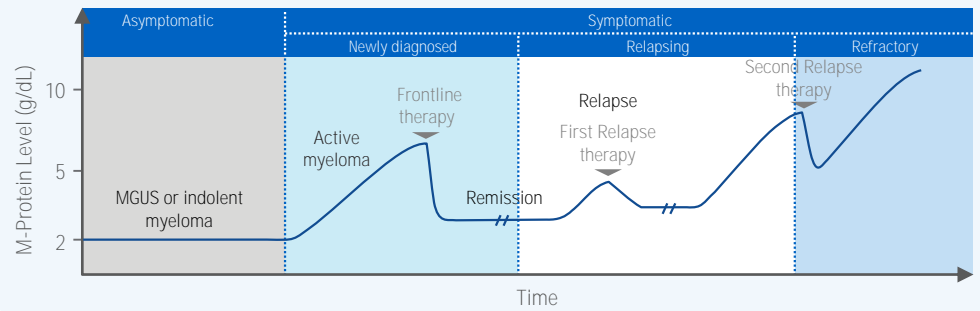


# Targeting BCMA as a Novel Therapeutic Strategy in Multiple Myeloma

Patients With Multiple Myeloma Eventually Relapse, Underscoring the Need for Novel Therapies<sup>1,2</sup>

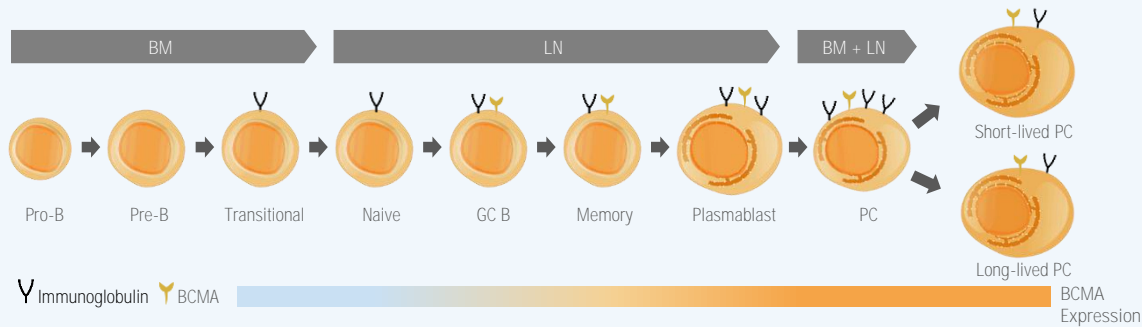
- Multiple myeloma (MM) is the second most common hematologic malignancy<sup>3</sup>
  - Estimated 160,000 new cases diagnosed and 106,000 deaths globally in 2018<sup>4</sup>
- Successful outcomes are hindered by the complexity of myeloma cell biology and changes to the BM microenvironment<sup>5-7</sup>
- While survival rates have improved in MM, almost all patients eventually relapse<sup>1-3</sup>

MM is Characterized by a Pattern of Recurrent Relapses<sup>1,2</sup>



BCMA Is a Cell Surface Protein That Is Selectively Expressed on Mature B Lymphocytes and Plasma Cells<sup>8</sup>

BCMA Expression During Plasma Cell Differentiation<sup>8</sup>

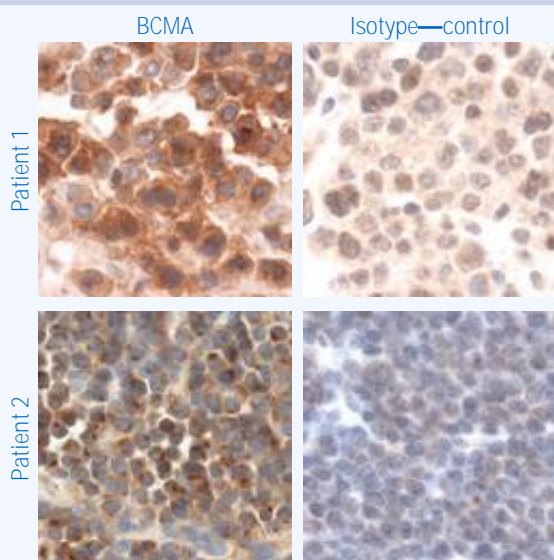


- BCMA is a transmembrane glycoprotein of the TNFR superfamily<sup>9</sup>
- BCMA is exclusively expressed on the cell membrane of late-stage B cells and plasma cells and regulates differentiation and survival of plasma cells<sup>8,10,11</sup>
  - BCMA is minimally expressed in hematopoietic stem cells and non-hematopoietic tissue<sup>12,13</sup>

BCMA is highly expressed on myeloma cells<sup>8</sup>

- BCMA membrane expression on myeloma cells was observed in almost all samples from MM patients<sup>13-15</sup>

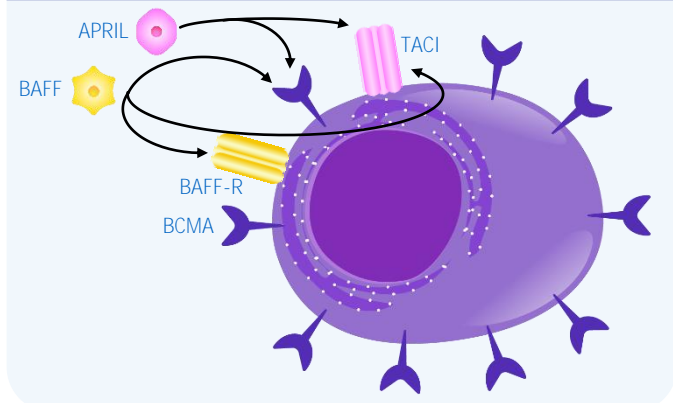
BCMA Expression on Neoplastic Plasma Cells From Patients With MM<sup>13</sup>



APRIL and BAFF Are BCMA Ligands<sup>8</sup>

- BCMA is part of a family of related receptors that includes BAFF-R and TACI<sup>8</sup>
- BCMA ligands, APRIL and BAFF, are produced in the BM microenvironment by osteoclasts, monocytes, and neutrophils<sup>8,16,17</sup>
- BCMA ligands have varying binding affinities: APRIL preferentially binds to BCMA with higher affinity than BAFF<sup>8</sup>
- APRIL and BAFF expression are increased in MM and correlate with increased BCMA expression<sup>8,18,19</sup>

BCMA Ligands and Related Receptors on Plasma Cells<sup>8</sup>

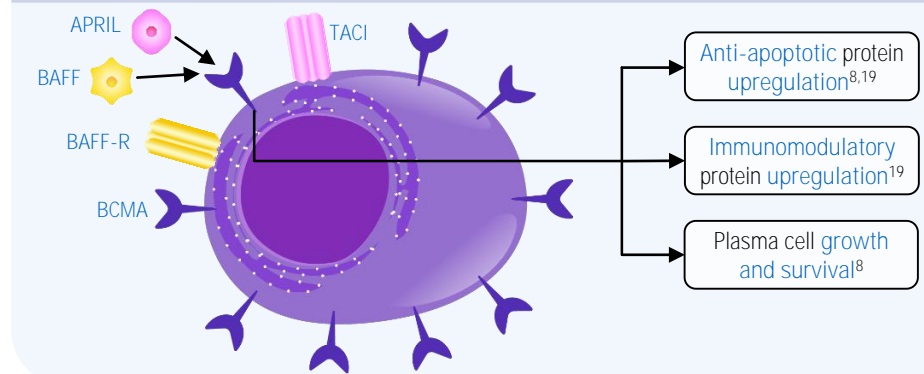


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## BCMA Activates Growth and Survival Signaling Cascades<sup>8,19</sup>

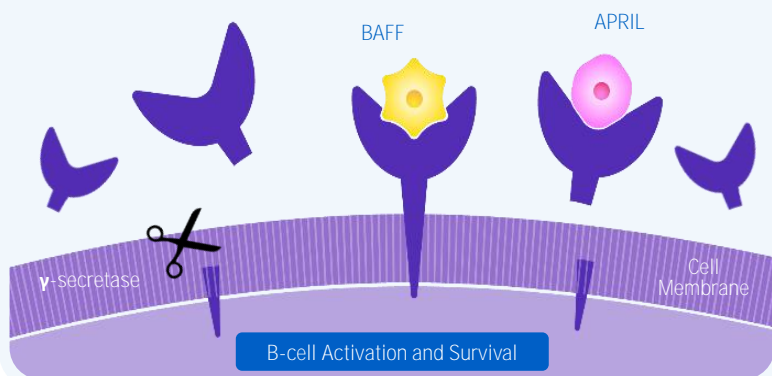
- Overexpression of BCMA in myeloma cells enhances tumor growth and survival<sup>8</sup>
- Upregulation of anti-apoptotic proteins (Bcl-2, Bcl-xL, and Mcl-1) and activation of the NF- $\kappa$ B pathway<sup>8,19</sup>
- Upregulation of immunomodulatory proteins (eg, PD-L1, IL-10, and TGF $\beta$ ), which may allow myeloma cells to evade immune detection<sup>19</sup>
- Preclinical studies suggest a pro-survival role of BCMA in myeloma cells<sup>8</sup>

## BCMA Signaling Pathway in Myeloma Cells<sup>8,19</sup>

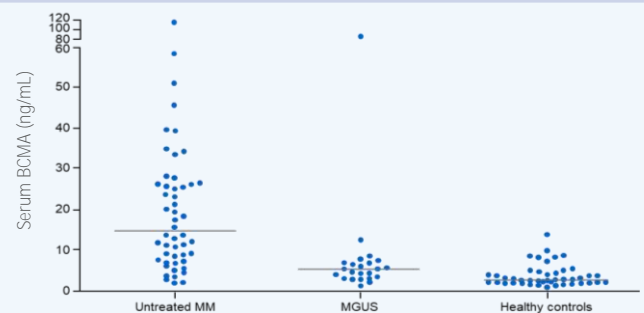


## High sBCMA Levels Correlate With Disease Burden in Patients With MM<sup>8</sup>

### $\gamma$ -secretase Cleaves BCMA to sBCMA<sup>8,20</sup>



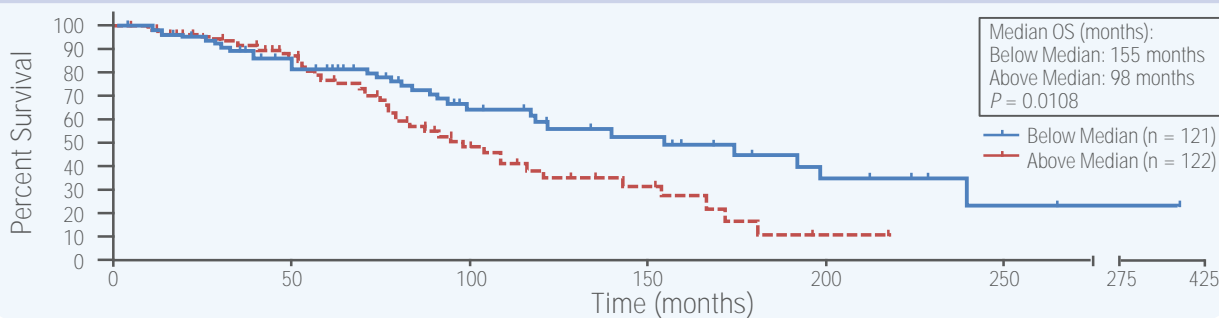
### Overexpression of sBCMA in Patient Populations With MM<sup>14</sup>



- sBCMA levels are highest in patients with active disease vs MGUS<sup>14</sup>
- sBCMA levels are lowest in those who achieve complete response and higher in those with progressive disease<sup>14</sup>

## High sBCMA Levels Correlate With Poor Prognosis in Patients With MM<sup>21</sup>

### sBCMA levels inversely correlate with OS in patients with MM<sup>21</sup>



- Patients with more sBCMA demonstrate reduced PFS relative to those with lower sBCMA levels<sup>14,21</sup>
- sBCMA may potentially serve as a biomarker for monitoring disease and predicting OS<sup>8,21</sup>

## BCMA as a Therapeutic Target in MM

- BCMA is a cell surface receptor expressed on mature B lymphocytes, plasma cells, and myeloma cells<sup>8</sup>
  - BCMA is minimally expressed in hematopoietic stem cells and non-hematopoietic tissue<sup>12,13</sup>
- BCMA expression is higher in myeloma cells than in normal plasma cells<sup>8</sup>
- Preliminary data suggest that BCMA supports myeloma cell survival<sup>8,11</sup>
- Amgen is currently investigating BiTE<sup>®</sup> molecules designed to target BCMA<sup>22-24</sup>

APRIL, a proliferation-inducing ligand; BAFF, B-cell activating factor; BAFF-R, BAFF-receptor; Bcl-2, B-cell lymphoma 2; Bcl-xL, B-cell lymphoma-extra large; BCMA, B-cell maturation antigen; BiTE, Bispecific T Cell Engager; BM, bone marrow;  $\gamma$ -secretase, gamma-secretase; GC, germinal center; IL, interleukin; LN, lymph node; Mcl-1, myeloid cell leukemia 1; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; NF- $\kappa$ B, nuclear factor kappa-light-chain-enhancer of activated B cells; OS, overall survival; PC, plasma cell; PD-L1, programmed death ligand 1; PFS, progression free survival; sBCMA, soluble BCMA; TACI, transmembrane activator and calcium modulator and cyclophilin ligand interactor; TGF $\beta$ , transforming growth factor  $\beta$ ; TNFR, tumor necrosis factor receptor.

1. Kumar SK, et al. *Nat Rev Dis Primers*. 2017;3:17046. 2. Durie BGM. *Concise Review of the Disease and Treatment Options*. 2018 ed. North Hollywood, CA: International Myeloma Foundation; 2018. 3. Kazandjian D. *Semin Oncol*. 2016;43:676-681. 4. Bray F, et al. *CA Cancer J Clin*. 2018;68:394-424. 5. Manier S, et al. *Curr Opin Hematol*. 2016;23:426-433. 6. Bianchi G, et al. *Blood*. 2015;125:3049-3058. 7. Morgan GJ, et al. *Nat Rev Cancer*. 2012;12:335-348. 8. Cho S-F, et al. *Front Immunol*. 2018;9:1821. 9. Hatzoglou A, et al. *J Immunol*. 2000;165:1322-1330. 10. Huang H-W, et al. *Proc Natl Acad Sci USA*. 2013;110:10928-10933. 11. Coquery CM, et al. *Crit Rev Immunol*. 2012;32:287-305. 12. Tai Y-T, et al. *Immunotherapy*. 2015;7:1187-1199. 13. Carpenter RO, et al. *Clin Cancer Res*. 2013;19:2048-2060. 14. Sanchez E, et al. *Br J Haematol*. 2012;158:727-738. 15. Tai Y-T, et al. *Expert Opin Biol Ther*. 2019. doi:10.1080/14712598.2019.1641196. 16. Belhouch E, et al. *J Immunol*. 2012;188:1283-1291. 17. Bolken L, et al. *Ann Hematol*. 2014;93:635-644. 18. Moreaux J, et al. *Blood*. 2004;103:3148-3157. 19. Tai Y-T, et al. *Blood*. 2016;127:3225-3236. 20. Laurent SA, et al. *Nat Commun*. 2015;6:7333. 21. Ghermezi M, et al. *Haematologica*. 2017;102:785-795. 22. Amgen. Amgen pipeline. <https://www.amgenpipeline.com/~media/amgen/full/www-amgenpipeline.com/charts/amgen-pipeline-chart.aspx>. Accessed August 12, 2019. 23. ClinicalTrials.gov. NCT03836053. <https://clinicaltrials.gov/ct2/show/record/NCT03836053>. Accessed August 12, 2019. 24. ClinicalTrials.gov. NCT03287908. <https://clinicaltrials.gov/ct2/show/record/NCT03287908>. Accessed August 12, 2019.