**Supplementary Table 2: List of approved Advanced Therapy Medicinal Products that have been granted a PRIME, breakthrough or a Sakigake designation (as of February 5th,2022)**

| **Technology** | **Product** | **Active Substance** | **Indication** | **Jurisdiction** | **Designation granted** | **Marketing Authorisation** | **Post-approval requirements/commitments** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| ***In vivo* gene therapy** | **Zolgensma** | Replication  deficient adeno-associated virus serotype 9 (AAV9) delivering a functional human survival motor neuron (*SMN*) gene. | Paediatric patients < 2 years with spinal muscular atrophy with bi-allelic  mutations in the survival motor neuron 1 (*SMN 1*) gene. | US | **Breakthrough Therapy**  (15 July 2016) | Yes  (24 May 2019) | * CMC post-approval commitments. * Safety and efficacy long-term follow-up studies. |
| EU | **PRIME**  (26 January 2017) | Yes – conditional approval  (18 May 2020) | * Prospective observational registry according to an agreed protocol. * Evaluation of final product specifications when additional primary and key secondary endpoint data from patients with two SMN2 copies are available; and tightening of release specifications accordingly. * Other CMC-related recommendations for investigations. |
| Japan | **Sakigake** (March 2018) | Yes  (19 March 2020) | * Post-marketing use-results survey covering all patients treated with the product, until data from a sufficient number of Japanese patients are collected, to identify the characteristics of patients using the product and collect data on the safety and efficacy of the product as early as possible. The results of analysis of the long-term data from post-marketing surveillance should be reported to the Ministry of Health, Labour and Welfare and the Pharmaceuticals and Medical Devices Agency. * Disseminate the proper use guide developed in cooperation with the relevant academic societies and take other necessary measures, so as to ensure that physicians with adequate knowledge of and experience in the treatment of spinal muscular atrophy fully understand the results from clinical trials of the product, adverse events reported, and other data. * Take necessary measures to ensure that relevant physicians are well informed of the Regulations on Type-1 Use so that the product is used in compliance with the approved Regulations on Type-1 Use. |
| **Oncolytic virus** | **Delytact (G47 Delta)** | Oncolytic herpes simplex virus-1 | malignant glioma | Japan | **Sakigake**  (February 2016) | Yes – conditional and time-limited approval (11 June 2021) | * Approval based on results of a single-arm phase 2 clinical trial in patients with residual or recurrent glioblastoma. * Post-marketing commitments not yet released. |
| **OBP-301** | Human telomerase reverse transcriptase gene (hTERT) promotor regulated oncolytic adenovirus | Oesophageal Cancer | Japan | **Sakigake**  (April 2019) | Not yet approved |  |
| **CAR-T** | **Kymriah** | Autologous T cells genetically  modified *ex vivo* using a lentiviral vector encoding an anti-CD19 chimeric antigen receptor (CAR). | CD19-positive relapsed or refractory  B-cell acute lymphoblastic leukaemia (ALL) and CD19-  positive relapsed or refractory diffuse large B-cell  lymphoma (DLBCL) | US | **Breakthrough Therapy**  (04 December 2017) | Yes  (2017) | * Implementation of a risk evaluation mitigation strategy (REMS) with elements to assure safe use (ETASU) for the management of toxicities (cytokine release syndrome (CRS) and neurologic toxicity). * A 15-year post-marketing observational study to monitor long-term toxicities of KYMRIAH and the potential risk of secondary malignancies linked to the use of a lentiviral vector for genetic modification. |
| EU | **PRIME** | Yes  (22 August 2018) | * Non-interventional post-authorisation safety study (PASS) in order to further characterise the safety (including long-term safety) of Kymriah. * Post-authorisation efficacy study (PAES) in order to further evaluate the efficacy and safety of Kymriah in ALL patients below the age of 3 years. * Prospective, observational study in patients with relapsed or refractory DLBCL based on data from registry with efficacy outcome measures including details of the manufacturing turnaround time (i.e. time from last relapse or confirmed refractory status, time from decision to treat, and time from leukapheresis to infusion). * In addition, in order to further characterise the long-term efficacy and safety of Kymriah in relapsed/refractory DLBCL, final clinical study report (CSR) including 5 years of follow-up should be submitted.   The results of study CCTL019H2301 – open-label, Phase III study of Kymriah versus standard of care in adult patients with relapsed or refractory aggressive B-cell non-Hodgkin lymphoma, are also expected to be submitted. |
| Japan | None | Yes  (26 March 2019) | * Requirement to ensure that the product is used by a physician with sufficient knowledge and experience in treatment of hematopoietic malignancies and hematopoietic stem cell transplantation at a medical institution that can properly respond to emergencies in an environment that ensures appropriate actions are taken (such as management of cytokine release syndrome). * Conduct a use-results survey covering all Japanese patients treated with the product after the market launch until data from a sufficient number of Japanese patients have been collected, in order to understand the characteristics of patients using the product, and to promptly collect safety and efficacy data so that the necessary measures are taken to ensure proper use of the product. |
| **Yescarta** | Autologous T cells genetically  modified *ex vivo* using a retroviral vector encoding an anti-CD19 CAR. | Relapsed or refractory large B-cell lymphoma | US | **Breakthrough Therapy**  (December 2015) | Yes  (18 October 2017) | * Risk evaluation mitigation strategy (REMS) with elements to assure safe use (ETASU) for the management of CRS and neurologic toxicity, training and assessment of sites and the use of tocilizumab. * A post-marketing observational study to primarily assess long-term toxicities of YESCARTA. |
| EU | **PRIME** | Yes  (23 August 2018) | * Non-interventional post-authorisation safety study (PASS) in order to assess the safety profile (including long-term safety) in patients with B-lymphocyte malignancies treated with YESCARTA in the post-marketing setting. |
| Japan | None | Yes  (22 January 2021) | Details not released. |
| **Tecartus** | Autologous peripheral blood T cells CD4 and CD8 selected and CD3 and CD28 activated transduced with retroviral vector expressing anti-CD19 CD28/CD3-zeta chimeric antigen receptor and cultured. | Adult patients with  relapsed or refractory mantle cell  lymphoma (MCL) | EU | **PRIME** | Yes  (14 December 2020) | * Confirm the long-term efficacy and safety of TECARTUS in adult patients with relapsed or refractory MCL and the Benefit/Risk balance in the female, elderly and severely diseased patients by conducting a prospective study investigating efficacy and safety based on data from the same registry used to characterise the long-term efficacy and safety of TECARTUS, according to an agreed protocol. * In order to confirm the long-term efficacy and safety of TECARTUS in adult patients with relapsed or refractory MCL, the Marketing Authorisation Holder (MAH) shall submit the 24 months follow-up data from all treated patients in cohort 1 of the pivotal study. |
| US | **Breakthrough Therapy**  (June  2018) | Yes  (24 July 2020) | * Conduct a multi-centre, prospective, observational safety study using a registry design, including 500 subjects enrolled within three months of the TECARTUS infusion over a period of five years. Enrolled subjects to be followed for 15 years post-TECARTUS infusion.   Other commitments:   * Complete additional follow-up of all 68 subjects treated with brexucabtagene autoleucel to a minimum of 18 months from the time of first response. Data will continue to be collected according to the protocol’s established schedule of assessments. * Conduct a study of brexucabtagene autoleucel treatment of subjects with relapsed or refractory mantle cell lymphoma who have not been exposed to a Bruton tyrosine kinase (BTK) inhibitor. A cohort of subjects naïve to BTK inhibitor therapy will be added to the ongoing study to fulfil this requirement. 86 subjects will be enrolled. The primary efficacy endpoint will be objective response rate with a supportive efficacy endpoint of duration of response based on a minimum follow-up of 18 months after first objective disease response. |
| **Abecma** | Genetically modified autologous human T cells transduced with lentiviral vector (LVV) encoding a CAR  that recognises B-cell maturation antigen. | Adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody. | US | **Breakthrough Therapy**  (19 September 2017) | Yes  (26 March 2021) | * Conduct a post-marketing, prospective, multi-centre, observational study to assess the long-term safety of ABECMA and the risk of secondary malignancies occurring after treatment with ABECMA. patients will be followed for 15 years after their ABECMA infusion.   The primary endpoint includes evaluation for secondary malignancy, which will include the collection and analysis of blood and/or biopsy specimens of certain malignancies for evaluation of insertional mutagenesis. Other important endpoints include the incidence and severity of CRS, neurologic toxicity (including the incidence and severity in  older adults 65 years and older), prolonged cytopenia (including the use of rescue stem cell transplantation, the outcome of hematopoietic reconstitution and survival (post-transplant) and  haemophagocytic lymphohistiocytosis/ Macrophage Activation Syndrome (HLH/MAS).  Other commitments:   * Characterise the efficacy and safety of ABECMA in the African-American/black population. The primary objective of the study is to evaluate the efficacy of ABECMA among the African-American/black population compared to the white population and the secondary objective is safety. |
| Adult patients with relapsed and refractory multiple myeloma  who have received at least three prior therapies, including an immunomodulatory agent, a proteasome  inhibitor and an anti-CD38 antibody and have demonstrated disease progression on the last therapy. | EU | **PRIME**  (10 November 2017) | Yes – conditional approval  (18 August 2021) | * Prospective study based on data from a registry, according to an agreed protocol, to further characterise the long-term efficacy and safety of ABECMA. * 24 months post-ABECMA infusion follow-up data (in the enrolled and treated population) of the pivotal study. * Results of the Phase 3 study comparing the efficacy and safety of ABECMA vs. standard triplet regimens in subjects with relapsed and refractory multiple myeloma. |
| **Breyanzi** | CD19-directed genetically modified autologous T cells. Also includes a non-functional truncated epidermal growth factor receptor (EGFRt) that is co-expressed on the cell surface with the CD19-specific CAR. | Relapsed or refractory large B-cell lymphoma and relapsed or refractory follicular lymphoma | US | **Breakthrough Therapy**  (15 December 2016)  **RMAT**  (20 October 2017) | Yes  (5 February 2021) | * CMC post-marketing commitment. * A post-marketing observational study to assess the long-term safety of BREYANZI, including the risk of secondary malignancies. |
| EU | **PRIME**  (15 December 2016) | CHMP positive opinion  (27 January 2022) |  |
| **T-Cell Receptor (TCR) gene therapy** | **TBI-1301** | NY-ESO-1 siTCR Gene Therapy | Synovial Sarcoma | Japan | **Sakigake**  (March 2018) | Not yet approved |  |
| **Other genetically modified cells** | **Zynteglo** | Autologous  CD 34 cell enriched population that contains hematopoietic  stem cells transduced with lentiglobin BB 305 lentiviral vector encoding  the beta AT87Q globin gene. | Treatment of transfusion  dependent  beta thalassaemia (also referred to  as beta thalassaemia major) | EU | **PRIME**  (15 September 2016) | Yes – conditional approval  (29 May 2019) | * Re-evaluation of the acceptance criteria for attributes related to potency tests using batch release data and clinical results after 6 months follow-up of 20 patients treated with commercial batches. * Non-interventional post-authorisation safety study (PASS) in patients 12 years and older with transfusion-dependent β-thalassaemia (TDT) who do not have a β0/β0 genotype. * Conduct and submit the results of a study based on data from a product registry and use data on human leukocyte antigen (HLA)-matched allogenic haematopoietic stem cell transplantation (HSCT) treated patients from an established European registry as a comparator group. |
| **Skysona** | Genetically modified autologous CD34+  cell-enriched population  that contains haematopoietic stem cells (HSCs) transduced *ex vivo* with lentiviral vector (LVV) encoding  ABCD1 complementary deoxyribonucleic acid (cDNA) for human adrenoleukodystrophy protein  (ALDP). | Early cerebral adrenoleukodystrophy in patients less than  18 years of age, with an ABCD1 genetic mutation, and for whom HLA-matched sibling HSC donor is not available. | EU | **PRIME**  (26 July 2018) | Yes  (16 July 2021) | * Non-interventional post-authorisation safety study (PASS) in patients with cerebral adrenoleukodystrophy – conduct and submit the results of a prospective observational Registry Study of patients with cerebral adrenoleukodystrophy treated with Skysona or allogeneic haematopoietic stem cell transplantation (allo-HSCT). * Long-term efficacy and safety of Skysona in patients with cerebral adrenoleukodystrophy. |
| **Autologous stem cells** | **Stemirac** | Human autologous bone  marrow-derived mesenchymal stem cells. | Improvement of neurological symptoms and functional disorders associated with spinal cord injury in patients with traumatic spinal cord injury and ASIA impairment Scale A, B or C. | Japan | **Sakigake**  (10 February 2016 ) | Yes – **Conditional/time-limited approval**  (28 December 2018) | * Used only for patients considered eligible for the treatment and only under the supervision of a specialist with sufficient knowledge and experience in diagnosis and treatment of spinal cord injury at medical institutions fully capable of emergency care where patients are appropriately monitored and managed by vital sign check and laboratory test. * Post-marketing evaluation in all patients treated with the product during the period after the conditional and time-limited approval until reapplication for marketing approval. |
| **JRM-001** | Human Autologous Cardiac  Progenitor/Stem Cells. | Paediatric congenital heart disease. | Japan | **Sakigake**  (February 2016) | Not yet approved |  |
| **Allogeneic stem cells** | **HLCM051** | Human allogeneic bone marrow  progenitor/stem cells | Respiratory Distress Syndrome, Adult | Japan | **Sakigake**  (February 2017) | Not yet approved |  |
| **SB623** | Adult allogeneic bone marrow-derived  mesenchymal stem cells | Chronic motor deficit resulting from traumatic brain injury (TBI). | Japan | **Sakigake**  (April 2019) | Not yet approved |  |
| **Induced pluripotent stem cell (iPSC)-derived** | Not defined | Human allogeneic iPS-derived  dopamine neural progenitor cells. | Parkinson’s Disease | Japan | **Sakigake**  (February 2017) | Not yet approved |  |
| **Other somatic cell therapies** | **CLBS12** | Human autologous CD34-positive  peripheral blood cells | Critical limb ischemia. | Japan | **Sakigake** (March 2018) | Not yet approved |  |
| **Tissue engineering** | **CLS2702C/D** | Human autologous oral mucosal  epithelial cell sheet | Extensive endoscopic  submucosa dissection (ESD) in  oesophageal cancer. | Japan | **Sakigake**  (February 2017) | Not yet approved |  |
| **STRATAGRAFT** | Allogeneic cultured keratinocytes and dermal fibroblasts in murine collagen- dsat | Indicated to promote durable wound closure & regenerative healing in the treatment of adult patients with debrided thermal burns that contain intact dermal elements, and for which surgical intervention is clinically indicated. | US | **RMAT**  (06 July 2017) | Yes  (15 June 2021) | * Viral clearance/inactivation to demonstrate clearance/inactivation of model viruses (parainfluenza virus type 3, pseudorabies virus and murine minute virus). * Commitment to implement method that can confirm the identity of the NIKS and normal human dermal fibroblast cell banks. * Commitment to develop validated tests that would be stability-indicating and predictive of the capability of the manufacturing process. |

AAV = adeno-associated virus, *SMN* = survival motor neuron, US = United States, EU = European Union, PRIME = PRIority MEdicines, CMC = Chemistry, Manufacturing and Controls, hTERT = human telomerase reverse transcriptase, ALL = acute lymphoblastic leukaemia, DLBCL = diffuse large B-cell lymphoma, REMS = risk evaluation mitigation strategy, ETASU = elements to assure safe use, CRS = cytokine release syndrome, PASS = post-authorisation safety study, PAES = post-authorisation efficacy study, CSR = clinical study report, MCL = mantle cell lymphoma, MAH = Marketing Authorisation Holder, BTK = Bruton tyrosine kinase, LVV = lentiviral vector, CAR = chimeric antigen receptor, HLH = haemophagocytic lymphohistiocytosis, MAS = macrophage activation syndrome, EGFRt = truncated epidermal growth factor receptor, RMAT = regenerative medicine advanced therapy, TCR = T-Cell Receptor, TDT = transfusion-dependent β-thalassaemia, HLA = human leukocyte antigen, HSCT = haematopoietic stem cell transplantation, cDNA = complementary deoxyribonucleic acid, ALDP = adrenoleukodystrophy protein, TBI = traumatic brain injury, iPSC = induced pluripotent stem cell, ESD = endoscopic submucosa dissection.