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## MarketVIEW: CAR-T cell therapy for multiple myeloma disease and pipeline summary (CAT: IOMV077)

Product Name	:	MarketVIEW: CAR-T cell therapy for multiple myeloma – disease and pipeline summary
Description	:	Disease and pipeline summary of CAR-T cell therapies for multiple myeloma
Contents	:	Executive presentation [~110 slides]
Therapeutic Area	:	Cancer immunotherapy
Publication date	:	February 2018
Catalogue No	:	IOMV077

### Background

**Multiple myeloma** is a cancer that develops from the plasma cells of the bone marrow and accounts for ~1% of all cancers and ~10% of all hematological malignancies. US estimates for multiple myeloma incidence in 2017 are >30,000 new cases diagnosed and approximately 12,500 deaths. The age adjusted incidence in the US is ~ 4 per 100,000 and, in the UK the value is ~9 per 100,000. The worldwide incidence of multiple myeloma was >114,000 new cases in 2012.

Despite significant improvements in treatments including the use of immunomodulatory drugs (e.g. lenalidomide, pomalidomide) and proteasome inhibitors (e.g. bortezomib, carfilzomib, ixazomib) in the first line setting, and the recent approvals for histone deacetylase inhibitors (e.g. panobinostat) and monoclonal antibodies (daratumumab and elotuzumab), most patients eventually relapse or are refractory and the management of the disease remains challenging.

Novel immunotherapeutic approaches in the treatment of multiple myeloma include checkpoint inhibitors, monoclonal antibodies, vaccines and adoptive T-cell therapies. Chimeric Antigen Receptor (CAR-T) approaches are also being investigated by several companies including **Novartis, Kite/Gilead, Juno Therapeutics/Celgene, Bluebird therapeutics/Celgene, Legend Biotech/J&J** as well as several companies in early stage clinical investigations (**Autolus, Poseida Therapeutics, Celyad**).

This **MarketVIEW** product consists of a comprehensive Executive presentation (~110 slides, .pdf) detailing the disease background, epidemiology of the disease, current therapies and treatment options, and novel immunotherapies with a focus on CAR-T. Also included is a summary and analysis of published and registered ongoing CAR-T clinical studies detailing the phases, targets under investigation, study status and summary of study protocols (patient numbers, dosing, study objectives). Key significant data available to date is discussed in further detail. 122 references are cited in this work.

## Methodology

iOnco Analytics has closely monitored all significant source material pertaining to multiple myeloma and CAR-T therapies as approaches to cancer immunotherapy. Source materials used are literature articles, government websites, medical bodies and associations, conference proceedings etc.

### PRODUCT CONTENTS:

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\*\*\*\*This product is composed of an **Executive Presentation (format: pdf)**<sup>1</sup>

#### Contents

##### Executive summary

##### Multiple Myeloma - Disease background and risk factors

Multiple myeloma: background  
Plasma cell disorders and multiple myeloma  
Amyloidosis Associated With Plasma Cell Neoplasms  
Multiple myeloma and plasma cell disorders  
Multiple myeloma Immunoglobulin (Ig) variants  
Multiple myeloma: molecular subtypes and oncogenes  
Multiple myeloma: risk factors

##### Multiple Myeloma - Diagnosis, symptoms, staging and prognosis

Multiple myeloma: diagnosis, staging and prognosis  
Multiple myeloma: diagnosis and prognosis  
Multiple myeloma: staging  
Multiple myeloma: recommended tests  
Multiple myeloma: symptoms

##### Multiple Myeloma – Epidemiology

Multiple myeloma: World incidence and mortality rates by region and sex  
Multiple myeloma: overall statistics in the US  
Multiple myeloma: new cases and deaths US  
Multiple myeloma estimated incidence versus other cancer types in US 2017  
Multiple myeloma: US incidence and death rate by age  
Multiple myeloma: US incidence by sex and race/ethnicity  
Multiple myeloma: US death rate by sex and race/ethnicity  
Multiple myeloma: US new cases and deaths 1975-2014 and five year survival  
Multiple myeloma: overall statistics UK  
Multiple myeloma: UK new cases and incidence rates by country (2014)  
Multiple myeloma: UK average number of new cases and age-specific incidence rates by age (2012-2014)  
Multiple myeloma: UK incidence and mortality rates over time  
Multiple myeloma: UK number of deaths and mortality rate by country and sex (2014)  
Multiple myeloma: incidence projections to 2035  
Multiple myeloma: mortality projections to 2035  
Multiple myeloma: UK prevalence statistics  
Multiple myeloma: European incidence by sex (2012)  
Multiple myeloma: European mortality by sex (2012)  
Multiple myeloma: Prevalence in Europe both sexes 2012  
Multiple myeloma: Prevalence in Europe by sex 2012  
Multiple myeloma: Canada- incidence and mortality statistics, 2012  
Multiple myeloma: Canada-prevalence statistics, 2012  
Multiple myeloma: Japan-incidence and mortality statistics, 2012  
Multiple myeloma: Japan-prevalence statistics, 2012  
Multiple myeloma: Australia-incidence and mortality statistics, 2012  
Multiple myeloma: Australia-prevalence statistics, 2012  
Multiple myeloma: Incidence and mortality comparison- US, Canada, Europe, Japan, Australia in 2012

<sup>1</sup>Presentation titles may apply to more than one slide

Continued....

**Multiple Myeloma - Treatment and unmet need**

Multiple myeloma: treatment

Multiple myeloma: treatment (transplant-eligible patients)

Multiple myeloma: treatment (transplant-ineligible patients)

Multiple myeloma: treatment of relapsed and refractory disease

Multiple myeloma: unmet need

**Novel treatments for Multiple Myeloma - Immunotherapy approaches**

Multiple myeloma: immunotherapies

Chimeric Antigen Receptor T cells (CAR-T) – overview

Chimeric Antigen Receptor T cells (CAR-T) - antigen selection

CAR-T cell therapy: potential issues and challenges

Steps in the manufacture of a CAR-T cell therapy

Multiple Myeloma targets for CAR-T cell therapy

CAR-T cell therapy for Multiple Myeloma - Published clinical studies

Pipeline analysis table: CAR-T studies for multiple myeloma on [clinicaltrials.gov](https://clinicaltrials.gov) (1)

Pipeline analysis table: CAR-T studies for multiple myeloma on [clinicaltrials.gov](https://clinicaltrials.gov) (2)

Pipeline analysis table: CAR-T studies for multiple myeloma on [clinicaltrials.gov](https://clinicaltrials.gov) (3)

Pipeline analysis table: CAR-T studies for multiple myeloma on [clinicaltrials.gov](https://clinicaltrials.gov) (4)

Pipeline analysis table: CAR-T studies for multiple myeloma on [clinicaltrials.gov](https://clinicaltrials.gov) (5)

Pipeline analysis table: CAR-T studies for multiple myeloma on [clinicaltrials.gov](https://clinicaltrials.gov) (6)

Pipeline analysis: Summary

Pipeline analysis: Key multiple myeloma CAR-T clinical studies targeting CD138: Chinese PLA General Hospital

Pipeline analysis: Key multiple myeloma CAR-T clinical studies targeting CD19: U. Penn/Novartis

Pipeline analysis: Key multiple myeloma CAR-T clinical studies targeting BCMA: National Cancer Institute

Pipeline analysis: Key multiple myeloma CAR-T clinical studies targeting BCMA: U. Penn/Novartis

Pipeline analysis: Key multiple myeloma CAR-T clinical studies targeting BCMA: Nanjing Legend Biotech Co./J&J

Pipeline analysis: Key multiple myeloma CAR-T clinical studies targeting BCMA: MSKCC, Fred Hutch, Juno Therapeutics, Inc.,

Pipeline analysis: Key multiple myeloma CAR-T clinical studies targeting BCMA: Autolus Ltd

Pipeline analysis: Key multiple myeloma CAR-T clinical studies targeting BCMA: Bluebird Bio/Celgene

Pipeline analysis: Key multiple myeloma CAR-T clinical studies targeting BCMA: Kite/Gilead

Pipeline analysis: Key multiple myeloma CAR-T clinical studies targeting BCMA: Poseida Therapeutics

Pipeline analysis: Key multiple myeloma CAR-T clinical studies targeting NKG2D Receptor CAR-T: Celyad

**Bibliography**

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**Slide number ~110**

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## BIBLIOGRAPHY:

- 1) ESMO Guidelines Working Group. Multiple myeloma: ESMO Clinical Practice Guidelines. Moreau P, San Miguel J, Sonneveld, M et al. 2017. *Ann Oncol* (2017) 28 (suppl 4): iv52–iv61
- 2) International Myeloma Working Group (IMWG) Criteria for the Diagnosis of Multiple Myeloma. Available at: <http://imwg.myeloma.org/international-myeloma-working-group-imwg-criteria-for-the-diagnosis-of-multiple-myeloma/>. Accessed Jan 2018
- 3) Information about plasma cell neoplasms. Available at: <https://www.cancer.gov/types/myeloma/hp/myeloma-treatment-pdq>. Accessed Jan 2018.
- 4) Clinical course and prognosis of smouldering (asymptomatic) multiple myeloma. Kyle R, Remstein E, Thernaeu T et al. 2007. *N Engl J Med*. 21;356(25):2582-9.0
- 5) Progression of a solitary plasmacytoma to multiple myeloma. A population-based registry of the northern Netherlands De Waal E, Leene M, Veger N et al. 2016 *Br J Haematol*. 175(4):661-667.
- 6) Solitary extramedullary plasmacytoma of the sinonasal region. Hazarika P, Balakrishnan R, Singh R, et al. 2011. *Indian J Otolaryngol Head Neck Surg*. 63(Suppl 1):33-5.
- 7) Monoclonal gammopathy of undetermined significance and smouldering multiple myeloma: emphasis on risk factors for progression. Kyle RA, Rajkumar SV. 2007. *Br J Haematol* 139(5): 730-43.
- 8) Comparison of extramedullary plasmacytomas with solitary and multiple plasma cell tumors of bone. Knowling MA, Harwood AR, Bergsagel DE. 1983. *J Clin Oncol* 1 (4): 255-62.
- 9) A practical approach to the diagnosis of systemic amyloidoses. Fernández de Larrea et al. 2015. *Blood* 125(14): 2239-44.
- 10) Review of 1027 patients with newly diagnosed multiple myeloma Kyle R, Gertz M, Witzig T, et al. 2003. *Mayo Clinic Proc.*78:21-33.
- 11) Multiple Myeloma: Diagnosis and Treatment. Rajkumar S and Kumar S. 2016. *Mayo Clin Proc*. 91(1):101-19.
- 12) Risk factors for multiple myeloma. Available at: <https://www.themmr.org/multiple-myeloma/multiple-myeloma-causes/myeloma-risk-factors/>. Accessed Jan 2018.
- 13) Risk factors for multiple myeloma. Available at: <https://www.cancer.org/cancer/multiple-myeloma/causes-risks-prevention/risk-factors.html>. Accessed Jan 2018.
- 14) Revised International Staging System for Multiple Myeloma: A Report From International Myeloma Working Group Palumbo A, Avet-Loiseau H, Oliva S et al. 2015. *J Clin Oncol*. 10;33(26):2863-9.
- 15) A clinical staging system for multiple myeloma: correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. Durie B and Salmon S. 1975. *Cancer* 36(3):842–854.
- 16) Mayo Clinic Risk stratification tool. Available at: <https://www.msmart.org/>. Accessed Jan 2018.
- 17) Management of newly diagnosed symptomatic multiple myeloma: updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) consensus guidelines. Mikhael J, Dingli D, Vivek R et al. 2013. *Mayo Clin Proc*. 88(4):360-76.
- 18) International staging system for multiple myeloma. Greipp P, San Miguel J, Durie B et al. 2005. *J. Clin. Oncol*. 23(15): 3412–20.
- 19) Information on multiple myeloma symptoms. Available at: [https://www.themmr.org/multiple-myeloma/symptoms/?qclid=EA1aIQobChMI2ZGzx8jS1qIV7b3tCh1sUAVzEAAYAiAAEgJf6PD\\_BwE](https://www.themmr.org/multiple-myeloma/symptoms/?qclid=EA1aIQobChMI2ZGzx8jS1qIV7b3tCh1sUAVzEAAYAiAAEgJf6PD_BwE). Accessed Jan 2018.
- 20) Globocan 2012: Estimated cancer incidence, mortality and prevalence worldwide. Available at: <http://globocan.iarc.fr/Pages/online.aspx>. Accessed Jan 2018.
- 21) Cancer statistics facts. Available at: <https://seer.cancer.gov/statfacts/html/mulmy.html>. Accessed Jan 2018.
- 22) Multiple myeloma incidence statistics. Available at: <http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma>. Accessed Jan 2018.
- 23) One, five and ten-year cancer prevalence by cancer network, UK, 2006. NCIN. Available at: <http://www.ncin.org.uk/view?rid=76>. Accessed Jan 2018.
- 24) EUCAN. Multiple myeloma. Available at: <http://eco.iarc.fr/eucan/Cancer.aspx?Cancer=39>. Accessed Jan 2018.
- 25) Information on multiple myeloma treatment. Available at: <https://www.cancer.gov/types/myeloma/hp/myeloma-treatment-pdq#section/107>. Accessed Jan 2018.
- 26) Myeloma today: Disease definitions and treatment advances. Rajkumar SV. 2016. *Am J Hematol*. 91(7):719-34.

- 27) Emerging drugs and combinations to treat multiple myeloma. Larocca A, Mina R, Gay F et al. 2017. *Oncotarget*. 15;8(36):60656-60672.
- 28) The clinical course of relapsed or refractory US multiple myeloma (RRMM) patients receiving two or more lines of therapy. Romanus D, Raju A, Seal B et al. *Haematologica*. 2016;101(suppl 1):532. Abstract E1287.
- 29) Superiority of the triple combination of bortezomib-thalidomide-dexamethasone over the dual combination of thalidomide-dexamethasone in patients with multiple myeloma progressing or relapsing after autologous transplantation: the MMVAR/IFM 2005-04 Randomized Phase III Trial from the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. Garderet L, Iacobelli S, Moreau P et al. *J Clin Oncol*. 2012.30:2475–82.
- 30) Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study. Cavo M, Tacchetti P, Patriarca F et al. *Lancet*. 2010.376:2075–85.
- 31) Bortezomib plus dexamethasone versus reduced-dose bortezomib, thalidomide plus dexamethasone as induction treatment before autologous stem cell transplantation in newly diagnosed multiple myeloma Moreau P, Avet-Loiseau H, Facon T et al. *Blood*. 2011.118:5752–8.
- 32) Safety and persistence of adoptively transferred autologous CD19-targeted T cells in patients with relapsed or chemotherapy refractory B-cell leukemias. . Brentjens R, Riviere I, Park JH, et al. 2011. *Blood*. 118:4817–28.
- 33) Tumor-targeted T cells modified to secrete IL-12 eradicate systemic tumors without need for prior conditioning. Pegram H, Lee J, Hayman E, et al. *Blood*. 2012. 119:4133–41.
- 34) Immune checkpoint blockade in hematologic malignancies. Armand P. 2015. *Blood*. 125(22):3393-400.
- 35) Promising therapies in multiple myeloma. Bianchi G, Richardson P, Anderson K. 2015. *Blood*.126(3):300-10.
- 36) US National Library of Medicine Clinical trials database. Available at: <https://clinicaltrials.gov/ct2/home>. Accessed Jan 2018.
- 37) Information on immunotherapies. Available at: <https://www.cancerresearch.org/scientists/science-of-immunotherapy/cancer-types/multiple-myeloma>. Accessed Jan 2018.
- 38) Monoclonal antibodies in the treatment of multiple myeloma: current status and future perspectives. Lonial S Durie B, Palumbo A and San-Miguel J. 2016. *J Leukaemia*. 30; 526-535.
- 39) Development of Novel Immunotherapies for Multiple Myeloma. Al-Hujaili E, Oldham R, Hari P and Medin J. 2016. *Int J Mol Sci*. 8;17(9)pii: E1506.
- 40) Expression of immunoglobulin-T-cell receptor chimeric molecules as functional receptors with antibody type specificity. Gross et al. *Proc Natl Acad Sci USA*. 1989; 86(24):10024-10028.
- 41) Manufacturing validation of biologically functional T cells targeted to CD19 antigen for autologous adoptive cell therapy. Hollyman et al. *J Immunother*. 2009; 32(2):169-80.
- 42) Chimeric antigen receptor therapy for cancer. Barrett et al. *Annu Rev Med*. 2014; 65:333-47.
- 43) CD28 costimulation improves expansion and persistence of chimeric antigen receptor-modified T cells in lymphoma patients. Savoldo et al. *J Clin Invest*. 2011; 121(5): 1822–1826.
- 44) Eradication of B-lineage cells and regression of lymphoma in a patient treated with autologous T cells genetically engineered to recognize CD19. Kochenderfer et al. *Blood*. 2010; 16(20):4099-4102.
- 45) Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia. Maude e al. *N Engl J Med*. 2014; 371(16): 1507–1517.
- 46) CD19-CAR Trials. Ramos et al. *Cancer J*. 2014; 20(2): 112–118.
- 47) CD19 antigen in leukemia and lymphoma diagnosis and immunotherapy. Scheuermann and Racila. 1995. *Leuk Lymphoma*. 18(5-6):385-97.
- 48) Construction of anti-CD20 single-chain antibody-CD28-CD137-TCRζ recombinant genetic modified T cells and its treatment effect on B cell lymphoma. Chen et al. 2015. *Med Sci Monit*, 21 p2110–2115.
- 49) Treatment of CD33-directed chimeric antigen receptor-modified T cells in one patient with relapsed and refractory acute myeloid leukemia. Wang et al. 2015. *Mol Ther*, 23:184–191.
- 50) Diverse solid tumors expressing a restricted epitope of L1-CAM can be targeted by chimeric antigen receptor redirected T lymphocytes. Hong et al. 2014. *J Immunother*, 37:93–104.
- 51) Chimeric antigen receptor (CAR) T cell therapy for malignant cancers: Summary and perspective. Aaron J. Smith. 2016. *J of Cellular Immunotherapy*, 2:(59–68).

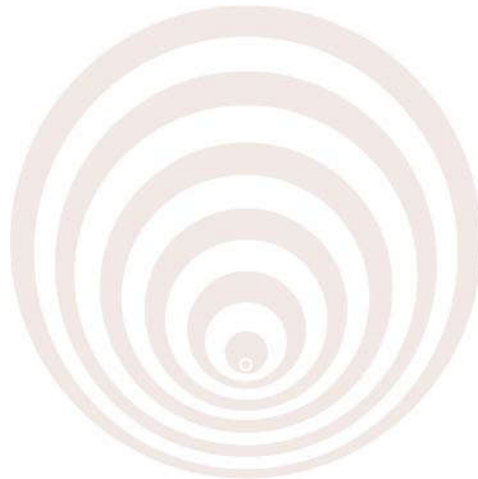
- 52) Genetically modified T cells in cancer therapy: opportunities and challenges. Sharpe and Mount. 2015. *Dis Model Mech.* Apr; 8(4): 337–350.
- 53) Toxicities of chimeric antigen receptor T cells: recognition and management. Brudno and Kochenderfer. 2016. *Blood.* 27(26):3321-3330.
- 54) Global Manufacturing of CAR T Cell Therapy. Bruce L. *Molecular Therapy: Methods & Clinical Development.* 2017; 4:92.
- 55) Commercialization of cellular immunotherapies for cancer. Walker et al. *Biochem Soc Trans.* 2016; 44(2):329-32.
- 56) Treating B-cell cancer with T cells expressing anti-CD19 chimeric antigen receptors. Kochenderfer JN, Rosenberg SA. 2013. *Nat Rev Clin Oncol*;10(5):267-276.
- 57) The basic principles of chimeric antigen receptor design. Sadelain M, Brentjens R, Riviere I. 2013. *Cancer Discov*; 3(4):388-398.
- 58) The prospects and promise of chimeric antigen receptor immunotherapy in multiple myeloma. Rotolo A, Caputo V, Karadimitris A. 2016. *Br J Haematol*; 173(3):350-364.
- 59) Antibody-modified T cells: CARs take the front seat for hematologic malignancies. Maus MV, Grupp SA, Porter DL, June CH. 2014. *Blood*; 123(17):2625-2635.
- 60) Heterogeneity of genomic evolution and mutational profiles in multiple myeloma. Bolli N, Avet-Loiseau H, Wedge DC, et al. 2014. *Nat Commun*; 5:2997.
- 61) Phenotypic identification of subclones in multiple myeloma with different chemoresistant, cytogenetic and clonogenic potential. Pa'ino T, Paiva B, Sayagués JM, et al. 2015. *Leukemia*; 29(5):1186-1194.
- 62) CD44v6-targeted T cells mediate potent antitumor effects against acute myeloid leukemia and multiple myeloma. Casucci M, Nicolis di Robilant B, Falcone L, et al. 2013. *Blood*;122(20):3461-3472.
- 63) CD44v6, a target for novel antibody treatment approaches, is frequently expressed in multiple myeloma and associated with deletion of chromosome arm 13q. Liebisch P, Eppinger S, Schöppflin C, et al. 2005. *Haematologica*;90(4):489-493.
- 64) Preclinical characterization of SGN-70, a humanized antibody directed against CD70. McEarchern JA, Smith LM, McDonagh CF, et al. 2008. *Clin Cancer Res.*;14(23):7763-7772.
- 65) T cells redirected against CD70 for the immunotherapy of CD70-positive malignancies. Shaffer DR, Savoldo B, Yi Z, et al. 2011. *Blood*; 117(16):4304-4314.
- 66) Plasma cells in multiple myeloma express a natural killer cell-associated antigen: CD56 (NKH-1; Leu-19). Van Camp B, Durie BG, Spier C, et al. 1990. *Blood*;76(2):377-382.
- 67) Distribution of myeloma plasma cells in peripheral blood and bone marrow correlates with CD56 expression. Rawstron A, Barrans S, Blythe D, et al. 1999. *Br J Haematol*;104(1):138-143.
- 68) CD56 targeted chimeric antigen receptors for immunotherapy of multiple myeloma [abstract]. Benjamin R, Condomines M, Gunset G, Sadelain M. 2012. *Cancer Res*;72(suppl 8). Abstract 3499.
- 69) CD38 and CD157: a long journey from activation markers to multifunctional molecules. Quarona V, Zaccarello G, Chillemi A, et al. 2013. *Cytometry B Clin Cytom*;84(4):207-217.
- 70) Pre-clinical evaluation of CD38 chimeric antigen receptor engineered T cells for the treatment of multiple myeloma. Drent E, Groen RW, Noort WA, et al. 2016. *Haematologica*;101(5):616-625.
- 71) A rational strategy for reducing on-target off-tumor effects of CD38-chimeric antigen receptors by affinity optimization. Drent E, Themeli M, Poels R, et al. 2017. *Mol Ther*;25(8):1946-1958.
- 72) CD138-directed adoptive immunotherapy of chimeric antigen receptor (CAR)-modified T cells for multiple myeloma. Guo B, Chen M, Han Q, et al. 2016. *J Cell Immunother*; 2(1):28-35.
- 73) CD138 (syndecan-1), a plasma cell marker immunohistochemical profile in hematopoietic and nonhematopoietic neoplasms. O'Connell FP, Pinkus JL, Pinkus GS. 2004. *Am J Clin Pathol*;121(2):254-263.
- 74) Multiple myeloma cells expressing low levels of CD138 have an immature phenotype and reduced sensitivity to lenalidomide. Kawano Y, Fujiwara S, Wada N, et al. 2012. *Int J Oncol*;41(3):876-884.
- 75) Chimeric antigen receptor T cells against CD19 for multiple myeloma. Garfall AL, Maus MV, Hwang WT, et al. 2015. *N Engl J Med*; 373(11): 1040-1047.
- 76) Pilot study of anti-CD19 chimeric antigen receptor T cells (CTL019) in conjunction with salvage autologous stem cell transplantation for advanced multiple myeloma [abstract]. Garfall AL, Stadtmauer EA, Maus MV, et al. 2016. *Blood*;128(22). Abstract 974.

- 77) Myeloma stem cell concepts, heterogeneity and plasticity of multiple myeloma. Hajek R, Okubote SA, Svachova H. 2013. Br J Haematol; 163(5):551-564.
- 78) Characterization of clonogenic multiple myeloma cells. Matsui W, Huff CA, Wang Q, et al. 2004. Blood;103(6):2332-2336.
- 79) Clinical responses with T lymphocytes targeting malignancy-associated k light chains. Ramos CA, Savoldo B, Torrano V, et al. 2016. J Clin Invest.;126(7):2588-2596.
- 80) Clonogenic multiple myeloma progenitors, stem cell properties, and drug resistance. Matsui W, Wang Q, Barber JP, et al. 2008. Cancer Res;68(1):190-197.
- 81) CS1, a potential new therapeutic antibody target for the treatment of multiple myeloma. Hsi ED, Steinle R, Balasa B, et al. 2008. Clin Cancer Res;14(9):2775-2784.
- 82) Genetic modification of T cells redirected toward CS1 enhances eradication of myeloma cells. Chu J, He S, Deng Y, et al. 2014. Clin Cancer Res;20(15):3989-4000.
- 83) First-in-human multicenter study of bb2121 anti-BCMA CAR T-cell therapy for relapsed/refractory multiple myeloma: updated results [abstract]. Berdeja JG, Lin Y, Raje NS, et al. 2017. J Clin Oncol;35(suppl 15). Abstract 3010.
- 84) Durable remissions with BCMA-specific chimeric antigen receptor (CAR)-modified T cells in patients with refractory/relapsed multiple myeloma [abstract]. Fan F, Zhao W, Liu J, et al. 2017. J Clin Oncol;35(suppl 18). Abstract LBA3001.
- 85) T cells expressing an anti-B-cell maturation antigen chimeric antigen receptor cause remissions of multiple myeloma. Ali SA, Shi V, Maric I, et al. 2016. Blood;128(13):1688-1700.
- 86) B-cell maturation antigen (BCMA)-specific chimeric antigen receptor T cells (CART-BCMA) for multiple myeloma (MM): initial safety and efficacy from a phase I study [abstract]. Cohen AD, Garfall AL, Stadtmauer EA, et al. 2016. Blood;128(22). Abstract 1147
- 87) Treatment of Chemotherapy Refractory Multiple Myeloma by CART-138 (CART-138). Available at: <https://clinicaltrials.gov/show/NCT01886976>. Accessed Jan 2018.
- 88) Toward an effective targeted chemotherapy for multiple myeloma. CD138\_multiple myeloma cells. Polson AG, Sliwkowski MX. 2009. Clin Cancer Res;15:3906e7.
- 89) CART-19 for Multiple Myeloma. Available at: <https://clinicaltrials.gov/show/NCT02135406>. Accessed Jan 2018.
- 90) CAR T-Cell Therapy Emerging in Multiple Myeloma. The ASCO post. 2017. Available at: <http://www.ascopost.com/issues/march-10-2017/car-t-cell-therapy-emerging-in-multiple-myeloma/>. Accessed Jan 2018.
- 91) B-cell maturation antigen is a promising target for adoptive T-cell therapy of multiple myeloma. Carpenter RO, Evbuomwan MO, Pittaluga S, et al. 2013. Clin Cancer Res;19(8):2048-2060.
- 92) Study of T Cells Targeting B-Cell Maturation Antigen for Previously Treated Multiple Myeloma. Available at: <https://clinicaltrials.gov/show/NCT02215967>. Accessed Jan 2018.
- 93) CART-BCMA Cells for Multiple Myeloma. Available at: <https://clinicaltrials.gov/show/NCT02546167>. Accessed Jan 2018.
- 94) B-cell maturation antigen (BCMA)-specific chimeric antigen receptor T cells (CART-BCMA) for multiple myeloma (MM): initial safety and efficacy from a phase I study [abstract]. Cohen AD, Garfall AL, Stadtmauer EA, et al. 2016. Blood;128(22). Abstract 1147
- 95) Safety and Efficacy of B-Cell Maturation Antigen (BCMA)-Specific Chimeric Antigen Receptor T Cells (CART-BCMA) with Cyclophosphamide Conditioning for Refractory Multiple Myeloma (MM). 2017. Cohen et al. ASH meeting abstract 505.
- 96) LCAR-B38M-02 Cells in Treating Relapsed/Refractory (R/R) Multiple Myeloma (LEGEND-2). Available at: <https://clinicaltrials.gov/show/NCT03090659>. Accessed Jan 2018.
- 97) CAR T-Cell Therapy in Multiple Myeloma Yields 100% Response Rate. The ASCO post. 2017. Available at: <http://www.ascopost.com/issues/july-10-2017/car-t-cell-therapy-in-multiple-myeloma-yields-100-response-rate/>. Accessed Jan 2018.
- 98) Janssen Enters Worldwide Collaboration and License Agreement with Chinese Company Legend Biotech to Develop Investigational CAR-T Anti-Cancer Therapy. Available at: <https://www.jnj.com/media-center/press-releases/janssen-enters-worldwide-collaboration-and-license-agreement-with-chinese-company-legend-biotech-to-develop-investigational-car-t-anti-cancer-therapy>. Accessed Jan 2018.
- 99) Juno Corporate Presentation. Jan 2018. Available at: <http://ir.junotherapeutics.com/static-files/9cbfd419-a834-4de0-93bd-eba8cf53d6c4>. Accessed Jan 2018.



100. BCMA Targeted CAR T Cells With or Without Lenalidomide for the Treatment of Multiple Myeloma. Available at: <https://clinicaltrials.gov/show/NCT03070327>. Accessed Jan 2018.
101. Immunotherapy With BCMA CAR-T Cells in Treating Patients With BCMA Positive Relapsed or Refractory Multiple Myeloma. Available at: <https://clinicaltrials.gov/ct2/show/record/NCT03338972>. Accessed Jan 2018.
102. APRIL CAR T Cells (AUTO2) Targeting BCMA and TACI for the Treatment of Multiple Myeloma (APRIL). Available at: <https://clinicaltrials.gov/show/NCT03287804>. Accessed Jan 2018.
103. Autolus Announces First-Dose Cohort Completed in APRIL Study of AUTO2: A Phase I/II Study in Patients with Multiple Myeloma. 2017. Available at: <https://www.autolus.com/news-and-events/press-releases/autolus-announces-first-dose-cohort-completed-april-study-auto2-phase-iii-study-patients-multiple-myeloma>. Accessed Jan 2018.
104. Celgene Corporation and bluebird bio Announce bb2121 Anti-BCMA CAR-T Cell Therapy Has Been Granted Breakthrough Therapy Designation from FDA and Prime Eligibility from EMA for Relapsed and Refractory Multiple Myeloma. 2017. Available at: <http://ir.celgene.com/releasedetail.cfm?releaseid=1049014>. Accessed Jan 2018.
105. Study of bb2121 in Multiple Myeloma. Available at: <https://clinicaltrials.gov/ct2/show/record/NCT02658929?term=NCT02658929&rank=1>. Accessed Jan 2018.
106. Longterm Follow-up of Subjects Treated With bb2121. Available at: <https://clinicaltrials.gov/ct2/show/record/NCT02786511?term=bb2121&rank=3>. Accessed Jan 2018.
107. Efficacy and Safety Study of bb2121 in Subjects With Relapsed and Refractory Multiple Myeloma (KarMMa) (bb2121). Available at: <https://clinicaltrials.gov/ct2/show/NCT03361748?term=bb2121&draw=2&rank=1>. Accessed Jan 2018.
108. Durable Clinical Responses in Heavily Pretreated Patients with Relapsed/Refractory Multiple Myeloma: Updated Results from a Multicenter Study of bb2121 Anti-Bcma CAR T Cell Therapy. 2017. Berdeja et al. ASH 2017. Abstract 740.
109. ASH: CAR T-Cell Tx Offers Durable Response in Pre-Treated MM. 2017. Available at: <https://www.medpagetoday.com/mastery-of-medicine/hematology-mastery-in-mm/69825>. Accessed Jan 2018.
110. Bluebird to seek approvals for three treatments by end of 2019. 2017. Available at: <https://uk.reuters.com/article/us-healthcare-conference-bluebird-bio/bluebird-to-see-approvals-for-three-treatments-by-end-of-2019-idUKKBN1EY2AJ>. Accessed Jan 2018.
111. Study of bb21217 in Multiple Myeloma. Available at: <https://clinicaltrials.gov/ct2/show/record/NCT03274219>. Accessed Jan 2018.
112. Bluebird bio Announces First Patient Treated with Second Anti-BCMA CAR T bb21217 in CRB-402 Phase 1 Study in Patients with Relapsed/Refractory Multiple Myeloma. 2017. Available at: <https://www.businesswire.com/news/home/20170928006294/en/bluebird-bio-Announces-Patient-Treated-Anti-BCMA-CAR>. Accessed Jan 2018.
113. Kite Submits Investigational New Drug (IND) Application for KITE-585, Anti-BCMA CAR-T Therapy Candidate for Multiple Myeloma. 2017. Available at: <http://ir.kitepharma.com/releasedetail.cfm?releaseid=1036443>. Accessed Jan 2018.
114. A Study Evaluating the Safety and Efficacy of KITE-585 in Subjects With Relapsed/Refractory Multiple Myeloma. Available at: <https://clinicaltrials.gov/ct2/show/record/NCT03318861>. Accessed Jan 2018.
115. P-BCMA-101 Tscm CAR-T Cells in the Treatment of Patients With Multiple Myeloma (MM). Available at: <https://clinicaltrials.gov/show/NCT03288493>. Accessed Jan 2018.
116. Poseida Therapeutics Presents Novel BCMA-Specific CAR-T Therapy at CAR-TCR Summit. 2017. Available at: <https://globenewswire.com/news-release/2017/09/06/1108317/0/en/Poseida-Therapeutics-Presents-Novel-BCMA-Specific-CAR-T-Therapy-at-CAR-TCR-Summit.html>. Accessed Jan 2018.
117. Gene Modification of Human T cells via piggyBac yields an anti-BCMA CARTyrin Cellular Product with Durable Efficacy in a TP53 KO MM model. 2017. Hermanson et al. Available at: [https://poseida.com/wp-content/uploads/2017/06/ASGCT-2017-Poster\\_Final.pdf](https://poseida.com/wp-content/uploads/2017/06/ASGCT-2017-Poster_Final.pdf). Accessed Jan 2018.
118. Poseida Awarded \$19.8 Million CIRM Grant to Support Clinical Trial of P-BCMA-101, a T Stem Cell Memory CAR-T Therapy for Multiple Myeloma. 2017. Available at: <http://poseida.com/2017/10/26/poseida-awarded-19-8-million-cirm-grant-support-clinical-trial-p-bcma-101-t-stem-cell-memory-car-t-therapy-multiple-myeloma/>. Accessed Jan 2018.
119. Poseida Therapeutics Announces First Patient Treated in Phase 1 Study of P-BCMA-101 CAR-T Stem Cell Memory Therapy in Patients with Multiple Myeloma. 2017. Available at: <https://poseida.com/2017/12/18/poseida-therapeutics-announces-first-patient-treated-phase-1-study-p-bcma-101-car-t-stem-cell-memory-therapy-patients-multiple-myeloma/>. Accessed Jan 2018.
120. NKG2D CARs as Cell Therapy for Cancer. Sentman and Meehan. 2014. Cancer J. 20(2): 156–159.
121. NKG2D ligands as therapeutic targets. Spear et al. 2013. Cancer Immun. 13: 8.

122. Safety Study of Chimeric Antigen Receptor Modified T-cells Targeting NKG2D-Ligands. Available at: <https://clinicaltrials.gov/show/NCT02203825>. Accessed Jan 2018.
123. A Dose Escalation Phase I Study to Assess the Safety and Clinical Activity of Multiple Cancer Indications (THINK). Available at: <https://clinicaltrials.gov/show/NCT03018405>. Accessed Jan 2018.
124. Celyad Announces Third Quarter 2017 Business Update. Available at: <https://www.celyad.com/en/news/celyad-announces-third-quarter-2017-business-update>. Accessed Jan 2018.
125. Celyad reports a first complete response in a relapsed refractory AML patient in the THINK trial. 2017. Available at: <https://www.celyad.com/en/news/celyad-reports-a-first-complete-response-in-a-relapsed-refractory-aml-patient-in-the-think-trial>. Accessed Jan 2018.





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iOnco Analytics – a trading division of **Assay Advantage (VacZine Analytics) Ltd** UK Company Number: 5807728 (Herein referred to as “The Company”). (Herein [enter client name] to as “The Client”).

1. This finished research product is provided is provided as a Service. Any additional Service required by the client will be subject to a new proposal being prepared.
2. The Service will commence after written (e-mail) or Fax confirmation stating the Client's acceptance of the Service according the description proposed by the Company.
3. **Cancellation policy.** The Company's cancellation policies are in accordance with the EU Consumer Protection (Distance Selling) Regulations 2000 (DSRs). Prior to acceptance of an order the Company will make available written information regarding Clients cancellation rights. This is posted on the Company website and is available for public review.
4. **Cancellation rights:** For finished documents - a Clients cancellation rights will last for **seven working days** counting from the day that the order was concluded. If the Services i.e. provision of the documents has taken place with the Clients agreement before this period the Client's cancellation rights have ended.
5. Invoicing will **100%** after submission of deliverables to the Client in a form reasonably acceptable to the Client.
6. If not purchased on line invoices are payable within **thirty days** of the invoice date.
7. All proposals are quoted in **\$USD dollars or £GBP** and invoices are to be settled in the same currency.
8. The Company agrees not to disclose to any third party confidential information acquired in the course of providing the services listed without the prior written consent of the Client. Exception occurs when the information is already in the public domain or when disclosure is necessary to help the Company's employees and agents with the performance of the Company's obligations to achieve satisfactory completion of the project and approved in writing by the Client.
9. Force Majeure: The Company will not be liable for any delay or failure to perform any obligation under this Agreement insofar as the performance of such obligation is prevented by an event beyond our reasonable control, included by not limited to, earthquake, fire, flood or any other natural disaster, labour dispute, riot, revolution, terrorism, acts of restraint of government or regulatory authorities, failure of computer equipment and failure or delay of sources from which data is obtained.
10. Please also refer to Master **TERMS and CONDITIONS** available upon request.

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## About iOnco Analytics:

**iOnco Analytics** is a subdivision of **VacZine Analytics** a world leading supplier of vaccine market analyses.

iOnco Analytics will provide a new suite of commercial analysis products focused on cancer immunotherapy.

Our role is to define market potential and strategy of new interventions in this space.

For more information please visit our website: [www.ionco-analytics.com](http://www.ionco-analytics.com)

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