD, Parekh S, Santomasso BD, et al. Incidence and management of CART neurotoxicity in patients with multiple myeloma treated with ciltacabtagene autoleucel in CARTITUDE studies. *Blood Cancer J* 2022;12:32.
- [55] Karschnia P, Miller KC, Yee AJ, et al. Neurologic toxicities following adoptive immunotherapy with BCMA-directed CAR

- T-cells. *Blood* 2023;2023020571. <https://doi.org/10.1182/blood.2023020571>.
- [56] Van Oekelen O, Aleman A, Upadhyaya B, et al. Neurocognitive and hypokinetic movement disorder with features of parkinsonism after BCMA-targeting CAR-T cell therapy. *Nat Med* 2021;27:2099–103.
- [57] Davis JA, Sborov DW, Wesson W, et al. Efficacy and Safety of CD341 Stem Cell Boost for Delayed Hematopoietic Recovery After BCMA Directed CAR T-cell Therapy. *Transplant Cell Ther* 2023. <https://doi.org/10.1016/j.jtct.2023.05.012>.
- [58] Kambhampati S, Sheng Y, Huang CY, et al. Infectious complications in patients with relapsed refractory multiple myeloma after BCMA CAR T-cell therapy. *Blood Adv* 2022;6:2045–54.
- [59] Mohan M, Chakraborty R, Bal S, et al. Recommendations on prevention of infections during chimeric antigen receptor T-cell and bispecific antibody therapy in multiple myeloma. *Br J Haematol* 2023;203(5):736–46.
- [60] Billadeau D, Ahmann G, Greipp P, et al. The bone marrow of multiple myeloma patients contains B cell populations at different stages of differentiation that are clonally related to the malignant plasma cell. *J Exp Med* 1993;178:1023–31.
- [61] Wang Y, Cao J, Gu W, et al. Long-Term Follow-Up of Combination of B-Cell Maturation Antigen and CD19 Chimeric Antigen Receptor T Cells in Multiple Myeloma. *J Clin Oncol* 2022;40:2246–56.
- [62] Du J, Jiang H, Dong B, et al. Updated results of a multicenter first-in-human study of BCMA/CD19 dual-targeting fast CAR-T GC012F for patients with relapsed/refractory multiple myeloma (RRMM). *J Clin Oncol* 2022;40:8005.
- [63] Chari A, Minnema MC, Berdeja JG, et al. Talquetamab, a T-Cell–Redirecting GPRC5D Bispecific Antibody for Multiple Myeloma. *N Engl J Med* 2022;387: 2232–44.
- [64] Mailankody S, Devlin SM, Landa J, et al. GPRC5D-Targeted CAR T Cells for Myeloma. *N Engl J Med* 2022;387:1196–206.
- [65] Zhang M, Wei G, Zhou L, et al. GPRC5D CAR T cells (OriCAR-017) in patients with relapsed or refractory multiple myeloma (POLARIS): a first-in-human, single-centre, single-arm, phase 1 trial. *Lancet Haematol* 2023;10:e107–16.
- [66] Xia J, Li H, Yan Z, et al. Anti-G Protein-Coupled Receptor, Class C Group 5 Member D Chimeric Antigen Receptor T Cells in Patients With Relapsed or Refractory Multiple Myeloma: A Single-Arm, Phase II Trial. *J Clin Oncol* 2023;41:2583–93.
- [67] Bal S, et al. BMS-986393 (CC-95266), a G protein-coupled receptor class C group5 member D (GPRC5D)-targeted CAR T-cell therapy for relapsed/refractory multiple myeloma (RRMM): results from a phase 1 study. *EHA Libr.* (2023).
- [68] Bahlis N, et al. Tumor Intrinsic Mechanisms of Antigen Escape to Anti-BCMA and Anti-GPRC5D Targeted Immunotherapies in Multiple Myeloma. (2023) doi:10.21203/rs.3.rs-2657360/v1.
- [69] Dimopoulos MA, Dytfield D, Grosicki S, et al. Elotuzumab plus Pomalidomide and Dexamethasone for Multiple Myeloma. *N Engl J Med* 2018;379:1811–22.
- [70] O’Neal J, Ritchey JK, Cooper ML, et al. CS1 CAR-T targeting the distal domain of CS1

- (SLAMF7) shows efficacy in high tumor burden myeloma model despite fratricide of CD81CS1 expressing CAR-T cells. *Leukemia* 2022;36:1625–34.
- [71] Wang X, Walter M, Urak R, et al. Lenalidomide Enhances the Function of CS1 Chimeric Antigen Receptor-Redirected T Cells Against Multiple Myeloma. *Clin Cancer Res* 2018;24:106–19.
- [72] Li C, Wang X, Wu Z, et al. Bispecific CS1-BCMA CAR-T Cells Are Clinically Active in Relapsed or Refractory Multiple Myeloma: An Updated Clinical Study. *Blood* 2022;140:4573–4.
- [73] Sallman DA, Kerre T, Havelange V, et al. CYAD-01, an autologous NKG2D-based CAR T-cell therapy, in relapsed or refractory acute myeloid leukaemia and myelodysplastic syndromes or multiple myeloma (THINK): haematological cohorts of the dose escalation segment of a phase 1 trial. *Lancet Haematol* 2023;10: e191–202.
- [74] Lonial S, Weiss BM, Usmani SZ, et al. Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial. *Lancet* 2016;387:1551–60.
- [75] Drent E, Themeli M, Poels R, et al. A Rational Strategy for Reducing On-Target Off-Tumor Effects of CD38-Chimeric Antigen Receptors by Affinity Optimization. *Mol Ther* 2017;25:1946–58.
- [76] Sun C, Mahendravada A, Ballard B, et al. Safety and efficacy of targeting CD138 with a chimeric antigen receptor for the treatment of multiple myeloma. *Oncotarget* 2019;10:2369–83.
- [77] Jiang D, Huang H, Qin H, et al. Chimeric antigen receptor T cells targeting FcRH5 provide robust tumour-specific responses in murine xenograft models of multiple myeloma. *Nat Commun* 2023;14:3642.
- [78] Radhakrishnan SV, Luetkens T, Scherer SD, et al. CD229 CAR T cells eliminate multiple myeloma and tumor propagating cells without fratricide. *Nat Commun* 2020;11:798.
- [79] Wong DP, Roy NK, Zhang K, et al. A BAFF ligand-based CAR-T cell targeting three receptors and multiple B cell cancers. *Nat Commun* 2022;13:217.
- [80] Shah N, Munshi NC, Berdeja JG, et al. Baseline Correlates of Complete Response to Idecabtagene Vicleucel (ide-cel, bb2121), a BCMA-Directed CAR T Cell Therapy in Patients with Relapsed and Refractory Multiple Myeloma: Subanalysis of the KarMMa Trial. *Blood* 2021;138:1739.
- [81] Rytlewski J, Fuller J, Mertz DR, et al. Correlative analysis to define patient profiles associated with manufacturing and clinical endpoints in relapsed/refractory multiple myeloma (RRMM) patients treated with idecabtagene vicleucel (ide-cel; bb2121), an anti-BCMA CAR T cell therapy. *J Clin Oncol* 2022;40:8021.
- [82] Dhodapkar KM, Cohen AD, Kaushal A, et al. Changes in Bone Marrow Tumor and Immune Cells Correlate with Durability of Remissions Following BCMA CAR T Therapy in Myeloma. *Blood cancer Discov* 2022;3:490–501.
- [83] Friedrich MJ, Neri P, Kehl N, et al. The pre-existing T cell landscape determines the response to bispecific T cell engagers in multiple myeloma patients. *Cancer Cell* 2023;41:711–25.e6.
- [84] Garfall AL, Dancy EK, Cohen AD, et al.

- T-cell phenotypes associated with effective CAR T-cell therapy in postinduction vs relapsed multiple myeloma. *Blood Adv* 2019;3:2812–5.
- [85] Samur MK, Fulciniti M, Aktas Samur A, et al. Biallelic loss of BCMA as a resistance mechanism to CAR T cell therapy in a patient with multiple myeloma. *Nat Commun* 2021;12:868.
- [86] Da Vià MC, Dietrich O, Truger M, et al. Homozygous BCMA gene deletion in response to anti-BCMA CAR T cells in a patient with multiple myeloma. *Nat Med* 2021;27:616–9.
- [87] Cowan AJ, Pont MJ, Sather BD, et al. g-Secretase inhibitor in combination with BCMA chimeric antigen receptor T-cell immunotherapy for individuals with relapsed or refractory multiple myeloma: a phase 1, first-in-human trial. *Lancet Oncol* 2023;24:811–22.
- [88] Fernández de Larrea C, Staehr M, Lopez AV, et al. Defining an Optimal DualTargeted CAR T-cell Therapy Approach Simultaneously Targeting BCMA and GPRC5D to Prevent BCMA Escape-Driven Relapse in Multiple Myeloma. *Blood cancer Discov* 2020;1:146–54.
- [89] Chong EA, Gerson JN, Nasta SD, et al. Outcomes with bendamustine lymphodepletion prior to brexucabtagene autoleucel for mantle cell lymphoma. *J Clin Oncol* 2023;41:e19540.
- [90] Zhang Q, Hresko ME, Picton LK, et al. A human orthogonal IL-2 and IL-2Rb system enhances CAR T cell expansion and antitumor activity in a murine model of leukemia. *Sci Transl Med* 2023;13:eabg6986.
- [91] Imbach KJ, Patel A, Levine AD. Ethical Considerations in the Translation of CAR-T Cell Therapies. *Cell Gene Ther Insights* 2018;4:295–307.
- [92] Derman BA, Parker WF. Fair Allocation of Scarce CAR T-Cell Therapies for Relapsed/Refractory Multiple Myeloma. *JAMA* 2023. <https://doi.org/10.1001/jama.2023.11846>.
- [93] Petersen CT, Hassan M, Morris AB, et al. Improving T-cell expansion and function for adoptive T-cell therapy using ex vivo treatment with PI3Kd inhibitors and VIP antagonists. *Blood Adv* 2018;2:210–23.
- [94] Yan Z, Cao J, Cheng H, et al. A combination of humanised anti-CD19 and antiBCMA CAR T cells in patients with relapsed or refractory multiple myeloma: a single-arm, phase 2 trial. *Lancet Haematol* 2019;6:e521–9.

9 造血干细胞移植在多发性骨髓瘤治疗中是否仍有重要地位

- [1] Singh S, Sharma R, Singh J, et al. Autologous stem cell transplantation for multiple myeloma in the novel agent era: Systematic review of Indian data and implications for resource constrained settings. *J Cancer Res Ther* 2023;19(Supplement):S12–s19.
- [2] Lamm W, Wohlfarth P, Bojic M, et al. Outcome in Multiple Myeloma Patients Eligible for Stem Cell Transplantation: A Single-Center Experience. *Oncology* 2015;89(4):196–204.
- [3] Belotti A, Ribolla R, Cancelli V, et al. Transplant eligibility in elderly multiple myeloma patients: Prospective external validation of the international myeloma working group frailty score and comparison with clinical judgment and other comorbidity scores in unselected patients aged 65-75 years. *Am J Hematol* 2020;95(7):759–65.
- [4] Vaxman I, Visram A, Kumar S, et al. Autologous stem cell transplantation for multiple myeloma patients aged 75 treated with novel agents. *Bone Marrow Transplant* 2021;56(5):1144–50.
- [5] Kumar L, Sahoo RK, Kumar S, et al. Autologous stem cell transplant for multiple myeloma: Impact of melphalan dose on the transplant outcome. *Leuk Lymphoma* 2023;64(2):378–87.
- [6] Zhai Y, Yan L, Jin S, et al. Autologous stem cell transplantation in multiple myeloma patients with renal impairment. *Ann Hematol* 2023;102(3):621–8.
- [7] Lazana I, Floro L, Christmas T, et al. Autologous stem cell transplantation for multiple myeloma patients with chronic kidney disease: a safe and effective option. *Bone Marrow Transplant* 2022;57(6):959–65.
- [8] Waszczuk-Gajda A, Gras L, de Wreede LC, et al. Safety and efficacy of autologous stem cell transplantation in dialysis-dependent myeloma patients-The DIADEM study from the chronic malignancies working party of the EBMT. *Bone Marrow Transplant* 2023;58(4):424–9.
- [9] Awada H, Hajj Ali A, Ali MF, et al. Validation of the role of corrected DLCO in predicting outcomes post autologous hematopoietic cell transplant for multiple myeloma. *Eur J Haematol* 2023;110(6):780–3.
- [10] Pasvolsky O, Saliba RM, Masood A, et al. Impact of gender on outcomes of patients with multiple myeloma undergoing autologous Haematopoietic stem cell transplant. *Br J Haematol* 2023;201(4):e37–41.
- [11] Prakash VS, Malik PS, Sahoo RK, et al. Multiple myeloma: risk adapted use of plerixafor for stem cell mobilization prior to autologous stem cell transplantation is effective and cost efficient. *Clin Lymphoma Myeloma Leuk* 2022;22(1):44–51.

- [12] Chhabra S, Callander N, Watts NL, et al. Stem cell mobilization yields with daratumumab- and lenalidomide-containing quadruplet induction therapy in newly diagnosed multiple myeloma: findings from the MASTER and GRIFFIN trials. *Transplant Cell Ther* 2022;06:06.
- [13] Thurlapati A, Roubal K, Davis JA, et al. Stem cell mobilization for multiple myeloma patients receiving daratumumab-based induction therapy: a real- world experience. *Transplant Cell Ther* 2023;29(5):340.e341–4.
- [14] Crees ZD, Rettig MP, Jayasinghe RG, et al. Motixafortide and G-CSF to mobilize hematopoietic stem cells for autologous transplantation in multiple myeloma: a randomized phase 3 trial. *Nat Med* 2023;29(4):869–79.
- [15] Gomez-Arteaga A, Mark TM, Guarneri D, et al. High-dose bendamustine and melphalan conditioning for autologous stem cell transplantation for patients with multiple myeloma. *Bone Marrow Transplant* 2019;54(12):2027–38.
- [16] Cailleteau A, Maingon P, Choquet S, et al. Phase 1 study of the combination of escalated total marrow irradiation using helical tomotherapy and fixed highdose melphalan (140 mg/m²) followed by autologous stem cell transplantation at first relapse in multiple myeloma. *Int J Radiat Oncol Biol Phys* 2023;115(3):677–85.
- [17] Li N, Liang L, Xiang P, et al. Clonal haematopoiesis of indeterminate potential predicts delayed platelet engraftment after autologous stem cell transplantation for multiple myeloma. *Br J Haematol* 2023;201(3):577–80.
- [18] Scordo M, Gilbert LJ, Hanley DM, et al. Open-label pilot study of romiplostim for thrombocytopenia after autologous hematopoietic cell transplantation. *Blood Adv* 2023;7(8):1536–44.
- [19] Pandya C, Hashmi S, Khera N, et al. Cost-effectiveness analysis of early vs. late autologous stem cell transplantation in multiple myeloma. *Clin Transplant* 2014;28(10):1084–91.
- [20] Asrar MM, Lad DP, Bansal D, et al. Health-related quality of life in transplant eligible multiple myeloma patients with or without early ASCT in the real-world setting. *Leuk Lymphoma* 2021;62(13):3271–7.
- [21] Yong K, Wilson W, de Tute RM, et al. Upfront autologous haematopoietic stem-cell transplantation versus carfilzomib-cyclophosphamide-dexamethasone consolidation with carfilzomib maintenance in patients with newly diagnosed multiple myeloma in England and Wales (CARDAMON): a randomised, phase 2, noninferiority trial. *Lancet Haematol* 2023;10(2):e93–106.
- [22] Lemieux C, Muffly LS, Iberri DJ, et al. Outcomes after delayed and second autologous stem cell transplant in patients with relapsed multiple myeloma. *Bone Marrow Transplant* 2021;56(11):2664–71.
- [23] Khan AM, Ozga M, Bhatt H, et al. Outcomes after salvage autologous hematopoietic cell transplant for patients with relapsed/refractory multiple myeloma: a single-institution experience. *Clin Lymphoma Myeloma Leuk* 2022;05:05.
- [24] Hashmi H, Atrash S, Jain J, et al. Daratumumab, pomalidomide, and dexamethasone (DPd) followed by high dose chemotherapy-Autologous Stem Cell

- Transplantation leads to superior outcomes when compared to DPd-alone for patients with Relapsed Refractory Multiple Myeloma. *Transplant Cell Ther* 2023;20:20.
- [25] Jain T, Sonbol MB, Firwana B, et al. High-dose chemotherapy with early autologous stem cell transplantation compared to standard dose chemotherapy or delayed transplantation in patients with newly diagnosed multiple myeloma: a systematic review and meta-analysis. *Biol Blood Marrow Transplant* 2019;25(2):239–47.
- [26] Khan S, Reece D, Atenafu EG, et al. Post salvage therapy autologous transplant for relapsed myeloma, ongoing relevance within modern treatment paradigms? *Clin Lymphoma Myeloma Leuk* 2023;23(2):e97–106. Role for Stem Cell Transplantation in Multiple Myeloma 417
- [27] Cook G, Ashcroft AJ, Cairns DA, et al. The effect of salvage autologous stem-cell transplantation on overall survival in patients with relapsed multiple myeloma (final results from BSBMT/UKMF Myeloma X Relapse [Intensive]): a randomised, open-label, phase 3 trial. *Lancet Haematol* 2016;3(7):e340–51.
- [28] Goldschmidt H, Baertsch MA, Schlenzka J, et al. Salvage autologous transplant and lenalidomide maintenance vs. lenalidomide/dexamethasone for relapsed multiple myeloma: the randomized GMMG phase III trial ReLApSE. *Leukemia* 2021;35(4):1134–44.
- [29] Richardson PG, Jacobus SJ, Weller EA, et al. Triplet therapy, transplantation, and maintenance until progression in myeloma. *N Engl J Med* 2022;387(2):132–47.
- [30] Stadtmauer EA, Pasquini MC, Blackwell B, et al. Autologous transplantation, consolidation, and maintenance therapy in multiple myeloma: results of the BMT CTN 0702 Trial. *J Clin Oncol* 2019;37(7):589–97.
- [31] Dispenzieri A, Krishnan A, Arendt B, et al. Mass-fix better predicts for PFS and OS than standard methods among multiple myeloma patients participating on the STAMINA trial (BMT CTN 0702/07LT). *Blood Cancer J* 2022;12(2):27.
- [32] Jung J, Kim K, Jung SH, et al. Cyclophosphamide, Bortezomib, and Dexamethasone Consolidation in Patients with Multiple Myeloma after Stem Cell Transplantation: The KMM130 Study. *Cancer Res Treat* 2023;55(2):693–703.
- [33] Lawless S, Iacobelli S, Knelange NS, et al. Comparison of autologous and allogeneic hematopoietic cell transplantation strategies in patients with primary plasma cell leukemia, with dynamic prediction modelling. *Haematologica* 2022;30:30.
- [34] Kriz T, Jungova A, Lysak D, et al. Allogeneic stem cell transplantation in patients with multiple myeloma-single center experience. *Neoplasma* 2023;23:23.
- [35] Gay F, Musto P, Rota-Scalabrini D, et al. Carfilzomib with cyclophosphamide and dexamethasone or lenalidomide and dexamethasone plus autologous transplantation or carfilzomib plus lenalidomide and dexamethasone, followed by maintenance with carfilzomib plus lenalidomide or lenalidomide alone for patients with newly diagnosed multiple myeloma (FORTE): a randomised, open-label, phase 2 trial. *Lancet Oncol* 2021;22(12):1705–20.
- [36] Lin CM, Chang LC, Shau WY, et al. Treatment benefit of upfront autologous

- stem cell transplantation for newly diagnosed multiple myeloma: a systematic review and meta-analysis. *BMC Cancer* 2023;23(1):446.37. Sato S, Tsunoda S, Kawahigashi T, et al. Clinical significance of high-dose chemotherapy with autologous stem cell transplantation in the era of novel agents in patients older than 65 years with multiple myeloma. *Ann Hematol* 2023;102(5):1185–91.
- [38] Pasvolsky O, Milton DR, Rauf M, et al. Impact of clonal plasma cells in autografts on outcomes in high-risk multiple myeloma patients. *Blood Cancer J* 2023;13(1):68.
- [39] Pasvolsky O, Gaballa MR, Milton DR, et al. Autologous Stem Cell Transplantation for Patients with Multiple Myeloma with Translocation (4;14): The MD Anderson Cancer Center Experience. *Transplant Cell Ther* 2023;29(4):260.e1-6.
- [40] Gertz MA, Buadi FK, Hayman SR, et al. Safety Outcomes for Autologous Stem Cell Transplant in Multiple Myeloma. *Mayo Clin Proc* 2018;93(1):56–8.
- [41] Kim DJ, Jeong S, Kong SG, et al. Incidence and risk factors of opportunistic infections after autologous stem cell transplantation: a nationwide, populationbased cohort study in Korea. *Sci Rep* 2023;13(1):2551.
- [42] D’Souza A, Brazauskas R, Stadtmauer EA, et al. Trajectories of quality of life recovery and symptom burden after autologous hematopoietic cell transplantation in multiple myeloma. *Am J Hematol* 2023;98(1):140–7.
- [43] Ullrich CK, Baker KK, Carpenter PA, et al. Fatigue in Hematopoietic Cell Transplantation Survivors: Correlates, Care Team Communication, and Patient-Identified Mitigation Strategies. *Transplant Cell Ther* 2023;29(3):200.e1-8.
- [44] Samur MK, Roncador M, Aktas Samur A, et al. High-dose melphalan treatment significantly increases mutational burden at relapse in multiple myeloma. *Blood* 2023;141(14):1724–36.
- [45] Nishimura KK, Barlogie B, van Rhee F, et al. Long-term outcomes after autologous stem cell transplantation for multiple myeloma. *Blood Adv* 2020;4(2):422–31.
- [46] Tang S, Lu Y, Zhang P, et al. Lenalidomide, bortezomib and dexamethasone followed by tandem- autologous stem cell transplantation is an effective treatment modality for multi-hit multiple myeloma. *Leuk Res* 2021;110:106710.
- [47] Blocka J, Hielscher T, Goldschmidt H, et al. Response Improvement Rather than Response Status after First Autologous Stem Cell Transplantation Is a Significant Prognostic Factor for Survival Benefit from Tandem Compared with Single Transplantation in Multiple Myeloma Patients. *Biol Blood Marrow Transplant* 2020;26(7):1280–7.
- [48] Mai EK, Benner A, Bertsch U, et al. Single versus tandem high-dose melphalan followed by autologous blood stem cell transplantation in multiple myeloma: long-term results from the phase III GMMG-HD2 trial. *Br J Haematol* 2016;173(5):731–41.
- [49] Cavo M, Gay F, Beksac M, et al. Autologous haematopoietic stem-cell transplantation versus bortezomib-melphalan-prednisone, with or without bortezomib-lenalidomide-dexamethasone consolidation therapy, and lenalidomide maintenance for newly diagnosed multiple myeloma (EMN02/HO95): a multicentre, randomised, open-

- label, phase 3 study. *Lancet Haematol* 2020;7(6):e456–68.
- [50] Baertsch M-A, Mai EK, Hielscher T, et al. Lenalidomide versus bortezomib maintenance after frontline autologous stem cell transplantation for multiple myeloma. *Blood Cancer J* 2021;11(1):1.
- [51] Dytfeld D, Wrobel T, Jamroziak K, et al. Carfilzomib, lenalidomide, and dexamethasone or lenalidomide alone as maintenance therapy after autologous stem-cell transplantation in patients with multiple myeloma (ATLAS): interim analysis of a randomised, open-label, phase 3 trial. *Lancet Oncol* 2023;24(2):139–50.
- [52] Mikulski D, Koscielny K, Nowicki M, et al. Neutrophil to lymphocyte ratio (NLR) impact on the progression-free survival and overall survival of multiple myeloma patients treated with high-dose chemotherapy and autologous stem cell transplantation. *Leuk Lymphoma* 2023;64(1):98–106.
- [53] D’Angelo C, Sudakaran S, Asimakopoulos F, et al. Perturbation of the gut microbiome and association with outcomes following autologous stem cell transplantation in patients with multiple myeloma. *Leuk Lymphoma* 2023;64(1):87–97.
- [54] Moreau P, Hulin C, Perrot A, et al. Maintenance with daratumumab or observation following treatment with bortezomib, thalidomide, and dexamethasone with or without daratumumab and autologous stem-cell transplant in patients with newly diagnosed multiple myeloma (CASSIOPEIA): an open-label, randomised, phase 3 trial. *Lancet Oncol* 2021;22(10):1378–90.
- [55] Voorhees PM, Kaufman JL, Laubach J, et al. Daratumumab, lenalidomide, bortezomib, and dexamethasone for transplant-eligible newly diagnosed multiple myeloma: the GRIFFIN trial. *Blood* 2020;136(8):936–45.
- [56] Jenner MW, Pawlyn C, Davies FE, et al. The addition of vorinostat to lenalidomide maintenance for patients with newly diagnosed multiple myeloma of all ages: results from ‘Myeloma XI’, a multicentre, open-label, randomised, phase III trial. *Br J Haematol* 2022;201(2):267–79.

10 巩固治疗和维持治疗的作用

- [1] Cavo M, Brioli A, Tacchetti P, et al. Role of consolidation therapy in transplant eligible multiple myeloma patients. *Semin Oncol* 2013;40(5):610–7.
- [2] Attal M, Harousseau JL, Stoppa AM, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. *N Engl J Med* 1996;335(2):91–7.
- [3] Child JA, Morgan GJ, Davies FE, et al. High-Dose Chemotherapy with Hematopoietic Stem-Cell Rescue for Multiple Myeloma. *N Engl J Med* 2003;348(19):1875–83.
- [4] Mellqvist UH, Gimsing P, Hjertner O, et al. Bortezomib consolidation after autologous stem cell transplantation in multiple myeloma: a Nordic Myeloma Study Group randomized phase 3 trial. *Blood* 2013;121(23):4647–54.
- [5] Cavo M, Pantani L, Petrucci MT, et al. Bortezomib-thalidomide-dexamethasone is superior to thalidomide-dexamethasone as consolidation therapy after autologous hematopoietic stem cell transplantation in patients with newly diagnosed multiple myeloma. *Blood* 2012;120(1):9–19.
- [6] Richardson PG, Weller E, Lonial S, et al. Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma. *Blood* 2010;116(5):679–86.
- [7] Roussel M, Robillard N, Moreau P, et al. Bortezomib, lenalidomide, and dexamethasone (VRD) consolidation and lenalidomide maintenance in frontline multiple myeloma patients: updated results of the IFM 2008 phase II VRD intensive program. *Blood* 2011;118(21):1872.
- [8] Attal M, Lauwers-Cances V, Hulin C, et al. Lenalidomide, bortezomib, and dexamethasone with transplantation for myeloma. *N Engl J Med* 2017;376(14):1311–20.
- [9] Stadtmauer EA, Pasquini MC, Blackwell B, et al. Autologous transplantation, consolidation, and maintenance therapy in multiple myeloma: results of the BMT CTN 0702 Trial. *J Clin Oncol* 2019;37(7):589–97.
- [10] Hari P, Pasquini MC, Stadtmauer EA, et al. Long-term follow-up of BMT CTN 0702 (STaMINA) of postautologous hematopoietic cell transplantation (autoHCT) strategies in the upfront treatment of multiple myeloma (MM). *J Clin Oncol* 2020;38(15_suppl):8506.
- [11] Sonneveld P, Dimopoulos MA, Beksac M, et al. Consolidation and maintenance in newly diagnosed multiple myeloma. *J Clin Oncol* 2021;39(32):3613–22.
- [12] Cavo M, Gay F, Beksac M, et al. Autologous haematopoietic stem-cell transplantation versus bortezomib-melphalan-prednisone, with or without bortezomib-lenalidomide-dexamethasone consolidation therapy, and lenalidomide maintenance for newly diagnosed multiple myeloma (EMN02/HO95): a multicentre, randomised, openlabel, phase 3 study. *Lancet Haematol*

- 2020;7(6):e456–68.
- [13] Dimopoulos M, Wang M, Maisnar V, et al. Response and progression-free survival according to planned treatment duration in patients with relapsed multiple myeloma treated with carfilzomib, lenalidomide, and dexamethasone (KRd) versus lenalidomide and dexamethasone (Rd) in the phase III ASPIRE study. *J Hematol Oncol* 2018;11(1):49.
- [14] Roussel M, Lauwers-Cances V, Willeme S, et al. Up-front carfilzomib, lenalidomide, and dexamethasone with transplant for patients with multiple myeloma: the IFM KRd final results. *Blood* 2021;138(2):113–21.
- [15] Gay F, Musto P, Rota-Scalabrini D, et al. Carfilzomib with cyclophosphamide and dexamethasone or lenalidomide and dexamethasone plus autologous transplantation or carfilzomib plus lenalidomide and dexamethasone, followed by maintenance with carfilzomib plus lenalidomide or lenalidomide alone for patients with newly diagnosed multiple myeloma (FORTE): a randomised, open-label, phase 2 trial. *Lancet Oncol* 2021;22(12):1705–20.
- [16] Voorhees PM, Kaufman JL, Laubach J, et al. Daratumumab, lenalidomide, bortezomib, and dexamethasone for transplant-eligible newly diagnosed multiple myeloma: the GRIFFIN trial. *Blood* 2020;136(8):936–45.
- [17] Moreau P, Attal M, Hulin C, et al. Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomised, openlabel, phase 3 study. *Lancet* 2019;394(10192):29–38.
- [18] Costa LJ, Chhabra S, Medvedova E, et al. Daratumumab, carfilzomib, lenalidomide, and dexamethasone with minimal residual disease response-adapted therapy in newly diagnosed multiple myeloma. *J Clin Oncol* 2022;40(25):2901–12.
- [19] Costa LJ, Chhabra S, Medvedova E, et al. Outcomes of MRD-adapted treatment modulation in patients with newly diagnosed multiple myeloma receiving daratumumab, carfilzomib, lenalidomide and dexamethasone (Dara-KRd) and autologous transplantation: extended follow up of the master trial. *Blood* 2022; 140(Supplement 1):7275–7.
- [20] Nørgaard JN, Abildgaard N, Lyse'n A, et al. Carfilzomib-Lenalidomide-Dexamethasone Consolidation in Myeloma Patients with a Positive FDG PET/CT after Upfront Autologous Stem Cell Transplantation: A Phase II Study (CONPET). *Blood* 2021;138:3939.
- [21] Holstein SA, Suman VJ, Hillengass J, et al. Future directions in maintenance therapy in multiple myeloma. *J Clin Med* 2021;10(11):2261.
- [22] Morgan GJ, Gregory WM, Davies FE, et al. The role of maintenance thalidomide therapy in multiple myeloma: MRC myeloma IX results and meta-analysis. *Blood* 2012;119(1):7–15.
- [23] Attal M, Lauwers-Cances V, Marit G, et al. Lenalidomide maintenance after stemcell transplantation for multiple myeloma. *N Engl J Med* 2012;366(19):1782–91.
- [24] Attal M, Lauwers VC, Marit G, et al. Maintenance treatment with lenalidomide after transplantation for MYELOMA: final

- analysis of the IFM 2005-02. *Blood* 2010; 116(21):310.
- [25] Holstein SA, Jung SH, Richardson PG, et al. Updated analysis of CALGB 100104 (Alliance): a randomised phase III study evaluating lenalidomide vs placebo maintenance after single autologous stem cell transplant for multiple myeloma. *Lancet Haematol* 2017;4(9):e431–42.
- [26] Palumbo A, Cavallo F, Gay F, et al. Autologous transplantation and maintenance therapy in multiple myeloma. *N Engl J Med* 2014;371(10):895–905.
- [27] McCarthy PL, Holstein SA, Petrucci MT, et al. Lenalidomide maintenance after autologous stem-cell transplantation in newly diagnosed multiple myeloma: a meta-analysis. *J Clin Oncol* 2017;35(29):3279–89.
- [28] Jackson GH, Davies FE, Pawlyn C, et al. Lenalidomide maintenance versus observation for patients with newly diagnosed multiple myeloma (Myeloma XI): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol* 2019;20(1):57–73.
- [29] Pawlyn C, Menzies T, Davies FE, et al. Defining the optimal duration of lenalidomide maintenance after autologous stem cell transplant - data from the myeloma XI trial. *Blood* 2022;140(Supplement 1):1371–2.
- [30] Atieh T, Hubben A, Faiman B, et al. Pomalidomide-based maintenance postautologous hematopoietic cell transplantation in multiple myeloma: a case series. *Ann Hematol* 2019;98(10):2457–9.
- [31] Garderet L, Kuhnowski F, Berge B, et al. Pomalidomide and dexamethasone until progression after first salvage therapy in multiple myeloma. *Br J Haematol* 2023;201(6):1103–15.
- [32] Sonneveld P, Schmidt-Wolf IGH, van der Holt B, et al. Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized phase III HOVON-65/GMMG-HD4 trial. *J Clin Oncol* 2012;30(24):2946–55.
- [33] Dimopoulos MA, Gay F, Schjesvold F, et al. Oral ixazomib maintenance following autologous stem cell transplantation (TOURMALINE-MM3): a double-blind, randomised, placebo-controlled phase 3 trial. *Lancet* 2019;393(10168):253–64.
- [34] Gregersen H, Peceliunas V, Remes K, et al. Carfilzomib and dexamethasone maintenance following salvage ASCT in multiple myeloma: A randomised phase 2 trial by the Nordic Myeloma Study Group. *Eur J Haematol* 2022;108(1):34–44.
- [35] Moreau P, Hulin C, Perrot A, et al. Maintenance with daratumumab or observation following treatment with bortezomib, thalidomide, and dexamethasone with or without daratumumab and autologous stem-cell transplant in patients with newly diagnosed multiple myeloma (CASSIOPEIA): an open-label, randomised, phase 3 trial. *Lancet Oncol* 2021;22(10):1378–90.
- [36] Clemens PL, Yan X, Lokhorst HM, et al. Pharmacokinetics of daratumumab following intravenous infusion in relapsed or refractory multiple myeloma after prior proteasome inhibitor and immunomodulatory drug treatment. *Clin Pharmacokinet* 2017;56(8):915–24.
- [37] Nooka AK, Kaufman JL, Muppidi S, et al. Consolidation and maintenance

- therapy with lenalidomide, bortezomib and dexamethasone (RVD) in high-risk myeloma patients. *Leukemia* 2014;28(3):690–3.
- [38] Joseph NS, Kaufman JL, Dhodapkar MV, et al. Long-term follow-up results of lenalidomide, bortezomib, and dexamethasone induction therapy and riskadapted maintenance approach in newly diagnosed multiple myeloma. *J Clin Oncol* 2020;38(17):1928–37.
- [39] Shah N, Patel S, Pei H, et al. Subcutaneous daratumumab (DARA SC) plus lenalidomide versus lenalidomide alone as maintenance therapy in patients (pts) with newly diagnosed multiple myeloma (NDMM) who are minimal residual disease (MRD) positive after frontline autologous stem cell transplant (ASCT): The phase 3 AURIGA study. *J Clin Oncol* 2021;39(15_suppl):TPS8054.
- [40] Krishnan A, Hoering A, Hari P, et al. Phase III Study of daratumumab/rhuph20 (nsc-810307) 1 lenalidomide or lenalidomide as post-autologous stem cell transplant maintenance therapy in patients with multiple myeloma (mm) using minimal residual disease to direct therapy duration (DRAMMATIC study): SWOG s1803. *Blood* 2020;136(Supplement 1):21–2.
- [41] Mina R, Musto P, Rota-Scalabrini D, et al. Carfilzomib induction, consolidation, and maintenance with or without autologous stem-cell transplantation in patients with newly diagnosed multiple myeloma: pre-planned cytogenetic subgroup analysis of the randomised, phase 2 FORTE trial. *Lancet Oncol* 2023;24(1):64–76.
- [42] Dytfeld D, Wrobel T, Jamroziak K, et al. Carfilzomib, lenalidomide, and dexamethasone or lenalidomide alone as maintenance therapy after autologous stem-cell transplantation in patients with multiple myeloma (ATLAS): interim analysis of a randomised, open-label, phase 3 trial. *Lancet Oncol* 2023;24(2):139–50.
- [43] Hajek R, Sliwka H, Stork M, et al. Patient characteristics and survival outcomes of lenalidomide exposed non-refractory vs. lenalidomide refractory multiple myeloma patients in the honeur federated data network. *Blood* 2022; 140(Supplement 1):7200–2.
- [44] van de Donk NWCJ, Agha ME, Cohen AD, et al. Biological correlative analyses and updated clinical data of ciltacabtagene autoleucel (cilta-cel), a BCMA directed CAR-T cell therapy, in patients with multiple myeloma (MM) and early relapse after initial therapy: CARTITUDE-2, cohort B. *J Clin Oncol* 2022; 40(16_suppl):8029.

11 新诊断多发性骨髓瘤管理的现状及未来

- [1] Kristinsson SY, Anderson WF, Landgren O. Improved long-term survival in multiple myeloma up to the age of 80 years. *Leukemia* 2014;28(6):1346–8.
- [2] Voorhees PM, Kaufman JL, Laubach J, et al. Daratumumab, lenalidomide, bortezomib, and dexamethasone for transplant-eligible newly diagnosed multiple myeloma: the GRIFFIN trial. *Blood* 2020;136(8):936–45.
- [3] Moreau P, Attal M, Hulin C, et al. Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomised, open-label, phase 3 study. *Lancet* 2019;394(10192):29–38.
- [4] Facon T, Kumar SK, Plesner T, et al. Daratumumab, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone alone in newly diagnosed multiple myeloma (MAIA): overall survival results from a randomised, open-label, phase 3 trial. *Lancet Oncol* 2021;22(11):1582–96.
- [5] Mateos MV, Cavo M, Blade J, et al. Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): a randomised, open-label, phase 3 trial. *Lancet* 2020;395(10218):132–41.
- [6] Fonseca R, Usmani SZ, Mehra M, et al. Frontline treatment patterns and attrition rates by subsequent lines of therapy in patients with newly diagnosed multiple myeloma. *BMC Cancer* 2020;20(1):1087.
- [7] Yong K, Delforge M, Driessen C, et al. Multiple myeloma: patient outcomes in real-world practice. *Br J Haematol* 2016;175(2):252–64.
- [8] Attal M, Lauwers-Cances V, Hulin C, et al. Lenalidomide, Bortezomib, and Dexamethasone with Transplantation for Myeloma. *N Engl J Med* 2017;376(14):1311–20.
- [9] Richardson PG, Jacobus SJ, Weller EA, et al. Triplet Therapy, Transplantation, and Maintenance until Progression in Myeloma. *N Engl J Med* 2022;387(2):132–47.
- [10] Gay F, Musto P, Rota-Scalabrini D, et al. Carfilzomib with cyclophosphamide and dexamethasone or lenalidomide and dexamethasone plus autologous transplantation or carfilzomib plus lenalidomide and dexamethasone, followed by maintenance with carfilzomib plus lenalidomide or lenalidomide alone for patients with newly diagnosed multiple myeloma (FORTE): a randomised, open-label, phase 2 trial. *Lancet Oncol* 2021;22(12):1705–20.
- [11] Perrot A, Lauwers-Cances V, Cazaubiel T, et al. Early Versus Late Autologous Stem Cell Transplant in Newly Diagnosed Multiple Myeloma: Long-Term Followup Analysis of the IFM 2009 Trial. *Blood* 2020;136(Supplement 1):39.
- [12] Palumbo A, Bringhen S, Mateos M-V, et al. Geriatric assessment predicts survival and toxicities in elderly myeloma patients: an International Myeloma Working Group

- report. *Blood* 2015;125(13):2068–74.
- [13] Engelhardt M, Domm AS, Dold SM, et al. A concise revised Myeloma Comorbidity Index as a valid prognostic instrument in a large cohort of 801 multiple myeloma patients. *Haematologica* 2017;102(5):910–21.
- [14] Durie BGM, Hoering A, Abidi MH, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. *Lancet* 2017;389(10068): 519–27.
- [15] Kumar S, Flinn I, Richardson PG, et al. Randomized, multicenter, phase 2 study(EVOLUTION) of combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide in previously untreated multiple myeloma. *Blood* 2012;119(19):4375–82.
- [16] Sidana S, Kumar S, Fraser R, et al. Impact of Induction Therapy with VRD versus VCD on Outcomes in Patients with Multiple Myeloma in Partial Response or Better Undergoing Upfront Autologous Stem Cell Transplantation. *Transplant Cell Ther* 2022;28(2):83.e1–9.
- [17] Chernaiewsky HM, Kukreti V, Reece D, et al. The survival impact of maintenance lenalidomide: an analysis of real-world data from the Canadian Myeloma Research Group national database. *Haematologica* 2021;106(6):1733–6.
- [18] Moreau P, Hulin C, Macro M, et al. VTD is superior to VCD prior to intensive therapy in multiple myeloma: results of the prospective IFM2013-04 trial. *Blood* 2016;127(21):2569–74.
- [19] Kumar SK, Jacobus SJ, Cohen AD, et al. Carfilzomib or bortezomib in combination with lenalidomide and dexamethasone for patients with newly diagnosed multiple myeloma without intention for immediate autologous stem-cell transplantation (ENDURANCE): a multicentre, open-label, phase 3, randomised, controlled trial. *Lancet Oncol* 2020;21(10):1317–30.
- [20] Sweeney NW, Sborov DW, Martí'nez JAH, et al. Real-world analysis of D-RVd v. RVd at induction for newly diagnosed transplant eligible multiple myeloma patients. *J Clin Oncol* 2023;41(16_suppl):e20024.
- [21] Costa LJ, Chhabra S, Medvedova E, et al. Daratumumab, Carfilzomib, Lenalidomide, and Dexamethasone With Minimal Residual Disease Response-Adapted Therapy in Newly Diagnosed Multiple Myeloma. *J Clin Oncol* 2022;40(25):2901–12.
- [22] Touzeau C, Perrot A, Hulin C, et al. Daratumumab carfilzomib lenalidomide and dexamethasone as induction therapy in high-risk, transplant-eligible patients with newly diagnosed myeloma: Results of the phase 2 study IFM 2018-04. *J Clin Oncol* 2022;40(16_suppl):8002.
- [23] Yimer H, Melear J, Faber E, et al. Daratumumab, cyclophosphamide, bortezomib, and dexamethasone for multiple myeloma: final results of the LYRA study. *Leuk Lymphoma* 2022;63(10):2383–92.
- [24] Kastiris E, Palladini G, Minnema MC, et al. Daratumumab-Based Treatment for Immunoglobulin Light-Chain Amyloidosis. *N Engl J Med* 2021;385(1):46–58.
- [25] Palladini G, Kastiris E, Maurer MS, et al. Daratumumab plus CyBorD for patients with

- newly diagnosed AL amyloidosis: safety run-in results of ANDROMEDA. *Blood* 2020;136(1):71–80.
- [26] Aurore Perrot VL-C, Touzeau C, Decaux O, et al. Daratumumab Plus Ixazomib, Lenalidomide, and Dexamethasone as Extended Induction and Consolidation Followed by Lenalidomide Maintenance in Standard - Risk Transplant Eligible Newly Diagnosed Multiple Myeloma (NDMM) Patients (IFM 2018-01): A Phase II Study of the Intergroupe Francophone Du Myeloma (IFM). Conference abstract presented at: ASH 2021; December 2021, Atlanta, USA; Session 1.
- [27] Goldschmidt H, Mai EK, Bertsch U, et al. Addition of isatuximab to lenalidomide, bortezomib, and dexamethasone as induction therapy for newly diagnosed, transplantation-eligible patients with multiple myeloma (GMMG-HD7): part 1 of an open-label, multicentre, randomised, active-controlled, phase 3 trial. *Lancet Haematol* 2022;9(11):e810–21.
- [28] Goldschmidt H, Mai EK, Bertsch U, et al. Elotuzumab in Combination with Lenalidomide, Bortezomib, Dexamethasone and Autologous Transplantation for Newly-Diagnosed Multiple Myeloma: Results from the Randomized Phase III GMMG-HD6 Trial. *Blood* 2021;138:486.
- [29] Usmani SZ, Hoering A, Ailawadhi S, et al. Bortezomib, lenalidomide, and dexamethasone with or without elotuzumab in patients with untreated, high-risk multiple myeloma (SWOG-1211): primary analysis of a randomised, phase 2 trial. *Lancet Haematol* 2021;8(1):e45–54.
- [30] Stuebig T, Kull M, Greil R, et al. Carfilzomib, lenalidomide, and dexamethasone (KRd) versus elotuzumab and KRd in transplant-eligible patients with newly diagnosed multiple myeloma: Post-induction response and MRD results from an open-label randomized phase 3 study. *J Clin Oncol* 2023;41(16_suppl):8000.
- [31] Moreau P, Hulin C, Perrot A, et al. Maintenance with daratumumab or observation following treatment with bortezomib, thalidomide, and dexamethasone with or without daratumumab and autologous stem-cell transplant in patients with newly diagnosed multiple myeloma (CASSIOPEIA): an open-label, randomised, phase 3 trial. *Lancet Oncol* 2021;22(10):1378–90.
- [32] Kaiser MF, Hall A, Walker K, et al. Depth of response and minimal residual disease status in ultra high-risk multiple myeloma and plasma cell leukemia treated with daratumumab, bortezomib, lenalidomide, cyclophosphamide and dexamethasone (Dara-CVRd): Results of the UK optimum/MUKnine trial. *J Clin Oncol* 2021;39(15_suppl):8001.
- [33] Cavo M, Gay F, Beksac M, et al. Autologous haematopoietic stem-cell transplantation versus bortezomib-melphalan-prednisone, with or without bortezomib-lenalidomide-dexamethasone consolidation therapy, and lenalidomide maintenance for newly diagnosed multiple myeloma (EMN02/HO95): a multicentre, randomised, openlabel, phase 3 study. *Lancet Haematol* 2020;7(6):e456–68.
- [34] Cavo M, Goldschmidt H, Rosinol L, et al. Double Vs Single Autologous Stem Cell Transplantation for Newly Diagnosed

- Multiple Myeloma: Long-Term Follow-up (10-Years) Analysis of Randomized Phase 3 Studies. *Blood* 2018;132:124.
- [35] Hari P, Pasquini MC, Stadtmauer EA, et al. Long-term follow-up of BMT CTN 0702 (STaMINA) of postautologous hematopoietic cell transplantation (autoHCT) strategies in the upfront treatment of multiple myeloma (MM). *J Clin Oncol* 2020;38(15_suppl):8506.
- [36] De La Torre A, Atenafu EG, Smith AC, et al. Myeloma Patients with Deletion of 17p: Impact of Tandem Transplant and Clone Size. *Blood* 2021;138(Supplement 1):460.
- [37] Mateos MV, Dimopoulos MA, Cavo M, et al. Daratumumab Plus Bortezomib, Melphalan, and Prednisone Versus Bortezomib, Melphalan, and Prednisone in Transplant-Ineligible Newly Diagnosed Multiple Myeloma: Frailty Subgroup Analysis of ALCYONE. *Clin Lymphoma, Myeloma & Leukemia* 2021;21(11):785–98.
- [38] Palumbo A, Anderson K. Multiple Myeloma. *N Engl J Med* 2011;364(11):1046–60.
- [39] Palumbo A, Bringhen S, Ludwig H, et al. Personalized therapy in multiple myeloma according to patient age and vulnerability: a report of the European Myeloma Network (EMN). *Blood* 2011;118(17):4519–29.
- [40] Benboubker L, Dimopoulos MA, Dispenzieri A, et al. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. *N Engl J Med* 2014; 371(10):906–17.
- [41] Durie BGM, Hoering A, Sexton R, et al. Longer term follow-up of the randomized phase III trial SWOG S0777: bortezomib, lenalidomide and dexamethasone vs. lenalidomide and dexamethasone in patients (Pts) with previously untreated multiple myeloma without an intent for immediate autologous stem cell transplant (ASCT). *Blood Cancer J* 2020;10(5):53.
- [42] O'Donnell EK, Laubach JP, Yee AJ, et al. Updated Results of a Phase 2 Study of Modified Lenalidomide, Bortezomib, and Dexamethasone (RVd-lite) in Transplant-Ineligible Multiple Myeloma. *Blood* 2019;134(Supplement_1):3178.
- [43] Chari A, Romanus D, Palumbo A, et al. Randomized Clinical Trial Representativeness and Outcomes in Real-World Patients: Comparison of 6 Hallmark Randomized Clinical Trials of Relapsed/Refractory Multiple Myeloma. *Clin Lymphoma, Myeloma & Leukemia* 2020;20(1):8–17.e16.
- [44] Lancman G, Sastow D, Aslanova M, et al. Effect of intravenous immunoglobulin on infections in multiple myeloma (MM) patients receiving daratumumab. *Blood* 2020;136:6–7.
- [45] Facon T, Vennet CP, Bahlis NJ, et al. Oral ixazomib, lenalidomide, and dexamethasone for transplant-ineligible patients with newly diagnosed multiple myeloma. *Blood* 2021;137(26):3616–28.
- [46] Munshi NC, Anderson LD, Shah N, et al. Idecabtagene Vicleucel in Relapsed and Refractory Multiple Myeloma. *N Engl J Med* 2021;384(8):705–16.
- [47] Rodriguez-Otero P, Ailawadhi S, Arnulf B, et al. Ide-cel or Standard Regimens in Relapsed and Refractory Multiple Myeloma. *N Engl J Med* 2023;388(11):1002–14.
- [48] Martin TG, Usmani SZ, Berdeja JG, et al. CARTITUDE-1 final results: Phase 1b/2 study of ciltacabtagene autoleucel in heavily pretreated patients with relapsed/refractory

- multiple myeloma. *J Clin Oncol* 2023;41(16_suppl):8009.
- [49] Yong K, Harrison SJ, Mateos M-V, et al. First phase 3 results from CARTITUDE-4:Cilta-cel versus standard of care (PVd or DPd) in lenalidomide-refractory multiple myeloma. *J Clin Oncol* 2023;41(17_suppl):LBA106.
- [50] Moreau P, Garfall AL, van de Donk N, et al. Teclistamab in Relapsed or Refractory Multiple Myeloma. *N Engl J Med* 2022;387(6):495–505.
- [51] Lancman G, Parsa K, Rodriguez C, et al. Infections and Severe Hypogammaglobulinemia in Multiple Myeloma Patients Treated with Anti-BCMA Bispecific Antibodies. *Blood* 2022;140(Supplement 1):10073–4.

12 克隆异质性对多发性骨髓瘤的影响

- [1] Palumbo A, Anderson K. Multiple Myeloma. *N Engl J Med* 2011;1046-60. <https://doi.org/10.1056/nejmra1011442>.
- [2] Rajkumar SV. Multiple myeloma: 2022 update on diagnosis, risk stratification, and management. *Am J Hematol* 2022;97(8):1086-107.
- [3] Sonneveld P, Avet-Loiseau H, Lonial S, et al. Treatment of multiple myeloma with high-risk cytogenetics: a consensus of the International Myeloma Working Group. *Blood* 2016;127(24):2955-62.
- [4] Lonial S. Relapsed Multiple Myeloma. *Hematology Am Soc Hematol Educ Program* 2010;2010(1):303-9.
- [5] Lannes R, Samur M, Perrot A, et al. In Multiple Myeloma, High-Risk Secondary Genetic Events Observed at Relapse Are Present From Diagnosis in Tiny, Undetectable Subclonal Populations. *J Clin Oncol* 2023;41(9):1695-702.
- [6] Cohen YC, Zada M, Wang S-Y, et al. Identification of resistance pathways and therapeutic targets in relapsed multiple myeloma patients through single-cell sequencing. *Nat Med* 2021;27(3):491-503.
- [7] Walker BA, Mavrommatis K, Wardell CP, et al. A high-risk, Double-Hit, group of newly diagnosed myeloma identified by genomic analysis. *Leukemia* 2019; 33(1):159-70.
- [8] Bolli N, Avet-Loiseau H, Wedge DC, et al. Heterogeneity of genomic evolution and mutational profiles in multiple myeloma. *Nat Commun* 2014;5:2997.
- [9] Lohr JG, Stojanov P, Carter SL, et al. Widespread genetic heterogeneity in multiple myeloma: implications for targeted therapy. *Cancer Cell* 2014;25(1): 91-101.
- [10] Morgan GJ, Walker BA, Davies FE. The genetic architecture of multiple myeloma. *Nat Rev Cancer* 2012;12(5):335-48.
- [11] Walker BA, Mavrommatis K, Wardell CP, et al. Identification of novel mutational drivers reveals oncogene dependencies in multiple myeloma. *Blood* 2018; 132(6):587-97.
- [12] Rasche L, Chavan SS, Stephens OW, et al. Spatial genomic heterogeneity in multiple myeloma revealed by multi-region sequencing. *Nat Commun* 2017; 8(1):268.
- [13] Rasche L, Schinke C, Maura F, et al. The spatio-temporal evolution of multiple myeloma from baseline to relapse-refractory states. *Nat Commun* 2022. <https://doi.org/10.1038/s41467-022-32145-y>.
- [14] Manier S, Salem KZ, Park J, et al. Genomic complexity of multiple myeloma and its clinical implications. *Nat Rev Clin Oncol* 2017;14(2):100-13.
- [15] Maura F, Bolli N, Angelopoulos N, et al. Genomic landscape and chronological reconstruction of driver events in multiple myeloma. *Nat Commun* 2019;10(1): 3835
- [16] Boyd KD, Ross FM, Chiecchio L, et al. A novel prognostic model in myeloma based on co-segregating adverse FISH lesions and the ISS: analysis of patients treated in the MRC Myeloma IX trial. *Leukemia* 2012;26(2):349-55.

- [17] Ross FM, Chiecchio L, Dagrada G, et al. The t(14;20) is a poor prognostic factor in myeloma but is associated with long-term stable disease in monoclonal gammopathies of undetermined significance. *Haematologica* 2010;95(7):1221-5.
- [18] Schinke C, Boyle EM, Ashby C, et al. Genomic analysis of primary plasma cell leukemia reveals complex structural alterations and high-risk mutational patterns. *Blood Cancer J* 2020;10(6):70.
- [19] Tuazon SA, Holmberg LA, Nadeem O, et al. A clinical perspective on plasma cell leukemia; current status and future directions. *Blood Cancer J* 2021; 11(2):23.
- [20] Wiedmeier-Nutor JE, Bergsagel PL. Review of Multiple Myeloma Genetics including Effects on Prognosis, Response to Treatment, and Diagnostic Workup. *Life* 2022;12(6). <https://doi.org/10.3390/life12060812>.
- [21] Chretien M-L, Corre J, Lauwers-Cances V, et al. Understanding the role of hyperdiploidy in myeloma prognosis: which trisomies really matter? *Blood* 2015; 126(25):2713-9.
- [22] Bolli N, Maura F, Minvielle S, et al. Genomic patterns of progression in smoldering multiple myeloma. *Nat Commun* 2018;9(1):3363.
- [23] Walker BA, Wardell CP, Melchor L, et al. Intracлона heterogeneity is a critical early event in the development of myeloma and precedes the development of clinical symptoms. *Leukemia* 2014;28(2):384-90.
- [24] Hanamura I. Multiple myeloma with high-risk cytogenetics and its treatment approach. *Int J Hematol* 2022;115(6):762-77.
- [25] Schmidt TM, Fonseca R, Usmani SZ. Chromosome 1q21 abnormalities in multiple myeloma. *Blood Cancer J* 2021;11(4):83.
- [26] Shaughnessy J. Amplification and overexpression of CKS1B at chromosome band 1q21 is associated with reduced levels of p27 Kip1 and an aggressive clinical course in multiple myeloma. *Hematology* 2005;10(sup1):117-26.
- [27] Chapman MA, Lawrence MS, Keats JJ, et al. Initial genome sequencing and analysis of multiple myeloma. *Nature* 2011;471(7339):467-72.
- [28] Jang JS, Li Y, Mitra AK, et al. Molecular signatures of multiple myeloma progression through single cell RNA-Seq. *Blood Cancer J* 2019;9(1):2.
- [29] Ledergor G, Weiner A, Zada M, et al. Single cell dissection of plasma cell heterogeneity in symptomatic and asymptomatic myeloma. *Nat Med* 2018;24(12): 1867-76.
- [30] de Jong MME, Kellermayer Z, Papazian N, et al. The multiple myeloma microenvironment is defined by an inflammatory stromal cell landscape. *Nat Immunol* 2021;22(6):769-80.
- [31] Liu R, Gao Q, Foltz SM, et al. Co-evolution of tumor and immune cells during progression of multiple myeloma. *Nat Commun* 2021;12(1):2559.
- [32] Merz M, Merz AMA, Wang J, et al. Deciphering spatial genomic heterogeneity at a single cell resolution in multiple myeloma. *Nat Commun* 2022;13(1):807.
- [33] Tirier SM, Mallm J-P, Steiger S, et al. Subclone-specific microenvironmental impact and drug response in refractory multiple myeloma revealed by single-cell transcriptomics. *Nat Commun* 2021;12(1):1-16.
- [34] Dang M, Wang R, Lee HC, et al. Single cell clonal and transcriptional evolution of

- multiple myeloma precursor disease. *Cancer Cell* 2023;41(6): 1032-47.e4.
- [35] Zamagni E, Tacchetti P, Cavo M. Imaging in multiple myeloma: How? When? *Blood* 2019;133(7):644-51.
- [36] Bartel TB, Haessler J, Brown TLY, et al. F18-fluorodeoxyglucose positron emission tomography in the context of other imaging techniques and prognostic factors in multiple myeloma. *Blood* 2009;114(10):2068-76.
- [37] Walker R, Barlogie B, Haessler J, et al. Magnetic resonance imaging in multiple myeloma: diagnostic and clinical implications. *J Clin Oncol* 2007;25(9):1121-8.
- [38] Rasche L, Angtuaco EJ, Alpe TL, et al. The presence of large focal lesions is a strong independent prognostic factor in multiple myeloma. *Blood* 2018;132(1): 59-66.
- [39] Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol* 2014;15(12):e538-48.
- [40] Zamagni E, Patriarca F, Nanni C, et al. Prognostic relevance of 18-F FDG PET/CT in newly diagnosed multiple myeloma patients treated with up-front autologous transplantation. *Blood* 2011;118(23):5989-95.
- [41] Ley TJ, Mardis ER, Ding L, et al. DNA sequencing of a cytogenetically normal acute myeloid leukaemia genome. *Nature* 2008;456(7218):66-72.
- [42] Waldschmidt JM, Yee AJ, Vijaykumar T, et al. Cell-free DNA for the detection of emerging treatment failure in relapsed/refractory multiple myeloma. *Leukemia* 2022;36(4):1078-87.
- [43] Deshpande S, Tytarenko RG, Wang Y, et al. Monitoring treatment response and disease progression in myeloma with circulating cell-free DNA. *Eur J Haematol* 2021;106(2):230-40.
- [44] Rasche L, Alapat D, Kumar M, et al. Combination of flow cytometry and functional imaging for monitoring of residual disease in myeloma. *Leukemia* 2019;33(7):1713-22.
- [45] Kaddoura M, Dingli D, Buadi FK, et al. Prognostic impact of posttransplant FDG PET/CT scan in multiple myeloma. *Blood Adv* 2021;5(13):2753-9.
- [46] Moreau P, Attal M, Caillot D, et al. Prospective Evaluation of Magnetic Resonance Imaging and [18F]Fluorodeoxyglucose Positron Emission Tomography-Computed Tomography at Diagnosis and Before Maintenance Therapy in Symptomatic Patients With Multiple Myeloma Included in the IFM/DFCI 2009 Trial: Results of the IMAJEM Study. *J Clin Oncol* 2017;35(25):2911-8.
- [47] Garca-Ortiz A, Rodriguez-Garcia Y, Encinas J, et al. The Role of Tumor Micro environment in Multiple Myeloma Development and Progression. *Cancers* 2021;13(2). <https://doi.org/10.3390/cancers13020217>
- [48] Schinke C, Weinhold N. The Immune Microenvironment in Multiple Myeloma Progression at a Single-cell Level. *Hemasphere* 2023;7(6):e894.
- [49] McGranahan N, Swanton C. Clonal Heterogeneity and Tumor Evolution: Past, Present, and the Future. *Cell* 2017;168(4):613-28.
- [50] Schinke C, Qu P, Mehdi SJ, et al. The Pattern of Mesenchymal Stem Cell Expres

- sion Is an Independent Marker of Outcome in Multiple Myeloma. *Clin Cancer Res* 2018;24(12):2913-9.
- [51] Adams HC 3rd, Stevenaert F, Krejcik J, et al. High-parameter mass cytometry evaluation of relapsed/refractory multiple myeloma patients treated with daratumumab demonstrates immune modulation as a novel mechanism of action. *Cytometry* 2019;95(3):279-89.
- [52] Chung DJ, Pronschinske KB, Shyer JA, et al. T-cell Exhaustion in Multiple Myeloma Relapse after Autotransplant: Optimal Timing of Immunotherapy. *Cancer Immunol Res* 2016;4(1):61-71.
- [53] Zavidij O, Haradhvala NJ, Mouhieddine TH, et al. Single-cell RNA sequencing reveals compromised immune microenvironment in precursor stages of multiple myeloma. *Nat Cancer* 2020;1(5):493-506.
- [54] Schinke C, Poos AM, Bauer M, et al. Characterizing the role of the immune microenvironment in multiple myeloma progression at a single-cell level. *Blood Adv* 2022;6(22):5873-83.
- [55] Bailur JK, McCachren SS, Doxie DB, et al. Early alterations in stem-like/resident T cells, innate and myeloid cells in the bone marrow in preneoplastic gammopathy. *JCI Insight* 2019;5(11). <https://doi.org/10.1172/jci.insight.127807>.
- [56] John L, Poos A, Brobeil A, et al. Resolving the spatial architecture of myeloma and its microenvironment at the single-cell level. *Nat Commun* 2023;14(1):5011.
- [57] Khoo WH, Ledergor G, Weiner A, et al. A niche-dependent myeloid transcriptome signature defines dormant myeloma cells. *Blood* 2019;134(1):30-43.
- [58] Greaves M, Maley CC. Clonal evolution in cancer. *Nature* 2012;481(7381):306-13.
- [59] Brioli A, Melchor L, Cavo M, et al. The impact of intra-clonal heterogeneity on the treatment of multiple myeloma. *Br J Haematol* 2014;165(4):441-54.
- [60] Keats JJ, Chesi M, Egan JB, et al. Clonal competition with alternating dominance in multiple myeloma. *Blood* 2012;120(5):1067-76.
- [61] Fonseca R, Barlogie B, Bataille R, et al. Genetics and cytogenetics of multiple myeloma: a workshop report. *Cancer Res* 2004;64(4):1546-58.
- [62] Hanamura I. Gain/Amplification of Chromosome Arm 1q21 in Multiple Myeloma. *Cancers* 2021;13(2). <https://doi.org/10.3390/cancers13020256>.
- [63] Mellors PW, Binder M, Ketterling RP, et al. Metaphase cytogenetics and plasma cell proliferation index for risk stratification in newly diagnosed multiple myeloma. *Blood Adv* 2020;4(10):2236-44.
- [64] Qiang Y-W, Ye S, Chen Y, et al. MAF protein mediates innate resistance to proteasome inhibition therapy in multiple myeloma. *Blood, The Journal of the American Society of Hematology* 2016;128(25):2919-30.
- [65] Qiang Y-W, Ye S, Huang Y, et al. MAFb protein confers intrinsic resistance to proteasome inhibitors in multiple myeloma. *BMC Cancer* 2018;18(1):724.
- [66] Bird SA, Pawlyn C. IMiD Resistance in Multiple Myeloma: Current Understanding of the Underpinning Biology and Clinical Impact. *Blood* 2023. <https://doi.org/10.1182/blood.2023019637>.
- [67] Barwick BG, Neri P, Bahlis NJ, et al. Multiple myeloma immunoglobulin lambda

- p>translocations portend poor prognosis.
- Nat Commun*
- 2019;10(1):1911.
- [68] Poos AM, Prokoph N, Przybilla MJ, et al. Resolving therapy resistance mechanisms in multiple myeloma by multi-omics subclone analysis. *Blood* 2023. <https://doi.org/10.1182/blood.2023019758>.
- [69] Vo JN, Wu Y-M, Mishler J, et al. The genetic heterogeneity and drug resistance mechanisms of relapsed refractory multiple myeloma. *Nat Commun* 2022;13(1): 3750.
- [70] Melchor L, Jones JR, Lenive O, et al. Spatiotemporal Analysis of Intracлонаl Heterogeneity in Multiple Myeloma: Unravelling the Impact of Treatment and the Propagating Capacity of Subclones Using Whole Exome Sequencing. *Blood* 2015;126(23):371.
- [71] Landau HJ, Yellapantula V, Diamond BT, et al. Accelerated single cell seeding in relapsed multiple myeloma. *Nat Commun* 2020;11(1):3617.
- [72] Ria R, Vacca A. Bone Marrow Stromal Cells-Induced Drug Resistance in Multiple Myeloma. *Int J Mol Sci* 2020;21(2). <https://doi.org/10.3390/ijms21020613>.
- [73] Di Marzo L, Desantis V, Solimando AG, et al. Microenvironment drug resistance in multiple myeloma: emerging new players. *Oncotarget* 2016;7(37):60698-711.
- [74] Chauhan D, Kharbanda S, Ogata A, et al. Interleukin-6 inhibits Fas-induced apoptosis and stress-activated protein kinase activation in multiple myeloma cells. *Blood* 1997;89(1):227-34.
- [75] Hideshima T, Mitsiades C, Tonon G, et al. Understanding multiple myeloma pathogenesis in the bone marrow to identify new therapeutic targets. *Nat Rev Cancer* 2007;7(8):585-98.
- [76] Katz B-Z. Adhesion molecules—The lifelines of multiple myeloma cells. *Semin Cancer Biol* 2010;20(3):186-95.
- [77] Hazlehurst LA, Damiano JS, Buyuksal I, et al. Adhesion to fibronectin via beta1 integrins regulates p27kip1 levels and contributes to cell adhesion mediated drug resistance (CAM-DR). *Oncogene* 2000;19(38):4319-27.
- [78] Neri P, Ren L, Azab AK, et al. Integrin β 7-mediated regulation of multiple myeloma cell adhesion, migration, and invasion. *Blood* 2011;117(23):6202-13.
- [79] Vaxman I, Gertz MA. How I approach smoldering multiple myeloma. *Blood* 2022;140(8):828-38.
- [80] Zingone A, Kuehl WM. Pathogenesis of monoclonal gammopathy of undetermined significance and progression to multiple myeloma. *Semin Hematol* 2011;48(1):4-12.
- [81] Visram A, Cook J, Warsame R. Smoldering multiple myeloma: evolving diagnostic criteria and treatment strategies. *Hematology Am Soc Hematol Educ Program* 2021;2021(1):673-81.
- [82] Prez-Persona E, Vidriales M-B, Mateo G, et al. New criteria to identify risk of progression in monoclonal gammopathy of uncertain significance and smoldering multiple myeloma based on multiparameter flow cytometry analysis of bone marrow plasma cells. *Blood. The Journal of the American Society of Hematology* 2007;110(7):2586-92.
- [83] Dispenzieri A, Kyle RA, Katzmann JA, et al. Immunoglobulin free light chain ratio is an independent risk factor for progression of smoldering (asymptomatic) multiple myeloma. *Blood* 2008;111(2):785-9.

- [84] Lakshman A, Rajkumar SV, Buadi FK, et al. Risk stratification of smoldering multiple myeloma incorporating revised IMWG diagnostic criteria. *Blood Cancer J* 2018;8(6):59.
- [85] Mateos M-V, Kumar S, Dimopoulos MA, et al. International Myeloma Working Group risk stratification model for smoldering multiple myeloma (SMM). *Blood Cancer J* 2020. <https://doi.org/10.1038/s41408-020-00366-3>
- [86] Mateos M-V, Hernández M-T, Giraldo P, et al. Lenalidomide plus dexamethasone versus observation in patients with high-risk smoldering multiple myeloma (QuiRedex): long-term follow-up of a randomised, controlled, phase 3 trial. *Lancet Oncol* 2016;17(8):1127-36.
- [87] Lonial S, Jacobus S, Fonseca R, et al. Randomized Trial of Lenalidomide Versus Observation in Smoldering Multiple Myeloma. *J Clin Oncol* 2020;38(11): 1126-37.
- [88] Landgren CO, Chari A, Cohen YC, et al. Daratumumab monotherapy for patients with intermediate-risk or high-risk smoldering multiple myeloma: a randomized, open-label, multicenter, phase 2 study (CENTAURUS). *Leukemia* 2020;34(7):1840-52.
- [89] Kumar SK, Abdallah A-O, Badros AZ, et al. Aggressive smoldering curative approach evaluating novel therapies (ASCENT): A phase 2 trial of induction, consolidation and maintenance in subjects with high risk smoldering multiple myeloma (SMM): Initial analysis of safety data. *Blood* 2020;136(Supplement 1):35-6.
- [90] Mateos M-V, Martínez López J, Rodríguez-Otero P, et al. Curative Strategy (GEM-CESAR) for High-Risk Smoldering Myeloma (SMM): Carfilzomib, Lenalidomide and Dexamethasone (KRd) As Induction Followed By HDT-ASCT, Consolidation with Krd and Maintenance with Rd. *Blood* 2021;138:1829.
- [91] Kazandjian D, Hill E, Dew A, et al. Carfilzomib, Lenalidomide, and Dexamethasone Followed by Lenalidomide Maintenance for Prevention of Symptomatic Multiple Myeloma in Patients With High-risk Smoldering Myeloma: A Phase 2 Nonrandomized Controlled Trial. *JAMA Oncol* 2021;7(11):1678-85.
- [92] Cherry BM, Korde N, Kwok M, et al. Modeling progression risk for smoldering multiple myeloma: results from a prospective clinical study. *Leuk Lymphoma* 2013;54(10):2215-8.
- [93] Dhodapkar MV, Sexton R, Waheed S, et al. Clinical, genomic, and imaging predictors of myeloma progression from asymptomatic monoclonal gammopathies (SWOG S0120). *Blood* 2014;123(1):78-85.
- [94] Zhan F, Huang Y, Colla S, et al. The molecular classification of multiple myeloma. *Blood* 2006;108(6):2020-8.
- [95] Kuiper R, Zweegman S, van Duin M, et al. Prognostic and predictive performance of R-ISS with SKY92 in older patients with multiple myeloma: the HOVON-87/NMSG-18 trial. *Blood Adv* 2020;4(24):6298-309.
- [96] Broyl A, Hose D, Lokhorst H, et al. Gene expression profiling for molecular classification of multiple myeloma in newly diagnosed patients. *Blood* 2010;116(14): 2543-53.
- [97] Usmani SZ, Crowley J, Hoering A, et al.

- Improvement in long-term outcomes with successive Total Therapy trials for multiple myeloma: are patients now being cured? *Leukemia* 2013;27(1):226-32.
- [98] Yellapantula V, Hultcrantz M, Rustad EH, et al. Comprehensive detection of recurring genomic abnormalities: a targeted sequencing approach for multiple myeloma. *Blood Cancer J* 2019;9(12):101.
- [99] Bolli N, Genuardi E, Ziccheddu B, et al. Next-Generation Sequencing for Clinical Management of Multiple Myeloma: Ready for Prime Time? *Front Oncol* 2020; 10:189.
- [100] Heuck CJ, Jethava Y, Khan R, et al. Inhibiting MEK in MAPK pathway-activated myeloma. *Leukemia* 2016;30(4):976-80
- [101] epulyte. R, uenka A, Peeliunas V. Combination of Dabrafenib and Trametinib for the Treatment of Relapsed and Refractory Multiple Myeloma Harboring BRAF V600E Mutation. *Case Rep Hematol* 2020;2020:8894031.
- [102] Giesen N, Chatterjee M, Scheid C, et al. A phase 2 clinical trial of combined BRAF/MEK inhibition for BRAFV600E-mutated multiple myeloma. *Blood* 2023; 141(14):1685-90.
- [103] Subbiah V, Kreitman RJ, Wainberg ZA, et al. Dabrafenib plus trametinib in BRAFV600E-mutated rare cancers: the phase 2 ROAR trial. *Nat Med* 2023; 29(5):1103-12.
- [104] Paner A, Patel P, Dhakal B. The evolving role of translocation t(11;14) in the biology, prognosis, and management of multiple myeloma. *Blood Rev* 2020; 41(100643):100643.
- [105] Kumar S, Kaufman JL, Gasparetto C, et al. Efficacy of venetoclax as targeted therapy for relapsed/refractory t(11;14) multiple myeloma. *Blood* 2017; 130(22):2401-9.
- [106] Kumar SK, Harrison SJ, Cavo M, et al. Venetoclax or placebo in combination with bortezomib and dexamethasone in patients with relapsed or refractory multiple myeloma (BELLINI): a randomised, double-blind, multicentre, phase 3 trial. *Lancet Oncol* 2020;21(12):1630-42.
- [107] Rogawski DS, Grembecka J, Cierpicki T. H3K36 methyltransferases as cancer drug targets: rationale and perspectives for inhibitor development. *Future Med Chem* 2016;8(13):1589-607.
- [108] Martinez-Garcia E, Popovic R, Min D-J, et al. The MMSET histone methyl transferase switches global histone methylation and alters gene expression in t(4;14) multiple myeloma cells. *Blood* 2011;117(1):211-20.
- [109] Popovic R, Martinez-Garcia E, Giannopoulou EG, et al. Histone methyltransferase MMSET/NSD2 alters EZH2 binding and reprograms the myeloma epigenome through global and focal changes in H3K36 and H3K27 methylation. *PLoS Genet* 2014;10(9):e1004566.
- [110] Rasche L, Wsch R, Munder M, et al. Novel immunotherapies in multiple myeloma: chances and challenges. *Haematologica* 2021;106(10):2555-65.
- [111] Da Vi MC, Dietrich O, Truger M, et al. Homozygous BCMA gene deletion in response to anti-BCMA CAR T cells in a patient with multiple myeloma. *Nat Med* 2021;27(4):616-9.
- [112] Samur MK, Fulciniti M, Aktas Samur A, et al. Biallelic loss of BCMA as a resistance mechanism to CAR T cell therapy in a patient with multiple myeloma. *Nat Commun* 2021;12(1):868.

[113] Bianchi G, Ghobrial IM. Biological and Clinical Implications of Clonal Heterogeneity and Clonal Evolution in Multiple

Myeloma. *Curr Cancer Ther Rev* 2014; 10(2):70-9.

13 多发性骨髓瘤可测量残留病和决策制订

- [1] Paiva B, Cedena MT, Puig N, et al. Minimal residual disease monitoring and immune profiling in multiple myeloma in elderly patients. *Blood* 2016;127(25): 3165 -74.
- [2] Lahuerta JJ, Paiva B, Vidriales MB, et al. Depth of Response in Multiple Myeloma: A Pooled Analysis of Three PETHEMA/ GEM Clinical Trials. *J Clin Oncol* 2017; 35(25):2900 -10.
- [3] Flores-Montero J, Sanoja-Flores L, Paiva B, et al. Next Generation Flow for highly sensitive and standardized detection of minimal residual disease in multiple myeloma. *Leukemia* 2017;31(10):2094 -103.
- [4] Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *Lancet Oncol* 2016;17(8):e328 -46.
- [5] Yanamandra U, Kumar SK. Minimal residual disease analysis in myeloma-when, why and where. *Leuk Lymphoma* 2017;1-13. <https://doi.org/10.1080/10428194.2017.1386304>.
- [6] Costa LJ, Chhabra S, Medvedova E, et al. Daratumumab, Carfilzomib, Lenalidomide, and Dexamethasone With Minimal Residual Disease Response-Adapted Therapy in Newly Diagnosed Multiple Myeloma. *J Clin Orthod* 2021. <https://doi.org/10.1200/JCO.21.01935>. JCO.21.01935.
- [7] Adaptive Biotechnologies Corporation. clonoSEQ Assay Technical Information. Available at: https://www.clonoseq.com/sites/default/files/clonoSEQ_TechnicalInformationSummary_21Sept2018.pdf.
- [8] Attal M, Lauwers-Cances V, Hulin C, et al. Lenalidomide, Bortezomib, and Dexamethasone with Transplantation for Myeloma. *N Engl J Med* 2017;376(14): 1311 -20.
- [9] Martinez-Lopez J, Lahuerta JJ, Pepin F, et al. Prognostic value of deep sequencing method for minimal residual disease detection in multiple myeloma. *Blood* 2014;123(20):3073 -9.
- [10] Avet-Loiseau H, Lauwers-Cances V, Corre J, et al. Minimal Residual Disease in Multiple Myeloma: Final Analysis of the IFM2009 Trial. *Blood* 2017;130(Suppl 1):435.
- [11] Perrot A, Lauwers-Cances V, Corre J, et al. Minimal residual disease negativity using deep sequencing is a major prognostic factor in multiple myeloma. *Blood* 2018;132(23):2456 -64.
- [12] Moreau P, Attal M, Caillot D, et al. Prospective Evaluation of Magnetic Resonance Imaging and [18F] Fluorodeoxyglucose Positron Emission Tomography-Computed Tomography at Diagnosis and Before Maintenance Therapy in Symptomatic Patients With Multiple Myeloma Included in the IFM/DFCI 2009 Trial: Results of the IMAJEM Study. *J Clin Oncol* 2017;35(25):2911 -8.
- [13] Zamagni E, Oliva S, Gay F, et al. Impact of minimal residual disease standardised

- assessment by FDG-PET/CT in transplant-eligible patients with newly diagnosed multiple myeloma enrolled in the imaging sub-study of the FORTE trial. *eClinicalMedicine* 2023;60. <https://doi.org/10.1016/j.eclinm.2023.102017>.
- [14] Kraeber-Bodr F, Zweegman S, Perrot A, et al. Prognostic value of positron emission tomography/computed tomography in transplant-eligible newly diagnosed multiple myeloma patients from CASSIOPEIA: the CASSIOPEIstudy. *Haematologica* 2023;108(2):621 -6.
- [15] Fonseca R, Arribas M, Wiedmeier-Nutor JE, et al. Integrated analysis of next generation sequencing minimal residual disease (MRD) and PET scan in transplant eligible myeloma patients. *Blood Cancer J* 2023;13(1):1 -9.
- [16] Rasche L, Angtuaco E, McDonald JE, et al. Low expression of hexokinase-2 is associated with false-negative FDG-positron emission tomography in multiple myeloma. *Blood* 2017;130(1):30 -4.
- [17] Sachpekidis C, Mosebach J, Freitag MT, et al. Application of (18)F-FDG PET and diffusion weighted imaging (DWI) in multiple myeloma: comparison of functional imaging modalities. *Am J Nucl Med Mol Imaging* 2015;5(5):479 -92.
- [18] Kaiser MF, Porta N, Sharma B, et al. Prospective comparison of whole body MRI and FDG PET/CT for detection of multiple myeloma and correlation with markers of disease burden: Results of the iTIMM trial. *J Clin Orthod* 2021;39(15_suppl): 8012.
- [19] Sanoja-Flores L, Flores-Montero J, Garcés JJ, et al. Next generation flow for minimally-invasive blood characterization of MGUS and multiple myeloma at diagnosis based on circulating tumor plasma cells (CTPC). *Blood Cancer J* 2018;8(12):117.
- [20] Garcés JJ, Cedena MT, Puig N, et al. Circulating Tumor Cells for the Staging of Patients With Newly Diagnosed Transplant-Eligible Multiple Myeloma. *J Clin Oncol* 2022;40(27):3151 -61.
- [21] Jelinek T, Bezdekova R, Zihala D, et al. More Than 2% of Circulating Tumor Plasma Cells Defines Plasma Cell Leukemia-Like Multiple Myeloma. *J Clin Orthod* 2023;41(7):1383 -92.
- [22] Bertamini L, Oliva S, Rota-Scalabrini D, et al. High Levels of Circulating Tumor Plasma Cells as a Key Hallmark of Aggressive Disease in Transplant-Eligible Patients With Newly Diagnosed Multiple Myeloma. *J Clin Oncol* 2022;40(27): 3120 -31.
- [23] Sanoja-Flores L, Flores-Montero J, Puig N, et al. Blood monitoring of circulating tumor plasma cells by next generation flow in multiple myeloma after therapy. *Blood* 2019;134(24):2218 -22.
- [24] Notarfranchi L, Zherniakova A, Lasa M, et al. Ultra-Sensitive Assessment of Measurable Residual Disease (MRD) in Peripheral Blood (PB) of Multiple Myeloma (MM) Patients Using Bloodflow. *Blood* 2022;140(Supplement 1): 2095 -7.
- [25] Vij R, Mazumder A, Klinger M, et al. Deep sequencing reveals myeloma cells in peripheral blood in majority of multiple myeloma patients. *Clin Lymphoma Myeloma Leuk* 2014;14(2):131 -9.e1.
- [26] Mazzotti C, Buisson L, Maheo S, et al. Myeloma MRD by deep sequencing from circulating tumor DNA does not correlate with results obtained in the bone marrow. *Blood Advances* 2018;2(21):2811 -3.

- [27] Dhakal B, Sharma S, Balcioglu M, et al. Assessment of Molecular Residual Disease Using Circulating Tumor DNA to Identify Multiple Myeloma Patients at High Risk of Relapse. *Front Oncol* 2022;12:786451.
- [31] Thoren KL. Mass spectrometry methods for detecting monoclonal immunoglobulins in multiple myeloma minimal residual disease. *Semin Hematol* 2018; 55(1):41 -3.
- [32] Kohlhagen MC, Barnidge DR, Mills JR, et al. Screening Method for M-Proteins in Serum Using Nanobody Enrichment Coupled to MALDI-TOF Mass Spectrometry. *Clin Chem* 2016;62(10):1345 -52.
- [33] Mills JR, Kohlhagen MC, Dasari S, et al. Comprehensive Assessment of M-Proteins Using Nanobody Enrichment Coupled to MALDI-TOF Mass Spectrometry. *Clin Chem* 2016;62(10):1334 -44.
- [34] Kohlhagen M, Dasari S, Willrich M, et al. Automation and validation of a MALDI- TOF MS (Mass-Fix) replacement of immunofixation electrophoresis in the clinical lab. *Clin Chem Lab Med* 2020;59(1):155 -63.
- [35] Barnidge DR, Dasari S, Botz CM, et al. Using Mass Spectrometry to Monitor Monoclonal Immunoglobulins in Patients with a Monoclonal Gammopathy. *J Proteome Res* 2014;13(3):1419 -27.
- [36] Zajec M, Langerhorst P, VanDuijn MM, et al. Mass Spectrometry for Identification, Monitoring, and Minimal Residual Disease Detection of M-Proteins. *Clin Chem* 2020;66(3):421 -33.
- [37] Li K, Barnidge D, Krevvata M, et al. Comparison of the Analytical Performance of EXENT®, a Mass Spectrometry-Based Assessment of M-Protein, to SPEP and NGS-Based MRD in Multiple Myeloma Patient Samples. *Blood* 2022; 140(Supplement 1):12446 -7.
- [38] Barnidge DR, Krick TP, Griffin TJ, et al. Using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry to detect monoclonal immunoglobulin light chains in serum and urine. *Rapid Commun Mass Spectrom* 2015;29(21): 2057 -60.
- [39] Eveillard M, Rustad E, Roshal M, et al. Comparison of MALDI-TOF mass spectrometry analysis of peripheral blood and bone marrow-based flow cytometry for tracking measurable residual disease in patients with multiple myeloma. *Br J Haematol* 2020;189(5):904 -7.
- [40] Puig N, Agull C, Contreras Sanfeliciano T, et al. Clinical Impact of Next Generation Flow in Bone Marrow Vs Qip-Mass Spectrometry in Peripheral Blood to Assess Minimal Residual Disease in Newly Diagnosed Multiple Myeloma Patients Receiving Maintenance As Part of the GEM2014MAIN Trial. *Blood* 2022; 140(Supplement 1):2098 -100.
- [41] Derman BA, Stefka AT, Jiang K, et al. Measurable residual disease assessed by mass spectrometry in peripheral blood in multiple myeloma in a phase II trial of carfilzomib, lenalidomide, dexamethasone and autologous stem cell transplantation. *Blood Cancer J* 2021;11(2):1 -4.
- [42] Puig N, Contreras Sanfeliciano T, Paiva B, et al. Assessment of Treatment Response By Ife, Next Generation Flow Cytometry and Mass Spectrometry Coupled with Liquid Chromatography in the GEM2012MENOS65 Clinical Trial. *Blood* 2021;138(Supplement 1):544.

- [43] Derman BA, Kansagra A, Zonder J, et al. Elotuzumab and Weekly Carfilzomib, Lenalidomide, and Dexamethasone in Patients With Newly Diagnosed Multiple Myeloma Without Transplant Intent: A Phase 2 Measurable Residual Disease-Adapted Study. *JAMA Oncol* 2022;8(9):1278 -86.
- [44] Liyasova M, McDonald Z, Taylor P, et al. A Personalized Mass Spectrometry-Based Assay to Monitor M-Protein in Patients with Multiple Myeloma (EasyM). *Clin Cancer Res* 2021;27(18):5028 -37.
- [45] McDonald Z, Taylor P, Liyasova M, et al. Mass Spectrometry Provides a Highly Sensitive Noninvasive Means of Sequencing and Tracking M-Protein in the Blood of Multiple Myeloma Patients. *J Proteome Res* 2021;20(8):4176 -85.
- [46] Bonifay V, Vimard V, Noori S, et al. P10 AN ULTRA-SENSITIVE METHOD FOR SEQUENCING AND MONITORING OF M-PROTEIN IN PERIPHERAL BLOOD (M-INSIGHT). *HemaSphere* 2023;7(S2):15.
- [47] Slade MJ, Khalid A, Fiala MA, et al. Clonotypic Mass Spectrometry with Easym Assay for Detection of Measurable Residual Disease in Multiple Myeloma. *Blood* 2022;140(Supplement 1):4376 -7.
- [48] Noori S, Wijnands C, Langerhorst P, et al. Dynamic monitoring of myeloma minimal residual disease with targeted mass spectrometry. *Blood Cancer J* 2023; 13(1):1 -3.
- [49] Kendrick F, Harding S, Chappell MJ, et al. Immunoglobulin G (IgG) and neonatal Fc-receptor (FcRn) dynamics in IgG multiple myeloma**Felicity Kendrick is a member of the Midlands Integrative Biosciences Training Partnership funded by the Biotechnology and Bi-ological Sciences Research Council (BBSRC). *IFAC-PapersOnLine* 2015;48(20):106 -11.
- [50] Kendrick F, Evans ND, Arnulf B, et al. Analysis of a Compartmental Model of Endogenous Immunoglobulin G Metabolism with Application to Multiple Myeloma. *Front Physiol* 2017;8:149.
- [51] van de Velde HJK, Liu X, Chen G, et al. Complete response correlates with long-term survival and progression-free survival in high-dose therapy in multiple myeloma. *Haematologica* 2007;92(10):1399 -406.
- [52] Gay F, Larocca A, Wijermans P, et al. Complete response correlates with long-term progression-free and overall survival in elderly myeloma treated with novel agents: analysis of 1175 patients. *Blood* 2011;117(11):3025 -31.
- [53] Lahuerta JJ, Mateos MV, Martinez-Lpez J, et al. Influence of pre- and post- transplantation responses on outcome of patients with multiple myeloma: sequential improvement of response and achievement of complete response are associated with longer survival. *J Clin Oncol* 2008;26(35):5775 -82.
- [54] Martinez-Lpez J, Paiva B, Lpez-Anglada L, et al. Critical analysis of the stringent complete response in multiple myeloma: contribution of sFLC and bone marrow clonality. *Blood* 2015;126(7):858 -62.
- [55] Cedena MT, Martin-Clavero E, Wong S, et al. The clinical significance of stringent complete response in multiple myeloma is surpassed by minimal residual disease measurements. *PLoS One* 2020;15(8):e0237155.
- [56] Jimnez Ubieto A, Paiva B, Puig N, et al. Validation of the IMWG standard

- p>response criteria in the PETHEMA/
-
- GEM2012MENOS65 study: are these
-
- times of change?
- Blood*
- 2021.
- [https://
doi.org/10.1182/blood.2021012319](https://doi.org/10.1182/blood.2021012319)
- .
-
- blood.2021012319*
- .
- [57] Munshi NC, Avet-Loiseau H, Rawstron
AC, et al. Association of Minimal Residual
Disease With Superior Survival Outcomes
in Patients With Multiple Myeloma: A Meta-
analysis. *JAMA Oncol* 2017;3(1):28.
- [58] Munshi NC, Avet-Loiseau H, Anderson KC,
et al. A large meta-analysis establishes the
role of MRD negativity in long-term survival
outcomes in patients with multiple myeloma.
Blood Advances 2020;4(23):5988 -99.
- [59] Bansal R, Baksh M, Larsen JT, et al.
Prognostic value of early bone marrow MRD
status in CAR-T therapy for myeloma. *Blood
Cancer J* 2023;13(1):1 -5.
- [60] Paiva B, Manrique I, Rytlewski J, et al.
Time-dependent prognostic value of sero-
logical and measurable residual disease
assessments after idecabtagene vicleucel.
Blood Cancer Discovery 2023. [https://doi.
org/10.1158/2643-3230.BCD-23-0044](https://doi.org/10.1158/2643-3230.BCD-23-0044).
BCD-23-0044.
- [61] Martin T, Usmani SZ, Berdeja JG, et
al. Ciltacabtagene Autoleucel, an Anti-
B-cell Maturation Antigen Chimeric
Antigen Receptor T-Cell Therapy, for
Relapsed/Refractory Multiple Myeloma:
CARTITUDE-1 2-Year Follow-Up. *JCO*
2022. [https:// doi.org/10.1200/JCO.22.00842](https://doi.org/10.1200/JCO.22.00842).
JCO.22.00842.
- [62] Lin Y, Martin TG, Usmani SZ, et al.
CARTITUDE-1 final results: Phase 1b/2
study of ciltacabtagene autoleucel in
heavily pretreated patients with relapsed/
refractory multiple myeloma. *J Clin Orthod*
2023;41(16_suppl):8009.
- [63] Gay F, Musto P, Rota-Scalabrini D, et
al. Carfilzomib with cyclophosphamide
and dexamethasone or lenalidomide
and dexamethasone plus autologous
transplantation or carfilzomib plus
lenalidomide and dexamethasone, followed
by maintenance with carfilzomib plus
lenalidomide or lenalidomide alone for
patients with newly diagnosed multiple
myeloma (FORTE): a randomised,
open-label, phase 2 trial. *Lancet Oncol*
2021;22(12):1705 -20.
- [64] San-Miguel J, Avet-Loiseau H, Paiva B, et al.
Sustained minimal residual disease negativity
in newly diagnosed multiple myeloma and
the impact of daratumumab in MAIA and
ALCYONE. *Blood* 2022;139(4):492 -501.
- [65] Avet-Loiseau H, San-Miguel J, Casneuf T, et
al. Evaluation of Sustained Minimal Residual
Disease Negativity With Daratumumab-
Combination Regimens in Relapsed and/
or Refractory Multiple Myeloma: Analysis
of POLLUX and CASTOR. *J Clin Oncol*
2021;39(10):1139 -49.
- [66] Mohan M, Kendrick S, Szabo A, et al.
Clinical implications of loss of bone marrow
minimal residual disease negativity in
multiple myeloma. *Blood Advances* 2022;
6(3):808 -17.
- [67] Diamond B, Korde N, Lesokhin AM, et
al. Dynamics of minimal residual disease
in patients with multiple myeloma on
continuous lenalidomide maintenance: a
single-arm, single-centre, phase 2 trial. *The
Lancet Haematology* 2021;8(6): e422 -32.
- [68] Paiva B, Manrique I, Dimopoulos MA, et
al. MRD dynamics during maintenance for
improved prognostication of 1280 patients

- with myeloma in the TOURMALINE-MM3 and -MM4 trials. *Blood* 2023;141(6):579-91.
- [69] Oliva S, Genuardi E, Paris L, et al. Prospective evaluation of minimal residual disease in the phase II FORTE trial: a head-to-head comparison between multiparameter flow cytometry and next-generation sequencing. *eClinicalMedicine* 2023;60.
- [70] Costa LJ, Derman BA, Bal S, et al. International harmonization in performing and reporting minimal residual disease assessment in multiple myeloma trials. *Leukemia* 2021;35(1):18-30.
- [71] Derman BA, Major A, Major S, et al. Prospective Trial Using Multimodal Measurable Residual Disease Negativity to Guide Discontinuation of Maintenance Therapy in Multiple Myeloma (MRD2STOP). *Blood* 2022;140(Supplement 1):2108-9.
- [72] Dispenzieri A, Krishnan A, Arendt B, et al. Mass-Fix better predicts for PFS and OS than standard methods among multiple myeloma patients participating on the STAMINA trial (BMT CTN 0702/07LT). *Blood Cancer J* 2022;12(2):1-8.
- [73] Claveau JS, Murray DL, Dispenzieri A, et al. Value of bone marrow examination in determining response to therapy in patients with multiple myeloma in the context of mass spectrometry-based M-protein assessment. *Leukemia* 2023;37(1):1-4.
- [74] Buyse M, Molenberghs G, Burzykowski T, et al. The validation of surrogate end-points in meta-analyses of randomized experiments. *Biostatistics* 2000;1(1): 49-67.
- [75] Etekal T, Koehn K, Sborov DW, et al. Time-to-event surrogate end-points in multiple myeloma randomised trials from 2005 to 2019: A surrogacy analysis. *Br J Haematol* 2023;200(5):587-94.
- [76] Xie W, Halabi S, Tierney JF, et al. A Systematic Review and Recommendation for Reporting of Surrogate Endpoint Evaluation Using Meta-analyses. *JNCI Cancer Spectr* 2019;3(1):kz002.
- [77] Paiva B, Zherniakova A, Nuez-Crdoaba JM, et al. Impact of treatment effect on MRD and PFS: an aggregate analysis from randomized clinical trials in multiple myeloma. *Blood Adv* 2023;1, bloodadvances.202301082.
- [78] Costa LJ, Chhabra S, Medvedova E, et al. Minimal residual disease response-adapted therapy in newly diagnosed multiple myeloma (MASTER): final report of the multicentre, single-arm, phase 2 trial. *Lancet Haematol* 2023;10(11): e890-901.
- [79] Research C for DE and. Hematologic Malignancies: Regulatory Considerations for Use of Minimal Residual Disease in Development of Drug and Biological Products for Treatment. U.S. Food and Drug Administration. Published January 24,2020. Available at: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/hematologic-malignancies-regulatory-considerations-use-minimal-residual-disease-development-drug-and>. Accessed June 30, 2023.
- [80] Dhakal B, Usmani S. Daratumumab and Lenalidomide Maintenance Guided by Minimal Residual Disease in Multiple Myeloma. *The Hematologist* 2021;18(6). <https://doi.org/10.1182/hem.V18.6.202166>.
- [82] Dytfield D, Wrbel T, Jamroziak K, et al. Carfilzomib, lenalidomide, and dexamethasone or lenalidomide alone as

- maintenance therapy after autologous stem-cell transplantation in patients with multiple myeloma (ATLAS): interim analysis of a randomised, open-label, phase 3 trial. *Lancet Oncol* 2023;24(2):139 -50.
- [83] Correia N, Dowling E, Popat R, et al. Functional and psychological impact of minimal residual disease assessment on patients with multiple myeloma. *Br J Haematol* 2023. <https://doi.org/10.1111/bjh.18948>.
- [84] Derman BA, Jakubowiak AJ, Thompson MA. Clinician survey regarding measurable residual disease-guided decision-making in multiple myeloma. *Blood Cancer J* 2022;12(7):108.
- [85] Martinez-Lopez J, Alonso R, Wong SW, et al. Making clinical decisions based on measurable residual disease improves the outcome in multiple myeloma. *J Hematol Oncol* 2021;14(1):126.
- [86] Derman BA, Major A, Rosenblatt J, et al. A Phase 2 Study of Extended Daratumumab, Carfilzomib, Lenalidomide, and Dexamethasone in Newly Diagnosed Multiple Myeloma. *Blood* 2021;138(Supplement 1):2759.
- [87] de Tute RM, Pawlyn C, Cairns DA, et al. Minimal Residual Disease After Autologous Stem-Cell Transplant for Patients With Myeloma: Prognostic Significance and the Impact of Lenalidomide Maintenance and Molecular Risk. *J Clin Orthod* 2022;40(25):2889 -900.
- [88] Alonso R, Cedena MT, Wong S, et al. Prolonged lenalidomide maintenance therapy improves the depth of response in multiple myeloma. *Blood Advances* 2020; 4(10):2163 -71.
- [89] Hahn TE, Wallace PK, Fraser R, et al. Minimal Residual Disease (MRD) Assessment before and after Autologous Hematopoietic Cell Transplantation (AutoHCT) and Maintenance for Multiple Myeloma (MM): Results of the Prognostic Immuno-phenotyping for Myeloma Response (PRIMeR) Study. *Biol Blood Marrow Transplant* 2019;25(3):S4 -6.
- [90] Paiva B, Puig N, Cedena MT, et al. Measurable Residual Disease by Next-Generation Flow Cytometry in Multiple Myeloma. *J Clin Orthod* 2019. <https://doi.org/10.1200/JCO.19.01231>. JCO.19.01231.

14 高危多发性骨髓瘤的治疗方法

- [1] Majithia N, Rajkumar SV, Lacy MQ, et al. Early relapse following initial therapy for multiple myeloma predicts poor outcomes in the era of novel agents. *Leukemia* 2016;30:2208–13.
- [2] Bygrave C, Pawlyn C, Davies F, et al. Early relapse after high-dose melphalan autologous stem cell transplant predicts inferior survival and is associated with high disease burden and genetically high-risk disease in multiple myeloma. *Br J Haematol* 2021;193:551–5.
- [3] Sonneveld P, Avet-Loiseau H, Lonial S, et al. Treatment of multiple myeloma with high-risk cytogenetics: a consensus of the International Myeloma Working Group. *Blood* 2016;127:2955–62.
- [4] Jagosky MH, Usmani SZ. Extramedullary disease in multiple myeloma. *Curr Hematol Malig Rep* 2020;15:62–71.
- [5] Bansal R, Rakshit S, Kumar S. Extramedullary disease in multiple myeloma. *Blood Cancer J* 2021;11:161.
- [6] Schinke C, Boyle EM, Ashby C, et al. Genomic analysis of primary plasma cell leukemia reveals complex structural alterations and high-risk mutational patterns. *Blood Cancer J* 2020;10:70.
- [7] Chng WJ, Dispenzieri A, Chim CS, et al. IMWG consensus on risk stratification in multiple myeloma. *Leukemia* 2014;28:269–77.
- [8] Greipp PR, San Miguel J, Durie BG, et al. International staging system for multiple myeloma. *J Clin Oncol* 2005;23:3412–20.
- [9] Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised international staging system for multiple myeloma: a report from International Myeloma Working Group. *J Clin Oncol* 2015;33:2863–9.
- [10] Boyle EM, Rosenthal A, Wang Y, et al. High-risk transcriptional profiles in multiple myeloma are an acquired feature that can occur in any subtype and more frequently with each subsequent relapse. *Br J Haematol* 2021;195:283–6.
- [11] D'Agostino M, Cairns DA, Lahuerta JJ, et al. Second Revision of the International Staging System (R2-ISS) for overall survival in multiple myeloma: a European Myeloma Network (EMN) report within the HARMONY Project. *J Clin Oncol* 2022;40:3406–18.
- [12] Pawlyn C, Morgan GJ. Evolutionary biology of high-risk multiple myeloma. *Nat Rev Cancer* 2017;17:543–56.
- [13] Maura F, Rustad EH, Boyle EM, et al. Reconstructing the evolutionary history of multiple myeloma. *Best Pract Res Clin Haematol* 2020;33:101145.
- [14] Melchor L, Brioli A, Wardell CP, et al. Single-cell genetic analysis reveals the composition of initiating clones and phylogenetic patterns of branching and parallel evolution in myeloma. *Leukemia* 2014;28:1705–15.
- [15] Walker BA, Wardell CP, Melchor L, et al. Intracлонаl heterogeneity is a critical early event in the development of myeloma

- and precedes the development of clinical symptoms. *Leukemia* 2014;28:384–90.
- [16] Landgren O, Morgan GJ. Biologic frontiers in multiple myeloma: from biomarker identification to clinical practice. *Clin Cancer Res* 2014;20:804–13.
- [17] Bergsagel PL, Kuehl WM, Zhan F, et al. Cyclin D dysregulation: an early and unifying pathogenic event in multiple myeloma. *Blood* 2005;106:296–303.
- [18] Zhan F, Huang Y, Colla S, et al. The molecular classification of multiple myeloma. *Blood* 2006;108:2020–8.
- [19] Joseph NS, Gentili S, Kaufman JL, et al. High-risk multiple myeloma: definition and management. *Clin Lymphoma Myeloma Leuk* 2017;17S:S80–7.
- [20] Maura F, Boyle EM, Rustad EH, et al. Chromothripsis as a pathogenic driver of multiple myeloma. *Semin Cell Dev Biol* 2022;123:115–23.
- [21] Maura F, Bolli N, Angelopoulos N, et al. Genomic landscape and chronological reconstruction of driver events in multiple myeloma. *Nat Commun* 2019;10:3835.
- [22] Shaughnessy JD Jr, Zhan F, Burington BE, et al. A validated gene expression model of high-risk multiple myeloma is defined by deregulated expression of genes mapping to chromosome 1. *Blood* 2007;109:2276–84.
- [23] Walker BA, Leone PE, Chiecchio L, et al. A compendium of myeloma-associated chromosomal copy number abnormalities and their prognostic value. *Blood* 2010;116:e56–65.
- [24] Walker BA, Mavrommatis K, Wardell CP, et al. A high-risk, double-hit, group of newly diagnosed myeloma identified by genomic analysis. *Leukemia* 2019;33: 159–70.
- [25] Panopoulou A, Cairns DA, Holroyd A, et al. Optimizing the value of lenalidomide maintenance by extended genetic profiling: an analysis of 556 patients in the Myeloma XI trial. *Blood* 2023;141:1666–74.
- [26] Panopoulou A, Easdale S, Ethell M, et al. Impact of ultra high-risk genetics on real-world outcomes of transplant-eligible multiple myeloma patients. *Hema- sphere* 2023;7:e831.
- [27] Messiou C, Giles S, Collins DJ, et al. Assessing response of myeloma bone disease with diffusion-weighted MRI. *Br J Radiol* 2012;85:e1198–203.
- [28] Giles SL, Messiou C, Collins DJ, et al. Whole-body diffusion-weighted MR imaging for assessment of treatment response in myeloma. *Radiology* 2014;271: 785–94.
- [29] Rasche L, Alapat D, Kumar M, et al. Combination of flow cytometry and functional imaging for monitoring of residual disease in myeloma. *Leukemia* 2019; 33:1713–22.
- [30] Dimopoulos M, Terpos E, Comenzo RL, et al. International myeloma working group consensus statement and guidelines regarding the current role of imaging techniques in the diagnosis and monitoring of multiple myeloma. *Leukemia* 2009;23:1545–56.
- [31] Rasche L, Angtuaco EJ, Alpe TL, et al. The presence of large focal lesions is a strong independent prognostic factor in multiple myeloma. *Blood* 2018;132: 59–66.
- [32] McDonald JE, Kessler MM, Gardner MW, et al. Assessment of total lesion glycolysis by (18)F FDG PET/CT significantly improves prognostic value of GEP and ISS in myeloma. *Clin Cancer Res* 2017;23:1981–7.
- [33] Morgan GJ, Walker BA, Davies FE. The

- genetic architecture of multiple myeloma. *Nat Rev Cancer* 2012;12:335–48.
- [34] Hoang PH, Dobbins SE, Cornish AJ, et al. Whole-genome sequencing of multiple myeloma reveals oncogenic pathways are targeted somatically through multiple mechanisms. *Leukemia* 2018;32:2459–70.
- [35] Stein CK, Pawlyn C, Chavan S, et al. The varied distribution and impact of RAS codon and other key DNA alterations across the translocation cyclin D subgroups in multiple myeloma. *Oncotarget* 2017;8:27854–67.
- [36] Heuck CJ, Jethava Y, Khan R, et al. Inhibiting MEK in MAPK pathway-activated myeloma. *Leukemia* 2016;30:976–80.
- [37] Hose D, Reme T, Hielscher T, et al. Proliferation is a central independent prognostic factor and target for personalized and risk-adapted treatment in multiple myeloma. *Haematologica* 2011;96:87–95.
- [38] Thanendrarajan S, Tian E, Qu P, et al. The level of deletion 17p and bi-allelic inactivation of TP53 has a significant impact on clinical outcome in multiple myeloma. *Haematologica* 2017;102:e364–7.
- [39] Dring AM, Davies FE, Fenton JA, et al. A global expression-based analysis of the consequences of the t(4;14) translocation in myeloma. *Clin Cancer Res* 2004;10:5692–701.
- [40] Woo JS, Alberti MO, Tirado CA. Childhood B-acute lymphoblastic leukemia: a genetic update. *Exp Hematol Oncol* 2014;3:16.
- [41] Topchu I, Pangeni RP, Bychkov I, et al. The role of NSD1, NSD2, and NSD3 histone methyltransferases in solid tumors. *Cell Mol Life Sci* 2022;79:285.
- [42] Popovic R, Martinez-Garcia E, Giannopoulou EG, et al. Histone methyltransferase MMSET/NSD2 alters EZH2 binding and reprograms the myeloma epigenome through global and focal changes in H3K36 and H3K27 methylation. *PLoS Genet* 2014;10:e1004566.
- [43] Walker BA, Wardell CP, Chiecchio L, et al. Aberrant global methylation patterns affect the molecular pathogenesis and prognosis of multiple myeloma. *Blood* 2011;117:553–62.
- [44] Pawlyn C, Kaiser MF, Heuck C, et al. The spectrum and clinical impact of epigenetic modifier mutations in myeloma. *Clin Cancer Res* 2016;22:5783–94.
- [45] Pawlyn C, Kaiser MF, Davies FE, et al. Current and potential epigenetic targets in multiple myeloma. *Epigenomics* 2014;6:215–28.
- [46] Pawlyn C, Bright MD, Buros AF, et al. Overexpression of EZH2 in multiple myeloma is associated with poor prognosis and dysregulation of cell cycle control. *Blood Cancer J* 2017;7:e549.
- [47] Ghamlouch H, Boyle EM, Blaney P, et al. Insights into high-risk multiple myeloma from an analysis of the role of PHF19 in cancer. *J Exp Clin Cancer Res* 2021; 40:380.
- [48] Mason MJ, Schinke C, Eng CLP, et al. Multiple myeloma DREAM Challenge reveals epigenetic regulator PHF19 as marker of aggressive disease. *Leukemia* 2020;34:1866–74.
- [49] Qiang YW, Ye S, Huang Y, et al. MAFb protein confers intrinsic resistance to proteasome inhibitors in multiple myeloma. *BMC Cancer* 2018;18:724.
- [50] Walker BA, Wardell CP, Murison A, et al. APOBEC family mutational signatures are associated with poor prognosis translocations in multiple myeloma. *Nat Commun*

- 2015;6:6997.
- [51] Maura F, Rustad EH, Yellapantula V, et al. Role of AID in the temporal pattern of acquisition of driver mutations in multiple myeloma. *Leukemia* 2020;34:1476–80.
- [52] Shou Y, Martelli ML, Gabrea A, et al. Diverse karyotypic abnormalities of the c-myc locus associated with c-myc dysregulation and tumor progression in multiple myeloma. *Proc Natl Acad Sci U S A* 2000;97:228–33.
- [53] Avet-Loiseau H, Gerson F, Magrangeas F, et al. Rearrangements of the c-myc oncogene are present in 15% of primary human multiple myeloma tumors. *Blood* 2001;98:3082–6.
- [54] Walker BA, Wardell CP, Brioli A, et al. Translocations at 8q24 juxtapose MYC with genes that harbor superenhancers resulting in overexpression and poor prognosis in myeloma patients. *Blood Cancer J* 2014;4:e191.
- [55] Affer M, Chesi M, Chen WG, et al. Promiscuous MYC locus rearrangements hijack enhancers but mostly super-enhancers to dysregulate MYC expression in multiple myeloma. *Leukemia* 2014;28:1725–35.
- [56] Misund K, Keane N, Stein CK, et al. MYC dysregulation in the progression of multiple myeloma. *Leukemia* 2020;34:322–6.
- [57] Maura F, Petljak M, Lionetti M, et al. Biological and prognostic impact of APOBEC-induced mutations in the spectrum of plasma cell dyscrasias and multiple myeloma cell lines. *Leukemia* 2018;32:1044–8.
- [58] Alexandrov LB, Nik-Zainal S, Wedge DC, et al. Signatures of mutational processes in human cancer. *Nature* 2013;500:415–21.
- [59] Bolli N, Avet-Loiseau H, Wedge DC, et al. Heterogeneity of genomic evolution and mutational profiles in multiple myeloma. *Nat Commun* 2014;5:2997.
- [60] Hoang PH, Cornish AJ, Dobbins SE, et al. Mutational processes contributing to the development of multiple myeloma. *Blood Cancer J* 2019;9:60.
- [61] Rustad EH, Yellapantula V, Leongamornlert D, et al. Timing the initiation of multiple myeloma. *Nat Commun* 2020;11:1917.
- [62] Cowan G, Weston-Bell NJ, Bryant D, et al. Massive parallel IGHV gene sequencing reveals a germinal center pathway in origins of human multiple myeloma. *Oncotarget* 2015;6:13229–40.
- [63] Rustad EH, Yellapantula VD, Glodzik D, et al. Revealing the impact of structural variants in multiple myeloma. *Blood Cancer Discov* 2020;1:258–73.
- [64] Morgan GJ. Jumping translocations and high-risk myeloma. *Blood* 2014;123: 2442–3.
- [65] Sawyer JR, Tian E, Heuck CJ, et al. Jumping translocations of 1q12 in multiple myeloma: a novel mechanism for deletion of 17p in cytogenetically defined high-risk disease. *Blood* 2014;123:2504–12.
- [66] Hanamura I, Stewart JP, Huang Y, et al. Frequent gain of chromosome band 1q21 in plasma-cell dyscrasias detected by fluorescence in situ hybridization: incidence increases from MGUS to relapsed myeloma and is related to prognosis and disease progression following tandem stem-cell transplantation. *Blood* 2006;108:1724–32.
- [67] Sawyer JR, Tian E, Walker BA, et al. An acquired high-risk chromosome instability phenotype in multiple myeloma: jumping 1q

- syndrome. *Blood Cancer J* 2019;9:62.
- [68] Hebraud B, Leleu X, Lauwers-Cances V, et al. Deletion of the 1p32 region is a major independent prognostic factor in young patients with myeloma: the IFM experience on 1195 patients. *Leukemia* 2014;28:675–9.
- [69] Hofman IJF, van Duin M, De Bruyne E, et al. RPL5 on 1p22.1 is recurrently deleted in multiple myeloma and its expression is linked to bortezomib response. *Leukemia* 2017;31:1706–14.
- [70] Boyd KD, Ross FM, Walker BA, et al. Mapping of chromosome 1p deletions in myeloma identifies FAM46C at 1p12 and CDKN2C at 1p32.3 as being genes in regions associated with adverse survival. *Clin Cancer Res* 2011;17:7776–84.
- [71] Inoue J, Otsuki T, Hirasawa A, et al. Overexpression of PDZK1 within the 1q12-q22 amplicon is likely to be associated with drug-resistance phenotype in multiple myeloma. *Am J Pathol* 2004;165:71–81.
- [72] Mani M, Carrasco DE, Zhang Y, et al. BCL9 promotes tumor progression by conferring enhanced proliferative, metastatic, and angiogenic properties to cancer cells. *Cancer Res* 2009;69:7577–86.
- [73] Marchesini M, Ogoti Y, Fiorini E, et al. ILF2 Is a regulator of RNA splicing and DNA damage response in 1q21-amplified multiple myeloma. *Cancer Cell* 2017;32:88–100 e6.
- [74] Teoh PJ, An O, Chung TH, et al. Aberrant hyperediting of the myeloma transcriptome by ADAR1 confers oncogenicity and is a marker of poor prognosis. *Blood* 2018;132:1304–17.
- [75] Samo AA, Li J, Zhou M, et al. MCL1 gene co-expression module stratifies multiple myeloma and predicts response to proteasome inhibitor-based therapy. *Genes Chromosomes Cancer* 2018;57:420–9.
- [76] Boyle EM, Blaney P, Stoeckle JH, et al. Multiomic Mapping of Acquired Chromosome 1 Copy-Number and Structural Variants to Identify Therapeutic Vulnerabilities in Multiple Myeloma. *Clin Cancer Res* 2023;29(19):3901–13.
- [77] Owen RG, Davis SA, Randerson J, et al. p53 gene mutations in multiple myeloma. *Mol Pathol* 1997;50:18–20.
- [78] Shah V, Johnson DC, Sherborne AL, et al. Subclonal TP53 copy number is associated with prognosis in multiple myeloma. *Blood* 2018;132:2465–9.
- [79] Thakurta A, Ortiz M, Blecura P, et al. High subclonal fraction of 17p deletion is associated with poor prognosis in multiple myeloma. *Blood* 2019;133:1217–21.
- [80] Martello M, Poletti A, Borsi E, et al. Clonal and subclonal TP53 molecular impairment is associated with prognosis and progression in multiple myeloma. *Blood Cancer J* 2022;12:15.
- [81] Kunkel EJ, Butcher EC. Plasma-cell homing. *Nat Rev Immunol* 2003;3:822–9.
- [82] Cyster JG. Homing of antibody secreting cells. *Immunol Rev* 2003;194:48–60.
- [83] Danziger SA, McConnell M, Gockley J, et al. Bone marrow microenvironments that contribute to patient outcomes in newly diagnosed multiple myeloma: A cohort study of patients in the Total Therapy clinical trials. *PLoS Med* 2020;17: e1003323.
- [84] Neri P, Ren L, Azab AK, et al. Integrin beta7-mediated regulation of multiple myeloma cell adhesion, migration, and invasion. *Blood* 2011;117:6202–13.
- [85] Gupta VA, Matulis SM, Conage-Pough JE, et

- al. Bone marrow microenvironment- derived signals induce Mcl-1 dependence in multiple myeloma. *Blood* 2017;129: 1969–79.
- [86] de Jong MME, Kellermayer Z, Papazian N, et al. The multiple myeloma microenvironment is defined by an inflammatory stromal cell landscape. *Nat Immunol* 2021;22:769–80.
- [87] Schinke C, Poos AM, Bauer M, et al. Characterizing the role of the immune microenvironment in multiple myeloma progression at a single-cell level. *Blood Adv* 2022;6:5873–83.
- [88] Zavidij O, Haradhvala NJ, Mouhieddine TH, et al. Single-cell RNA sequencing reveals compromised immune microenvironment in precursor stages of multiple myeloma. *Nat Cancer* 2020;1:493–506.
- [89] Friedrich MJ, Neri P, Kehl N, et al. The pre-existing T cell landscape determines the response to bispecific Tcell engagers in multiple myeloma patients. *Cancer Cell* 2023;41:711–725 e6.
- [90] Moreau P, Attal M, Hulin C, et al. Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomised, open- label, phase 3 study. *Lancet* 2019;394:29–38.
- [91] Voorhees PM, Kaufman JL, Laubach J, et al. Daratumumab, lenalidomide, bortezomib, and dexamethasone for transplant-eligible newly diagnosed multiple myeloma: the GRIFFIN trial. *Blood* 2020;136:936–45.
- [92] Costa LJ, Chhabra S, Medvedova E, et al. Daratumumab, carfilzomib, lenalidomide, and dexamethasone with minimal residual disease response-adapted therapy in newly diagnosed multiple myeloma. *J Clin Oncol* 2022;40:2901–12.
- [93] Gay F, Musto P, Rota-Scalabrini D, et al. Carfilzomib with cyclophosphamide and dexamethasone or lenalidomide and dexamethasone plus autologous transplantation or carfilzomib plus lenalidomide and dexamethasone, followed by maintenance with carfilzomib plus lenalidomide or lenalidomide alone for patients with newly diagnosed multiple myeloma (FORTE): a randomised, open- label, phase 2 trial. *Lancet Oncol* 2021;22:1705–20.
- [94] Usmani SZ, Hoering A, Ailawadhi S, et al. Bortezomib, lenalidomide, and dexamethasone with or without elotuzumab in patients with untreated, high-risk multiple myeloma (SWOG-1211): primary analysis of a randomised, phase 2 trial. *Lancet Haematol* 2021;8:e45–54.
- [95] Brown S, Sherratt D, Hinsley S, et al. MUKnine OPTIMUM protocol: a screening study to identify high-risk patients with multiple myeloma suitable for novel treatment approaches combined with a phase II study evaluating optimised combination of biological therapy in newly diagnosed high-risk multiple myeloma and plasma cell leukaemia. *BMJ Open* 2021;11:e046225.
- [96] Croft J, Ellis S, Sherborne AL, et al. Copy number evolution and its relationship with patient outcome-an analysis of 178 matched presentation-relapse tumor pairs from the Myeloma XI trial. *Leukemia* 2021;35:2043–53.
- [97] Chavan SS, He J, Tytarenko R, et al. Biallelic inactivation is more prevalent at

- relapse in multiple myeloma, identifying RB1 as an independent prognostic marker. *Blood Cancer J* 2017;7:e535.
- [98] Bird S, Pawlyn C. IMiD resistance in multiple myeloma: current understanding of the underpinning biology and clinical impact. *Blood* 2023;142:131–40.
- [99] Da Via MC, Dietrich O, Truger M, et al. Homozygous BCMA gene deletion in response to anti-BCMA CAR T cells in a patient with multiple myeloma. *Nat Med* 2021;27:616–9.
- [100] Swamydas M, Murphy EV, Ignatz-Hoover JJ, et al. Deciphering mechanisms of immune escape to inform immunotherapeutic strategies in multiple myeloma. *J Hematol Oncol* 2022;15:17.

15 复发难治性多发性骨髓瘤的新疗法涌现

- [1] Kumar SK, Dispenzieri A, Lacy MQ, et al. Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. *Leukemia* 2014;28(5):1122 -8.
- [2] Binder M, Nandakumar B, Rajkumar SV, et al. Mortality trends in multiple myeloma after the introduction of novel therapies in the United States. *Leukemia* 2022;36(3):801 -8.
- [3] Ravi P, Kumar SK, Cerhan JR, et al. Defining cure in multiple myeloma: a comparative study of outcomes of young individuals with myeloma and curable hematologic malignancies. *Blood Cancer J* 2018;8(3):26.
- [4] Mateos M-V, Weisel K, De Stefano V, et al. LocoMMotion: a prospective, non-interventional, multinational study of real-life current standards of care in patients with relapsed and/or refractory multiple myeloma. *Leukemia* 2022;36(5):1371 -6.
- [5] Gandhi UH, Cornell RF, Lakshman A, et al. Outcomes of patients with multiple myeloma refractory to CD38-targeted monoclonal antibody therapy. *Leukemia* 2019;33(9):2266 -75.
- [6] Chari A, Vogl DT, Gavriatopoulou M, et al. Oral Selinexor -Dexamethasone for Triple-Class Refractory Multiple Myeloma. *N Engl J Med* 2019;381(8):727 -38.
- [7] Lonial S, Lee HC, Badros A, et al. Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): a two-arm, randomised, open-label, phase 2 study. *Lancet Oncol* 2020;21(2):207 -21.
- [8] Dimopoulos M, Bringhen S, Anttila P, et al. Isatuximab as monotherapy and combined with dexamethasone in patients with relapsed/refractory multiple myeloma. *Blood* 2021;137(9):1154 -65.
- [9] Moreau P, Garfall AL, van de Donk NWCJ, et al. Teclistamab in Relapsed or Refractory Multiple Myeloma. *N Engl J Med* 2022;387(6):495 -505.
- [10] Chari A, Minnema MC, Berdeja JG, et al. Talquetamab, a T-Cell -Redirecting GPRC5D Bispecific Antibody for Multiple Myeloma. *N Engl J Med* 2022; 387(24):2232 -44.
- [11] Lesokhin AM, Tomasson MH, Arnulf B, et al. Elranatamab in relapsed or refractory multiple myeloma: phase 2 MagnetisMM-3 trial results. *Nat Med* 2023. <https://doi.org/10.1038/s41591-023-02528-9>.
- [12] San-Miguel J, Dhakal B, Yong K, et al. Cilta-cel or Standard Care in Lenalidomide-Refractory Multiple Myeloma. *N Engl J Med* 2023;389(4):335 -47.
- [13] Rodriguez-Otero P, Ailawadhi S, Arnulf B, et al. Ide-cel or Standard Regimens in Relapsed and Refractory Multiple Myeloma. *N Engl J Med* 2023;388(11): 1002 -14.
- [14] Touzeau C, Dousset C, Le Gouill S, et al. The Bcl-2 specific BH3 mimetic ABT-199: a promising targeted therapy for t(11;14) multiple myeloma. *Leukemia* 2014;28(1):210 -2.
- [15] Cleyneen A, Samur M, Perrot A, et al. Variable BCL2/BCL2L1 ratio in multiple myeloma with t(11;14). *Blood* 2018;132(26):2778 -80.

- [16] Fonseca R, Blood EA, Oken MM, et al. Myeloma and the t(11;14)(q13;q32); evidence for a biologically defined unique subset of patients. *Blood* 2002;99(10): 3735-41.
- [17] Kumar S, Kaufman JL, Gasparetto C, et al. Efficacy of venetoclax as targeted therapy for relapsed/refractory t(11;14) multiple myeloma. *Blood* 2017;130(22): 2401-9.
- [18] Punnoose EA, Leverson JD, Peale F, et al. Expression Profile of BCL-2, BCL-XL, and MCL-1 Predicts Pharmacological Response to the BCL-2 Selective Antagonist Venetoclax in Multiple Myeloma Models. *Mol Cancer Ther* 2016;15(5): 1132-44.
- [19] Moreau P, Chanan-Khan A, Roberts AW, et al. Promising efficacy and acceptable safety of venetoclax plus bortezomib and dexamethasone in relapsed/refractory MM. *Blood* 2017;130(22):2392-400.
- [20] Kumar SK, Harrison SJ, Cavo M, et al. Venetoclax or placebo in combination with bortezomib and dexamethasone in patients with relapsed or refractory multiple myeloma (BELLINI): a randomised, double-blind, multicentre, phase 3 trial. *Lancet Oncol* 2020;21(12):1630-42.
- [21] Kumar S, Harrison SJ, Cavo M, et al. Final Overall Survival Results from BELLINI, a Phase 3 Study of Venetoclax or Placebo in Combination with Bortezomib and Dexamethasone in Relapsed/Refractory Multiple Myeloma. *Blood* 2021;138:84.
- [22] Bahlis NJ, Baz R, Harrison SJ, et al. Phase I Study of Venetoclax Plus Daratumumab and Dexamethasone, With or Without Bortezomib, in Patients With Relapsed or Refractory Multiple Myeloma With and Without t(11;14). *J Clin Oncol* 2021; 39(32):3602-12.
- [23] Kaufman JL, Quach H, Baz RC, et al. An Updated Safety and Efficacy Analysis of Venetoclax Plus Daratumumab and Dexamethasone in an Expansion Cohort of a Phase 1/2 Study of Patients with t(11;14) Relapsed/Refractory Multiple Myeloma. *Blood* 2022;140(Supplement 1):7261-3.
- [24] Costa LJ, Davies FE, Monohan GP, et al. Phase 2 study of venetoclax plus carfilzomib and dexamethasone in patients with relapsed/refractory multiple myeloma. *Blood Advances* 2021;5(19):3748-59.
- [25] Mateos M-V, Moreau P, Dimopoulos MA, et al. A phase III, randomized, multicenter, open-label study of venetoclax or pomalidomide in combination with dexamethasone in patients with t(11;14)-positive relapsed/refractory multiple myeloma. *J Clin Oncol* 2020;38(15_suppl):TPS8554.
- [26] Lopez-Girona A, Mendy D, Ito T, et al. Cereblon is a direct protein target for immunomodulatory and antiproliferative activities of lenalidomide and pomalidomide. *Leukemia* 2012;26(11):2326-35.
- [27] Bjorklund CC, Lu L, Kang J, et al. Rate of CRL4CRBN substrate Ikaros and Aiolos degradation underlies differential activity of lenalidomide and pomalidomide in multiple myeloma cells by regulation of c-Myc and IRF4. *Blood Cancer J* 2015; 5(10):e354.
- [28] Matyskiela ME, Zhang W, Man H-W, et al. A Cereblon Modulator (CC-220) with Improved Degradation of Ikaros and Aiolos. *J Med Chem* 2018;61(2):535-42.
- [29] Hansen JD, Correa M, Nagy MA, et al. Discovery of CRBN E3 Ligase Modulator CC-92480 for the Treatment of Relapsed and

- Refractory Multiple Myeloma. *J Med Chem* 2020;63(13):6648 -76.
- [30] Amatangelo M, Bjorklund CC, Kang J, et al. Iberdomide (CC-220) Has Synergistic Anti-Tumor and Immunostimulatory Activity Against Multiple Myeloma in Combination with Both Bortezomib and Dexamethasone, or in Combination with Daratumumab in Vitro. *Blood* 2018;132(Supplement 1):1935.
- [31] Bjorklund CC, Kang J, Amatangelo M, et al. Iberdomide (CC-220) is a potent cereblon E3 ligase modulator with antitumor and immunostimulatory activities in lenalidomide- and pomalidomide-resistant multiple myeloma cells with dysregulated CRBN. *Leukemia* 2020;34(4):1197 -201.
- [32] Wong L, Narla RK, Leisten J, et al. CC-92480, a Novel Cereblon E3 Ligase Modulator, Is Synergistic with Dexamethasone, Bortezomib, and Daratumumab in Multiple Myeloma. *Blood* 2019;134:1815.
- [33] Lonial S, Popat R, Hulin C, et al. Iberdomide plus dexamethasone in heavily pretreated late-line relapsed or refractory multiple myeloma (CC-220-MM-001): a multicentre, multicohort, open-label, phase 1/2 trial. *Lancet Haematol* 2022; 9(11):e822 -32.
- [34] Lonial S, Richardson PG, Popat R, et al. OAB-013: Iberdomide (IBER) in combination with dexamethasone (DEX) and daratumumab (DARA), bortezomib (BORT), or carfilzomib (CFZ) in patients (pts) with relapsed/refractory multiple myeloma (RRMM). *Clin Lymphoma, Myeloma & Leukemia* 2021;21:S9.
- [35] Lonial S, Quach H, Dimopoulos MA, et al. EXCALIBER-RRMM: A phase 3, two-stage study of iberdomide, daratumumab, and dexamethasone (IberDd) versus daratumumab, bortezomib, and dexamethasone (DVd) in patients (pts) with relapsed/refractory multiple myeloma (RRMM). *J Clin Oncol* 2023;41(16_suppl):TPS8069.
- [36] Richardson PG, Vangsted AJ, Ramasamy K, et al. First-in-human phase I study of the novel CELMoD agent CC-92480 combined with dexamethasone (DEX) in patients (pts) with relapsed/refractory multiple myeloma (RRMM). *J Clin Oncol* 2020; 38(15_suppl):8500.
- [37] Wong L, Lamba M, Jimenez Nuez MD, et al. Dose- and Schedule-Dependent Immunomodulatory Effects of the Novel Celmod Agent CC-92480 in Patients with Relapsed/Refractory Multiple Myeloma. *Blood* 2020;136(Supplement 1):47 -8.
- [38] Richardson PG, Trudel S, Quach H, et al. Mezigdomide (CC-92480), a Potent, Novel Cereblon E3 Ligase Modulator (CELMoD), Combined with Dexamethasone (DEX) in Patients (pts) with Relapsed/Refractory Multiple Myeloma (RRMM): Preliminary Results from the Dose-Expansion Phase of the CC-92480-MM-001 Trial. *Blood* 2022;140(Supplement 1):1366 -8.
- [39] Richardson P, Sandhu I, Oriol A, et al. OAB-053: Mezigdomide (MEZI; CC-92480) in combination with dexamethasone (DEX) and bortezomib (BORT) or carfilzomib (CFZ) in patients (pts) with relapsed/refractory multiple myeloma (RRMM). *Clin Lymphoma, Myeloma & Leukemia* 2022;22:S33.
- [40] Amatangelo M, Berenson JR, Cerchione C, et al. A phase 3, two-stage, randomized

- study of mezigdomide, carfilzomib, and dexamethasone (MeziKd) versus carfilzomib and dexamethasone (Kd) in relapsed/refractory multiple myeloma (RRMM): SUCCESSOR-2. *J Clin Oncol* 2023;41(16_suppl):TPS8070.
- [41] Bruins WSC, Rentenaar R, Collins S, et al. Modakafusp Alfa (TAK-573), a Novel CD38-Targeting Attenuated Interferon-Alpha Immunocytokine, Kills MM Cells Via NK Cell Activation. *Blood* 2022;140(Supplement 1):4236 -7.
- [42] Vogl DT, Kaufman JL, Holstein SA, et al. TAK-573, an Anti-CD38/Attenuated Ifna Fusion Protein, Has Clinical Activity and Modulates the Ifna Receptor (IFNAR) Pathway in Patients with Relapsed/Refractory Multiple Myeloma. *Blood* 2020;136(Supplement 1):37 -8.
- [43] Pogue SL, Taura T, Bi M, et al. Targeting Attenuated Interferon-alpha to Myeloma Cells with a CD38 Antibody Induces Potent Tumor Regression with Reduced Off-Target Activity. *PLoS One* 2016;11(9):e0162472.
- [44] Vogl DT, Atrash S, Holstein SA, et al. Final Results from the First-in-Human Phase 1/2 Study of Modakafusp Alfa, an Immune-Targeting Attenuated Cytokine, in Patients(Pts) with Relapsed/Refractory Multiple Myeloma (RRMM). *Blood* 2022;140(Supplement 1):1357 -9.

16 多发性骨髓瘤免疫活性小鼠模型：治疗意义

- [1] Kuehl WM, Bergsagel PL. Molecular pathogenesis of multiple myeloma and its premalignant precursor. *J Clin Invest* 2012;122(10):3456–63.
- [2] Huang J, Chan SC, Lok V, et al. The epidemiological landscape of multiple myeloma: a global cancer registry estimate of disease burden, risk factors, and temporal trends. *Lancet Haematol* 2022;9(9):e670–7.
- [3] Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International myeloma working group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol* 2014;15(12):e538–48.
- [4] Bolli N, Martinelli G, Cerchione C. The molecular pathogenesis of multiple myeloma. *Hematol Rep* 2020;12(3):9054.
- [5] Misund K, Keane N, Stein CK, et al. MYC dysregulation in the progression of multiple myeloma. *Leukemia* 2020;34(1):322–6.
- [6] Keats JJ, Fonseca R, Chesi M, et al. Promiscuous mutations activate the non-canonical NF-kappaB pathway in multiple myeloma. *Cancer Cell* 2007;12(2): 131–44.
- [7] Maura F, Coffey DG, Stein CK, et al. The Vk*MYC Mouse Model recapitulates human multiple myeloma evolution and genomic diversity. *bioRxiv preprint* 2023. <https://doi.org/10.1101/2023.07.25.550482>.
- [8] Maura F, Petljak M, Lionetti M, et al. Biological and prognostic impact of APOBEC-induced mutations in the spectrum of plasma cell dyscrasias and multiple myeloma cell lines. *Leukemia* 2018;32(4):1044–8.
- [9] Hideshima T, Mitsiades C, Tonon G, et al. Understanding multiple myeloma pathogenesis in the bone marrow to identify new therapeutic targets. *Nat Rev Cancer* 2007;7(8):585–98.
- [10] O'Connor BP, Raman VS, Erickson LD, et al. BCMA is essential for the survival of long-lived bone marrow plasma cells. *J Exp Med* 2004;199(1):91–8.
- [11] Sklavenitis-Pistofidis R, Haradhvala NJ, Getz G, et al. Inflammatory stromal cells in the myeloma microenvironment. *Nat Immunol* 2021;22(6):677–8.
- [12] de Jong MME, Kellermayer Z, Papazian N, et al. The multiple myeloma microenvironment is defined by an inflammatory stromal cell landscape. *Nat Immunol* 2021;22(6):769–80.
- [13] Zhu YX, Braggio E, Shi CX, et al. Cereblon expression is required for the antimyeloma activity of lenalidomide and pomalidomide. *Blood* 2011;118(18):4771–9.
- [14] Oliver AM, Martin F, Kearney JF. Mouse CD38 is down-regulated on germinal center B cells and mature plasma cells. *J Immunol* 1997;158(3):1108–15.
- [15] Raje N, Berdeja J, Lin Y, et al. Anti-BCMA CAR T-Cell Therapy bb2121 in Relapsed or Refractory Multiple Myeloma. *N Engl J Med* 2019;380(18):1726–37.
- [16] Carpenter RO, Evbuomwan MO, Pittaluga S, et al. B-cell maturation antigen is a promising target for adoptive T-cell therapy

- of multiple myeloma. *Clin Cancer Res* 2013;19(8):2048–60.
- [17] Seckinger A, Delgado JA, Moser S, et al. Target Expression, Generation, Preclinical Activity, and Pharmacokinetics of the BCMA-T Cell Bispecific Antibody EM801 for Multiple Myeloma Treatment. *Cancer Cell* 2017;31(3):396–410.
- [18] Radl J, Hollander CF. Homogeneous immunoglobulins in sera of mice during aging. *J Immunol* 1974;112(6):2271–3.
- [19] van den Akker TW, de Glopper-van der Veer E, Radl J, et al. The influence of genetic factors associated with the immunoglobulin heavy chain locus on the development of benign monoclonal gammopathy in ageing IgH-congenic mice. *Immunology* 1988;65(1):31–5.
- [20] Asosingh K, Radl J, Van Riet I, et al. The 5TMM series: a useful in vivo mouse model of human multiple myeloma. *Hematol J* 2000;1(5):351–6.
- [21] Maes K, Boeckx B, Vlummens P, et al. The genetic landscape of 5T models for multiple myeloma. *Sci Rep* 2018;8(1):15030.
- [22] Vanderkerken K, De Raeve H, Goes E, et al. Organ involvement and phenotypic adhesion profile of 5T2 and 5T33 myeloma cells in the C57BL/KaLwRij mouse. *Br J Cancer* 1997;76(4):451–60.
- [23] Amend SR, Wilson WC, Chu L, et al. Whole Genome Sequence of Multiple Myeloma-Prone C57BL/KaLwRij Mouse Strain Suggests the Origin of Disease Involves Multiple Cell Types. *PLoS One* 2015;10(5):e0127828.
- [24] Noll JE, Hewett DR, Williams SA, et al. SAMS1 is a tumor suppressor gene in multiple myeloma. *Neoplasia* 2014;16(7):572–85.
- [25] Friend NL, Hewett DR, Panagopoulos V, et al. Characterization of the role of Samsn1 loss in multiple myeloma development. *FASEB Bioadv* 2020;2(9):554–72.
- [26] Oyajobi BO, Franchin G, Williams PJ, et al. Dual effects of macrophage inflammatory protein-1 α on osteolysis and tumor burden in the murine 5TGM1 model of myeloma bone disease. *Blood* 2003;102(1):311–9.
- [27] Van Valckenborgh E, Schoupe E, Movahedi K, et al. Multiple myeloma induces the immunosuppressive capacity of distinct myeloid-derived suppressor cell subpopulations in the bone marrow. *Leukemia* 2012;26(11):2424–8.
- [28] Menu E, De Leenheer E, De Raeve H, et al. Role of CCR1 and CCR5 in homing and growth of multiple myeloma and in the development of osteolytic lesions: a study in the 5TMM model. *Clin Exp Metastasis* 2006;23(5–6):291–300.
- [29] Hewett DR, Vandyke K, Lawrence DM, et al. DNA Barcoding Reveals Habitual Clonal Dominance of Myeloma Plasma Cells in the Bone Marrow Microenvironment. *Neoplasia* 2017;19(12):972–81.
- [30] Khoo WH, Ledergor G, Weiner A, et al. A niche-dependent myeloid transcriptome signature defines dormant myeloma cells. *Blood* 2019;134(1):30–43.
- [31] Merwin RM, Algire GH. Induction of plasma-cell neoplasms and fibrosarcomas in BALB/c mice carrying diffusion chambers. *Proc Soc Exp Biol Med* 1959;101(3): 437–9.
- [32] Kishimoto T. The biology of interleukin-6. *Blood* 1989;74(1):1–10.
- [33] Potter M. Neoplastic development in plasma

- cells. *Immunol Rev* 2003;194: 177–95.
- [34] Dechow T, Steidle S, Gotze KS, et al. GP130 activation induces myeloma and col- laborates with MYC. *J Clin Invest* 2014;124(12):5263–74.
- [35] Zhang S, Ramsay ES, Mock BA. Cdkn2a, the cyclin-dependent kinase inhibitor encoding p16INK4a and p19ARF, is a candidate for the plasmacytoma suscep- tibility locus, Pctr1. *Proc Natl Acad Sci U S A* 1998;95(5):2429–34.
- [36] Shen-Ong GL, Keath EJ, Piccoli SP, et al. Novel myc oncogene RNA from abor- tive immunoglobulin-gene recombination in mouse plasmacytomas. *Cell* 1982; 31(2 Pt 1):443–52.
- [37] Kobayashi H, Potter M, Dunn TB. Bone lesions produced by transplanted plasma-cell tumors in BALB/c mice. *J Natl Cancer Inst* 1962;28:649–77.
- [38] Hofgaard PO, Jodal HC, Bommert K, et al. A novel mouse model for multiple myeloma (MOPC315.BM) that allows noninvasive spatiotemporal detection of os- teolytic disease. *PLoS One* 2012;7(12):e51892.
- [39] Cheung WC, Kim JS, Linden M, et al. Novel targeted deregulation of c-Myc co- operates with Bcl-X(L) to cause plasma cell neoplasms in mice. *J Clin Invest* 2004;113(12):1763–73.
- [40] Carrasco DR, Sukhdeo K, Protopopova M, et al. The differentiation and stress response factor XBP-1 drives multiple myeloma pathogenesis. *Cancer Cell* 2007;11(4):349–60.
- [41] Chesi M, Robbiani DF, Sebag M, et al. AID- dependent activation of a MYC trans- gene induces multiple myeloma in a conditional mouse model of post-germinal center malignancies. *Cancer Cell* 2008;13(2):167–80.
- [42] Chesi M, Matthews GM, Garbitt VM, et al. Drug response in a genetically engi- neered mouse model of multiple myeloma is predictive of clinical efficacy. *Blood* 2012;120(2):376–85.
- [43] Chesi M, Mirza NN, Garbitt VM, et al. IAP antagonists induce anti-tumor immunity in multiple myeloma. *Nat Med* 2016;22(12):1411–20.
- [44] Meermeier EW, Welsh SJ, Sharik ME, et al. Tumor burden limits bispecific anti- body efficacy through T cell exhaustion averted by concurrent cytotoxic therapy. *Blood Cancer Discovery* 2021;2(4):354–69, bloodcandisc. BCD-21-0038-E.2021.
- [45] Calcinotto A, Brevi A, Chesi M, et al. Microbiota-driven interleukin-17-producing cells and eosinophils synergize to accelerate multiple myeloma progression. *Nat Commun* 2018;9(1):4832.
- [46] Nakamura K, Kassem S, Cleynen A, et al. Dysregulated IL-18 Is a Key Driver of Immunosuppression and a Possible Therapeutic Target in the Multiple Myeloma Microenvironment. *Cancer Cell* 2018;33(4):634–648 e635.
- [47] Minnie SA, Kuns RD, Gartlan KH, et al. Myeloma escape after stem cell transplan- tation is a consequence of T-cell exhaustion and is prevented by TIGIT blockade. *Blood* 2018;132(16):1675–88.
- [48] Guillerey C, Harjunpaa H, Carrie N, et al. TIGIT immune checkpoint blockade re- stores CD8(+) T-cell immunity against multiple myeloma. *Blood* 2018;132(16): 1689–94.
- [49] Chesi M, Stein CK, Garbitt VM, et al.

- Monosomic loss of MIR15A/MIR16-1 is a driver of multiple myeloma proliferation and disease progression. *Blood Cancer Discov* 2020;1(1):68–81.
- [50] Wen Z, Rajagopalan A, Flietner ED, et al. Expression of NrasQ61R and MYC transgene in germinal center B cells induces a highly malignant multiple myeloma in mice. *Blood* 2021;137(1):61–74.
- [51] Morito N, Yoh K, Maeda A, et al. A novel transgenic mouse model of the human multiple myeloma chromosomal translocation t(14;16)(q32;q23). *Cancer Res* 2011;71(2):339–48.
- [52] Winkler W, Farre Diaz C, Blanc E, et al. Mouse models of human multiple myeloma subgroups. *Proc Natl Acad Sci U S A* 2023;120(10). e2219439120.
- [53] Larrayoz M, Garcia-Barchino MJ, Celay J, et al. Preclinical models for prediction of immunotherapy outcomes and immune evasion mechanisms in genetically heterogeneous multiple myeloma. *Nat Med* 2023;29(3):632–45.
- [54] Watanabe H, Numata K, Ito T, et al. Innate immune response in Th1- and Th2- dominant mouse strains. *Shock* 2004;22(5):460–6.
- [55] Hartmann W, Blankenhaus B, Brunn ML, et al. Elucidating different pattern of immunoregulation in BALB/c and C57BL/6 mice and their F1 progeny. *Sci Rep* 2021;11(1):1536.