Virtuelle Jahrestagung 2020 – Best Abstracts

274 - FLYSYN: Ergebnisse der Erstanwendungsstudie des Fc-optimierten FLT3 Antikörper FLYSYN zur Behandlung der akuten myeloischen Leukämie mit minimaler Resterkrankung / Phase I trial of the Fc-optimized FLT3 antibody FLYSYN in acute myeloid leukemia (AML) patients with measurable residual disease

Preisträger - Anneliese Gaebel-Preis

Heitmann J.S.*[1], Dörfel D.[1,2], Kayser S.[3,4], Döhner K.[5], Heuser M.[6], Thol F.[6], Kapp-Schwoerer S.[5], Bethge W.[2], Große-Hovest L.[7], Steiner M.[7], Märklin M.[1], Walz J.[1,2], Schlenk R.[8,9], Jung G.[10], Salih H.[1]

[1]Clinical Collaboration Unit Translational Immunology, German Cancer Consortium (DKTK), University Hospital Tübingen, Tübingen, Germany, [2] Department of Hematology and Oncology, University Hospital Tübingen, Tübingen, Germany, [3]Department of Hematology, University Hospital of Leipzig, Leipzig, Germany, [4]German Cancer Research Center (DKFZ), Heidelberg, Germany, [5]Department of Internal Medicine III, University Hospital of Ulm, Ulm, Germany, [6]Department of Hematology, Hemostasis, Oncology, and Stem Cell Transplantation, Hannover Medical School, Hannover, Germany, [7]Synimmune GmbH, Tübingen, Germany, [8]National Center for Tumor Diseases, Heidelberg, Germany, [9]Department of Internal Medicine V, University Hospital of Heidelberg, Heidelberg, Germany, [10]Department for Immunology, Eberhard Karls University, Tübingen, Germany

Upon achievement of complete remission (CR), roughly half of AML patients display measurable residual disease (MRD) and eventually relapse. FLT3/CD135 is a highly selective target antigen for immunotherapy expressed on AML cells in almost all patients, whereas expression on healthy tissues is limited to low levels on dendritic cells, monocytes and progenitor cells. Here we report the results of an open-label, single-arm, first in man multicenter trial (recruitment March 2017 to March 2020) evaluating safety/tolerability and efficacy of the Fc-optimized FLT3 antibody FLYSYN in patients with AML (NCT02789254). Morphological CR with stable or increasing MRD in two sequential measurements using central RT-qPCR and/or NGS constituted the main inclusion criterion. FLYSYN was administered i.v. over 3 h (cohort 1-5: single application of 0.5 mg/m², 1.5 mg/m², 5 mg/m², 15 mg/m², 45 mg/m²; cohort 6: 15 mg/m² on day 1, 15 and 29). Three patients were treated per cohort except for cohorts 4 and 6, which were expanded to 9 and 10 patients, respectively. Response was defined as ≥1 log MRD reduction or negativity in bone marrow (BM). 31 patients (median age 58 years; range, 21-80 years; 20 (65%) females) were enrolled, of which 27, 3 and 1 were MRD positive for mutated *NPM1*, mutated *IDH2* and *RUNX1-RUNX1T1*, respectively. The half-life of FLYSYN was estimated to be 6.5 days. In 8 patients (26%), a transient decrease of neutrophil count (2 adverse event (AE) grade 3, others ≤ grade 2) was observed. Of note, in the so far analyzed subset of patients (n=24), no relevant effect on stem cell reserve as assessed by CFU assays was detected. No other AEs ≥ grade 3 or dose-limiting toxicity were observed. The most frequent AEs were unspecific and comprised fatigue and flu like symptoms (12%), musculoskeletal symptoms (8%) and laboratory abnormalities (42%). Overall, molecular response to treatment was achieved in

11/31 patients (35%), with so far two patients achieving MRD negativity documented one year after treatment. Upon application of 45 mg/m² FLYSYN (in total, single or repetitive dosing), objective responses were achieved in 46% (6/13) of the patients, whereas 28% (5/18) responded to treatment with lower doses. The results of our phase I trial demonstrate that FLYSYN is safe and very well tolerated as monotherapy in AML patients with molecular MRD. Early efficacy data are promising and warrant further evaluation in an up-coming phase II clinical trial.

483 - PET adaptierter Verzicht auf Radiotherapie beim intermediären Hodgkin Lymphom: Ergebnisse der HD17- Studie der German Hodgkin Study Group / Positron emission tomography guided omission of radiotherapy in early-stage unfavorable Hodgkin Lymphoma: Final results of the international, randomized Phase III HD17 trial by the German Hodgkin Study Group

Borchmann P.[1], Kobe C.[2], Plütschow A.[3], Greil R.[4], Meissner J.[5], Topp M.S.[6], Ostermann H.[7], Dierlamm J.[8], Mohm J.[9], Thiemer J.[10], Sökler M.[11], Kerkhoff A.[12], Ahlborn M.[13], Halbsguth T.[14], Martin S.[15], Keller U.[16], Balabanov S.[17], Pabst T.[18], Vogelhuber M.[19], Hüttmann A.[20], Wilhem M.[21], Zijlstra J.M.[22], Moccia A.[23], Bröckelmann P.J.[24], von Tresckow B.[25], Fuchs M.[25], Eich H.[26], Baues C.[27], Hallek M.[28], Diehl V.[29], Dietlein M.[30], Engert A.[31]

[1]University of Cologne, Department I of Internal Medicine and Center of Integrated Oncology Aachen, Bonn, Cologne, Düsseldorf, German Hodgkin Study Group, Faculty of Medicine and University Hospital of Cologne, Cologne, Germany, [2]Faculty of Medicine and University Hospital Cologne, University Hospital of Cologne, Department of Nuclear Medicine, Cologne, Germany, [3]University Hospital of Cologne, German Hodgkin Study Group (GHSG) and Department I of Internal Medicine, Cologne, Germany, [4]IIIrd Medical Department, Paracelcus Medical University and Salzburg Cancer Research Institute and AGMT (Arbeitsgemeinschaft Medikamentöse Tumortherapie, Salzburg, Austria, [5]Medicine V, University of Heidelberg, Heidelberg, Germany, [6]Medizinische Klinik und Poliklinik II, Universitätsklinikum Würzburg, Würzburg, Germany, [7]LMU, University Hospital of Munich, Munich, Germany, [8]Department of Oncology and Hematology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [9]Onkopraxis Dresden, Dresden, Germany, [10]Department of Hematology and Oncology, Klinikum der Philipps-Universität Marburg, Marburg, Germany, [11]Innere Medizin II, University Hospital Tübingen, Tübingen, Germany, [12]Medizinische Klinik A, University Hospital Muenster, Muenster, Germany, [13]Medizinische Klinik III, Städtisches Klinikum Braunschweig, Braunschweig, Germany, [14]Department of Medicine II, Hematology/ Oncology, Goethe University Hospital, Frankfurt/M., Frankfurt, Germany, [15]Department of Hematology and Oncology, Robert-Bosch-Hospital, Stuttgart, Germany, [16]Klinikum rechts der Isar der TU München, München, Germany, [17]Department of Medical Oncology and Hematology, University Hospital Zurich, Zurich, Switzerland, [18]Department of Medical Oncology, Institute of Medical Oncology, Berne, Switzerland, [19]Klinik und Poliklinik für Innere Medizin III, Universitätsklinik Regensburg, Regensburg, Germany, [20]Department of Hematology, University Hospital of Essen, Essen, Germany, [21]Klinikum Nurnberg, Nurnberg, Germany, Nurnberg, Germany, [22]Department of Hematology, Amsterdam UMC, Vrije Universiteit Amsterdam, Cancer Center Amsterdam, Amsterdam, Netherlands, [23]Oncology Institute of Southern Switzerland, Bellinzona, Switzerland, [24]German Hodgkin Study Group (GHSG) and Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Düsseldorf (CIO ABCD), University of Cologne, Cologne, Germany, [25]German Hodgkin Study Group (GHSG) and Department I of Internal Medicine, Center of Integrated Oncology Aachen Bonn Cologne Düsseldorf (CIO ABCD), University of Cologne, Cologne, Germany, [26]Department of Radiotherapy, University Hospital of Muenster, Muenster, Germany, [27]Department of Radiooncology and Cyberknife Center, Faculty of Medicine and University Hospital Cologne, University Hospital Cologne, Cologne, Germany, [28]Department I of Internal Medicine and Center of Integrated Oncology Aachen, Bonn, Cologne, Düsseldorf, German CLL Study Group, Faculty of Medicine and University Hospital of Cologne, University of Cologne, Cologne, Germany, [29]German Hodgkin Study Group (GHSG), University of Cologne, Cologne, Germany, [30]Department of Nuclear Medicine, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany, [31]German Hodgkin Study Group (GHSG), Germany and Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Düsseldorf (CIO ABCD), Faculty of Medicine and University Hospital of Cologne, University of Cologne, Cologne, Germany

Introduction: Combined-modality treatment (CMT) comprising of chemotherapy (CTx) followed by radiotherapy (RT) is standard of care for patients with early-stage unfavorable Hodgkin lymphoma (HL). Overall, this strategy yields a good primary cure rate, but the use of

radiotherapy raises concern about long-term sequelae. We asked in the current HD17 study, whether radiotherapy can be safely omitted in patients achieving a complete metabolic response after chemotherapy.

Methods: 1100 patients with newly diagnosed, early-stage unfavorable HL were included in this international, randomized phase III trial. Patients were assigned to CMT with 4 cycles of chemotherapy followed by 30Gy involved-field RT or PET-guided treatment, omitting RT in iPET-negative patients (DS, Deauville score, < 3). Primary objectives were (1) non-inferiority of the iPET-guided strategy in a per protocol (PP) analysis of both treatment groups and (2) to confirm iPET positivity (DS ≥3) as a risk factor in an intention-to-treat (ITT) analysis.

Results: Of 979 patients with confirmed iPET result, 651 (66.5%) were iPET-negative, 238 (24.3%) had DS3, and 90 (9.2%) DS4. In the standard CMT group (PP, n=428), 5-year PFS was estimated at 97.3% (95% CI, 94.5% to 98.7%), as compared to 95.1% (95% CI, 92.0% to 97.0%) in the iPET-guided treatment group (PP, n=477). The 5-year PFS difference between the two groups was -2.2% (95%-CI, -5.3% to 0.9%), excluding the lower margin of -8%. In the CMT/CTx+RT group (n=646), 5-year PFS was estimated at 94.2% (95%-CI, 90.1% to 96.6%) for iPET positive patients (n=328) as compared to 97.6% (95%-CI, 94.0% to 99.9%) for iPET-negative patients (n=318). The Hazard ratio for the difference was 3.03 (95% CI, 1.1% to 8.3%) confirming iPET as significant risk factor. The difference was more pronounced when DS4 was used as cut-off for positivity: 5-year PFS rates were 81.6% (95%-CI, 67.9% to 89.9%) for DS4 patients versus 98.1% (95%-CI, 95.9% to 99.1%) in DS1-3 patients.

Conclusion: In early-stage unfavorable HL treated with “2+2” chemotherapy, a positive iPET indicates a risk for treatment failure, particularly for the small proportion of patients (90/979, 9.2%) with DS4. In iPET-negative patients, PFS for patients treated with chemotherapy alone is non-inferior to standard CMT. In conclusion, the iPET-guided individualized treatment approach allows omission of radiotherapy for most patients while maintaining the very high primary cure rate.

619 - Stromales SFRP1 steuert das Verhalten von hämatopoetischen Stammzellen über die PP2A-vermittelte Regulation von CTNNB1 / EP300 / Microenvironmental SFRP1 controls repopulating activity of Hematopoietic Stem Cells via PP2A-mediated regulation of CTNNB1/EP300

Hettler F.[1], Schreck C.[1], Romero Marquez S.[1], Sippenauer T.[1], Koller F.[1], Demir E.[2], Bassermann F.[1], Istvanffy R.[2], Oostendorp R.[1]

[1]Klinikum rechts der Isar der Technischen Universität München, III. Med. Klinik, München, Germany, [2]Klinikum rechts der Isar der Technischen Universität München, II. Med. Klinik, München, Germany

We have previously found that a Sfrp1 knock-out environment fails to support the regeneration of hematopoietic stem cells (HSC) with serial to repopulate secondary recipients (Renström et al., 2009). In order to dissect cell specific requirements of the *Sfrp1* gene we established the $Sfrp1^{flox/flox}$ mouse strain and deleted Sfrp1 gene in $Osterix^{+}$ (Sp7) osteolineage cells. In these Osx-Cre, $Sfrp1^{\Delta/\Delta}$ (OS1Δ/Δ) mice, the number of MSCs is reduced, but these show an increased proportion of colony forming units (CFU-F). Furthermore, stromal cells grown *ex-vivo* show increased senescence-associated b-galactosidase staining. In addition, the CFU-F-derived stromal cells differentiated spontaneously into adipocytes. These findings indicate altered functionality of stromal cells from OS1Δ/Δ mice. In the hematopoietic compartment of these mice, we found a decrease in myeloid progenitors in the bone marrow (BM) with concomitant increase in $CD11b^{+}$ $GR1^{hi}$ granulocytes in peripheral blood. Although the number of primitive $CD34^{-}$ $CD48^{-}$ $CD150^{+}$ HSCs (LT-HSCs) in the BM was unchanged, LT-HSCs from OS1Δ/Δ mice failed to repopulate in wild type recipients. In single cell cultures, we found that LT-HSCs from OS1Δ/Δ mice show decreased proliferation with concomitant increased differentiation into mature myeloid cells, which was associated with increased DNA damage as shown with comet tail assays and staining for gammaH2.AX. On a molecular level, we found that LT-HSCs from OS1Δ/Δ mice show increased CTNNB1 protein levels. CTNNB1 regulates cell differentiation and proliferation of stem cells by binding to Ep300 or CBP respectively (Miyabayashi et al., 2007). Interestingly, CBP protein level was decreased in LT-HSCs from OS1Δ/Δ mice while Ep300 was increased, suggesting overactivation of the CTNNB1/Ep300 axis. Indeed, blocking CTNNB1/Ep300 binding with specific PP2A inhibitor IQ-1, we not only rescued the aberrant behavior of OS1Δ/Δ LT-HSC *in vitro*, but we also restored the repopulating activity of these LT-HSCs *in vivo*. Our results suggest that deletion of stromal SFRP1 diminishes the repopulating activity of LT-HSCs by increasing differentiation through PP2A-mediated dephosphorylation of the phospho-Ep300-binding site with CTNNB1.

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Both last mentioned authors: Joint senior authors

577 - Klinische Ergebnisse nach autologer hematopoetischer Stammzelltransplantation mit betibeglogene autotemcel (beti-cel, LentiGlobin für β-thalassämie) Gentherapie in Phase 3 Nothstar-2 und Northstar-3 Studien in transfusions-abhängiger β-thalassämie (TDT) / Clinical outcomes following autologous hematopoietic stem cell transplantation with betibeglogene autotemcel (beti-cel, LentiGlobin for β-thalassemia) gene therapy in the phase 3 Northstar-2 and Northstar-3 studies for transfusion-dependent β-thalassemia (TDT)

***Kulozik A.E.*[1,2], *Locatelli F.*[3], *Kunz J.*[1,2], *Kwiatkowski J.L.*[4,5], *Thompson A.A.*[6,7], *Yannaki E.*[8], *Sauer M.G.*[9], *Schambach A.*[10], *Schmidt M.*[11], *Porter J.B.*[12], *Thuret I.*[13], *Hongeng S.*[14], *Lal A.*[15], *Thrasher A.J.*[16], *Tao G.*[17], *Liu W.*[17], *Colvin R.A.*[17], *Walters M.C.*[15]**

[1]Department of Pediatric Oncology, Hematology, and Immunology and Hopp-Children's Cancer Research Center (KiTZ), University of Heidelberg, Heidelberg, Germany, [2]Molecular Medicine Partnership Unit (MMPU), European Molecular Biology Laboratory, University of Heidelberg, Heidelberg, Germany, [3]Department of Gene Therapy, IRCCS Bambino Gesù Children's Hospital, Rome, Italy, [4]Department of Pediatrics, University of Pennsylvania Perelman School of Medicine, Philadelphia, United States, [5]Division of Hematology, Children's Hospital of Philadelphia, Philadelphia, United States, [6]Department of Pediatrics (Hematology, Oncology, and Stem Cell Transplantation), Northwestern University Feinberg School of Medicine, Chicago, United States, [7]Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, United States, [8]Gene and Cell Therapy Center of the Hematology Dept /Hematopoietic Cell Transplantation Unit, G. Papanicolaou Hospital, Thessaloniki, Greece, [9]Pediatric Hematology and Oncology, Medizinische Hochschule Hannover, Hannover, Germany, [10]Institut Experimentelle Hämatologie, Medizinische Hochschule Hannover, Hannover, Germany, [11]GeneWerk GmbH, Heidelberg, Germany, [12]Haematology Department, University College London Hospitals, London, United Kingdom, [13]Pediatric Hematology, Hôpital de la Timone, Marseille, France, [14]Mahidol University, Ramathibodi Hospital, Bangkok, Thailand, [15]USCF, Benioff Children's Hospital Oakland, Oakland, United States, [16]UCL Great Ormond Street Institute of Child Health, London, United Kingdom, [17]bluebird bio, Inc., Cambridge, United States

Introduction: In the phase 1/2 Northstar study (HGB-204) of beti-cel, patients achieving transfusion independence (TI) showed improved erythropoiesis and reductions from baseline to 48 months in median serum ferritin (4829 [n=10] to 937 [n=7] pmol/L) and liver iron levels (6.3 [n=11] to 2.0 [n=7] mg/g dw). We present interim phase 3 results of Northstar-2 (NCT02906202; HGB-207; non-β^0/β^0 genotypes) and Northstar-3 (NCT03207009; HGB-212; β^0/β^0, $\beta^0/\beta^{+\text{ IVS-I-110}}$ or $\beta^{+\text{ IVS-I-110}}/\beta^{+\text{ IVS-I-110}}$).

Methods: CD34+ hematopoietic stem cells collected via mobilization/apheresis were transduced with BB305 lentiviral vector, and infused into patients following PK-adjusted, single-agent busulfan myeloablation. Statistics are median (min-max).

Results: As of 03 Mar 2020, 38 patients (25 ≥12 years old) were treated in Northstar-2 and -3, with 19.4 (1.2-36.2) and 14.4 (1.1-24.0) months follow-up.
In Northstar-2, 20/22 patients with ≥6 months follow-up stopped transfusions. 17/19 evaluable patients achieved the primary endpoint (TI: weighted average Hb ≥9 g/dL without RBC transfusions ≥12 months); ongoing TI duration was 19.4 (12.3-31.4) months. Weighted

average Hb during TI was 11.9 (9.4-12.9) g/dL. Gene therapy-derived HbA^{T87Q} (*in patients with no RBC transfusion ≥60 days) was 8.7, 8.9, 9.3 g/dL at Months 6 (n=19), 12 (n=19), 18 (n=15), respectively. Myeloid:erythroid ratios in patients achieving TI were 1:1.2 and 1:1.1 at Months 12 (n=16) and 24 (n=8), vs 1:3 at baseline (n=17), indicating improved erythropoiesis.
In Northstar-3, 11/13 patients have been off transfusions >6 months. Total Hb* and HbA^{T87Q}* were 10.1 (8.5-13.2) and 8.6 (3.8-12.0) g/dL at Month 6 (n=12), and 10.5 (7.9-14.0) and 8.7 (4.4-12.6) g/dL at Month 12 (n=10). 6/8 evaluable patients achieved TI.
Non-hematologic grade ≥3 AEs in ≥3 patients in either study were stomatitis (n=19), febrile neutropenia (n=17), epistaxis (n=6), pyrexia (n=5), veno-occlusive liver disease (n=3). Drug product-related AEs were abdominal pain (n=3), thrombocytopenia (n=3), leukopenia (n=1), neutropenia (n=1), tachycardia (n=1), pain in extremity (n=1). All samples showed polyclonal vector integration.

Conclusions: After beti-cel gene therapy, 20/22 patients (non-β^0/β^0) and 11/13 patients (β^0/β^0, $\beta^0/\beta^{+\text{ IVS-I-110}}$ or $\beta^{+\text{ IVS-I-110}}/\beta^{+\text{ IVS-I-110}}$) with TDT and ≥6 months follow-up have stopped transfusions. 89% and 75% of evaluable patients in Northstar-2 and -3 achieved TI. Safety is consistent with that of single-agent busulfan myeloablation.

302 - Therapie mit CD19-gerichteten chimären Antigen-Rezeptor (CAR) T-Zellen der dritten Generation - Ergebnisse der Heidelberger CAR-1 (HD-CAR-1)-Studie / Treatment with CD19-directed third-generation chimeric antigen receptor (CAR) T cells - results of the Heidelberg trial 1 (HD-CAR-1 Trial)

***Schubert M.-L.*[1], Schmitt A.[1], Neuber B.[1], Hückelhoven-Krauss A.[1], Kunz A.[1], Wang L.1, Gern U.[1], Michels B.[1], Hofmann S.[1], Pavel P.[2], Ho A.D.[1,3], Müller-Tidow C.[1,3], Dreger P.[1,3], Schmitt M.[1,3]**

[1]Universitätsklinikum Heidelberg, Heidelberg, Germany, [2]Institut für Klinische Transfusionsmedizin und Zelltherapie (IKTZ), DRK-Blutspendedienst Baden-Württemberg - Hessen, Heidelberg, Germany, [3]Deutsches Konsortium für Translationale Krebsforschung (DKTK), Heidelberg, Germany

Introduction: HD-CAR-1 is an investigator-initiated phase I/II trial designed to study the safety and feasibility of a third-generation CD19 CAR construct (SFG.CD19.CD28-4-1BBzeta) comprising the costimulatory domains CD28 and 4-1BB (CD137). Leukapheresis, manufacturing and administration of CAR T cells (CARTs), patient monitoring and follow-up of HD-CAR-1 are performed in-house.

Methods: Patients with relapsed or refractory (r/r) acute lymphoblastic leukemia (ALL) or r/r non-Hodgkin lymphoma (NHL) including chronic lymphocytic leukemia (CLL), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL) or mantle cell lymphoma (MCL) were eligible. HD-CAR-1 evaluated escalating CART doses (1-20×10^6 CARTs/m^2) after lympho-depletion with fludarabine and cyclophosphamide (90 mg/m^2 and 1500 mg/m^2, respectively). Patients were monitored for cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS) and other toxicities. In vivo function, survival and anti-tumor efficacy of CARTs were assessed.

Results: 22 patients have been enrolled and 19 patients (9 adult ALL patients, 2 CLL, 3 MCL, 4 DLBCL, 1 FL) have received CARTs (6 patients 10^6 CARTs/m^2; 6 patients 5×10^6 CARTs/m^2; 7 patients 20×10^6 CARTs/m^2). CART production was successful for all patients enrolled. Two patients did not receive treatment due to progression or uncontrolled hepatitis B infection. One patient is awaiting treatment. Two patients developed CRS ≥ III°. Both patients were treated with tocilizumab, one additionally with steroids. No ICANS ≥ III° was observed. CARTs were detectable in the peripheral blood (PB) of 18 of 19 analyzed patients. Overall response rate (ORR) of treated patients was 63%, with 42% achieving a complete response (CR). With regards to disease entities, ALL patients reached an ORR of 77% (all CRs) with 66% displaying MRD-negativity. An ORR of 50% was achieved in the NHL cohort. Response was associated with a higher CART dose as 79% of patients treated with 20×10^6 CARTs/m^2 responded to treatment. For dose levels I (10^6 CARTs/m^2) and II (5×10^6 CARTs/m^2) responses were achieved in 66% and 50% of patients, respectively.

Conclusion: Leukapheresis and third-generation CART manufacturing were effective for all enrolled patients. Particularly ALL patients responded to treatment in a dose-dependent manner. HD-CAR-1 CART product appeared efficient even at low dose levels and displayed an excellent safety profile.

202 - Entrectinib bei NTRK-Fusions-positivem Sarkom: Integrierte Analyse der STATRK-2, STARTRK-1 und ALKA-372-001 Studien / Entrectinib in *NTRK* fusion-positive sarcoma: integrated analysis of patients enrolled in STATRK-2, STARTRK-1 and ALKA-372-001

***Wolf J.*[1], Liu S.V.[2], Paz-Ares L.[3], Hu J.[4], Cho B.C.[5], Krzakowski M.[6], Chung C.H.[7], Patel M.[8], Taylor M.[9], Zeuner H.[10], Aziez A.[10], Huang X.[11], Osborne S.[10], Farago A.[12]**

[1]Center for Integrated Oncology, University Hospital of Cologne, Cologne, Germany, [2]Georgetown University, Washington, United States, [3]Hospital Universitario 12 de Octubre, Madrid, Spain, [4]University of Southern California/Norris Cancer Center, Los Angeles, United States, [5]Yonsei University/Yonsei Cancer Center, Seoul, Korea, Republic of, [6]Maria Skłodowska-Curie Institute of Oncology, Warsaw, Poland, [7]Moffitt Cancer Center Magnolia Campus, Tampa, United States, [8]University of Minnesota, Department of Medicine, Minneapolis, United States, [9]Earle A. Chiles Research Institute/Providence Cancer Institute, Portland, United States, [10]F. Hoffmann-La Roche, Basel, Switzerland, [11]Genentech Inc., San Fancisco, United States, [12]Massachusetts General Hospital, Boston, United States

Introduction: *NTRK* gene fusions in *NTRK1, NTRK2* and *NTRK3* act as oncogenic drivers in different tumour types, including sarcomas, and are potential therapeutic targets. Entrectinib is a CNS-active, potent inhibitor of TRKA/B/C and ROS1. We present integrated efficacy and safety data from three trials of entrectinib in *NTRK* fusion-positive solid tumours focusing on sarcomas.

Methods: Pts with locally advanced/metastatic *NTRK*-fusion positive tumours (with/without baseline CNS disease) confirmed by nucleic acid-based methods were enrolled in three global phase 1/2 entrectinib trials (>150 sites/15 countries: ALKA-372-001 [EudraCT 2012-000148-88], STARTRK-1 [NCT02097810], STARTRK-2 [NCT02568267]). The integrated efficacy evaluable population included TRK inhibitor-naïve adults with extracranial solid tumours harbouring a single, in frame *NTRK* fusion with measurable disease at baseline. Disease burden was assessed per BICR using RECIST v1.1 after cycle 1 (4 weeks) and every 8 weeks thereafter. Primary endpoints were ORR and DOR by BICR. Secondary endpoints included PFS, OS, and safety.

Results: The efficacy-evaluable population comprised 54 pts (10 tumour types; >19 histopathologies). In 13 pts with *NTRK*-fusion positive sarcomas, *NTRK1* and *NTRK3* gene fusions were detected (53.8% and 46.2%). Six subtypes of soft tissue sarcoma and 7 cases of sarcoma 'not otherwise specified' were reported. Median age was 53 years (range 21-81), 46.2% of pts reported ≥2 prior systemic therapies, and all had an ECOG performance status of 0/1 (61.5%/38.5%). No pt had baseline CNS metastases. ORR by BICR was 46.2% (95% CI 19.22-74.87), all were PRs. Four pts (30.8%) had SD, 1 (7.7%) had disease progression, and 2 had missing/unevaluable data. Median (95% CI) DOR, PFS and OS were: 10.3 (4.6-15.0), 11.0 (6.5-15.7), and 16.8 (10.6-20.9) months. Median treatment duration was 4.6 months. The safety population (355 pts) received ≥1 dose of entrectinib; pts reported grade 1/2 (60.5%), grade 3 (27.6%), grade 4 (3.4%), and no grade 5 treatment-related AEs (TRAEs). The most frequent TRAEs were dysgeusia (41.4%), fatigue (27.9%), dizziness (25.4%) and constipation (23.7%). TRAEs led to dose reductions in 27.3%, interruptions in 25.4% and discontinuations in 3.9% of pts.

Conclusion: In this integrated analysis of global multicentre clinical trials, entrectinib was well tolerated and induced clinically meaningful, durable responses in pts with *NTRK*-fusion positive sarcomas.