****Published March 2017****

MarketVIEW: CAR-T therapy overview (CAT: VAMV073)

Product Name	:	**MarketVIEW: CAR-T therapy overview**
Description	:	Overview of therapeutic cancer vaccines
Contents	:	Executive presentation + 1 Excel workbook
Therapeutic Area	:	Cancer immunotherapy
Publication date	:	March 2017
Catalogue No	:	VAMV073

Background

CAR-T or Chimeric Antigen Receptor T cells are a sub component of **Adoptive T Cell therapy (ACT)**, a promising new treatment intervention for cancer. In **ACT**, a patient's individual T cells are removed and manipulated so they have an increased capacity to fight cancer. The therapy is usually personalized (autologous) for a specific patient.

Chimeric antigen receptor T cells present hybrid receptors consisting of an antigen binding domain of an antibody (e.g. directed to CD19) fused to the T-cell receptor signalling domain. So far, the technology has undergone four generations of development, where second-generation approaches have shown remarkable responses in clinical studies[1],[2]. Complete remission in up to 90% of patients have been reported for relapsed or refractory B-cell Acute Lymphoblastic Leukaemia (B-ALL).[1] Since 2015/2016 commercial interest has heightened in the development of CAR-T therapies with companies such as **Novartis**, **Pfizer (Cellectis)**, **Medimmune**, **Juno Therapeutics**, and **Kite Pharma** involved in clinical studies, mainly against hematological cancers.

This **MarketVIEW** product consists of a detailed Executive presentation (~91 slides) and MS-Excel work book summarizing latest developments in CAR-T therapies with a full review of the field to date. A searchable database of nearly **200** CAR trials has been compiled with analysis by start date, current phase, indication and sponsor type (industry and/or academic). For the hematological cancers, detailed case studies are provided looking at clinical trial parameters and data presented to date. Future perspectives, key risks, and challenges along with summary and conclusions are provided. This analysis is ideal for those wishing to gain an up-to-date understanding of the CAR-T landscape.

[1] Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia. Maude e al. 2014. N Engl J Med. 371(16): 1507–1517.
[2] CD19-CAR Trials. 2014. Ramos et al. Cancer J. 20(2): 112–118

Methodology

VacZine Analytics has closely monitored all significant source material pertaining to 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 one Excel workbook[3] and an executive presentation[4]

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Chimeric Antigen Receptors (CAR) - In depth review of key industry sponsored programmes

[3] Contents available on request
[2] Presentation titles may apply to more than one slide

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Continued……

Slide number = 99

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BIBLIOGRAPHY

1. Clinical Cancer Advances 2017. Available at: https://www.asco.org/research-progress/reports-studies/clinical-cancer-advances#/message-ascos-president-0. Accessed January 2017.
2. Harnessing the immune system to improve cancer therapy. Papaioannou et al. Ann Transl Med. 2016. 4(14):261
3. Adoptive T Cell Immunotherapy for Cancer. Perica et al. Rambam Maimonides Med J. 2015. 6(1):e0004
4. Durable complete responses in heavily pretreated patients with metastatic melanoma using T-cell transfer immunotherapy. Rosenberg et al. 2011. Clin Cancer Res. 1;17(13):4550-7
5. Cancer immunotherapy based on mutation-specific CD4+ T cells in a patient with epithelial cancer. Tran et al. 2014. Science. 9;344(6184):641-5
6. Generation of tumor-infiltrating lymphocyte cultures for use in adoptive transfer therapy for melanoma patients. 2003. Dudley ME et al. J Immunother. 26(4):332-42
7. T-cell tolerance: central and peripheral. Xing and Hogquist. Cold Spring Harb Perspect Biol. 2012. 4(6).
8. Natural regulatory T cells and de novo-induced regulatory T cells contribute independently to tumor-specific tolerance. Zhou G., Levitsky. 2007. J. Immunol. 178, 2155–2162.
9. Genetically modified T cells in cancer therapy: opportunities and challenges. Sharpe and Mount. Dis Model Mech. 2015. Apr; 8(4): 337–350.
10. Gene therapy with human and mouse Tcell receptors mediates cancer regression and targets normal tissues expressing cognate antigen. Johnson et al. 2009. Blood 114, 535–546.
11. Cancer regression and neurological toxicity following anti MAGEA3 TCR gene therapy. 2013. Morgan et al. J. Immunother. 36, 133–151.
12. Tumor regression in patients with metastatic synovial cell sarcoma and melanoma using genetically engineered lymphocytes reactive with NYESO1. 2011. Robbins et al. J. Clin. Oncol. 29, 917–924.
13. Expression of immunoglobulin-T-cell receptor chimeric molecules as functional receptors with antibodytype specificity. Gross et al. 1989. Proc Natl Acad Sci USA. 86(24):10024-10028.
14. Manufacturing validation of biologically functional T cells targeted to CD19 antigen for autologous adoptive cell therapy. Hollyman et al. 2009. J Immunother. 32(2):169-80.
15. Chimeric antigen receptor therapy for cancer. Barrett et al. 2014. Annu Rev Med. 65:333-47.
16. A phase I study on adoptive immunotherapy using gene-modified T cells for ovarian cancer. Kershaw et al. 2006. Clin. Cancer Res. 12:6106–6115.
17. Adoptive transfer of chimeric antigen receptor re-directed cytolytic T lymphocyte clones in patients with neuroblastoma. Park et al. 2007. Mol. Ther. 15:825–833.
18. Signals through T cell receptor-zeta chain alone are insufficient to prime resting T lymphocytes. Brocker and Karjalainen. 1995. J Exp Med. 181(5):1653-1659.
19. CD28 costimulation improves expansion and persistence of chimeric antigen receptor-modified T cells in lymphoma patients. Savoldo et al. 2011. J Clin Invest. 121(5): 1822–1826.
20. 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. 2010. Blood. 16(20):4099-4102.
21. Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia. Maude e al. 2014. N Engl J Med. 371(16): 1507–1517.
22. CD19-CAR Trials. 2014. Ramos et al. Cancer J. 20(2): 112–118.
23. Chimeric receptors containing CD137 signal transduction domains mediate enhanced survival of T cells and increased antileukemic efficacy in vivo. Milone et al. 2009. Mol Ther. 17(8):1453–64.
24. Third-generation CD28/4-1BB chimeric antigen receptor T cells for chemotherapy relapsed or refractory acute lymphoblastic leukaemia: a non-randomised, open-label phase I trial protocol. Tang et al. 2016. BMJ Open 6:e013904.
25. CD20-specific adoptive immunotherapy for lymphoma using a chimeric antigen receptor with both CD28 and 4–1BB domains: pilot clinical trial results. Till et al. 2012. Blood, 119 3940–3950.
26. TRUCKs: the fourth generation of CARs. Chmielewski and Abken. 2015. Expert Opin Biol Ther. 15(8):1145-54.

27. IL-12 release by engineered T cells expressing chimeric antigen receptors can effectively muster an antigen-independent macrophage response on tumor cells that have shut down tumor antigen expression. Chmielewski et al. 2011. Cancer Res. 71, 5697–5706.
28. Chimeric antigen receptor-redirected T cells engineered to deliver inducible IL-12 modulate the tumour stroma to combat cancer. Chmielewski. 2012. Cancer Immunol. Immunother. 61, 1269–1277.
29. CD19 antigen in leukemia and lymphoma diagnosis and immunotherapy. Scheuermann and Racila. 1995. Leuk Lymphoma. 18(5-6):385-97.
30. 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.
31. 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.
32. 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.
33. Chimeric antigen receptor (CAR) T cell therapy for malignant cancers: Summary and perspective. Aaron J. Smith. 2016. J.of Cellular Immunotherapy, 2:(59–68).
34. Genetically modified T cells in cancer therapy: opportunities and challenges. Sharpe and Mount. 2015. Dis Model Mech. Apr; 8(4): 337–350.
35. Toxicities of chimeric antigen receptor T cells: recognition and management. Brudno and Kochenderfer. 2016. Blood. 27(26):3321-3330.
36. Adoptive transfer of effector CD8+ T cells derived from central memory cells establishes persistent T cell memory in primates. Berger et al. 2008. J. Clin. Investig. 118, 294–305.
37. Adoptive transfer of gene-engineered CD4+ helper T cells induces potent primary and secondary tumor rejection. Moeller et al. 2005. Blood: 106, 2995–3003.
38. Different Subsets of T Cells, Memory, Effector Functions, and CAR-T Immunotherapy. Golubovskaya and Wu. 2015. Cancers 2016, 8, 36.
39. T cell exclusion, immune privilege, and the tumor microenvironment. Joyce and Fearon. 2015. Science : 348, Issue 6230, pp. 74-80.
40. CD19-targeted T cells rapidly induce molecular remissions in adults with chemotherapy-refractory acute lymphoblastic leukemia. Brentjens et al. 2013. Sci Transl Med. 5(177): 177ra38.
41. T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial. Lee et al. 2015. The Lancet, 385, No. 9967, p517–528.
42. B-cell depletion and remissions of malignancy along with cytokine-associated toxicity in a clinical trial of anti-CD19 chimeric-antigen-receptor–transduced T cells. Kochenderfer et al. 2012. Blood. 119(12):2709-2720.
43. Chemotherapy-Refractory Diffuse Large B-Cell Lymphoma and Indolent B-Cell Malignancies Can Be Effectively Treated With Autologous T Cells Expressing an Anti-CD19 Chimeric Antigen Receptor. Kochenderfer et al. 2014. J Clin Oncol 33:540-549.
44. Leukaemia (all subtypes combined) incidence statistics. Available at: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia/incidence#heading-Seven. Accessed January 2017.
45. Relapsed childhood acute lymphoblastic leukaemia. Bhojwani and Pui. 2013. Lancet Oncol. 14 (6):e205-e217.
46. Where do we stand in the treatment of relapsed acute lymphoblastic leukemia? Raetz and Bhatla. 2012. Hematology Am Soc Hematol EducProgram. 2012:29-136.
47. Cancer Immunotherapy. Leukemia. Available at: http://www.cancerresearch.org/cancer-immunotherapy/impacting-all-cancers/leukemia. Accessed January 2017.
48. The Hodgkin and Reed/Sternberg cell. Küppers and Hansmann. 2005. Int J Biochem Cell Biol. 37(3):511-7.
49. GLOBOCAN 2012: Estimated cancer incidence, mortality and prevalence worldwide in 2012. Estimated incidence, mortality and 5-year prevalence: both sexes. Available at: http://globocan.iarc.fr/Pages/fact_sheets_population.aspx. Accessed January 2017.
50. Lymphoma. Available at: http://www.cancerresearchuk.org/about-cancer/type/lymphoma/. Accessed January 2017.
51. TREATING MULTIPLE MYELOMA. Available at: https://www.cancer.org/cancer/multiple-myeloma/treating/chemotherapy.html. Accessed February 2017.

52. Bluebird bio Presents Pre-Clinical and Manufacturing Data from CAR T Oncology Programs at ASH Annual Meeting. Presented at the 57th American Society of Hematology Annual Meeting. 2016. Accessed via http://investor.bluebirdbio.com/phoenix.zhtml?c=251820&p=irol-newsArticle&ID=2120416. Accessed February 2017.
53. Tolerance and efficacy of autologous or donor derived T cells expressing CD19 chimeric antigen receptors in adult B-ALL with extramedullary leukemia. Dai et al. 2015. OncoImmunology, 4:11, e1027469.
54. NKG2D CARs as Cell Therapy for Cancer. Sentman and Meehan. 2014. Cancer J. 20(2): 156–159.
55. NKG2D ligands as therapeutic targets. Spear et al. 2013. Cancer Immun. 13: 8.
56. Diagram reproduced from: Celyad Update. Developing engineered celltherapies for life-threatening diseases. Steve Buckanavage: http://car-tcr-summit.com/wp-content/uploads/sites/125/2016/09/YES-Buckanavage-9-14-16-10.10.pdf. Accessed February 2017.
57. Celyad Announces Positive New Data from its CAR-T NKR-2 Phase I Trial at 2016 ASH Annual Meeting. Available at: http://www.celyad.com/news/celyad-announces-positive-new-data-from-its-car-t-nkr-2-phase-i-trial-at-2016-ash-annual-meeting. Accessed February 2017.
58. Celyad Announces Registration of the first patient in the Belgian THINK trialAvailable at: http://www.celyad.com/news/celyad-announces-registration-of-the-first-patient-in-the-belgian-think-trial. Accessed February 2017.
59. Celyad Announces Registration of the First Pancreatic Cancer Patient in its CAR-T NKR-2 THINK Trial in Belgium. Available at: http://www.celyad.com/news/celyad-announces-registration-of-the-first-pancreatic-cancer-patient-in-its-car-t-nkr-2-think-trial-in-belgium. Accessed February 2017.
60. Juno Therapeutics Presents Data From TRANSCEND Study Showing 60% Complete Response in Patients with Relapsed or Refractory Aggressive CD19+ Non-Hodgkin Lymphoma. Available at: http://ir.junotherapeutics.com/phoenix.zhtml?c=253828&p=irol-newsArticle&ID=2227607. Accessed February 2017.
61. Juno Therapeutics Highlights Progress with Best-in-Class Strategy in B-Cell Malignancies at ASH. Available at: http://ir.junotherapeutics.com/phoenix.zhtml?c=253828&p=irol-newsArticle&ID=2228009. Accessed February 2017.
62. JUNO'S CAR T AND TCR INVESTIGATIONAL PRODUCT CANDIDATES DEMONSTRATE PROMISING OUTCOMES IN CLINICAL TRIALS IN PATIENTS WITH B-CELL CANCERS. Available at: https://www.junotherapeutics.com/junos-car-t-and-tcr-investigational-product-candidates-demonstrate-promising-outcomes-in-clinical-trials-in-patients-with-b-cell-cancers/. Accessed February 2017.
63. Immunotherapy of non-Hodgkin's lymphoma with a defined ratio of CD8+ and CD4+ CD19-specific chimeric antigen receptor–modified T cells. Turtle et al. 2016. Science Translational Medicine Vol. 8, Issue 355:355ra116.
64. Kite Pharma Receives FDA Breakthrough Therapy Designation for KTE-C19 for the Treatment of Refractory, Aggressive Non Hodgkin Lymphoma (NHL). Available at: http://ir.kitepharma.com/releasedetail.cfm?ReleaseID=945790. Accessed February 2017.
65. Phase 1 Results of ZUMA-1: A Multicenter Study of KTE-C19 Anti-CD19 CAR T Cell Therapy in Refractory Aggressive Lymphoma. Locke et al. 2017. Molecular Therapy Vol. 25 No 1 January 2017.
66. 1227 Production of Anti-CD19 CAR T Cells for ZUMA-3 and -4: Phase 1/2 Multicenter Studies Evaluating KTE-C19 in Patients With Relapsed/Refractory B-Precursor Acute Lymphoblastic Leukemia (R/R ALL). Available at: https://ash.confex.com/ash/2016/webprogram/Paper93708.html. Accessed February 2017.
67. Kite Pharma Reports 82 Percent of Patients Achieved Complete Remission in Preliminary Analysis from Phase 1 ZUMA-3 and ZUMA-4 Trials of KTE-C19 in Adult and Pediatric Patients with High Burden Relapsed/Refractory Acute Lymphoblastic Leukemia. Available at: http://ir.kitepharma.com/releasedetail.cfm?releaseid=1002521. Accessed February 2017.
68. Novartis announces new CTL019 study data demonstrating overall response in adult patients with certain types of lymphoma. Available at: https://www.novartis.com/news/media-releases/novartis-announces-new-ctl019-study-data-demonstrating-overall-response-adult. Accessed February 2017.
69. Sustained Remissions Following Chimeric Antigen Receptor Modified T Cells Directed Against CD19 (CTL019) in Patients with Relapsed or Refractory CD19+ Lymphomas [oral presentation]. Schuster, Stephen J. et al. 2015. 57th American Society of Hematology Annual Meeting & Exposition: Abstract 183.
70. Novartis highlights new CTL019 Phase II data demonstrating 93% complete remission in pediatric patients with r/r ALL. Available at: https://www.novartis.com/news/media-releases/novartis-highlights-new-ctl019-phase-ii-data-demonstrating-93-complete-remission. Accessed February 2017.
71. A Multidrug-resistant Engineered CAR T Cell for Allogeneic Combination Immunotherapy. Valton et al. 2015. Molecular Therapy vol. 23 no. 9, 1507–1518

72. In Vivo Proof of Concept of Activity and Safety of UCART19, an Allogeneic “Off-the-Shelf” Adoptive T-Cell Immunotherapy Against CD19+ B-Cell Leukemias. Gouble et al. 2014. Blood 124:4689
73. Molecular remission of infant B-ALL after infusion of universal TALEN gene-edited CAR T cells. Qasim. 2017. Sci. Transl. Med. 9, eaaj2013.
74. ENGINEERED CAR-T THERAPIES A NEW PARADIGM IN ONCOLOGY. 2017. Available at: https://www.cellectis.com/sites/default/files/cellectis_healthcare17.pdf. Accessed February 2017.
75. FDA Grants Cellectis IND Approval to Proceed with the Clinical Development of UCART123, the First Gene Edited Off-the-Shelf CAR T-Cell Product Candidate developed in the U.S. 2017. Available at: https://www.cellectis.com/en/content/fda-grants-cellectis-ind-approval-proceed-clinical-development-ucart123-first-gene-edited-0. Accessed February 2017.

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