



****Published May 2017*** MarketVIEW: CAR-T г/г B-ALL global market forecast (сат: юмvо74)

Product Name	:	MarketVIEW: CAR-T r/r B-ALL commercial market forecast
Description	:	Commercial assessment of new CAR-T therapies in relapsed/refractory B-acute lymphoblastic leukaemia
Contents	:	Executive presentation [130 slides] + 1 MS Excel workbook
Therapeutic Area	:	Cancer immunotherapy
Publication date	:	May 2017
Catalogue No		IOMV074

Background

B-ALL Acute Lymphoblastic Leukaemia (ALL) is a hematologic malignancy characterised by the proliferation and accumulation of lymphoid progenitor cells (lymphoblasts) or lymphocytes in the bone marrow, blood or in various extramedullary sites. ALL, which mainly affects the <20 yrs age group represents about 0.4% of all new cancer cases in the US with around 6500 new cases per year and ~1400 deaths (SEER, Cancer Stat Facts). Rates for ALL have been rising ~0.6% each year for the last 10 years although the 5-year survival rate shows an increasing trend.

Despite a plethora of treatment strategies and a relatively high cure rate in children (60-90%), the prognosis of those individuals with relapsing/refractory disease (r/r) is still poor. In adults, long term survival (5 year rates) are often below 10%. No current standard approach exists. **CAR-T** or Chimeric Antigen Receptor T cells are a promising new treatment intervention for r/r B-ALL with companies such as Novartis, Pfizer (Cellectis), Medimmune, Juno Therapeutics, and Kite Pharma involved in clinical studies. Recently, Novartis has received a FDA priority review for **CTL019 (tisagenlecleucel-T)** upon BLA filing for pediatric and young adult patients for r/r B-cell ALL.

This **MarketVIEW** product consists of a detailed Executive presentation (~130 slides) and MS-Excel workbook forecasting the commercial potential (\$ 000s) of novel CAR-T therapies (per competitor) in both pediatric and adult r/r B-ALL(new cases) across 9 major Western¹ markets to 2030. A patient-based flow methodology has been devised where **three possible intervention scenarios** for CAR-T introduction are visualized so that the optimum product positioning can be assessed. In addition, an up-to-date review of B-ALL disease background, epidemiology, current and future treatments is presented along with a comprehensive review of the CAR-T landscape. Pricing and cost effectiveness considerations are also discussed. All assumptions are clearly provided.

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 $^{^1}$ US, Canada, UK, France, Germany, Italy, Spain, UK, Australia and Japan





Methodology

iOnco Analytics has closely monitored all significant source material pertaining to B-ALL 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: Published May 2017 (CAT No: IOMV074)

****This product is composed of one Excel workbook² and an executive presentation³

Contents Executive summary CAR-T treatment for r/r B-ALL - commercial model: key outputs CAR-T cell therapy: projected ALL revenue forecast per scenario (\$000s) (0-19yrs) to 2030 (Global) CAR-T cell therapy: projected ALL revenue forecast per scenario (\$000s) (0-19yrs) to 2030 (Europe) CAR-T cell therapy: projected ALL revenue forecast per scenario (\$000s) (0-19yrs) to 2030 (US) CAR-T cell therapy: projected ALL revenue forecast per scenario (\$000s) (19-65yrs) to 2030 (Global) CAR-T cell therapy: projected ALL revenue forecast per scenario (\$000s) (19-65yrs) to 2030 (Europe) CAR-T cell therapy: projected ALL revenue forecast per scenario (\$000s) (19-65yrs) to 2030 (US) CTL019: projected ALL revenue forecast per scenario (\$000s) (0-19yrs) to 2030 (Global) CTL019: projected ALL revenue forecast per scenario (\$000s) (19-65yrs) to 2030 (Global) CAR-T cell therapy: revenues per competitor, 2025 snapshot (US & M5EU) CAR-T cell therapy: projected ALL patient numbers (0-19yrs) to 2030 (Global) CAR-T cell therapy: projected ALL patient numbers (19-65yrs) to 2030 (Global) CAR-T cell therapy: projected ALL revenue forecast - price sensitivity analysis B-ALL: Disease background and epidemiology Leukaemia: Background Acute Lymphoblastic Leukaemia: Background Lymphocytes and the development of ALL Lymphocyte development and ALL Molecular genetics of ALL Molecular genetics of ALL: common mutations [7 slides] Molecular genetics of B cell ALL: Chromosomal abnormalities in children and adults with B-cell ALL and their relative frequencies Epidemiology: overall ALL statistics in the US 2016 ALL incidence vs other common cancer types in the US Age related distribution of ALL in the US Childhood ALL statistics in the US Childhood ALL statistics and genetic risk factors [2 slides] ALL deaths in the US with distribution by age ALL distribution by race, ethnicity and sex in the US [2 slides] ALL new cases and deaths in the US Five-year survival rate of ALL in the US Epidemiology: overall ALL statistics in the UK Incidence of ALL in the UK by age Incidence of ALL by UK country and sex ALL incidence rate trends in the UK over time, by age and sex ALL incidence and deprivation in England 2006-2010 New leukaemia cases and deaths in the UK (2014) (all subtypes*) New leukaemia cases and deaths in the US (2016) (all subtypes*) ALL incidence comparison in UK, France, Germany, Italy and Spain ALL mortality comparison in UK, France, Germany, Italy and Spain ALL prevalence comparison in UK, France, Germany, Italy and Spain

² Contents available on request

² Presentation titles may apply to more than one slide

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Continued.....

Clinical presentation and diagnosis of ALL Diagnosis of ALL Methods of classification of ALL ALL classification subtypes Factors affecting the prognosis of ALL Factors affecting the prognosis of ALL (cont..) Current cure rates of ALL Treatment of ALL: Chemotherapy phases and regimens [2 slides] Treatment of ALL: following chemotherapy [2 slides] ALL treatment summary Treatment of ALL: the expression of CD antigens and targeted therapies [3 slides] The development of monoclonal antibodies in ALL treatment [4 slides] Tyrosine Kinase inhibitors in ALL treatment and their application Treatment of T cell ALL Treatment of relapsed/refractory (r/r) ALL [2 slides] The unmet need in ALL treatment - adult The unmet need in ALL treatment - pediatric The unmet need in ALL treatment – outlook Novel treatments for r/r B-ALL: CAR-T cells Chimeric Antigen Receptors T-cells (CAR-T) Cancer Immunotherapy Adoptive T cell therapy - T cells Antigen selection for a CAR-T approach CAR-T cell therapy - Potential issues and challenges Steps in the manufacture of a CAR-T cell therapy Chimeric Antigen Receptor T cells (CAR-T) - Review of Key Successful Clinical Trials CAR-T cell therapy - successful clinical trials for CD19-CAR-T targeting acute lymphoblastic leukaemia [3 slides] Chimeric Antigen Receptors (CAR) - Current R&D pipeline CAR-T Therapy - pipeline analysis methodology [2 slides] CAR-T Therapy: pipeline analysis results Current pipeline analysis: industry sponsored CAR-T studies for ALL Current pipeline analysis: industry sponsored CAR-T studies for Leukaemia In depth review of key industry sponsored programmes for ALL Cellular Biomedicine Group Ltd: C-CAR011 [2 slides] Juno Therapeutics Inc, Celgene Corporation: JCAR017 [3 slides] Kite Pharma: KTE-C19 Novartis: CTL019 Novartis: CD19 CAR-T Long Term Follow Up/BLA filing Servier, Cellectis, Pfizer: UCART19 [4 slides] Cellectis: additional UCARTS CAR-T treatment for r/r B-ALL: modelling commercial potential Modelling rationale: CAR-T therapy CAR-T cell therapy: Target product profiles (TPPs) [2 slides] Modelling approach: methodology Modelling approach: markets modelled in this analysis B-ALL model development: Age group 0-19 yrs [2 slides] Patient flow: potential CAR-T treatment scenarios (0-19 yrs) B-ALL model development: Age group 19-65 yrs [2 slides] Patient flow: potential CAR-T treatment scenarios (19-65 yrs) CAR-T cell therapy: potential pricing policies [2 slides] Pricing CAR-T therapies: comparable analysis CAR-T cell therapy: pricing analogues used (LO, BASE, HI) Key CAR-T clinical pipeline summary Potential CAR-T launch sequence Competitor market share assumptions/rationale Model caveats and limitations Model validations Bibliography About iOnco Analytics Disclaimer Slide number ~130

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BIBLIOGRAPHY

- 1. Clinical Cancer Advances 2017. Available at: <u>https://www.asco.org/research-progress/reports-studies/clinical-cancer-advances#/message-ascos-president-0. Accessed January 2017</u>
- Exploring the assessment and appraisal of regenerative medicines and cell therapy products. March 2016. Available at: https://www.nice.org.uk/Media/Default/About/what-we-do/Science%20policy%20and%20research/Regenerative-medicinestudy-march-2016.pdf. Accessed March 2017.
- 3. The assessment and appraisal of regenerative medicines and cell therapy products: an exploration of methods for review, economic evaluation and appraisal. Hettle et al. 2017. Heath Technology Assessment. Volume 21 Issue 7. Available at: https://www.ncbi.nlm.nih.gov/books/NBK424722/. Accessed April 2017
- 4. Leukaemia (all subtypes combined) incidence statistics. Available at: http://www.cancerresearchuk.org/healthprofessional/cancer-statistics/statistics-by-cancer-type/leukaemia/incidence#heading-Seven. Accessed January 2017.
- 5. Adult Acute Lymphoblastic Leukemia Treatment (PDQ®)–Health Professional Version. Available at: https://www.cancer.gov/types/leukemia/hp/adult-all-treatment-pdq. Accessed March 2017.
- 6. Treatment of Acute Lymphoblastic Leukemia in Adults: Applying Lessons Learned in Children. Aldoss et al. 2016. Available at http://www.cancernetwork.com/oncology-journal/treatment-acute-lymphoblastic-leukemia-adults-applying-lessons-learned-children. Accessed March 2017.
- Genetic abnormalities associated with acute lymphoblastic leukemia. Yokota and Kanakura. 2016. Cancer Sci 107 (2016) 721–725.
- 8. A population-based cytogenetic study of adults with acute lymphoblastic leukemia. Moorman et al. 2010. Blood. 115:206-214.
- 9. Ph-like Acute Lymphoblastic Leukemia in Older Adults. Herold et al. 2014. N Engl J Med: 371:2235.
- Incidence and clinical outcome of children with BCR/ABL-positive acute lymphoblastic leukemia (ALL). A prospective RT-PCR study based on 673 patients enrolled in the German pediatric multicenter therapy trials ALL-BFM-90 and CoALL-05-92. Schlieben et al. 1996. Leukemia:10:957-63
- 11. Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia in Childhood. Koo. 2011. Korean J Pediatr: 54(3):106-110
- 12. Deletion of IKZF1 and Prognosis in Acute Lymphoblastic Leukemia. Mullighan et al. 2009. N Engl J Med: 360:470-80.
- 13. Targetable kinase-activating lesions in Ph-like acute lymphoblastic leukemia. Roberts et al. 2014. N Engl J Med:371:1005-15
- 14. TKI dasatinib monotherapy for a patient with Ph-like ALL bearing ATF7IP/PDGFRB translocation. Kobayashi et al. 2015. Pediatr Blood Cancer: 62:1058-60.
- 15. CRLF2 and JAK2 in B-Progenitor Acute Lymphoblastic Leukemia: A Novel Association in Oncogenesis. Devon Roll and Reuther. 2010. Cancer Res. 70(19): 7347–7352
- 16. How Is Acute Lymphocytic Leukemia Classified? Available at: https://www.cancer.org/cancer/acute-lymphocyticleukemia/detection-diagnosis-staging/how-classified.html. Accessed March 2017.
- 17. World Health Organization Classification of Tumours. Pathology and genetics. Tumours of hematopoietic and lymphoid tissues. IARC Press, Jaffe et al. 2001 Lyon, pp 181–184.
- 18. ETV6-RUNX1-positive childhood acute lymphoblastic leukemia: improved outcome with contemporary therapy. Bhojwani et al. 2012. Leukemia: 26(2): 265–270
- 19. Cancer Stat Facts: Acute Lymphocytic Leukemia (ALL). Available at: https://seer.cancer.gov/statfacts/html/alyl.html Accessed March 2017.
- 20. Childhood Acute Lymphoblastic Leukemia Treatment (PDQ®)–Health Professional Version. Available at: https://www.cancer.gov/types/leukemia/hp/child-all-treatment-pdq#cit/section_1.4. Accessed March 2017.
- 21. SEER Cancer Statistics Review (CSR) 1975-2013. Howlader N, Noone AM, Krapcho M. Bethesda, Md: National Cancer Institute, 2015. Available at: https://seer.cancer.gov/csr/1975_2013/. Accessed March 2017.
- 22. Down syndrome and acute lymphoblastic leukaemia. Whitlock JA. 2006. Br J Haematol 135 (5): 595-602.
- 23. The management of neoplastic disorders of haematopoiesis in children with Down's syndrome. Lange, B. 2000. British Journal of Haematology, 110, 512–524
- 24. Acute leukaemia in children with Down syndrome: a population-based Nordic study. Zeller et al. 2005. Br J Haematol 128 (6): 797-804.
- 25. Outcome in children with Down's syndrome and acute lymphoblastic leukemia: role of IKZF1 deletions and CRLF2 aberrations. Buitenkamp et al. 2012. Leukemia. 10:2204-11

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- Down syndrome acute lymphoblastic leukemia, a highly heterogeneous disease in which aberrant expression of CRLF2 is associated with mutated JAK2: a report from the International BFM Study Group. Hertzberg. 2010. Blood. 115(5):1006-17.
- 27. cof JAK2 mutations in Down syndrome acute lymphoblastic leukaemia. Gaikwad et al. 2009. Br J Haematol. 144(6):930-2.
- 28. Adult acute lymphoblastic leukemia. Jabbour et al. 2005. Mayo Clin Proc: 80(11):1517-1527.
- Acute lymphoblastic leukaemia (ALL) incidence statistics. Available at: http://www.cancerresearchuk.org/healthprofessional/cancer-statistics/statistics-by-cancer-type/leukaemia-all/incidence#heading-One. Accessed March 2017.
- 30. Cancer Research UK and National Cancer Intelligence Network. Cancer by Deprivation in England. Available at: Cancer by deprivation in England: Incidence, 1996-2010, Mortality, 1997-2011). Accessed March 2017.
- 31. Leukaemia. Available at: http://eco.iarc.fr/eucan/Cancer.aspx?Cancer=40#block-map-a. Accessed March 2017.
- 32. Cancer Stat Facts: Leukemia. Available at: https://seer.cancer.gov/statfacts/html/leuks.html. Accessed March 2017.
- 33. Adult Acute Lymphoblastic Leukemia. Paul et al. 2016. Mayo Clin Proc: 91(11):1645-1666
- 34. Adult Acute Lymphoblastic Leukemia. Concepts and Strategies. Faderl et al. 2010. Cancer. 116(5): 1165–1176.
- Central Nervous System Involvement in Adult Acute Lymphoblastic Leukemia: Diagnostic Tools, Prophylaxis, and Therapy. Del Principe et al. 2014. Mediterr J Hematol Infect Dis: 1;6(1):e2014075.
- 36. French American British (FAB) morphological classification of childhood lymphoblastic leukaemia and its clinical importance. Lilleyman et al. 1986. J Clin Pathol:39(9):998-1002.
- 37. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, Fourth Edition. Swerdlow et al. 2008.
- Prognostic Factors in Childhood Leukemia (ALL or AML). Available at: https://www.cancer.org/cancer/leukemia-inchildren/detection-diagnosis-staging/prognostic-factors.html. Accessed March 2017.
- New Insights into the Pathophysiology and Therapy of Adult Acute Lymphoblastic Leukemia. Jabbour et al. 2015. Cancer:121:2517-28
- 40. Improved outcome of adult Burkitt lymphoma/leukemia with rituximab and chemotherapy: report of a large prospective multicenter trial. Hoelzer et al. 2014. Blood: 124:3870-3879.
- Chemoimmunotherapy with a modified hyper-CVAD and rituximab regimen improves outcome in de novo Philadelphia chromosome–negative precursor B-lineage acute lymphoblastic leukemia. Thomas et al. 2010. J Clin Oncol: 28:3880-3889.
- 42. The combination of hyper-CVAD plus nelarabine as frontline therapy in adult T-cell acute lymphoblastic leukemia and Tlymphoblastic lymphoma: MD Anderson Cancer Center experience. Jain et al. 2014. Leukemia.: 28:973-975.
- 43. Results of treatment with hyper-CVAD, a dose-intensive regimen, in adult acute lymphocytic leukemia. Kantarjian et al. 2000. J Clin Oncol.:18(3): 547-561
- 44. Acute Lymphoblastic Leukemia Treatment Protocols. Available at: http://emedicine.medscape.com/article/2004705overview. Accessed March 2017.
- 45. Improved outcome in adult B-cell acute lymphoblastic leukemia. Hoelzer et al. 1996. Blood:87(2):495-508.
- 46. Results of treatment with hyper-CVAD, a dose-intensive regimen, in adult acute lymphocytic leukemia. Kantarjian et al. 2000. J Clin Oncol.:18(3): 547-561
- 47. Secondary brain tumors in children treated for acute lymphoblastic leukemia at St Jude Children's Research Hospital. 1998. Walter et al. J Clin Oncol.: 6(12):3761-3767.
- 48. In adults with standard-risk acute lymphoblastic leukemia (ALL) the greatest benefit Progress in Acute Lymphoblastic is achieved from a matched sibling allogeneic transplant in first complete remission (CR) and an autologous transplant is less effective than conventional consolidation/maintenance chemotherapy in all patients: final results of the international ALL trial (MRC UKALL XII/ECOG 2993). Goldstone et al. 2008. Blood: 111:1827-1833.
- 49. Current approach to relapsed acute lymphoblastic leukemia in children. Fuster. 2014. World J Hematol: 3(3): 49-70
- 50. Improved risk classification for risk-specific therapy based on the molecular study of minimal residual disease (MRD) in adult acute lymphoblastic leukemia (ALL). Bassan et al. 2009. Blood:113:4153-1162.
- 51. Minimal Residual Disease in Acute Lymphoblastic Leukemia. Campana. 2010. Hematology Am Soc Hematol Educ Program: 2010:7-12.
- 52. Current Concepts in Pediatric Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia. Bernt and Hunger. 2014. Front Oncol: 4: 54
- 53. Diagnosis and subclassification of acute lymphoblastic leukemia. Chiaretti et al. 2014. Mediterr J Hematol Infect Dis, 6; Open Journal System
- 54. A simple guide to the terminology and application of leucocyte monoclonal antibodies. Chan et al. 1988. Histopathology. 12 (5): 461–480
- 55. CD19: a biomarker for B cell development, lymphoma diagnosis and therapy. Wang et al. 2012. Experimental Hematology & Oncology, 1:36
- 56. CD19 function in central and peripheral B-cell development. Del Nagro et al. 2005. Immunol Res 2005, 31(2):119–131

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- 57. Differential phosphorylation of functional tyrosines in CD19 modulates B-lymphocyte activation. Ishiura et al. 2010. Eur J Immunol 2010, 40(4):1192–1204
- 58. The B cell surface molecule B1 is functionally linked with B cell activation and differentiation. Tedder et al. 1985. J Immunol. 135(2):973-9.
- 59. Antibodies reactive with the B1 molecule inhibit cell cycle progression but not activation of human B lymphocytes. Et al. 1986. Eur J Immunol. 16(8):881-7.
- 60. CD22, a B lymphocyte-specific adhesion molecule that regulates antigen receptor signaling. Tedder et al. 1997. Annu Rev Immunol. 15:481-504
- 61. CD52 antigen a review. Domagała and Kurpisz. 2001. Med Sci Monit, 7(2): 325-331
- 62. Chemoimmunotherapy with hyper-CVAD plus rituximab for the treatment of adult Burkitt and Burkitt-type lymphoma or acute lymphoblastic leukemia. Thomas et al. 2006. Cancer: 2006;106(7):1569-1580.
- 63. Chemoimmunotherapy in acute lymphoblastic leukemia. Hoelzer and Gokbuget. 2012. Blood Rev: 26(1):25-32.
- 64. Alliance for Clinical Trials In Oncology (ACTION). Improved efficacy using rituximab and brief duration, high intensity chemotherapy with filgrastim support for Burkitt or aggressive lymphomas: cancer and Leukemia Group B study 10 002. Rizzieri et al. 2014. Br J Haematol: 165(1):102-111.
- 65. Phase II study of the hyper-CVAD regimen in combination with ofatumumab as frontline therapy for adults with CD-20 positive acute lymphoblastic leukemia [abstract]. Jabbour et al. 2014. J Clin Oncol. Abstract 7065.
- 66. Chemoimmunotherapy Reinduction With Epratuzumab in Children With Acute Lymphoblastic Leukemia in Marrow Relapse: A Children's Oncology Group Pilot Study. Raetz et al. 2008. J Clin Oncol 26:3756-3762.
- 67. Southwest Oncology Group Study S0910: a phase 2 trial of clofarabine/cytarabine/epratuzumab for relapsed/refractory acute lymphocytic leukemia. Advani et al. 2014. Br J Haematol: 65(4):504-509.
- 68. Inotuzumab ozogamicin in the treatment of B-cell acute lymphoblastic leukemia. Thomas. 2012. Expert Opin Investig Drugs:21(6):871-878.
- 69. Inotuzumab ozogamicin, an anti-CD22-calecheamicin conjugate, for refractory and relapsed acute lymphocytic leukaemia: a phase 2 study. Kantarjian et al. 2012. Lancet Oncol:13(4):403-411
- 70. Results of inotuzumab ozogamicin, a CD22 monoclonal antibody, in refractory and relapsed acute lymphocytic leukemia. Kantarjian et al. 2013. Cancer:1;119(15):2728-36
- 71. A Phase 1 Study of Denintuzumab Mafodotin (SGN-CD19A) in Adults with Relapsed or Refractory B-Lineage Acute Leukemia (B-ALL) and Highly Aggressive Lymphoma. Fathi et al. Blood: 126:1328
- 72. Remission of adult acute lymphocytic leukaemia with Alemtuzumab. Laporte et al. 2004. Leukemia:18, 1557–1558
- 73. Current status of antibody therapy in ALL. Ai. 2015. Br J Haematol: 168(4):471-80
- 74. Alternating versus concurrent schedules of imatinib and chemotherapy as front-line therapy for Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL). Wassmann et al. Blood. 2006;108:1469-77.
- 75. Overriding imatinib resistance with a novel ABL kinase inhibitor. Shah et al. 2004. Science: 305:399–401.
- 76. Management of adults with T-cell lymphoblastic leukemia. Marks and Rowntree. 2017. Blood: 129(9):1134-1142
- 77. Acute leukemia incidence and patient survival among children and adults in the United States, 2001-2007. Dores et al. 2012. Blood:119(1):34-43
- 78. Outcome of patients treated for relapsed or refractory acute lymphoblastic leukemia: a Therapeutic Advances in Childhood Leukemia Consortium study. Ko et al. 2010. J Clin Oncol: 28:648–54
- 79. Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study. Topp et al. 2015. Lancet Oncol. 16:57-66.
- Targeted therapy with the T-cell-engaging antibody blinatumomab of chemotherapy-refractory minimal residual disease in B-lineage acute lymphoblastic leukemia patients results in high response rate and prolonged leukemia-free survival. Topp et al. 2011. J Clin Oncol: 29:2493-8.
- 81. Outcome of 609 adults after relapse of acute lymphoblastic leukemia (ALL); an MRC UKALL12/ECOG 2993 study. Fielding et al. 2007. Blood: 109(3):944-50
- 82. GETLALA Group; Swiss Group for Clinical Cancer Research SAKK; Australasian Leukaemia and Lymphoma Group. Outcome of treatment after first relapse in adults with acute lymphoblastic leukemia initially treated by the LALA-94 trial. Tavernier et al. 2007. Leukemia: 21(9):1907-1914.
- Outcome of children and adolescents with a second or third relapse of acute lymphoblastic leukemia (ALL): a populationbased analysis of the Austrian ALL-BFM (Berlin-Frankfurt-Munster) study group. Reismuller et al. 2013. J Pediatr Hematol Oncol:35:e200–4
- 84. Pathways through relapses and deaths of children with acute lymphoblastic leukemia: role of allogeneic stem-cell transplantation in Nordic data. Saarinen-Pihkala et al. 2006. J Clin Oncol:24:5750–62

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- 85. How I treat adults with relapsed or refractory Philadelphia chromosome-negative acute lymphoblastic leukemia. Frey and Luger. 2015. Blood 2015 126:589-596
- 86. 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.
- 87. 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.
- 88. 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.
- 89. 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.
- 90. Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia. Maude e al. 2014. N Engl J Med. 371(16): 1507–1517.
- 91. CD19-CAR Trials. 2014. Ramos et al. Cancer J. 20(2): 112-118.
- 92. CD19 antigen in leukemia and lymphoma diagnosis and immunotherapy. Scheuermann and Racila. 1995. Leuk Lymphoma. 18(5-6):385-97.
- 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.
- 94. 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.
- 95. 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.
- Chimeric antigen receptor (CAR) T cell therapy for malignant cancers: Summary and perspective. Aaron J. Smith. 2016. J.of Cellular Immunotherapy, 2:(59–68).
- 97. Genetically modified T cells in cancer therapy: opportunities and challenges. Sharpe and Mount. 2015. Dis Model Mech. Apr; 8(4): 337–350.
- 98. Toxicities of chimeric antigen receptor T cells: recognition and management. Brudno and Kochenderfer. 2016. Blood. 27(26):3321-3330.
- 99. Global Manufacturing of CAR T Cell Therapy. Bruce L. 2017. Molecular Therapy: Methods & Clinical Development :4:92
- 100.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.
- 101.Efficacy and Toxicity Management of 19-28z CAR T Cell Therapy in B Cell Acute Lymphoblastic Leukemia. Davila et al. 2014. Sci Transl Med: 6(224): 224ra25
- 102.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.
- 103.Phase I Trial (CALL-1) for C-CAR011 in Adult Patients with Relapsed or Refractory B-cell Acute Lymphoblastic Leukemia (ALL) in China. Available at: http://www.cellbiomedgroup.com/newsroom/phase-i-trial-call-1-for-c-car011-in-adult-patients-with-relapsed-or-refractory-b-cell-acute-lymphoblastic-leukemia-all-in-china/. Accessed March 2017.
- 104. 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. Oncolmmunology, 4:11, e1027469.
- 105. 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.
- 106.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-candidatesdemonstrate-promising-outcomes-in-clinical-trials-in-patients-with-b-cell-cancers/. Accessed March 2017.
- 107.Juno Therapeutics Reports Fourth Quarter and 2016 Financial Results. 2016. Available at: http://ir.junotherapeutics.com/phoenix.zhtml?c=253828&p=irol-newsArticle&ID=2250772. Accessed March 2017.
- 108. 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.
- 109. 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.
- 110.1227 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.

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- 111.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.
- 112.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.
- 113.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.
- 114.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-93complete-remission. Accessed February 2017.
- 115.Novartis presents results from first global registration trial of CTL019 in pediatric and young adult patients with r/r B-ALL. Available at: https://www.novartis.com/news/media-releases/novartis-presents-results-first-global-registration-trial-ctl019pediatric-and. Accessed March 2017.
- 116.Novartis announces first CAR-T cell therapy BLA for pediatric and young adult patients with r/r B-cell ALL granted FDA Priority Review. Available at: https://www.novartis.com/news/media-releases/novartis-announces-first-car-t-cell-therapy-blapediatric-and-young-adult. Accessed March 2017.
- 117.A Multidrug-resistant Engineered CAR T Cell for Allogeneic Combination Immunotherapy. Valton et al. 2015. Molecular Therapy vol. 23 no. 9, 1507–1518.
- 118.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.
- 119.Molecular remission of infant B-ALL after infusion of universal TALEN gene-edited CAR T cells. Qasim. 2017. Sci. Transl. Med. 9, eaaj2013.
- 120. Engineered CAR-T therapies. A new paradigm in oncology. 2017. Available at: http://www.cellectis.com/sites/default/files/170223_corppres.pdf. Accessed March 2017.
- 121. Servier and Pfizer announce FDA clearance of IND application for UCART19 in Adult Relapsed/Refractory Acute Lymphoblastic Leukemia. March 2017. Available at: https://www.cellectis.com/en/content/servier-and-pfizer-announce-fdaclearance-ind-application-ucart19-adult-relapsedrefractory-0. Accessed March 2017.
- 122.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/fdagrants-cellectis-ind-approval-proceed-clinical-development-ucart123-first-gene-edited-0. Accessed March 2017.
- 123. The United States Census Bureau. Available at https://www.census.gov/population/international/index.html. Accessed March 2017.
- 124. Treatment of Pediatric Acute Lymphoblastic Leukemia. Cooper et al. Pediatr Clin North Am. 2015 Feb; 62(1): 61-73.
- 125. Clinical outcome of children with newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia treated between 1995 and 2005. Aricò et al. 2010. J Clin Oncol:28(4755-61).
- 126. Current Treatment of Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia. Fielding. 2011. Hematology:231
- 127. Outcome after relapse of acute lymphoblastic leukemia in adult patients included in four consecutive risk-adapted trials by the PETHEMA Study Group. Oriol et al. 2010. Haematologica: 95:589-596
- 128. Treatment of adult acute lymphoblastic leukemia (ALL): long-term follow-up of the GIMEMA ALL 0288 randomized study. Annino L et al. 2002. Blood: 99:863-871.
- 129.Sipuleucel-T (Provenge) Injection The First Immunotherapy Agent (Vaccine) For Hormone-Refractory Prostate Cancer. Anassi et al. 2011. P T. 36(4): 197–202.
- 130.Clofarabine (Evoltra®) for acute lymphoblastic leukaemia. Available at: https://www.scottishmedicines.org.uk/Press_Statements/Clofarabine_Evoltra__for_acute_lymphoblastic_leukaemia. Accessed April 2017.
- 131. The Cost of Hematopoietic Stem Cell Transplantation and Associated Conditioning Regimens. Quock et al. 2015. 57th American Society of Hematology Annual Meeting & Exposition December 5–8, 2015. Available at: http://www.pharllc.com/wp-content/uploads/2015/12/HSCT-Poster_FINAL-ASH-2015.pdf. Accessed April 2017.
- 132. Amgen slaps record-breaking \$178K price on rare leukemia drug Blincyto. Available at: http://www.fiercepharma.com/marketing/amgen-slaps-record-breaking-178k-price-on-rare-leukemia-drug-blincyto. Accessed April 2017.
- 133.Assessing the Cost–Benefit of Immune Checkpoint Inhibitors. Available at: http://www.valuebasedcancer.com/issuearchive/2016/september-2016-vol-7-no-8/assessing-the-cost-benefit-of-immune-checkpoint-inhibitors/. Accessed April 2017.

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134.Novartis Pharmaceuticals. Q1 2017 Results Presentation. Available at: https://www.novartis.com/sites/www.novartis.com/files/q1-2017-ir-presentation.pdf. Accessed May 2017



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TERMS and CONDITIONS:

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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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