SUPPLEMENTARY INFORMATION

Table 1. Clinical trials of cancer immunotherapy using NK cells.

Identifier/ Reference	Status: Active/Completed	Title	Disease	IMPD (IMP: Investigational Medicinal Product Dossier)	Dose /number of doses	Administration route	Number of patients recruited/estimated	Publications	Safety and efficacy results
Krause et al. Clin Cancer Res, 2004	Completed. Phase I	Treatment of colon and lung cancer patients with ex-vivo heat shock protein 70-peptide- activated, autologous natural killer cells: a clinical phase I trial.	Metastatic colorectal cancer and nonsmall cell lung cancer.	Autologous NK cells from mononuclear cells of peripheral blood	(0.001-0.3) $x10^{9}$ cells/dose. From 1 to 4 doses/cycle, from 1 to 6 cycles.	Intravenous	12		No significant toxicity.
Park et al. Clin Cancer Res, 2011	Completed. Phase I	Adoptive transfer of autologous natural killer cells leads to high levels of circulating natural killer cells but does not mediate tumour regression.	Metastatic melanoma, metastatic renal cell carcinoma.	Autologous NK cells from mononuclear cells of peripheral blood	(4.70 ±2.10) $x10^{10}$ cells	Intravenous	8		No significant toxicity.
NCT00717184	Completed. Phase I	A Pilot Study of Autologous Ex Vivo Activated NK Cell Infusion in the Treatment of Metastatic Nasopharyngeal Carcinoma	Metastatic nasopharyngeal cancer	Autologous NK cells from mononuclear cells of peripheral blood		Intravenous		There are no published results	There are no published results
NCT00720785	Active. Recruiting patients. Phase I	Safety and the Anti-Tumour Effects of Escalating Doses of Adoptively Infused Ex Vivo Expanded Autologous Natural Killer (NK) Cells Against Metastatic Cancers or Hematological Malignancies Sensitized to NK TRAIL Cytotoxicity with Bortezomib	Metastatic tumours. Hematologic malignancies.	Autologous NK cells from mononuclear cells of peripheral blood		Intravenous		There are no published results	There are no published results
NCT00909558	Suspended. Phase I	A Phase I Open Label, Single Site, Safety and Efficacy Study of the Effects of Autologous Natural Killer and Natural Killer T Cell Immunotherapy on Malignant Disease	Breast cancer, Hepatocellular cancer, squamous cell lung cancer, pancreatic cancer, colon cancer, prostate cancer	Autologous NK cells from mononuclear cells of peripheral blood		Intravenous	24	There are no published results	There are no published results

Iliopoulou et al. Cancer Immunol Immunother 2010		A phase I trial of adoptive transfer of allogenic natural killer cells in patients with advanced non-small cell lung cancer.	Advanced stage nonsmall cell lung cancer	Allogeneic NK cells from mononuclear cells of peripheral blood.	(0.2-29) x10^6 cells/kg/dose. From 2 to 4 doses	Intravenous	15		Clinically effective. No significant toxicity.
NCT00187096	Completed. Phase I	Pilot Study of Haplo-Identical Natural Killer Cell Transplantation for Acute Myeloid Leukemia	Acute myeloid leukemia	Allogeneic NK cells from mononuclear cells of peripheral blood.		Intravenous	49	Rubnitz JE, Inaba H, Ribeiro RC, Pounds S, Rooney B, Bell T, Pui CH, Leung W. NKAML: a pilot study to determine the safety and feasibility of haploidentical natural killer cell transplantation in childhood acute myeloid leukemia. J Clin Oncol. 2010 Feb 20;28(6):955-9	Successful graft. The nonhematologic toxicity was not significant. There were no cases of graft-versus-host disease.
NCT00383994	Completed. Phase I	Immunotherapy with NK Cell, Rituximab and Rhu-GMCSF in Non-Myeloablative Allogeneic Stem Cell Transplantation	Lymphoma, leukemia, stem cell transplantation	Allogeneic NK cells from mononuclear cells of peripheral blood.		Intravenous	6	There are no published results	There are no published results
NCT00586690	Completed. Phase I	Safety Trial of Natural Killer (NK) Cell Donor Lymphocyte Infusions (DLI) From 6/6 Human Leukocyte Antigen (HLA) Matched Family Member Following Nonmyeloablative Allogeneic Stem Cell Transplantation (ASCT)	Lymphoma	Allogeneic NK cells from mononuclear cells of peripheral blood.	1x10^7 cells/kg.	Intravenous	47	Rizzieri DA, Storms R, Chen DF, Long G, Yang Y, Nikcevich DA, Gasparetto C, Horwitz M, Chute J, Sullivan K, Hennig T, Misra D, Apple C, Baker M, Morris A, Green PG, Hasselblad V, Chao NJ. Natural killer cell-enriched donor lymphocyte infusions from A 3-6/6 HLA matched family member following nonmyeloablative allogeneic stem cell transplantation. Biol	Improvement of immunologic recovery. No evidence of toxicity.

								Blood Marrow Transplant. 2010 Aug;16(8):1107-14.	
NCT00640796	Completed. Phase I	Pilot Study of Expanded, Activated Haploidentical Natural Killer Cell Infusions for Non-B Lineage Hematologic Malignancies and Solid Tumours	Acute myeloid leukemia. Acute lymphocytic leukemia. Juvenile T-cell myelomonocytic leukemia. Lymphoblastic lymphoma. Myelodysplastic syndrome	Allogeneic NK cells from mononuclear cells of peripheral blood.		Intravenous	22	There are no published results	There are no published results
NCT00660166	Completed. Phase I	HLA Class I Haplotype Mismatched Natural Killer Cell Infusions After Autologous Stem Cell Transplant for Hematological Malignancies	Lymphoma, myeloma, leukemia.	Allogeneic NK cells from mononuclear cells of peripheral blood.		Intravenous	13	There are no published results	There are no published results
NCT00697671	Completed. Phase I	Pilot Study of Haploidentical Natural Killer Cell Infusions for Poor Prognosis Non-AML Hematologic Malignancies	Acute lymphoblastic leukemia, Chronic myeloid leukemia, Juvenile myelomonocytic leukemia, myelodysplastic syndrome, non-Hodgkin's lymphoma.	Allogeneic NK cells from mononuclear cells of peripheral blood.		Intravenous	48	There are no published results	There are no published results
NCT00799799	Unknown. Phase I	Adoptive Immunotherapy of High Risk Acute Myeloblastic Leukemia Patients Using Haploidentical KIR Ligand-mismatched Natural Killer Cells	Acute myeloid leukemia	Allogeneic NK cells from mononuclear cells of peripheral blood.	(1-5) x10^{b} cells/kg	Intravenous	13	Curti A, Ruggeri L, D'Addio A, Bontadini A, Dan E, Motta MR, Trabanelli S, Giudice V, Urbani E, Martinelli G, Paolini S, Fruet F, Isidori A, Parisi S, Bandini G, Baccarani M, Velardi A, Lemoli RM. Successful transfer of alloreactive haploidentical KIR ligand-mismatched	No evidence of toxicity. There were no cases of graft-versus-host disease.

								natural killer cells after infusion in elderly high risk acute myeloid leukemia patients. Blood. 2011 Sep 22;118(12):3273-9.	
NCT00877110	Active. Phase I	Phase I Study of Anti-GD2 3F8 Antibody and Allogeneic Natural Killer Cells for High-Risk Neuroblastoma	Neuroblastoma	Allogeneic NK cells from mononuclear cells of peripheral blood.		Intravenous	72	There are no published results	There are no published results
NCT00995137	Completed. Phase I	Pilot Study of Genetically Modified Haploidentical Natural Killer Cell Infusions for B-Lineage Acute Lymphoblastic Leukemia	Acute lymphoblastic leukemia	Allogeneic NK cells from mononuclear cells of peripheral blood.		Intravenous	14	There are no published results	There are no published results
NCT01212341	Completed. Phase I	A Phase I Study of Allogeneic NK Cell Therapy in Patients with Refractory/Relapsed Lymphoma or Solid Tumour	Lymphomas, solid tumours	Allogeneic NK cells from mononuclear cells of peripheral blood.	Infusion of single dose: Cohort 1: $1x10^6$ cells/kg; Cohort 2: $1x10^7$ cells/kg; Infusion of multiple doses: Cohort 3: $1x10^6$ cells/kg; Cohort 5: $1x10^7$ cells/kg; Cohort 6: $3x10^7$ cells/kg.	Intravenous	18	There are no published results	There are no published results
NCT01287104	Active. Recruiting patients. Phase I	A Phase I Study of NK Cell Infusion Following Allogeneic Peripheral Blood Stem Cell Transplantation from Related or Matched Unrelated Donors in Pediatric Patients with Hematologic Malignancies	Leukemia, Lymphoma, neuroblastoma, sarcoma,	Allogeneic NK cells from mononuclear cells of peripheral blood.	$1x10^5$ cells/kg $1x10^6$ cells/kg $1x10^7$ cells/kg	Intravenous	86	There are no published results	There are no published results

NCT01576692	Active. Not recruiting. Phase I	A Safety/Feasibility Trial of the Addition of the Humanized Anti-GD2 Antibody (hu14.18K322A) With and Without Natural Killer Cells to Chemotherapy in Children and Adolescents with Recurrent/Refractory Neuroblastoma.	Neuroblastoma	Allogeneic NK cells from mononuclear cells of peripheral blood.	Minimum: $0.1x10^6$ cells/kg. Maximum: $400x10^6$ $CD45^+$ cells/kg, in single dose.	Intravenous	20	There are no published results	There are no published results
NCT01619761	Active. Phase I	Natural Killer Cells in Allogeneic Cord Blood Transplantation	Chronic lymphocytic leukemia	Allogeneic NK cells from mononuclear cells of peripheral blood.	(3-7) $x10^8$ cells.	Intravenous	13	There are no published results	There are no published results
NCT00303667	Completed. Phase I/II	Reduced Intensity Haploidentical Hematopoietic Stem Cell Transplantation (HSCT) Supplemented with Donor Natural Killer (NK) Cell Infusions in Patients with High Risk Myeloid Malignancies Who Are Unsuitable for Fully Myeloablative Transplantation	Acute myeloid leukemia	Allogeneic NK cells from mononuclear cells of peripheral blood.	(2-3) $x10^7$ cells/kg	Intravenous	50	There are no published results	There are no published results
NCT00625729	Completed. Phase I/II	MT2007-12 Allogeneic Natural Killer Cells with Rituximab in Patients with CD20 Positive Relapsed Non-Hodgkin Lymphoma or Chronic Lymphocytic Leukemia. Strategies to Increase Sensitivity of CLL Tumour Cells to Natural Killer Cell-Immune-Mediated Cytolysis	Lymphoma. Leukemia	Allogeneic NK cells from mononuclear cells of peripheral blood.	(1.5-8) $x10^7$ NK cells/kg	Intravenous	6	There are no published results	There are no published results

NCT00823524	Completed. Phase I/II	Donor NK Cell Infusion for Progression/Recurrence of Underlying Malignant Disorders After HLA-haploidentical HCT - a Phase 1-2 Study	Central nervous system tumours. Chronic myeloproliferative disorders. Leukemia. Lymphoma. Lymphoproliferative disorder. Multiple myeloma. Myeloproliferative/ myelodysplastic neoplasia syndromes	Allogeneic NK cells from mononuclear cells of peripheral blood.		Intravenous	47	There are no published results	There are no published results
NCT00846833	Completed. Phase I/II	Phase I/II Study of Haploidentical Natural Killer Cell Infusion in Patients with Refractory or Relapsed Malignant Melanoma	Melanoma	Allogeneic NK cells from mononuclear cells of peripheral blood.		Intravenous	12	There are no published results	There are no published results
NCT01040026	Active. Recruiting patients. Phase I/II	A Phase I/II Single Center Study to Assess Tolerability and Feasibility of Infusions of Allogeneic Expanded Haploidentical Natural Killer (NK) Cells in Patients Treated with High Dose Melphalan Chemotherapy and Autologous Stem Cell Transplantation for a Multiple Myeloma	Multiple myeloma	Allogeneic NK cells from mononuclear cells of peripheral blood.	($1.5x10^6$ cells/kg; $1.5x10^7$ cells/kg and $1x10^8$ cells/kg); if the doses are safe, the therapy continues with a maximum of 7 doses of $1x10^8$ cells/kg.	Intravenous	10	There are no published results	There are no published results
NCT01220544	Unknown	Transplantation of Hematopoietic Stem Cells and Infusion of CD56+CD3- NK Cells from Haploidentical Donors for Patients with Hematological Malignancies	Acute myeloid leukemias. Advanced hematologic neoplasms. Indication for allogeneic stem cell transplantation without HLA-identical donor available.	Allogeneic NK cells from mononuclear cells of peripheral blood.	$1x10^7$ cells/kg	Intravenous	30	There are no published results	There are no published results

NCT01337544	Completed. Phase I/II	Haploidentical Stem Cell Transplantation and IL-15 NK Cell Infusion for Paediatric Refractory Solid Tumours	Pediatric solid tumours	Allogeneic NK cells from mononuclear cells of peripheral blood.		Intravenous	6	Pérez-Martínez A, de Prada Vicente I, Fernández L, González-Vicent M, Valentín J, Martín R, Maxwell H, Sevilla J, Vicario JL, Díaz MÁ. Natural killer cells can exert a graft-vs-tumour effect in haploidentical stem cell transplantation for pediatric solid tumours.	Beneficial effect of haploidentical stem cells transplantation in refractory solid tumours. Safety: 50% of the patients (3 of 6) developed acute degree I-II GVHD. One patient developed severe acute GVHD. Two patients developed chronic GVHD. One patient died due to acute severe intestinal GVHD.
NCT01386619	Active but not recruiting patients. Phase I/II	Natural Killer Cell Selected T-cell Depleted Donor Lymphocyte Infusions (NK-DLI) in Patients After HLA-haploidentical Allogeneic Stem Cell Transplantation	Acute myeloid leukemia, myelodysplastic syndromes, lymphoma, neuroblastoma, rhabdomyosarcoma.	Allogeneic NK cells from mononuclear cells of peripheral blood.	≥1x10^{7} NK cells/kg	Intravenous	15	Stern M, Passweg JR, Meyer-Monard S, Esser R, Tonn T, Soerensen J, Paulussen M, Gratwohl A, Klingebiel T, Bader P, Tichelli A, Schwabe D, Koehl U. Pre-emptive immunotherapy with purified natural killer cells after haploidentical SCT: a prospective phase II study in two centers. Bone Marrow Transplant. 2013 Mar;48(3):433-8.	When compared with the historic controls, infusions of NK cells had no apparent effect on the graft failure rates or relapse. The adoptive transfer of allogeneic NK cells is safe and feasible, but more studies are needed to determine the optimal dosage and moment for the NK cell therapy. Moreover, NK cell activation/expansion might be necessary to achieve a clinical benefit.
NCT01520558	Active. Recruiting patients. Phase I/II	A Phase 1/2 Study of CNDO-109-Activated Allogeneic Natural Killer Cells in Patients with High Risk Acute Myeloid Leukemia in First Complete Remission (CR1)	Acute myeloid leukemia.	Allogeneic NK cells from mononuclear cells of peripheral blood.	1x10^{6} NK cells/kg or 3x10^{6} cells/kg.	Intravenous	33	There are no published results	There are no published results

Geller et al. Cytotherapy. 2011	Completed. Phase II	A phase II study of allogeneic natural killer cell therapy to treat patients with recurrent ovarian and breast cancer.	Ovarian cancer, Breast cancer.	Allogeneic NK cells from mononuclear cells of peripheral blood.	(8.33-39.41) x10^6 NK cells/kg	Intravenous	20	Geller MA, Cooley S, Judson PL, Ghebre R, Carson LF, Argenta PA, Jonson AL, Panoskaltsis-Mortari A, Curtsinger J, McKenna D, Dusenbery K, Bliss R, Downs LS, Miller JS. A phase II study of allogeneic natural killer cell therapy to treat patients with recurrent ovarian and breast cancer. Cytotherapy. 2011 Jan;13(1):98-107.	Partial response: 4 patients. Stabilization of the disease: 12 patients. Disease progression: 3 patients.
NCT00186875	Active. Not recruiting patients. Phase II	A Study of Therapy for Pediatric Relapsed or Refractory Acute Lymphoblastic Leukemia	Acute lymphoblastic leukemia, lymphoma.	Allogeneic NK cells from mononuclear cells of peripheral blood.		Intravenous	47	There are no published results	There are no published results
NCT00328861	Completed. Phase II	Phase II Study in Metastatic Melanoma or Kidney Cancer Using Autologous Natural Killer Cells Plus Aldesleukin (IL-2) Following a Lymphodepleting Chemotherapy	Metastatic melanoma. Metastatic renal cell carcinoma.	Allogeneic NK cells from mononuclear cells of peripheral blood.		Intravenous	8	There are no published results	There are no published results
NCT00376805	Completed. Phase II	Allogeneic Natural Killer Cells in Patients with Advanced Metastatic Breast Cancer	Breast cancer	Allogeneic NK cells from mononuclear cells of peripheral blood.	(1.5-8.0) x10^7 NK cells/kg	Intravenous	6	There are no published results	There are no published results

NCT00526292	Completed. Phase II	Phase II Trial of HLA Haploidentical Natural Killer Cell Infusion for Treatment of Relapsed or Persistent Leukemia Following Allogeneic Hematopoietic Stem Cell Transplant	Leukemia, myelodysplastic syndromes	Allogeneic NK cells from mononuclear cells of peripheral blood.		Intravenous	12	There are no published results	There are no published results
NCT00652899	Completed. Phase II	MT2007-19R: WCC #53 Allogeneic Natural Killer Cells in Patients with Recurrent Ovarian Cancer, Fallopian Tube, and Primary Peritoneal Cancer	Fallopian tube cancer, ovarian cancer, peritoneal cancer.	Allogeneic NK cells from mononuclear cells of peripheral blood.	(1.5-8.1) x10^7 NK cells/kg	Intravenous	14	There are no publications.	Safety analysis: SAEs were reported in 9 of the 14 patients.
NCT00698009	Completed. Phase II	Study to Infuse Haploidentical Natural Killer Cells in Patients with Relapsed or Refractory Neuroblastoma	Neuroblastoma	Allogeneic NK cells from mononuclear cells of peripheral blood.		Intravenous	1	There are no publications.	There are no publications.
NCT00941928	Completed. Phase II	Adoptive Transfer of Haploidentical NK Cells in Combination with Epratuzumab for the Treatment of Relapsed Acute Lymphoblastic Leukemia	Leukemia, pediatric tumours	Allogeneic NK cells from mononuclear cells of peripheral blood.		Intravenous	2	There are no publications.	There are no publications.

NCT01105650	Completed. Phase II	Lymphodepleting Chemotherapy and T-Cell Suppression Followed by Allogeneic Natural Killer Cells and IL-2 in Patients with Recurrent Ovarian, Fallopian Tube, Primary Peritoneal Cancer and Advanced Metastatic Breast Cancer (MT2009-30)	Fallopian tube cancer, ovarian cancer, primary peritoneal cancer, breast cancer.	Allogeneic NK cells from mononuclear cells of peripheral blood.	$8.0x10^{7}$ cells/kg	Intravenous	13	There are no publications.	There are no publications.
NCT01106950	Completed. Phase II	Adoptive Transfer of Haploidentical Natural Killer Cells to Treat Refractory or Relapsed AML MT2010-02	Acute myeloid leukemia	Allogeneic NK cells from mononuclear cells of peripheral blood.	$\leq 8.0x10^{7}$ nucleated cells/kg	Intravenous	15	Bachanova V, Cooley S, Defor TE, Verneris MR, Zhang B, McKenna DH, Curtsinger J, Panoskaltsis-Mortari A, Lewis D, Hippen K, McGlave P, Weisdorf DJ, Blazar BR, Miller JS. Clearance of acute myeloid leukemia by haploidentical natural killer cells is improved using IL-2 diphtheria toxin fusion protein. Blood. 2014 Jun 19;123(25):3855-63	Efficacy: 53% of the patients showed full remission of the disease. 33% showed disease-free survival evaluated at 6 months after completing the therapy. Safety: 12 of the 15 patients had an SAE, 33% due to hematological abnormalities. In terms of AEs, 100% had grade I pulmonary infiltrates.
NCT01181258	Active. Recruiting patients. Phase II	Lymphodepleting Chemotherapy with Rituximab and Allogeneic Natural Killer Cells for Patients with Refractory Lymphoid Malignancies (MT2009-15)	Non-Hodgkin's lymphoma, Chronic lymphocytic leukemia.	Allogeneic NK cells from mononuclear cells of peripheral blood.	(1.5-8.0) $x10^{7}$ cells/kg	Intravenous	34	There are no publications.	There are no publications.
NCT01370213	Active. Recruiting patients. Phase II	Multi-Center Phase II Trial of NK Cell Based Non-Myeloablative Haploidentical Transplantation for Patients with High-Risk Acute Myeloid Diseases	Acute myeloid leukemia, myelodysplastic syndrome	Allogeneic NK cells from mononuclear cells of peripheral blood.		Intravenous	43	There are no publications.	There are no publications.

NCT01390402	Completed. Phase II	Natural Killer (NK) Cells and Nonmyeloablative Stem Cell Transplantation for Chronic Myelogenous Leukemia (CML)	Leukemia, chronic myeloid leukemia	Allogeneic NK cells from mononuclear cells of peripheral blood.		Intravenous	6	There are no publications.	There are no publications.
NCT01593670	Active. Not recruiting patients. Phase II	Decitabine and Vorinostat With CD3/CD19 Depleted Haploidentical Donor Natural Killer (NK) Cells for the Treatment of High-Risk Myelodysplastic Syndromes (MDS)	Myelodysplastic syndrome	Allogeneic NK cells from mononuclear cells of peripheral blood.		Intravenous	46	There are no publications.	There are no publications.
2013-003421-28	Active. Phase II	Randomised controlled phase-2 trial to determine the efficacy of adoptive immunotherapy with haploidentical natural killer cells in high-risk acute myeloid leukemia	Recently diagnosed high-risk AML and acute promyelocytic leukemia, ≥20% of blast cells	NK cells-CD3 negative / CD56-positive of HLA-haploidentical family donors.		Intravenous	56	There are no publications.	There are no publications.
2011-001514-34	Active.	Infusion of IL-15 activated NK cells after allogeneic stem cell transplantation in children transplanted for relapsed/refractory leukemia: a feasibility study	Acute leukemia in relapse	NK cells activated with IL-15	$10x10^6$ cells/kg	Intravenous	12	There are no publications.	There are no publications.

2011-003181-32	Completed	In vivo expansion and efficacy of adoptive natural killer cell-based immunotherapy for high-risk myeloid diseases	Acute myeloid leukemia and myelodysplastic syndrome	Activated NK cells		Intravenous	12	Björklund AT, Carlsten M, Sohlberg E, Liu LL, Clancy T, Karimi M, Cooley S, Miller JS7, Klimkowska M8, Schaffer M2, Watz E9, Wikström K10, Blomberg P10,11, Wahlin BE, Palma M, Hansson L, Ljungman P, Hellström-Lindberg E, Ljunggren HG, Malmberg KJ. Complete Remission with Reduction of High-Risk Clones following Haploidentical NK-Cell Therapy against MDS and AML. Clin Cancer Res. 2018 Apr 15;24(8):1834-1844	Efficacy: Six patients achieved objective responses with complete remission (CR), marrow CR, or partial remission (PR). Five patients proceeded to allogeneic hematopoietic stem cell transplantation (HSCT). Three patients are still free from disease >3 years after treatment. Safety: The NK-cell infusions were well tolerated with transient (<6 hours) grade 3-4 toxicities, including chills and nausea, observed in 2 out of 16 patients.
2012-005146-38	Active.	"LANK-2": IMMUNOTHERAPY WITH ACTIVATED AND EXPANDED NATURAL KILLER CELLS ALONG WITH SALVAGE CHEMOTHERAPY IN CHILDREN, ADOLESCENTS AND YOUNG ADULTS WITH ACUTE LEUKEMIA IN RELAPSE OR REFRACTORINESS	ACUTE LEUKEMIA IN RELAPSE OR REFRACTORINESS	Haploidentical allogeneic adult differentiated NK cells from peripheral blood, expanded and activated with IL-15		Intravenous	10	There are no publications.	There are no publications.
2012-000054-63	Active	Salvage therapy with chemotherapy and Natural Killer cells in relapsed/refractory paediatric T cell lymphoblastic leukaemia and lymphoma.	REFRACTORY LEUKEMIA/T LYMPHOMA in children	NK cells	≥50,000,000	Intravenous	16	There are no publications.	There are no publications.