Background: VTd is a standard of care for transplant-eligible newly diagnosed multiple myeloma (NDMM) patients. Daratumumab (DARA), a CD38 mAb, significantly reduced the risk of progression or death and improved complete response (CR) and minimal residual disease (MRD)-negative rates in relapsed refractory multiple myeloma or transplant-ineligible NDMM in phase 3 studies. Aims: We report the primary and final analysis of Part 1 of the CASSIOPEIA trial for NDMM.

Methods: In Part 1, transplant-eligible NDMM patients 18–65 years old were randomized 1:1 to VTd [6 28-day cycles [C]; 4 autologous stem cell transplantation (ASCT) induction, 2 post-ASCT consolidation] of V 1.3 mg/m2 SC BIW Week [W] 1–2; T 100 mg PO QD; d 40–80 mg/week PO or IV W 1–4 C 1–2, W 1–3 C 3–6] + DARA (16 mg/kg IV QW C 1–2, Q2W C 3–6). Melphalan 200 mg/m2 was pre-ASCT therapy. The primary endpoint was the rate of post-consolidation stringent complete response (sCR) assessed at Day 100 post-ASCT. Part 2 (maintenance) is ongoing.

Results: A cohort of 1085 patients (D-VTd, 543; VTd, 542) was randomized. The Day 100 post-ASCT sCR rate was significantly higher for the D-VTd arm versus the VTd arm (28.9% vs 20.3%; P = 0.0010; Table). With 18.8-months median follow-up, progression-free survival (PFS) from first randomization favored D-VTd with a hazard ratio (HR) of 0.67 (95% CI, 0.50–0.89; P = 0.0043). PFS rates ≥VGPR, and MRD negativity supported the use of D-VTd in transplant-eligible NDMM. CASSIOPEIA is the first study to demonstrate the clinical benefit of daratumumab plus VTd in transplant-eligible NDMM. CASSIOPEIA supports the use of D-VTd in transplant-eligible newly diagnosed multiple myeloma or transplant-ineligible NDMM in phase 3 studies.

Background: Transient abnormal myelopoiesis (TAM) arises from fetal hematopoietic cells in 5–30% of neonates with Down syndrome (DS) and is characterized by the accumulation of immature megakaryoblasts with the triad of fetal origin, GATA1 s mutation and trisomy 21 being necessary and sufficient for its induction. Yet, molecular mechanisms underlying this cooperation are incompletely understood. Aims: We aimed to identify the oncogenic factors on human chromosome 21 (Hsa21) and unravel their molecular synergy with GATA1 s during the development of TAM/ML-DS.

Methods: To study the mechanisms underlying the cooperation between GATA1 s and trisomy 21 in TAM/ML-DS pathogenesis, we performed a CRISPR-Cas9 screening targeting the 218 currently annotated coding genes on Hsa21 with 1090 sgRNAs in both a ML-DS and control cell line. The top ML-DS-specific candidates were functionally and molecularly validated in vitro and in vivo.

Results: Comprehensive CRISPR-Cas9 loss-of-function screening of the Hsa21 coding genes (n = 218) revealed a strong and specific RUNX1 dependency indicated by the depletion of the ML-DS cell line CMK with minor effect on non-DS leukemia cells (K562), RNA-sequencing followed by isoform-specific, qRT-PCR validation in leukemic blasts from ML-DS patients demonstrated deregulation of the RUNX1 isoform equilibrium compared to other types of leukemia or hematopoietic stem and progenitor cells (HSPCs) from healthy donors. In an in vitro set up using Gata1 s-mutated, pre-leukemic murine fetal HSPCs, we observed that ectopic deregulation of RUNX1 isoforms by overexpression synergized with Gata1 s, resulting in enhanced proliferation and accumulation of immature megakaryocytic progenitors. Accordingly, ectopic expression of the ML-DS-mutant RUNX1 isoform in human CD34+ HSPCs led to a loss of mature megakaryocytes and increased monocytic differentiation. Inversely, shifting the expression towards the main hematopoietic RUNX1 isoform induced megakaryocytic differentiation and impaired proliferation of HSPCs. The same was observed in ML-DS patient blasts. Restoring the expression of the main hematopoietic RUNX1 isoform induced differentiation and cell cycle arrest of ML-DS blasts, while further elevating the expression of the ML-DS-mutant RUNX1 isoform enhanced proliferation and accumulation of a megakaryocytic CD41+CD117+ population. Importantly, overexpression of the RUNX1 isoform in Gata1 s fetal HSPCs was sufficient to induce a leukemic phenotype upon transplantation into syngeneic C57BL/6j recipients after a short latency of 40 days and high penetrance (100%). The leukemic cells engrafted in secondary recipients and displayed a megakaryocytic progenitor-like phenotype (CD41+CD117+CD34−CD16/32low). Moreover, global gene expression profiling by RNA-sequencing confirmed a ML-DS-like RNA expression profile of the murine leukemias. Using ChIP-sequencing of tagged versions of GATA1 s and GATA1 s, we could determine differential chromatin occupancy at the RUNX1 locus implicating a feed-forward loop driving the expression of specific RUNX1 isoforms in GATA1 s-mutated cells. Similarly, pulldown assays of tagged GATA1 s revealed isoform-specific interactions with RUNX1.

Summary/Conclusion: Our Hsa21-wide CRISPR screening in combination with functional validation in vitro and in vivo places a specific RUNX1 isoform in the center of an interaction network with mutated GATA1 s during the transformation of fetal HSPCs in the background of trisomy 21. Our data highlight the importance of alternative splicing in leukemias and will guide the development of truly specific and targeted therapies.
S148 TFR2-HAPLOINSUFFICIENCY ENHANCES THE BENEFICIAL EFFECT OF EFV-INDUCED ANTISENSE OLIGONUCLEOTIDE TREATMENT IN BETA-THALASSEMA MICE

M. Pettinato1, M. Aghajan3, M. R. Lidonnici4, V. Olivari2, L. Silvestri2, S. Guo, G. Ferrari1, C. Camaschella1, A. Nai1,2
1Vita-Salute San Raffaele University, 2Division of Genetics and Cell Biology, Ospedale San Raffaele, Milan, Italy, 3Ionis Pharmaceuticals, Inc., Carlsbad, United States, 4University of Illinois at Chicago, Chicago, Illinois, 5University of Alabama at Birmingham, Birmingham, United States, 6American University at Beirut Medical Center, Beirut, Lebanon, 7“Guy’s and St Thomas’ NHS Foundation Trust and King’s College, London, United Kingdom

Background: Involuntary cell disease (SCD) is an inherited disorder caused by a single amino acid substitution in the b-chain of hemoglobin (Hb) resulting in the production of sickle hemoglobin (HbS). When deoxygenated, HbS polymerizes, leading to red blood cell sickling and damage. This results in a triad of clinical features (anemia, hemolysis, and vaso-occlusion), which contribute to the acute and chronic manifestations of SCD. These long-term complications contribute to the decreased quality of life and reduced life expectancy observed in patients with SCD. Voxelotor is an oral, once-daily hemoglobin-oxygen affinity modulator designed to inhibit HbS polymerization, thus improving anemia and reducing hemolysis. The randomized phase 3 HOPE trial (NCT03036813) evaluates the efficacy and safety of voxelotor in patients with SCD aged 12 to 65 years.

Aims: To present the results of the pre-specified Part A analysis of the first approximately 150 randomized patients in the HOPE trial.

Methods: Patients with SCD (HbSS, HbSC, HbSb0 thalassemia, or other variants), Hb ≥ 5.5 and ≤10.5 g/dL, and between 1 and 10 vaso-occlusive crises in the prior 12 months were eligible. Concurrent hydroxyurea was allowed if the dose had been stable for ≥90 days. Patients were randomly assigned to receive voxelotor 1500 mg/day, 900 mg/day, or placebo for at least 24 weeks. The primary endpoint was the proportion of patients with a ≥1.0-g/dL increase in Hb from baseline at week 24. Secondary endpoints included change from baseline to week 24 in measures of hemolysis (absolute and percent reticulocyte counts, indirect bilirubin levels, and lactate dehydrogenase levels) and safety.

Results: 154 patients were included in the preliminary Part A analysis; median age was 25 years (range, 12–59), and 42% were male. Most patients were HbSS/HbSb0: 92% (1500 mg), 94% (900 mg), and 90% (placebo). Hydroxyurea use at study entry was 62% (1500 mg), 67% (900 mg), and 64% (placebo), and median baseline Hb was 8.6 g/dL (1500 mg; range, 5.9–10.8), 8.3 g/dL (900 mg; range, 6.3–10.8), and 8.5 g/dL (placebo; range, 6.1–10.4). At week 24, the proportion of patients with a ≥0.5-g/dL increase in Hb from baseline was significantly higher for both voxelotor 1500 mg (63%; P = 0.0001) and 900 mg (33%; P = 0.0159) compared with placebo (10%) (Figure). The mean change in Hb from baseline to week 24 was 1.5 g/dL with 1500 mg, 0.6 g/dL with 900 mg, and 0 g/dL with placebo. Consistent with improvement in Hb, voxelotor also resulted in concordant improvements in measures of hemolysis (Table). Overall, the treatment-emergent adverse events (TEAEs) were similar across all treatment arms except for diarrhea, which was higher with voxelotor (1500 mg, 21%; 900 mg, 19%) compared with placebo (10%). The majority of TEAEs were grade 1 or 2 in severity. The efficacy and safety data from the full patient population of the phase 3 HOPE trial (N = 274) will be presented.

Summary/Conclusion: Voxelotor treatment demonstrated a dose-dependent increase in Hb, with the majority of patients on voxelotor 1500 mg achieving a ≥1.0-g/dL improvement in Hb from baseline to week 24. In addition, there was a dose-dependent decrease in measures of hemolysis with voxelotor. Furthermore, voxelotor was generally well tolerated. This suggests the potential to be disease-modifying by improving anemia and reducing hemolysis and their associated morbidity and mortality.

S149 FIXED-DURATION VENETOCLAX PLUS OBINUTUZUMAB IMPROVES PROGRESSION-FREE SURVIVAL AND MINIMAL RESIDUAL DISEASE NEGATIVITY IN PATIENTS WITH PREVIOUSLY UNTREATED CLL AND COMORBIDITIES

K. Fischer1,2, O. Al-Sawaf1, J. Bahlo1, A.-M. Fink1, M. Tandon2, M. Dixon2, S. Robrecht1, S. Warburton2, K. Humphrey2, O. Samoylova, A. M. Liberati3, J. Pinilla-Ibarz4, S. Opal5, L. Svikhvatova, K. Le Doan6, L. Maria Fogliatto, C. Uottf Niemans7, R. Winkvole1, S. Robinson1, J. J Kipps1, S. Boettcher1, E. Tauscher1, W. L. Schiery1, B. Eichhorst4,5, M. Wendorfer1, A. W. Langerak6,7,8, K.-A. Kreuzer9, V. Goede9, S. Stilgenbauer10,12, M. Mobasher11, M. Fitgen1,10, M. Hallek1
1Department 1 of Internal Medicine and Center of Integrated Oncology Cologne Bonn, University Hospital, Cologne, Germany, 2Roche Products Limited, 3Wetten Garden City, United Kingdom, 4Regional Clinical Hospital N.A. Senashko, Naryn, Kyrgyzstan, 5Ospedale San Raffaele, Milan, Italy, 6Department of Malignant Hematology, Ospedale San Raffaele, Milan, Italy, 7Department of Hematology and Clinical Immunology, Ospedale San Raffaele, Milan, Italy, 8Division of Hematology, Oncology and Transplantation, Stanford University School of Medicine, Stanford, California, United States, 9Division of Hematology-Oncology, University of California, San Francisco, Department of Medicine, San Francisco, California, United States, 10Department of Haematology and Medical Oncology, Academic Medical Center, Amsterdam, Netherlands, 11Department of Haematology, University of Perugia, Perugia, Italy, 12Department of Gynaecological Oncology, Veneto Institute of Oncology Ospedale San Raffaele, Milan