7001 **Oral Abstract Session, Tue, 8:00 AM-11:00 AM**

Impact of baseline mutations on response to ponatinib and end of treatment mutation analysis in patients with chronic myeloid leukemia.

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Background: BCR-ABL kinase domain mutations frequently cause tyrosine kinase inhibitor (TKI) failure in chronic myeloid leukemia (CML). Ponatinib, a potent oral pan-BCR-ABL TKI, has shown preclinical activity against all single mutants tested, including T315I. The impact of baseline (BL) mutations on response to ponatinib (45 mg once daily) and end of treatment (EOT) mutations in pts discontinuing treatment were evaluated in the phase II PACE trial. **Methods**: Heavily pretreated chronic phase (CP) CML pts (93% received ≥2 prior TKIs, 60% ≥3) resistant or intolerant to dasatinib or nilotinib (N=203) or with T315I confirmed at BL (N=64) were enrolled. The primary endpt was major cytogenetic response (MCyR). Min follow up at analysis (9 Nov 2012) was 12 mos (median 15 [0.1-25]). Sanger sequencing was done at one central laboratory. **Results**: At BL, no mutations were detected in 51% of pts, 1 mutation in 39%, and ≥2 mutations in 10%; 26 unique mutations were observed. Responses were observed regardless of BL mutation status. MCyR rates were: 56% overall, 49% in pts with no mutations, 64% 1 mutation, 62% ≥2 mutations; 57% in pts with mutation(s) other than T315I, 74% T315I only, 57% T315I + other mutation(s). Responses were seen against each of the 15 mutations present in >1 pt at BL, including T315I, E255V, F359V, Y253H. 99 pts discontinued, 56 had EOT mutations assessed. 5 pts lost a mutation, 46 had no change, 5 gained mutations (Table). 11 pts lost MCyR (none with T315I); of the 6 discontinuing, 4 had EOT mutations assessed and no changes from BL were seen. **Conclusions**: Responses to ponatinib were observed regardless of BL mutation status. No single mutation conferring resistance to ponatinib in CP-CML has been observed to date. Data with a minimum follow up of 18 mos, including pts with advanced disease, will be presented. Clinical trial information: NCT01207440.

Relevant mutation history	BL mutation(s)	EOT mutation(s)[a]
E255V	None	E255V [10%][b]
T315I	None	T315I/F359V [100%/90%][c]
T315I	T315I	T315I/M351T [100%/40%][b]
T315I	F359V	T315I [100%][d]
Y253H	V299L/F359V	Y253H/F359V [100%/100%][d]

[a]Gained mutation = bold; % of transcripts with mutation = [%]. Reason for discontinuation: [b]Other. [c]AE. [d]Progressive disease.

7002 **Oral Abstract Session, Tue, 8:00 AM-11:00 AM**

A randomized study of lenalidomide (LEN) with or without EPO in RBC transfusion dependent (TD) IPSS low and int-1 (lower risk) myelodysplastic syndromes (MDS) without del 5q resistant to EPO.

Andrea Toma, Sylvie Chevret, Olivier Kosmider, Jacques Delaunay, Aspasia Stamatoullas, Christian Rose, Odile Beyne-Rauzy, Anne Banos, Agnes Guercy-Bresler, Eric Jourdan, Veronique Sardnal, Denis Caillot, Kamel Laribi, Benoit De Renzis, Dominique Bordessoule, Borhane Slama, Laurence Sanhes, Michaela Fontenay, Pierre Fenaux, Francois Dreyfus; Hopital Henri Mondor-APHP, Universite Paris 12, Creteil, France; DBIM Hopital Saint Louis, Paris, France; Service d'Hématologie Biologique, Hopital Cochin, Paris, France; University of Nantes, Nantes, France; Centre Henri Becquerel, Rouen, France; Centre Hospitalier Universitaire, Lille, France; Purpan University Hospital, Toulouse, France; Hematology, Centre Hospital de la Côte Basque, Bayonne, France; Centre Hospitalier Universitaire, Nancy, France; Centre Hospitalier Universitaire de Nîmes, Nîmes, France; Hopital Cochin, Paris, France; Hematology Department, CHU Le Bocage, Dijon, France; Centre Hospitalier du Mans, Le Mans, France; Centre Hospitalier Universitaire Estaing, Clermont Ferrand, France; Hématologie Clinique et Thérapie Cellulaire, Limoges, France; GINECO, Avignon, France; Hematology, Hopital de Perpignan, Perpignan, France; Hopital Cochin, Paris, Eritrea; Hôpital Avicenne, Université Paris XIII, Bobigny, France; Hematology, Hopital Cochin APHP, University of Paris 5, Paris, France

Background: ESAs, the first line treatments of anemia in non del 5q lower risk MDS, yield only 40-50% responses. LEN gives RBC transfusion independence (TI) in about 25% of ESA resistant (or relapsing) TD lower risk MDS without del 5q (Raza, Blood, 2008), and a gene expression signature can predict response (Ebert, Plos Med 2008). We randomized in this patient population LEN alone and LEN+EPO. **Methods:** In this prospective multicenter open-label phase II study (NCT01718379), lower risk MDS patients without del 5q, with TD (≥4 RBC units during the previous 8 weeks (w)) with ESA resistance or relapse after a response were randomized between LEN alone, 10mg/d x 21 d/4 w (L arm) or LEN (same schedule) + EPO beta, 60 000 U/w (LE arm). The primary endpoint was erythroid response (HI-E, IWG 2006 criteria) after 4 treatment cycles. Secondary objectives included identification of biomarkers of response. **Results:** Between July 2010 and June 2012, 132 patients (pts, 66 / arm), median age 73 (range 46-88), M/F: 88/44 were enrolled. Median TD was 6 RBC units/8w (range 2-18). IPSS was Low in 45% and Int-1 in 55% pts. Pretreatment characteristics did not differ between the 2 groups. All but 3 pts, who withdrew consent (2L+1LE), were evaluable for response. In this ITT population, HI-E was obtained in 15 pts (23.4%) in L arm and 26 (40.0%) in LE arm (RR= 1.7, p= 0.043, chi2 test), and TI in 9 (14.1%) versus 16 (24.6%) pts (RR=1.7, p= 0.13). In the 99 pts who completed 4 treatment cycles, 41 achieved HI-E, including 15/49 (30.6%) in L arm versus 26/50 (52.0%) in LE arm (p= 0.03), and TI in 9 (18.4%) versus 16 (32.0%) pts (RR= 1.7, p=0.12). Side effects (cytopenias and 1 DVT/arm) were similar in the 2 arms. A 29-gene expression profile signature predicting HI-E to L or LE, different from that previously published, was identified and a polymorphism in the CRBN gene (Kosmider, submitted) was significantly associated with HI-E in the entire cohort (p=0.034). **Conclusions:** LEN + EPO yielded a significantly better erythroid response than LEN alone in lower risk MDS patients with anemia resistant to ESA alone. A gene expression signature and a CRBN gene polymorphism correlated with the erythroid response. Clinical trial information: NCT01718379.

7003 **Oral Abstract Session, Tue, 8:00 AM-11:00 AM**

Final results of a phase I study of idelalisib (GSE1101) a selective inhibitor of PI3Kδ, in patients with relapsed or refractory CLL.

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Background: Signals through PI3K-delta regulate activation, proliferation and survival of B cells, critically influence homing and retention of B cells in lymphoid tissues, and are hyperactive in many BEcell malignancies. Idelalisib (GS-1101) is a first-in-class, selective, oral inhibitor of PI3Kδ that reduces proliferation, enhances apoptosis, and inhibits homing and retention of malignant B cells. **Methods:** Pts with relapsed/refractory CLL were treated continuously with single-agent oral idelalisib from 50E350 mg/dose (QD or BID). Response evaluated by investigators per Hallek (2008) and Cheson (2012). **Results:** 54 pts (9F/45M) median (range) age 63 (37E82) years enrolled with: bulky lymphadenopathy (80%), refractory disease (70%), extensive prior therapies (median: 5, range: 2E14), unmutated IgHV (91%), del17p and/or TP53 mutation (24%), del11q (28%), NOTCH1 mutation (17%). The median (range) exposure was 9 (0E41+) months. 25 (46%) pts completed the primary study, 23 (43%) enrolled into an extension study. ORR was 30/54 (56%, 2 CR, 28 PR). Of the 28 PR, 22 met Hallek (2008) and 6 met PR with lymphocytosis Cheson (2012). 44/54 (81%) showed a lymph node response (≥50% reduction in the nodal SPD). 21/54 were SD and 3/54 NE. The median (range) time to first response was 1.9 (0.9-12.9) months. Median PFS was 17 months and median DOR was 18 months. Idelalisib treatment resulted in resolution of splenomegaly (14/20, 70%) and normalization of cytopenias: anemia (17/25, 68%); thrombocytopenia (27/34 79%), neutropenia (15/15, 100%). Most common AEs independent of causality (any Grade/≥Gr 3) included fatigue (31%/2%), diarrhea (30%/6%), pyrexia (30%/4%), rash (22%/0%), upper respiratory tract infection (22%/0%), pneumonia (20%/19%). 2% of pts had ≥Gr 3 ALT/AST elevation. 15% of pts discontinued due to AEs, 7% potentially treatment-related. There were no dose-limiting toxicities. **Conclusions:** Idelalisib shows substantial clinical activity and a favorable safety profile in heavily pretreated, refractory and highErisk pts with CLL. Phase 3 trials with idelalisib in combination with rituximab or bendamustine/rituximab are ongoing. Clinical trial information: NCT01539512, NCT01569295.

Obinutuzumab (GA101) plus chlorambucil (Clb) or rituximab (R) plus Clb versus Clb alone in patients with chronic lymphocytic leukemia (CLL) and preexisting medical conditions (comorbidities): Final stage 1 results of the CLL11 (BO21004) phase III trial.

Valentin Goede, Kirsten Fischer, Kathryn Humphrey, Elina Asikanius, Raymonde Busch, Anja Engelke, Clemens M. Wendtner, Olga Samoylova, Tatiana Chagorova, Marie-Sarah Dilhuydy, Javier De La Serna Torroba, Thomas Illmer, Stephen Opat, Carolyn Owen, Karl A Kreuzer, Anton W Langerak, Matthias Ritgen, Stephan Stilgenbauer, Michael Wenger, Michael Hallek; German CLL Study Group, Dept. I of Internal Medicine, Center of Integrated Oncology Cologne-Bonn, University Hospital Cologne, Cologne, Germany; Department I of Internal Medicine and Center of Integrated Oncology Cologne Bonn, University of Cologne, Cologne, Germany; F. Hoffmann-La Roche Ltd, Welwyn, England; F. Hoffmann-La Roche Ltd, Basel, Switzerland; Institute of Medical Statistics and Epidemiology, Technical University Munich, Munich, Germany; Department of Hematology and Oncology, Schwabing Hospital Munich, Munich, Germany; Hematology, Regional Clinical Hospital N.A. Semashko, Nizhny Novgorod, Russia; Penza Regional Oncology Dispensary, Penza, Russia; Hopital De Haut Leveque, Hematologie Clinique, Pessac, France; Hospital Univ 12 De Octubre, Servicio De Hematologia, Madrid, Spain; Private Oncology Practice, Dresden, Germany; Monash Medical Centre, Haematology, Clayton, Australia; Tom Baker Cancer Centre, Calgary, AB, Canada; Deptartment I of Internal Medicine, Center of Integrated Oncology Cologne-Bonn, University Hospital Cologne, Cologne, Germany; Department of Immunology, Erasmus Medical Center Rotterdam, Rotterdam, Netherlands; Medical Department II, University of Schleswig Holstein, City Hospital Kiel, Kiel, Germany; Department of Internal Medicine III, University of Ulm, Ulm, Germany

Background: Chemoimmunotherapy (CIT) is standard of care in young and physically fit patients (pts) with CLL. Development of CIT for older and less fit CLL pts is ongoing, but data from phase III trials are sparse. CLL11 is the largest trial to evaluate three treatments in previously untreated CLL pts with comorbidities: Clb alone, GA101 + Clb (GClb), R + Clb (RClb). The final analysis of CLL11 stage 1 efficacy and safety results is presented here. **Methods:** Treatment-naïve CLL pts with a Cumulative Illness Rating Scale (CIRS) total score >6 and/or an estimated creatinine clearance (CrCl) <70 mL/min were eligible. Pts received Clb alone (0.5 mg/kg po d1, d15 q28 days, 6 cycles), GClb (100 mg iv d1, 900 mg d2, 1000 mg d8, d15 of cycle 1, 1000 mg d1 cycles 2-6), or RClb (375 mg/m^2 iv d1 cycle 1, 500 mg/m^2 d1 cycles 2-6). Primary endpoint was investigator-assessed progression-free survival (PFS). **Results:** Median age, CIRS score, and CrCl at baseline were 73 years, 8, and 61.1 mL/min for stage 1a (Clb vs GClb, 356 pts) and 73 years, 8, and 62.1 mL/min for stage 1b (Clb vs RClb, 351 pts, triggered by a different event rate). Key efficacy and safety results are shown in the Table.Grade 3-4 infusion-related reactions with GClb occurred at first infusion only. Management required splitting the first dose over 2 days. **Conclusions:** CIT with GClb or RClb significantly prolongs PFS vs Clb alone. The results demonstrate that GClb and RClb are very active in CLL and superior treament options in this population. GClb vs RClb will be compared in stage 2 analysis with more follow-up available. Clinical trial information: NCT01010061.

	Stage 1a		Stage 1b	
Total stage 1 N=589	Clb N=118	GClb N=238	Clb N=118	RClb N=233
Median observation time, months	13.6	14.5	14.2	15.3
Overall response rate, %	30.2	75.5	30.0	65.9
Complete responses, %	0	22.2	0	8.3
Median PFS, months	10.9	23.0*	10.8	15.7
HR, CI, p	0.14, 0.09-0.21, <.0001		0.32, 0.24-0.44, <.0001	
Grade 3-5 adverse events during treatment, %	41	67	41	46
Infusion-related reaction	-	21	-	4
Neutropenia	15	34	15	25
Infections	11	6	11	8

* Still immature, < 20% at risk at time of median.

7005 **Oral Abstract Session, Tue, 8:00 AM-11:00 AM**

A phase II study of the selective phosphatidylinositol 3-kinase delta (PI3Kδ) inhibitor idelalisib (GS-1101) in combination with rituximab (R) in treatment-naive patients (pts) ≥65 years with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

Susan Mary O'Brien, Nicole Lamanna, Thomas J. Kipps, Ian Flinn, Andrew David Zelenetz, Jan Andreas Burger, Leanne Holes, David Michael Johnson, Jessie Gu, Roger D. Dansey, Ronald L. Dubowy, Steven E. Coutre; The University of Texas MD Anderson Cancer Center, Houston, TX; Memorial Sloan-Kettering Cancer Center, New York, NY; UC San Diego Moores Cancer Center, La Jolla, CA; Sarah Cannon Research Institute, Nashville, TN; Gilead Sciences, Inc., Seattle, WA; Stanford Cancer Institute, Stanford, CA

Background: PI3K-delta is critical for activation, proliferation and survival of B cells and plays a role in homing and retention in lymphoid tissues. PI3Kδ signaling is hyperactive in many B-cell malignancies. Idelalisib is a first-in-class, selective oral inhibitor of PI3Kδ. When combined with R in 19 relapsed/refractory patients with CLL, the ORR was 78% (Coutre, ASH 2012). **Methods:** Treatment-naive pts ≥65 yrs with CLL or SLL were treated with R 375 mg/m^2 weekly x 8 and idelalisib 150 mg bid continuously for 48 weeks (primary study). Pts completing 48 wks w/o progression could continue to receive idelalisib on an extension study. Responses and progression were based on investigator assessment using IWCLL criteria (Hallek, Blood 2008). **Results:** Data is presented here on the first 50 of 64 pts enrolled, 48 CLL/2 SLL, median age 71 yrs (range: 65-89), M/F 70/30 (%), Rai stage III/IV 10/32 (%), nodes ≥5 cm in 16%, WHO 0/1/2 in 34/64/2 (%); del(17p) in 6 pts and del(11q) in 13 pts. 32 pts completed 48 wks (18 discontinued, 11 due to AE, 4 due to death and 3 other); 30 pts entered the extension study and 26 remain on treatment. The median time on treatment was 16 months (range 0.8-27.5). The ORRwas 96% with 4% nonevaluable; median time to response was 1.9 mos (range 1.0-6.5). There have been no on-study relapses. The Kaplan-Meier estimated PFS is 91% at 24 mos. Of note, 6/6 pts with del(17p) responded (1 CR, 5 PR) and 3 remain on treatment for more than 21 months. 13/14 (93%) pts with thrombocytopenia and 12/12 (100%) pts with anemia at baseline responded. Of 20 pts with B symptoms at baseline, 13 (65%) were asymptomatic by 8 wks. Most frequent AEs (total%/ ≥G3%) were diarrhea (including reported as colitis) (46/16), pyrexia (42/4), chills (34/0), fatigue (34/2), rash (34/10), pneumonia (30/20) and nausea (28/0). Elevated ALT/AST was seen in 60%, Gr ≥3 in 22%. **Conclusions:** Idelalisib + R is highly active, resulting in durable disease control in treatment-naïve older pts with CLL. These results support the further development of idelalisib in frontline CLL. Clinical trial information: NCT01203930.

7006 **Oral Abstract Session, Tue, 8:00 AM-11:00 AM**

Multi-institutional study of allogeneic bone marrow transplantation using myeloablative busulfan (Bu)/fludarabine (Flu) conditioning and short-course, single-agent graft-versus-host disease (GVHD) prophylaxis with high-dose, post-transplantation cyclophosphamide (PTCy).

Christopher George Kanakry, Paul V. O'Donnell, Marcos J.G. De Lima, Wei Wei, Terry Furlong, Marta Medeot, Richard J. Jones, Peter F. Thall, Borje Andersson, Leo Luznik; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD; Fred Hutchinson Cancer Research Center, Seattle, WA; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: The clinical efficacy of 1) myeloablative BuFlu and 2) PTCy as GVHD prophylaxis have been independently shown in multiple single-center studies. Here, we sought to combine these two promising strategies in the context of a multi-institutional clinical trial. **Methods:** IV Bu was given in pharmacokinetically adjusted doses to achieve a targeted steady-state concentration. PTCy at 50mg/kg on Days +3 and +4 was administered as sole GVHD prophylaxis. Ninety-two patients (median age 49, range 21-65) receiving HLA-matched allografts (49% related and 51% unrelated) were enrolled at three institutions: 42 at Johns Hopkins, 38 at Fred Hutchinson, and 12 at MD Anderson. Diagnoses included 37 patients with de novo AML (40%), 16 with secondary AML (17%), 15 with acute lymphoblastic leukemia (16%), 13 with myelodysplastic syndrome (14%), 5 with chronic myelogenous leukemia (5%), two with chronic myelomonocytic leukemia (2%), three with non-Hodgkin lymphoma (3%), and one with multiple myeloma (1%). Twenty-five patients (27%) were not in remission by morphologic criteria at the time of allogeneic transplantation and an additional 17 patients (18%) had flow cytometric, cytogenetic, or molecular evidence of disease. **Results:** Five patients (5.4%) had primary graft failure. The cumulative incidences of grades 2-4 and 3-4 acute GVHD were 51% and 16%, respectively, and the cumulative incidence of chronic GVHD was 14%. GVHD was the primary cause of death in two patients, and one patient died of veno-occlusive disease. The 100 day and 1 year non-relapse mortality were 9.8% and 16%, respectively. Relapse occurred in 24% of these high-risk patients. At 1 year, the EFS was 64% and the OS was 72%. For the 50 patients in complete remission without MRD, at 1 year the EFS was 77% and the OS was 78%. **Conclusions:** This multi-institutional trial confirms the efficacy of high-dose PTCy as single-agent GVHD prophylaxis and demonstrates that it can be safely and effectively combined with the myeloablative BuFlu conditioning regimen. Clinical trial information: NCT00809276.

7007 **Oral Abstract Session, Tue, 8:00 AM-11:00 AM**

Long-term safety and survival outcomes after TK-expressing donor lymphocyte infusion (TK-DLI) in allogeneic hematopoietic stem cell transplantation (HSCT).

Fabio Ciceri, Maria Teresa Lupo-Stanghellini, Giacomo Oliveira, Raffaella Greco, Luca Vago, Attilio Bondanza, Antonio Lambiase, Claudio Bordignon, Chiara Bonini; Hematology and BMT Unit, San Raffaele Scientific Institute, Milan, Italy; Cancer Immunotherapy and Gene Therapy Program, San Raffaele Scientific Institute, Milan, Italy; MolMed, Milan, Italy

Background: Suicide gene therapy (SGT) was firstly applied to allogeneic HSCT, addressing the need for modulation of graft vs host disease (GvHD) reactions while preserving graft vs leukemia (GvL) effect of alloreactive T cells. HSV-TK gene insertion in donor T-cells modulates alloreactivity by selectively destroying dividing alloreactive cells involved in GvHD. **Methods:** Long-term safety and survival was assessed in 128 pts entering worldwide 10 phase I-II trials that used TK-DLI to improve GvL, immune reconstitution (IR) and GvHD control. In all, 57 pts received TK DLI at our Institution: 23 to treat relapse after HLA-identical HSCT (Ciceri, 2007) and 34 to improve IR after haploidentical HSCT (Ciceri, Bonini, 2009). **Results:** SGT was feasible, safe and effective in promoting a dynamic and specific modulation of alloreactivity. TK-DLI clinical benefit, defined by chimerism, tumor response and/or IR, was achieved by 65 pts (51%). Grade 2 to 4 GvHD (n=28, 22%) was fully controlled by SGT. TK-DLI engrafted in 51 pts (90%) and, being detectable at low frequency up to 14 yrs, no SGT-related adverse events occurred. In HLA-identical setting (n=23; median follow-up, 15 yrs), 11 pts (48%) had disease response and 2 pts (9%) were alive in complete response (CR). In haploidentical setting (n=34; median follow-up, 7 yrs), 25 pts (73%) had IR and 9 pts (26%) were alive in CR. All pts were monitored according to guidelines on long-term survivors (Majhail, 2012). There were no major infections, while 3 pts had a second tumor. Immunity against TK-DLI was reported exclusively after HLA-identical allo-HSCT indicating that TK-DLI is not limited by SGT-specific immunity after haploidentical HSCT. **Conclusions:** Long-term follow-up confirms the high benefit to risk ratio of TK-DLI. A phase III trial is ongoing in haploidentical HSCT (NCT00914628). Clinical trial information: NCT00423124.

7008 **Oral Abstract Session, Tue, 8:00 AM-11:00 AM**

Impact of allogeneic hematopoietic stem cell transplant (HSCT) on patients harboring the spliceosome mutation *SRSF2*.

Betty Ky Hamilton, Ali Tabarroki, Paul Elson, Edy Hasrouni, Valeria Visconte, Shawnda Tench, Matt E. Kalaycio, Mikkael A. Sekeres, Ronald M. Sobecks, Hien Kim Duong, Brian Thomas Hill, Brian James Bolwell, Edward Alan Copelan, Ramon Velasquez Tiu; Department of Hematologic Oncology and Blood Disorders, Cleveland Clinic Taussig Cancer Institute, Cleveland, OH; Department of Translational Hematology and Oncology Research, Cleveland Clinic Taussig Cancer Institute, Cleveland, OH; Cleveland Clinic Quantitative Health Sciences, Cleveland, OH; Cleveland Clinic Taussig Cancer Institute, Cleveland, OH

Background: Molecular predictors of outcome are increasingly important in determining optimal therapy for myeloid neoplasms. Mutations (mut) in spliceosome genes *U2AF1* and *SRSF2* predict poor outcome in MDS and related diseases. The purpose of this study was to investigate the role of HCT on the prognostic impact of *U2AF1* and *SRSF2* in myeloid malignancies. **Methods:** 123 patients (pts) with MDS (33%), AML (51%), MPN (10%), and MDS/MPN (5%) receiving an allogeneic HCT from 2003-2012 for whom genomic DNA was available from a time when the disease was active, were evaluated for mut in *U2AF1* and *SRSF2* by direct sequencing. Data were analyzed using competing risks methods (relapse and non-relapse mortality, NRM), proportional hazards (overall survival, OS) and logistic regression models (GVHD). **Results:** Median time of follow up was 38 months (range 1.5-108). Median age at HCT was 51 yrs (range 18-71). 53 (43%) pts were in remission and 70 (57%) had active disease prior to HCT. 20 (16%) pts had low, 48 (39%) intermediate and 32 (26%) high risk cytogenetics respective to their disease, (per CALGB criteria for AML, IPSS-MF for MPN and IPSS-R for MDS), with missing data on 23 (19%) pts. 89 (72%) had myeloablative transplants, and 34 (28%) received reduced intensity regimens. 54 (44%) had related, 52 (42%) unrelated and 17 (14%) cord blood donors. *SRSF2* mut were detected in 13 (11%) pts and *U2AF1* in 2 (2%) pts. Due to the low incidence of *U2AF1* mut in our cohort, further analysis was focused on *SRSF2*. There were no significant differences in baseline characteristics between mut and wild-type (wt) pts except *SRSF2* mut tended to occur in older AML pts (median age 64 vs 50 yrs, $p=0.0004$). *SRSF2* mut and wt had similar OS ($p=0.95$), relapse ($p=0.28$), NRM ($p=0.45$) and rates of acute ($p=0.41$) and chronic ($p=0.67$) GVHD. Results were similar, adjusting for factors such as age, disease type, cytogenetics, comorbidity, transplant type and stem cell source. **Conclusions:** *SRSF2* has previously been associated with dismal outcomes in MDS pts, with 5 yr-OS of $<20\%$. In this cohort of transplanted pts, *SRSF2* mut had similar outcomes to wt, suggesting HSCT may compensate for the adverse impact of *SRSF2*.

7009 **Poster Discussion Session (Board #1), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM**

Incidence of posttransplantation lymphoproliferative disorder (PTLD) following allogeneic blood or marrow transplantation (alloBMT) using post-transplantation cyclophosphamide (PT-Cy) for graft-versus-host disease (GVHD) prophylaxis.

Jennifer Ann Kanakry, Yvette L. Kasamon, Lode J. Swinnen, Javier Bolanos-Meade, Douglas Gladstone, Heather J. Symons, Huzefa J. Mogri, Christopher George Kanakry, Christopher D Gocke, Leo Luznik, Ephraim Joseph Fuchs, Richard J. Jones, Richard F. Ambinder; Johns Hopkins School of Medicine, Baltimore, MD; The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD; Johns Hopkins Hospital, Baltimore, MD; Johns Hopkins University, Baltimore, MD

Background: Immunosuppression to prevent graft rejection and GVHD is associated with an increased incidence of PTLD in the first year after alloBMT. AlloBMTs using partially HLA-mismatched or unrelated donor grafts, particularly when coupled with selective T-cell depletion approaches and/or anti-thymocyte globulin therapy, are associated with PTLD rates of 4-8%. The incidence of PTLD after umbilical cord blood alloBMT ranges from 2-7%. We evaluated the incidence of PTLD associated with the use of PT-Cy as GVHD prophylaxis at Johns Hopkins Hospital. **Methods:** After IRB approval, the Blood and Marrow Transplant Research database was queried for adult patients (age $>$ 18) who received PT-Cy as GVHD prophylaxis. Medical records from the first year after alloBMT, including clinical notes, pathology reports, and laboratory assays for Epstein-Barr virus (EBV), were reviewed. **Results:** From 2000-2011, 765 alloBMT patients received PT-Cy (50 mg/kg/day on days 3 and 4 after alloBMT) as GVHD prophylaxis. Of these, 734 patients had 1-year follow-up or death. In patients receiving myeloablative conditioning and HLA-matched grafts (n=289, 117 unrelated donors), PT-Cy was the sole GVHD prophylaxis. Other patients undergoing alloBMT received mycophenolate mofetil and tacrolimus in addition to PT-Cy. These included recipients of HLA-matched (n=63) or haploidentical (n=352) grafts who were conditioned with reduced intensity regimens, as well as recipients of HLA-haploidentical grafts who received myeloablative regimens (n=30). Forty-one patients with CD20(+) tumors received rituximab after alloBMT as part of a clinical protocol. There were no cases of PTLD. **Conclusions:** The absence of PTLD in this series, even among high-risk recipients of haploidentical or unrelated donor grafts, suggests that PT-Cy is less associated with PTLD than other GVHD prophylaxis strategies. We hypothesize that multiple mechanisms may account for the lack of PTLD with PT-Cy, including destruction of B cells that harbor EBV, sparing of EBV-specific memory T cells, and rapid immune reconstitution.

7010 Poster Discussion Session (Board #2), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Impact of monosomal karyotype and FLT3 status on post-transplant relapse in acute myeloid leukemia (AML).

Antonio Martin Jimenez, Marcos De Lima, Uday R. Popat, Gautam Borthakur, Lynne Abruzzo, Borje Andersson, Guillermo Garcia-Manero, Elias Jabbour, Julianne Chen, Qaiser Bashir, Stefan O. Ciurea, Partow Kebriaei, Sairah Ahmed, Issa F. Khouri, Piyanuch Kongtim, Muzaffar H. Qazilbash, Gabriela Rondon, Elizabeth J. Shpall, Richard E. Champlin, Betul Oran; Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, TX; University Hospitals Seidman Cancer Center, Cleveland, OH; Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Hematopathology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Relapse remains the major cause of treatment failure in AML patients (pts) undergoing allogeneic hematopoietic stem cell transplantation (allo-HCT). We aimed to identify prognostic factors for relapse and leukemia free survival (LFS) after allo-HCT in AML pts. **Methods:** We retrospectively analyzed 987 consecutive pts who underwent their first allo-HCT for AML between January 2001 and June 2012. 124 pts had monosomal karyotype (MK+), 440 had other cytogenetic abnormalities (core-binding factor [CBF] n=67; MK-, n=373). 113 pts had diploid cytogenetics and FLT3 mutations (CN-FLT3+), 235 were diploid without FLT3 mutations (CN-FLT3-); FLT3 data was unavailable for 75 CN pts. Pts were stratified based on disease status at HCT: complete remission (CR, n=627) and active disease (n=360). **Results:** In this cohort, median age was 52 years (range: 19 – 76) and 191 pts (20%) had secondary AML (sAML). Conditioning intensity was non-myeloablative in 230 pts (23%). On multivariate analysis in pts with CR at HCT (adjusted for age, donor type and conditioning intensity) factors that predicted inferior LFS included: sAML (HR=1.5, 95% CI=1.1-2.2, p=0.009), >=CR2 vs. CR1 (HR=1.6, 95% CI=1.2-2.1, p=0.002), CN-FLT3+ (HR=1.7, 95% CI=1.1-2.5, p=0.02), MK- (HR=1.4, 95% CI=1.1-2.0, p=0.04) and MK+ disease (HR=2.1, 95% CI=1.4-3.2, p <0.001). Three-year LFS rates for CN-FLT3+ and MK+ were 45.3% and 34% *vs.* 53.3% for CN-FLT3- pts. For pts with active disease; CN-FLT3+ (HR=2.6, 95% CI= 1.5-4.2, p<0.001) and MK+ (HR=2.3, 95% CI= 1.5-3.5, p<0.001) predicted worse 3-year LFS: 10% and 6% vs. 30.8% in pts with CN-FLT3- . For CR pts, cumulative incidence of relapse (CIR) was higher for those with CN–FLT3+ (HR=1.9, 95% CI=1.1-3.1, p=0.01) and MK+ disease (HR=2.1, 95% CI=1.2-3.5, p=0.005). Among active disease pts, CN-FLT3+ (HR=2.5, 95% CI=1.4-4.3, p=0.002) and MK+ (HR=1.9, 95% CI=1.2-3.0, p=0.009) also predicted for higher CIR. **Conclusions:** Although pts with CN-FLT3+ and MK+ represent a high risk group for decreased LFS with increased relapse incidence after allo-HCT, they may still enjoy LFS of 30% - 45% if transplanted in CR. Post-transplant strategies to minimize the risk of relapse should be investigated in this setting

7011 Poster Discussion Session (Board #3), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Allogeneic transplantation for myelofibrosis: Benefit of dose intensity.

Uday R. Popat, Roland Bassett, Julianne Chen, Amin Majid Alousi, Paolo Anderlini, Stefan O. Ciurea, Chitra Hosing, Roy B. Jones, Partow Kebriaei, Issa F. Khouri, Sergej Konoplev, Marcos De Lima, Yago Nieto, Betul Oran, Muzaffar H. Qazilbash, Gabriela Rondon, Elizabeth J. Shpall, Srdan Verstovsek, Borje Andersson, Richard E. Champlin; Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Hematopathology Adm, The University of Texas MD Anderson Cancer Center, Houston, TX; University Hospitals Seidman Cancer Center, Cleveland, OH; Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: We did a prospective study of busulfan (bu) and fludarabine (flu) conditioning in patients with myelofibrosis. After observing a high relapse rate in the initial cohort, we increased the intensity of conditioning regimen for subsequent patients, hypothesizing that increased dose intensity delivered with PK guidance will reduce relapse rate without increasing non relapse mortality (NRM), thereby improving overall outcome. **Methods:** Patients with intermediate or high risk MF were eligible if they had adequate organ function and at least 9/10 matched related or unrelated donor. Of the 46 consecutive patients, 15 (bu low group) received IV busulfan 130 mg/m^2 x 2 (day -3,-2). Of the remaining 31 (bu high group), 27 received IV busulfan dose to a target daily AUC of 4000 μmol.min x 4 (day -5 to -2) and 4 patients received a fixed dose of 100 mg/m^2 x 4 (days -5 to -2). All patients received fludarabine 40mg/m^{2}x 4 (day -5 to -2). **Results:** 23 males and 23 females with a median age of 58 years (27-74) had intermediate (25) or high-risk (21) disease. Donors were matched sibs (19), matched unrelated (23), or mismatched unrelated (4). With a median follow-up of 2.1 years (range 0.1-6 years), 3-year overall survival(OS), event-free survival (EFS), cumulative incidence (CI) of non-relapse mortality (NRM), and CI of relapse were 69%, 50% , 13%, and 37%, respectively. Multivariate Cox regression analysis showed that Bu-high dose (HR 0.41; p=0.04) and peripheral blood CD 34 count (HR 1.7; p=0.03) were significantly associated with EFS, and high CD-34 count was significantly associated with OS (HR 1.87; p=0.04). Table shows details of 3-year outcomes of low-dose and high-dose group. All patients engrafted with a median time to neutrophil engraftment of 13 (0-27) days and a median time to platelet engraftment of 24 (0-268) days. Cumulative incidence (CI) of grade II-IV, grade III, IV acute GVHD, and Chronic GVHD were 22%, 5%, and 39%, respectively. **Conclusions:** Higher dose busulfan, delivered with pharmacokinetic dose adjustment, reduces relapse without increasing non-relapse mortality, resulting in better EFS in patients with MF. Clinical trial information: NCT00475020.

@ 3 years	Bu-High (n=31)	Bu-low (n=15)
OS	75%	60%
EFS	61%	27%
CI of relapse	29%	53%
CI of NRM	10%	20%

7012 **Poster Discussion Session (Board #4), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM**

Response rate and bridging to hematopoietic stem cell transplantation (HSCT) with quizartinib (AC220) in patients with FLT3-ITD positive or negative relapsed/ refractory AML after second-line chemotherapy or previous bone marrow transplant.

Jorge E. Cortes, Alexander E. Perl, Hervé Dombret, Hartmut Dohner, Bjoern Steffen, Philippe H. Rousselot, Giovanni Martinelli, Elihu Estey, Neil P. Shah, Alan K. Burnett, Guy Gammon, Denise Trone, Mark J. Levis; The University of Texas MD Anderson Cancer Center, Houston, TX; University of Pennsylvania, Philadelphia, PA; Hematologie Adultes, Hôpital Saint-Louis, Paris, France; Department of Internal Medicine III, University Hospital of Ulm, Ulm, Germany; Department of Medicine, Hematology/Oncology, Goethe University of Frankfurt, Frankfurt, Germany; Service d'Hématologie et Oncologie, Hôpital de Versailles, Université Versailles Saint Quentin en Yvelines, Le Chesnay, France; Seragnoli Institute of Hematology, Bologna University School of Medicine, Bologna, Italy; Division of Hematology, University of Washington, Fred Hutchinson Cancer Research Center, Seattle, WA; University of California, San Francisco, San Francisco, CA; Department of Medical Genetics, Haematology and Pathology, Cardiff University School of Medicine, Cardiff, United Kingdom; Ambit Biosciences Corporation, San Diego, CA; Department of Oncology, Division of Hematologic Malignancies, Johns Hopkins University School of Medicine, Baltimore, MD

Background: FMS-like tyrosine kinase 3 internal tandem duplication (FLT3-ITD) in acute myeloid leukemia (AML) is associated with early relapse after chemotherapy and poor survival. Relapse after HSCT or failure of salvage chemotherapy in FLT3-ITD AML is rarely associated with subsequent HSCT or durable survival. Quizartinib, an oral FLT3 inhibitor, shows promising activity; a Ph 2 study (n=333) of quizartinib monotherapy (Levis et al, ASH 2012) reported that quizartinib often bridged patients (pts) to HSCT. **Methods:** 136 FLT3-ITD(+) and 40 FLT3-ITD(-) pts, relapsed/refractory after HSCT or 1-second line regimen, were included. The response category of composite complete remission (CRc) comprised complete remission [CR] + complete remission with incomplete platelet recovery [CRp] + complete remission with incomplete hematologic recovery [CRi]. **Results:** Quizartinib was discontinued for HSCT in 47/136 FLT3-ITD(+) pts (35%), with 44/47 having at least a PR (2 CRp, 24 CRi, 18 PR). Median overall survival (OS) was 41.5 wks for pts with CRc prior to HSCT and 29 wks for pts with PR. The 1y survival rate was 39% for both response groups. Pts with a CRc (n=36) or PR (n=20) but no HSCT, respectively, had a median OS of 24.5 and 20.9 wks and 1y survival rates of 25% and 5%. Of 27 pts with OS >52 wks, 17 (63%) had HSCT. Quizartinib was discontinued for HSCT in 14/40 FLT3-ITD(-) pts (35%), with 13/14 having at least a PR (1 CR, 1 CRp, 7 CRi, 4 PR). Median OS was not yet reached for pts with CRc, and was 40.7 wks for pts with PR. The 1y survival rate was 78% for pts with CRc and 50% for pts with PR. 8 of these 14 pts had detectable ITD mutation but the level was below the prespecified 10% cutoff. **Conclusions:** Of clinical significance in these heavily pretreated pts who had failed salvage chemotherapy or HSCT, approximately 1/3 were successfully bridged to potentially curative HSCT, with encouraging 1y survival rates. To extend the potential benefits of FLT3 inhibitor therapy in combination with allogeneic HSCT, studies of maintenance quizartinib to prevent relapse post HSCT are ongoing. Clinical trial information: NCT00989261.

7013 **Poster Discussion Session (Board #5), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM**

Efficacy and safety of cladribine: Subcutaneous versus intravenous administration in hairy cell leukemia.

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Background: Hairy cell leukemia (HCL) is rare B-cell lymphoproliferative disorder. Its treatment has evolved from splenectomy with time to failure (TTF) of 19 months to Cladribine that increased complete remission (CR) rate to 90%, with only small percentage of patients relapsing at 30 months. Cladribine (CDA) is originally administered intravenously as continuous infusion for 7 days; Subsequently, it was administered subcutaneously. This study aims at comparing efficacy and toxicity of Subcutaneous (SC) versus Intravenous (IV) administration of CDA in treatment of HCL. **Methods:** This retrospective study included HCL patients presented to National Cancer Institute and Nasser Institute, Cairo, Egypt, during period 2004-2010. Included patients received CDA as 1st or 2nd line with minimum follow up of 12 months. All files were reviewed for baseline clinical & laboratory parameters, route of administration, response, adverse events and survival. **Results:** This study included 49 eligible patients, 41 patients received CDA as 1^{st} line treatment, while 8 patients as 2^{nd} line. Eighteen patients were treated by continuous IV infusion whereas 31 patients by SC injections. Both groups were comparable regarding baseline clinical and laboratory parameters with no statistically significant difference. At median follow up period of 33.5 months, complete remission rate was 94% in IV group versus 97% in SC group ($p=0.691$); median TTF for IV group was 52.9 months while that for SC group was not reached ($p=0.035$). The median time to achieve CR in both arms was similar. By analyzing different factors affecting TTF using multivariate analysis, route of administration proved to be the only statistically significant factor ($P=0.006$). Regarding adverse events, there was no difference between both groups in hematological toxicities. IV route was associated with a significant higher incidence of mucositis ($p=0.02$) and viral infections ($p=0.01$). Hepatotoxicity and neurotoxicity were higher in SC group but difference was not statistically significant. **Conclusions:** SC administration of cladribine is an alternative route to IV in treatment of HCL with similar response rate, longer time to treatment failure and better tolerability.

7014 **Poster Discussion Session (Board #6), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM**

Use of tumor genomic profiling to reveal mechanisms of resistance to the BTK inhibitor ibrutinib in chronic lymphocytic leukemia (CLL).

Betty Y Chang, Richard R. Furman, Marc Zapatka, Jacqueline Claudia Barrientos, Daniel Li, Susanne Steggerda, Karl Eckert, Michelle Francesco, Jennifer Ann Woyach, Amy J Johnson, Danelle Frances James, Matthias Versele, John C. Byrd, Stephan Stilgenbauer, Joseph J. Buggy; Pharmacyclics, Inc., Sunnyvale, CA; Weill Cornell Medical College, New York, NY; German Cancer Research Center (DKFZ), Heidelberg, Germany; Hofstra North Shore-LIJ School of Medicine, Hyde Park, NY; The Ohio State University, Columbus, OH; The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, Columbus, OH; Pharmacyclics, Sunnyvale, CA; Janssen Research & Development, LLC, Beerse, Belgium; Department of Internal Medicine III, University of Ulm, Ulm, Germany

Background: Ibrutinib interacts covalently with cysteine 481 of Bruton tyrosine kinase (BTK), resulting in targeted inhibition of B cell receptor signaling. Early trials of ibrutinib mono- or combination therapy enrolled 246 CLL patients receiving a median of 14 months of ibrutinib. 20 patients (8%) experienced progressive disease (PD), including 8 patients with Richter's transformation. Here we examine changes to the CLL genome in 3 patients that acquired resistance to ibrutinib. **Methods:** Ibrutinib resistance was defined as patients achieving partial response (PR) or better lasting $\geq$ 6 months, then developing PD without Richter's transformation. RNAseq and whole exome sequencing (WES) followed by comparative genome analysis was performed at baseline and after PD and confirmed by Sanger sequencing. RNAseq and WES data were aligned using TopHat and BWA software. Single nucleotide variations (SNVs) were identified using SAMtools mpileup. **Results:** Compared to patients who relapsed from conventional chemotherapy, minimal genomic changes were acquired in ibrutinib resistant patients, reflecting relative genomic stability. SNVs were discovered in 3 patients specific to the relapse sample (Table). 2 out of 3 patients had distinct SNVs that each encode a cysteine-to-serine substitution at position 481of BTK (C481S). Homologous cysteine residues in BMX, ITK, TEC and BLK were wild-type (WT). Ibrutinib inhibited recombinant C481S 25 fold less potently than WT, and could not covalently bind C481S expressed in cells. The third patient had WT BTK, but acquired a potential gain-of-function mutation encoding a R665W substitution in PLCg2, a substrate of BTK, consistent with constitutive PLCg2 activation. **Conclusions:** Although rare, the acquisition of C481S BTK and R665W PLCg2 mutations in the setting of resistance confirms BTK as an important pharmacologic target of ibrutinib, and suggests mechanisms of ibrutinib resistance.

Study	RXn	Duration on ibrutinib	Best response	Mutation
PCYC-04753	Ibrutinib 560 mg daily	575 days	PR	C481S BTK
PCYC-1102	Ibrutinib 420 mg daily	581 days	PR	R665W PLCg2
PCYC-1108	Ibrutinib 420 mg daily + bendamustine/rituximab x 6 cycles	388 days	CR	C481S BTK

7015 Poster Discussion Session (Board #7), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

A comprehensive prognostic index for patients with CLL.

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Background: Besides clinical staging, a number of biomarkers predicting OS in CLL have been identified. The multiplicity of markers, limited information on their independent value, and a lack of understanding of how to interpret discordant markers are major barriers to use in routine clinical practice. We developed an integrated prognostic index using the database of the German CLL Study Group (GCLLSG), which was subsequently validated in a cohort of untreated CLL patients (pts) from the Mayo Clinic. **Methods:** The analysis was based on a dataset collected between 1997 and 2006 in 3 GCLLSG phase III trials. The external validation was performed on a series of newly diagnosed CLL pts managed at Mayo Clinic. **Results:** The GCLLSG dataset (1,948 physically fit pts at early and advanced stage; median age: 60 yr (range 30-81); median observation time 63.4 mo) was used as a training dataset. 7 parameters were identified as independent predictors for OS: sex, age, ECOG status, del 17p, del 11q, *IGHV* mutation status, thymidine kinase and β_2-microglobulin. By using a weighted grading a prognostic index was derived separating four different pts groups: low risk (score 0 - 2), intermediate risk (score 3-5), high risk (score 6-10) and very high risk (score 11-14) with significant different OS rates (95.2%, 86.9%, 67.7% and 18.7% OS after 5 yr for the low, intermediate, high and very high risk group respectively ($p<0.001$). This prognostic index was validated in a cohort of 676 newly diagnosed, untreated pts from the Mayo Clinic (median age 61.5 yr (range 32 - 89); median observation time 47.0 mo). The 4 risk groups were reproduced with 98.3%, 95.4%, 75.4% and 10.8% OS after 5 yr. The prognostic index predicts OS independent of Rai/Binet stage and provides accurate estimations regarding time to first treatment (TTF). C-statistic is 0.75. **Conclusions:** Using a multi-step process including external validation, we developed a comprehensive prognostic index combining clinical, serum, and molecular information into a single risk score for pts with untreated CLL. The prognostic index provides more accurate prediction of both TTF and OS. To our knowledge it is the first prognostic model in CLL to reach the C-statistic threshold ($c > 0.70$) necessary to have utility at the level of the individual.

7016 **Poster Discussion Session (Board #8), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM**

Which treatment options impact outcomes in elderly chronic lymphocytic leukemia patients with high prevalence of comorbidity?

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Background: Therapy selection in chronic lymphocytic leukemia (CLL) patients is based on disease severity as well as patient characteristics such as age and comorbidity. While treatment outcomes are mostly available from clinical trial data in younger patients, less is known about the effect of comorbidities on outcomes in elderly CLL patients in the real-world setting. **Methods:** The linked Surveillance, Epidemiology, and End Results (SEER)-Medicare database was utilized in this retrospective cohort analysis of 3,366 first primary CLL patients. Patients were diagnosed between 1/1/1998-12/31/2007, were >66 years, continuously enrolled in Medicare Part A and B with no HMO coverage in the year prior to diagnosis and received first-line treatment with any oral or infused therapy. CLB is covered by Medicare Part D and data for its use were only available from 2007-2009 in the dataset. Cox regression with backward elimination and propensity score weighted Cox regression estimated the relative risk of death. Date of last follow-up was 12/31/2009. **Results:** There were 153 CLB, 606 R-mono, 702 R+IV Chemo, and 1,905 IV Chemo-only patients. CLB and R-mono patients were older at diagnosis with mean age of 77 compared to R+IV Chemo (73 years) and IV Chemo-only (76 years; $p<.0001$). Patients administered R-mono had a higher comorbidity burden and more advanced disease compared with other treatment groups. In the survival analysis we compared CLB to R-mono during the time period 2007-2009 and R+IV Chemo to IV Chemo-only during the time period 1998-2009. The adjusted multivariate survival analysis revealed a significant mortality risk reduction with R+IV Chemo compared with IV Chemo-only patients (HR, 0.72; 95% CI, 0.62-0.84) while a non-significant mortality risk reduction was noted with R-mono compared to CLB patients (HR, 0.47; 95% CI, 0.21-1.05). Older age and increasing comorbidity score were significantly associated with higher mortality. **Conclusions:** These findings suggest that chemo-immunotherapy is more effective than chemotherapy in an elderly population with a high prevalence of comorbidity. This extends the conclusions from clinical trials in younger, medically fit patients.

7017 Poster Discussion Session (Board #9), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Update on a phase I study of the selective PI3Kδ inhibitor idelalisib (GS-1101) in combination with rituximab and/or bendamustine in patients with relapsed or refractory CLL.

Jacqueline Claudia Barrientos, Richard R. Furman, John Leonard, Ian Flinn, Kanti Roop Rai, Sven De Vos, Marshall T. Schreeder, Nina D. Wagner-Johnston, Jeff Porter Sharman, Thomas E. Boyd, Nathan Hale Fowler, Leanne Holes, David Michael Johnson, Daniel Li, Roger D. Dansey, Thomas Michael Jahn, Steven E. Coutre; Hofstra North Shore-LIJ School of Medicine, Hyde Park, NY; Weill Cornell Medical College, New York, NY; Sarah Cannon Research Institute, Nashville, TN; University of California, Los Angeles Medical Center, Los Angeles, CA; Clearview Cancer Institute, Huntsville, AL; Washington University School of Medicine in St. Louis, St. Louis, MO; Willamette Valley Cancer Institute/US Oncology Research, Springfield, OR; Yakima Valley Memorial Hospital/North Star Lodge Cancer Center, Yakima, WA; The University of Texas MD Anderson Cancer Center, Houston, TX; Gilead Sciences, Inc., Seattle, WA; Stanford Cancer Institute, Stanford, CA

Background: PI3K-delta signaling is critical for proliferation, survival, homing and tissue retention of malignant B cells. Idelalisib is a first-in-class, selective, oral inhibitor of PI3Kδ that has shown considerable monotherapy activity in pts with heavily pretreated CLL. **Methods:** This phase I study evaluated idelalisib continuously given at 150 mg BID in combination with rituximab (R, 375 mg/m^2 every wk x 8), bendamustine (B, 70 or 90 mg/m^2 x 2, every 4 wks x 6) or BR (every 4 wks x 6) for relapsed/refractory CLL. Pts still on treatment after 48 weeks were eligible to continue idelalisib on an extension study. Clinical response was evaluated according to published criteria (Hallek 2008; Cheson 2012). **Results:** 52 pts (23F/29M) with a median (range) age of 64 (41-87) years were enrolled. Adverse disease characteristics included bulky lymphadenopathy (62%), refractory disease (50%), multiple prior therapies (median 3, range: 1-14) with 96% receiving prior R and 44% receiving prior B. As of 14 Jan 2013, the median (range) treatment duration was 18 (1-33) months. 31/52 (60%) pts enrolled into the extension study; of those, 24/52 (46%) pts are continuing idelalisib treatment on the extension study. The ORR was 81%, with 1 CR, and a median (range) time to response of 1.9 (1.5-8.3) months. The 2-year PFS and OS were 62% and 85%, respectively. At 2 years follow up, 71% of responses were still enduring. There was no difference in outcomes for pts with <3 prior treatments (n=21) vs ≥ 3 prior treatments (n=31). The most common TEAEs (any Grade/$\geq$Gr 3, independent of causality) included pyrexia (44%/6%), diarrhea (40%/14%), cough (31%/2%), fatigue (29%/2%), nausea (29%/0%). Pneumonia (any Gr/$\geq$Gr 3) occurred in 15%/12% and rash was seen in 15%/0%. 10% of patients experienced $\geq$Gr 3 ALT/AST elevation based on laboratory values. **Conclusions:** A lack of overlapping toxicities allowed idelalisib to be co-administered with R, B, or BR, and all 3 combination regimens were highly active, resulting in durable tumor control in pts with heavily pretreated relapsed/refractory CLL. Phase III trials evaluating the efficacy of idelalisib in combination with R or BR are ongoing. Clinical trial information: NCT01088048.

7018 Poster Discussion Session (Board #10), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Updated results of a phase I first-in-human study of the BCL-2 inhibitor ABT-199 (GDC-0199) in patients with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL).

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Background: Targeting BCL-2 is a promising strategy for treating CLL, including disease refractory to fludarabine (F), or with (del(17p). ABT-199 is a selective BCL-2 inhibitor with >500-fold higher affinity for BCL-2 (K_i<0.10 nM) than for BCL-X_L (K_i=48 nM). **Methods:** Objectives of this Ph I dose-escalation study include evaluations of safety, pharmacokinetics and preliminary efficacy of ABT-199 in patients (pts) with R/R CLL. A single oral dose was given followed by 6 days off drug, before continuous once daily dosing. After cohort 1, the initial dose was reduced and daily dosing modified to include a 2 or 3 step dose-escalation to the target dose for each cohort. **Results:** As of January 11, 2013, 56 pts have been enrolled; median age 67 y (range 36-86); 41 males; median 3.5 prior therapies (range 1-10). 16 (29%) had del(17p) and 18 (32%) F-refractory CLL. Median follow up is 6.3 months (range 0.03-16.5); 7 pts have been on study for more than 1 yr. 13 pts discontinued; 7 due to PD, 6 for other reasons: tumor lysis syndrome (TLS; 2), other illness (2), thromboembolic event (1), consent withdrawal (1). The most common non-hematological AEs (>15% pts) were nausea (36%), diarrhea (30%), fatigue (25%), upper respiratory tract infection (23%), and cough (16%). Grade 3/4 AEs occurring in > 5 pts were neutropenia 21(38%), thrombocytopenia 6 (11%) and TLS 5 (9%). TLS occurred in 3/3 pts in cohort 1 and 2/53 pts with the modified stepped dosing schedule (DLTs). Additionally, 1 fatal AE occurred within 48 hrs of dose-escalation to 1200 mg in a pt with laboratory evidence of TLS (DLT). 46 of 54 pts (85%) evaluable for efficacy achieved a response to ABT-199; 7 (13%) a CR or CR with incomplete count recovery and 39 (72%) a PR (30 confirmed by consecutive scans). 14/16 (88%) and 12/16 (75%) of pts with del(17p) and F-refractory CLL, respectively, achieved at least a PR. **Conclusions:** ABT-199 is highly active achieving a 85% overall response rate in R/R CLL, independent of high risk markers such as del(17p) and F-refractory disease. Additional dosing and scheduling modifications are currently being explored to minimize the risk of TLS. Clinical trial information: NCT01328626.

7019 Poster Discussion Session (Board #11), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Aberrant NFAT2 signaling in chronic lymphocytic leukemia.

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Background: CLL is a malignancy of mature B cells and constiututes the most common leukemia in adults. It is characterized by a progressive accumulation of clonal B cells, which coexpress CD19, CD23 and CD5. NFAT is a family of highly phosphorylated transcription factors residing in the cytoplasm of resting cells. Upon dephosphorylation by calcineurin, NFAT proteins translocate to the nucleus where they orchestrate developmental and activation programs in diverse cell types. In this study, we investigated the significance of NFAT signaling in B-CLL. **Methods:** NFAT2 expression and aberrant nuclear translocation in CLL cells (n=30) was assessed by Western Blotting and immunofluorescence. In addition, NFAT2 mRNA levels were measured by qRT-PCR and its DNA binding capacity was assessed using an electrophoretic mobility shift assay. Transcriptional activity of NFAT2 proteins in CLL cells was further analyzed by determining the expression of several well characterized NFAT target genes. **Results:** We detected a profound overexpression of NFAT2 mRNA and protein in all CLL samples. Using qRT-PCR we found that CD19+CD5+ CLL cells exhibited a significant overexpression of NFAT2 as compared to CD19+ B cells isolated from healthy donors (8-200fold). This overexpression of NFAT2 in CLL cells could also be confirmed on the protein level. We could further demonstrate that even under resting conditions significant amounts of NFAT2 protein had translocated to the nucleus in CLL cells, whereas virtually all NFAT2 was in the cytoplasm in non-malignant B cells. Nuclear NFAT2 in CLL cells was able to bind DNA but its transcriptional activity with respect to several apoptosis-regulating genes (i.e. Spp1, Pdcd1) was severely compromised. **Conclusions:** These results provide strong evidence that the Ca^{2+}/NFAT signalling axis is constitutively activated in CD5+CD19+ CLL cells. Reduced expression of several apoptosis regulators which are known target genes of NFAT2 links deregulation of this signaling cascade to CLL progression. Further investigation is warranted to investigate the therapeutic potential of modulating Ca^{2+}/Calcineurin/ NFAT signaling in CLL.

7020 Poster Discussion Session (Board #12), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Immunopharmacodynamic response to blinatumomab in patients with relapsed/refractory B-precursor acute lymphoblastic leukemia (ALL).

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Background: Blinatumomab is an anti-CD19/anti-CD3 bispecific T cell engager (BiTE) that induces target cell-dependent, polyclonal T cell activation and proliferation, resulting in redirected lysis of $CD19^+$ target cells. **Methods:** In a phase 2 study, adult patients (N=36) with relapsed/refractory B-precursor ALL received continuous blinatumomab IV infusion for 28 days in ≤5 treatment/consolidation cycles. Whole blood and serum samples were collected throughout treatment and analyzed for lymphocyte subpopulations, cytokines, granzyme B, and blinatumomab serum concentrations. **Results:** Lymphocytes in all patients responded in a similar fashion. After infusion start, peripheral B cell counts dropped to ≤1 B cell/μL in <1 week and remained undetectable throughout treatment. Peripheral T cells showed a redistribution characterized by swift disappearance within the first 2-6 hrs and subsequent recovery to baseline within several days. Otherwise, T cell counts remained at least stable in most patients. In some patients even an expansion of the T cell compartments was observed, most likely due to specific proliferation of activated T cells but could not be defined as prerequisite for treatment efficacy. During the first infusion days, a significant proportion of T cells newly expressed the activation marker CD69, and the T cell effector molecule granzyme B was detectable in serum. Additionally, a transient cytokine release dominated by IL-10, IL-6 and IFN-γ was observed in most patients shortly after first infusion start, which was alleviated or absent in subsequent cycles. Blinatumomab serum steady state concentrations (mean±SD) were 198±61 pg/mL and 694±236 pg/mL at doses of 5 and 15 μg/m²/d, respectively, which is comparable to those from previous studies. **Conclusions:** Immunopharmacodynamic response to blinatumomab was characterized by B cell depletion, T cell activation and redistribution, and release of granzyme B and cytokines, suggesting T cell engagement according to the expected BiTE mode of action. The tested pharmacodynamic markers did not allow for predictive differentiation between patients achieving a hematologic response and those who did not. Clinical trial information: NCT01209286.

7021 Poster Discussion Session (Board #13), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Effect of quizartinib (AC220) on response rates and long-term survival in elderly patients with FLT3-ITD positive or negative relapsed/refractory acute myeloid leukemia.

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Background: Advanced age and FMS-like tyrosine kinase 3 internal tandem duplications (FLT3-ITD) in acute myeloid leukemia (AML) are associated with early relapse after standard chemotherapy and poor survival. Quizartinib (AC220), an oral FLT3 inhibitor active against ITD mutant and wild type FLT3, has shown promising activity in Ph 1 and 2 studies. **Methods:** Patients (pts) in a Ph 2 open label study (N = 333) of quizartinib monotherapy included 154 aged ≥60 y with known FLT3-ITD status and AML relapsed in <1 y or refractory to 1st line chemotherapy. Median duration of treatment was 14.2 wks (range 0.1–70.6 wks) for FLT3-ITD(+) pts and 9.5 wks (range 1.1–77.0 wks) for FLT3-ITD(-) pts. The composite complete remission (CRc) rate included complete remission (CR), complete remission with incomplete platelet recovery (CRp), and complete remission with incomplete hematologic recovery (CRi). **Results:** Of 110 FLT3-ITD(+) pts, 63 (57%) had a CRc (3 CR, 4 CRp, 56 CRi). Of 44 FLT3-ITD(-) pts, 16 (36%) had a CRc (2 CR, 1 CRp, 13 CRi). Median overall survival (OS) in FLT3-ITD(+) pts was 25.3 wks and 16/110 (15%) survived >52 wks. The median age of these pts surviving >52 wks was 69.5 y (range 66–80 y) and median OS was 76.3 wks (range 56.9–96.0 wks). All of these pts responded to quizartinib (2 CR, 2 CRp, 8 CRi, 4 partial remission [PR]). 2 pts were still alive >1 ½ y (OS 93.0 and 96.0 wks). Median OS in FLT3-ITD(-) pts was 19.1 wks and 6/44 FLT3-ITD(-) pts (14%) survived >52 wks. The median age of these pts was 70.0 y (range 65–77 y) and their median survival was 76.6 wks (range 54.9–98.4 wks). 5 of these pts responded to quizartinib (1 CR, 3 CRi, 1 PR). **Conclusions:** These data for an FLT3-targeted agent show encouraging survival in a subset of elderly pts with relapsed/refractory FLT3-ITD(+) AML. Clinical trial information: NCT00989261.

Efficacy in elderly relapsed/refractory AML pts.

	FLT3-ITD(+) (N=110)	FLT3-ITD(-) (N=44)
Cumulative CRc, n (%)	63 (57)	16 (36)
CRc+PR, n (%)	86 (78)	20 (56)
Median CRc duration, wk (95% CI)	12.1 (6.3, 15.7)	10.8 (8.1, 26.1)
Median overall survival, wk (95% CI)	25.3 (21.3, 30.0)	19.1 (12.0, 29.4)

Abbreviations: CRc = composite complete remission; PR = partial remission.

7022 Poster Discussion Session (Board #14), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

BH3 profiling as a predictive biomarker for response to cytarabine-based treatment of acute myelogenous leukemia.

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Background: Acute myelogenous leukemia (AML) is the most frequently diagnosed of the leukemias with approximately 13,000 new cases per year in the U.S. Although intense therapeutic discovery efforts have been directed towards AML, cytarabine-based treatment remains unchanged as the standard-of-care (SOC). As patient response to SOC is variable, segregating patients based on biomarker-driven predicted response may lead to improved clinical outcomes. One personalized diagnostic approach that may provide actionable information in patient management is BH3 profiling, a surrogate functional biomarker assay that assesses cell mitochondrial response to pro-apoptotic signaling. **Methods:** Blinded to outcomes, we profiled an AML cohort (n=63) treated with cytarabine-based therapy using a panel of BH3 peptides with response as a primary endpoint. Peripheral blood mononuclear cell (PBMC) or bone marrow aspirate (BM) specimens were obtained from newly diagnosed AML patients and viably preserved. Specimens were assayed by flow cytometry following cell permeabilization and incubation with potentiometric JC-1 mitochondrial dye and individual BH3 peptides. **Results:** Mann-Whitney analysis indicates BH3 profiling biomarkers are correlated with response to induction therapy. Among BH3 peptides, BIM was highly significant ($p=2X10^{-6}$; CI[0.73,0.94]) with a notable sensitivity/specificity profile (AUC=0.84; $p=2X10^{-10}$). Multivariate analysis indicates improved profiles for BIM + patient age (AUC=0.89; CI[0.81,0.97])and BIM + patient age +cytogenetic status (AUC=0.91; CI[0.83,0.98]). When patients were stratified by cytogenetic status, BIM was significant for both intermediate (p=0.0017; AUC=0.88; CI[0.71,1.04]) and unfavorable (p=0.016; AUC=0.80; CI[0.60,1.00]), demonstrating that the predictive power of the assay is independent of cytogenetics. **Conclusions:** Here, BH3 profiling predicts patient response to cytarabine-based treatment regimens with accuracies of 90%. Thus, patients may potentially benefit from being given alternate therapies while at the same time spared the toxicities, cost, and time lost associated with a therapy less likely to exhibit response.

7023 Poster Discussion Session (Board #15), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Efficacy and safety of quizartinib (AC220) in patients age ≥ 70 years with FLT3-ITD positive or negative relapsed/refractory acute myeloid leukemia (AML).

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Background: Advanced age and FMS-like tyrosine kinase 3 internal tandem duplication (FLT3-ITD) in AML are each associated with early relapse after standard chemotherapy and poor survival. Quizartinib, an oral FLT3 inhibitor active against ITD mutant and wild type FLT3, has shown promising activity in Ph 1 and 2 studies. **Methods:** We provide detailed analysis from a Ph 2 study (N = 333) of quizartinib monotherapy, focusing on patients (pts) aged ≥ 70 y with AML that relapsed and/or was refractory to prior therapy. **Results:** A total of 83 pts age ≥70 y included 60 (72%) FLT3-ITD(+) and 23 (28%) FLT3-ITD(-). Median duration of treatment was 14.6 wks for FLT3-ITD(+) pts and 5.9 wks for FLT3-ITD(-) pts. Composite complete remission (CRc) rate included complete remission (CR), complete remission with incomplete platelet recovery (CRp), and complete remission with incomplete hematologic recovery (CRi). Of 60 FLT3-ITD(+) pts, 32 (53%) had a CRc (1 CR, 3 CRp, 28 CRi). Of 23 FLT3-ITD(-) pts, 10 (43%) had a CRc (2 CR, 1 CRp, 7 CRi). 12/27 FLT3-ITD(+) pts (44%) and 5/10 FLT3-ITD(-) pts (50%) refractory to prior therapy responded to quizartinib, and 12/83 (14%) survived >1 y. The most common (≥10%) Grade 3 or 4 treatment-related adverse events (TRAEs) were febrile neutropenia (22%), anemia (20%), transient QT interval prolongation (17%; no Grade 4), and thrombocytopenia (12%). 15 pts (18%) had TRAEs resulting in discontinuation. **Conclusions:** Because AML in the elderly, particularly in those aged ≥70 y, is genetically heterogeneous and often follows a myelodysplastic syndrome, there is a wide assumption that it may be less amenable to FLT3-targeted therapy than AML in younger pts. Our data argue against these conclusions and show that pts aged ≥70 y with chemotherapy-resistant AML have preserved high response rates, and promising survival to quizartinib. Clinical trial information: NCT00989261.

Efficacy in relapsed/refractory AML pts ≥ 70 Y.

	FLT3-ITD(+) (N=60)	FLT3-ITD(-) (N=23)
Cumulative CRc, n (%)	32 (53)	10 (43)
CRc+PR, n (%)	41 (68)	12 (52)
Median CRc duration, wk (95% CI)	13.9 (8.0, 16.5)	8.3 (4.1, 26.1)
Median overall survival, wk (95% CI)	21.0 (17.0, 25.4)	19 (7.6, 28.9)

Abbreviations: CRc, composite complete remission; PR, partial remission.

7024 Poster Discussion Session (Board #16), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Phase II study of combination of hyperCVAD with ponatinib in frontline therapy of patients (pts) with Philadelphia chromosome (Ph) positive acute lymphoblastic leukemia (ALL).

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Background: Combination of chemotherapy with TKIs was evaluated and appears to be effective in Ph+-ALL. Ponatinib is a more potent inhibitor and suppresses the T315I clones, a common cause of relapse in pts with Ph+- ALL. Clinical trials of ponatinib have demonstrated its high activity and limited toxicity in pts with Ph+-leukemia failing 2-3 TKIs and in those with a T315I mutation. Combinations of chemotherapy regimens and ponatinib may be associated with better response rates and higher likelihood of eradication of MRD. **Methods:** In this phase II trial, pts with newly diagnosed Ph+ ALL receive ponatinib 45 mg po QD for the first 14 days of cycle 1 then continuously for the subsequent 7 cycles. Pts in CR receive maintenance with ponatinib 45 mg po QD and vincristine and prednisone monthly for 2 years followed by ponatinib indefinitely. MRD monitoring is conducted. **Results:** To date 20 pts with untreated Ph+ ALL have received a median of 6 cycles; 5 pts are receiving maintenance in CR. Median age is 49 years. Median WBC at diagnosis was 2.45 x 10^9/L. All pts were in CR after 1 cycle. 15 of the 17 pts (88%) known to be Ph+ by cytogenetic analysis at baseline achieved CCyR after 1 cycle; 1 had mCyR only and 1 had no cytogenetic analysis at CR, both of them achieved CCyR after cycles 2; 3 had a diploid karyotype at the start. To date, 17 pts (85%) have achieved MMR, of whom 11 (55%) have achieved CMR at a median of 10 weeks from initiation of treatment. MRD assessment by flow cytometry is negative in 18 (90%) pts at a median of 3 weeks. Median time to neutrophil and platelet recovery for cycle 1 was 18 and 22 days, and 16 and 22 days for subsequent cycles, respectively. Grade $\geq$3 toxicity included increase of LFT's/hyperbilirubinemia in 8 pts, thrombosis in 3, skin rash in 2, pancreatitis in 1, and pericardial effusion in 1. With a median follow up of 6 months, 19 pts are alive and in CR; 1 pt died in CR from an unrelated cardiac event. 1 pt has undergone an allogeneic transplant. The 1-year PFS and OS rates were 100% and 95%, respectively. **Conclusions:** The combination of hyperCVAD with ponatinib is safe and highly effective in achieving molecular remissions in pts with Ph+ ALL. Clinical trial information: NCT01424982.

7025 Poster Discussion Session (Board #17), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Rate of complete hematological response of elderly Ph+ acute lymphoblastic leukemia (ALL) patients by sequential use of nilotinib and imatinib: A GIMEMA protocol LAL 1408.

Cristina Papayannidis, Alfonso Piciocchi, Antonella Vitale, Ilaria Iacobucci, Simona Soverini, Francesco Di Raimondo, Stefania Paolini, Giovanni Pizzolo, Angelo Michele Carella, Mario Cazzola, Antonio Cuneo, Pietro Leoni, Mario Luppi, Enrica Morra, Giorgina Specchia, Loredana Elia, Robin Foa, Michele Baccarani, Giovanni Martinelli; Institute of Hematology, Bologna, Italy; Gimema Data Center, Rome, Italy; Italian Multiple Myeloma Network, GIMEMA, Catania, Italy; Department of Medicine, Section of Hematology, Verona, Italy; Azienda Ospedaliera Universitaria S Martino di Genova, Genova, Italy; Division of Hematology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; Università degli Studi Ferrara, Arcispedale Sant'Anna, Ferrara, Italy; Division of Hematology, Nuovo Ospedale "Torrette", Ancona, Italy; Department of Oncology, Haematology and Respiratory Diseases, Section of Haematology, University of Modena and Reggio Emilia, Modena, Italy; Division of Hematology, "Ca Granda Niguarda Hospital", Milan, Italy; Department of Hematology, Bari, Italy; Department of Cellular Biotechnologies and Hematology, Sapienza University of Rome, Rome, Italy

Background: We have explored if the administration of two TKIs, Nilotinib (NIL) and Imatinib (IM) can improve the results without increasing the toxicity in the elderly Ph+ Acute Lymphoblastic Leukemia (ALL) patients. We investigate the type and number of BCR-ABL kinase domain mutations developing during and after the study. **Methods:** We have designed a study (ClinicalTrials.gov. NCT01025505) in which patients more than 60 years old or unfit for intensive chemotherapy and SCT where treated with two TKIs, NIL 400 mg twice daily, and IM 300 mg twice daily, alternating for 6 weeks for a minimum of 24 weeks (study core) and indefinitely in case of response. The 6-weeks rotation schedule was respected, irrespectively of temporary discontinuations. The primary end-point was the rate of Disease Free Survival (DFS) at 24 weeks (4 courses of treatment); the secondary end points included the evaluation of CHR, CCgR and CMR rates. **Results:** 39 patients have been enrolled in 15 Italian hematologic Centers (median age 66 years, range 28-84). Among these, 8 patients were unfit for standard chemotherapy or SCT (median age 50 years, range 28-59). 27 patients were p190, 5 were p210 and 7 were p190/p210. After 6 weeks of treatment, 36 patients were evaluable for response: 34 were in CHR (94%) and 2 in PHR (6%). 23 patients have already completed the study core (24 weeks), 87% were in CHR and 17 are currently continuing therapy in the protocol extension phase. Thus, the OS at 1 year is 79%, and 64% at 2 years. Overall, 1 patient was primarily resistant and 13 patients have relapsed, with a median time to relapse of 7.6 months (range 0.8-16.1 months), for a DFS of 51.3% at 12 months. **Conclusions:** In this small cohort of Ph+ ALL elderly/unfit patients, the rates of relapse and progression were not likely to be different from the rates observed with Imatinib alone. Acknowledgements: ELN, AIL, AIRC, PRIN. Clinical trial information: NCT01025505.

7026 Poster Discussion Session (Board #18), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Variations in FLT3 ligand levels during the course of AML treatment.

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Background: FLT3 ligand (FL) is a hematopoietic growth factor expressed in many tissues. AML patients who are administered myeloablative therapy exhibit a marked and transient rise in plasma FL concentrations. Furthermore, the presence of high concentrations (1000 pg/mL) of FL impedes the efficacy of FLT3 tyrosine kinase inhibitors in vitro. However, the behavior of FL concentrations throughout the course of AML treatment remains unknown. This pilot study was undertaken to track the relationship between AML therapy and FL levels over time. **Methods:** Ten AML patients were enrolled in an IRB-approved procurement protocol. Blood samples were collected at weekly intervals for one year, and plasma was isolated by centrifugation. Plasma FL and stem cell factor (SCF) concentrations were measured by ELISA. **Results:** We observed four distinct patterns in FL fluctuations. First, in all cases where induction or consolidation chemotherapy resulted in an aplastic bone marrow (nine patients), FL concentrations rose markedly and consistently to levels >1000 pg/mL following the administration of chemotherapy. Second, in three of four patients whose leukemia was refractory to induction chemotherapy, FL concentrations remained below 500 pg/mL during induction. Third, in two patients receiving the FLT3 TKI sorafenib, FL concentrations did not rise above 500 pg/mL while on this medication. Fourth, in one patient receiving the hypomethylating agent 5-azacitidine, FL concentrations remained below 100 pg/mL throughout the course of therapy. SCF concentrations did not vary throughout the course of chemotherapy. **Conclusions:** An "FL surge" was seen when cytotoxic chemotherapy resulted in aplasia. This FL surge was not seen with sorafenib or 5-azacitidine. In addition, the FL surge was attenuated in three patients whose leukemia was refractory to chemotherapy. These observations give rise to two new hypotheses regarding FL: 1) It is possible to maintain lower FL levels with targeted agents than with chemotherapy; and 2) Residual leukemia appears to inhibit the FL surge, providing indirect evidence of cross-talk between leukemia and the stromal microenvironment. This inhibition may be the explanation for why AML patients develop pancytopenia early in relapse.

7027 Poster Discussion Session (Board #19), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Use of Axl, a therapeutic target in AML, to mediate stroma-induced chemoresistance.

Isabel Ben Batalla, Alexander Schultze, Mark Wroblewski, Robert Erdmann, Michael Heuser, Kristoffer Riecken, Mascha Binder, Miguel Cubas-Cordova, Janning Melanie, Jasmin Wellbrock, Boris Fehse, Christian Hagel, Jürgen Krauter, James B. Lorens, Arnold Ganser, Walter M. Fiedler, Peter Carmeliet, Klaus Pantel, Carsten Bokemeyer, Sonja Loges; II. Medical Clinic & Institute of Tumor Biology, Campus Forschung, University Hospital Hamburg-Eppendorf, Hamburg, Germany; Department of Hematology, Hemostasis, Oncology, and Stem Cell Transplantation, Hannover Medical School, Hannover, Germany; Research Department Cell and Gene Therapy, Campus Forschung, University Hospital Hamburg-Eppendorf, Hamburg, Germany; II. Medical Clinic, Campus Forschung, University Hospital Hamburg-Eppendorf, Hamburg, Germany; Department of Neuropathology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; The Department of Biomedicine, Faculty of Medicine and Dentistry, University of Bergen, Bergen, Norway; Katholieke Universiteit Leuven, Leuven, Belgium; Institute of Tumor Biology, Campus Forschung, University Hospital Hamburg-Eppendorf, Hamburg, Germany

Background: Axl, the receptor for Growth Arrest-specific protein 6 (Gas6) plays a role in AML pathobiology (Blood Suppl. Nov 2011; 118: 940). Here, we investigated whether Axl represents a therapeutic target in AML. **Methods:** Gas6 levels were measured by ELISA and immunohistochemistry. Axl expression was detected by flow cytometry. Co-cultures of (murine) BM stroma cells (primary, OP9, S17) with Mv4-11 and OCI-AML5 cell lines were performed. **Results:** We found (i) higher expression of Axl in AML BM compared to healthy BM donors (66.20 ± 10.87 vs. 0.65 ± 0.10 %; n=8/6; $p<0.05$); (ii) Axl expression by 68 ± 31% of AML blasts and (iv) higher expression of Axl by $CD34^+CD38^-$ AML stem cells compared to healthy $CD34^+CD38^-$ BM stem cells (58.43 ± 4.63 % vs. 6.00 ± 2.01 %; n=7/6; $p<0.05$). The Axl inhibitor BGB324 dose-dependently inhibited proliferation of primary AML cells with a mean IC50 of 1.8 μM. Sensitivity to BGB324 (i.e. a lower IC50) correlated with Axl expression on leukemia cells (Pearson's r = -0.9656, $p<0.05$). Combination therapy with BGB324 and cytarabine exerted an additive therapeutic effect and BGB324 could chemosensitize cytarabine-resistant AML cells. Analyses of BM sections revealed that Gas6 expression was low in AML cells, similar to healthy hematopoietic cells while it was abundantly expressed in AML BM stromal cells with fibroblastic/mesenchymal morphology (BMDSCs). Gas6 expression was considerably lower in control BMDSCs (86 ± 14 % vs. 20 ± 20 %; n=5/7; $p<0.05$) thus suggesting a possible paracrine interaction between AML cells and BMDSCs leading to Gas6 upregulation in the stroma compartment. Co-culture experiments indicated specific upregulation of murine (m)Gas6 in BMDSCs via leukemia-cell derived IL-10 and M-CSF. This stroma-derived Gas6 could mediate chemoresistance of AML cells in co-culture, which was abrogated by sAxl or by BGB324. Thus, interaction between stroma-derived Gas6 and Axl^+leukemia cells forms a chemoprotective niche for leukemia cells. In line with these findings Axl blockade chemosensitizes Mv4-11 cells for treatment with doxorubicine in vivo. **Conclusions:** Axl represents a therapeutic target in AML and Axl inhibition by BGB324 holds potential to treat chemosensitive and chemoresistant AML.

7028 Poster Discussion Session (Board #20), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

SWOG S0919: A phase II study of idarubicin and cytarabine in combination with pravastatin for relapsed acute myeloid leukemia (AML).

Anjali S. Advani, Shannon McDonough, Edward Copelan, Cheryl L. Willman, Deborah A. Mulford, Alan F. List, Mikkael A. Sekeres, Megan Othus, Harry P. Erba, Frederick R. Appelbaum; Cleveland Clinic Taussig Cancer Institute, Cleveland, OH; SWOG Statistical Center, Seattle, WA; Levine Cancer Institute, Carolinas Healthcare System, Charlotte, NC; University of New Mexico Cancer Center, Albuquerque, NM; University of Rochester Medical Center, Rochester, NY; H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; University of Alabama at Birmingham, Birmingham, AL; Fred Hutchinson Cancer Research Center, Seattle, WA

Background: Inhibition of cholesterol synthesis and uptake sensitizes AML blasts to chemotherapy (Blood 104: 1816, 2004). A prior Phase 1 study demonstrated the safety of high dose pravastatin given with idarubicin and cytarabine in patients with AML and also reported an encouraging response rate (Blood 109: 2999, 2007). SWOG S0919 therefore evaluated the complete remission (CR) rate in a larger number of pts with relapsed AML treated with the pravastatin dose arrived at in the Phase 1 trial. **Methods:** Pts were treated at SWOG institutions from Aug 2009 through Nov 2012. Pravastatin was supplied by Bristol-Meyers Squibb. The protocol was approved by each institution's review board. Eligibility: age $\geq$ 18 yrs, relapsed AML, cardiac ejection fraction $\geq$ 45%, CR/ CR with incomplete count recovery (CRi) following most recent chemotherapy lasting $\geq$ 3 months, no prior hematopoietic cell transplant. Treatment: oral pravastatin 1280 mg Days 1-8, idarubicin 12 mg/m^2/d IV Days 4-6, and cytarabine 1.5 g/m^2/d continuous IV infusion Days 4-7. Pts achieving a CR could receive 2 cycles of consolidation. CR and CRi were defined by IWG criteria. Fifty eligible pts were to be accrued. If $\geq$ 21 pts achieved CR or CRi, the regimen would be considered sufficiently effective (critical level = 4.8% if true CR rate = 30% and power of 90% if true CR rate = 50%). **Results:** The study closed to accrual on Nov 1, 2012 after meeting the defined criterion for a positive study. Thirty-six pts with a median age of 59 yr (range 23-78) were enrolled. Seventeen pts (47%) were male and the median WBC was 2800/ uL (range 700-110,600). The median time from initial dx to registration was 18 mo (range 5-136). Relapse status: 1st: 17 pts (47%), 2nd: 15 (42%), 3rd: 2 (5.5%), and 4th: 2 (5.5%). Eighteen pts have died, 3 during treatment. The response rate was 75% (95% CI 58-88%; 20 CR, 7 CRi); and the median overall survival was 10 mo. The p-value comparing 75% to 30% (null response rate) is 3.356×10^{-8}. Duration of last CR ($\leq$ 6 months) and prior high dose cytarabine exposure did not affect response to protocol treatment. **Conclusions:** The CR/ CRi in this relapsed population is encouraging. We plan to evaluate the efficacy of this regimen in higher-risk patients. Clinical trial information: NCT00840177.

7029^ Poster Discussion Session (Board #21), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Activity and tolerability of SL-401, a targeted therapy directed to the interleukin-3 receptor on cancer stem cells and tumor bulk, as a single agent in patients with advanced hematologic malignancies.

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Background: SL-401 is a novel biologic targeted therapy directed to the interleukin-3 receptor (IL-3R). IL-3R is overexpressed on cancer stem cells (CSCs) and tumor bulk relative to normal hematopoietic cells in a wide range of hematologic malignancies including AML and blastic plasmacytoid dendritic cell neoplasm (BPDCN). Since SL-401 targets both leukemia blasts and CSCs, tumor regression and improvement in long-term outcome is expected. The clinical activity and side effect profile of SL-401 were evaluated in a multicenter Phase I/II trial of patients with advanced hematologic cancers. **Methods:** Eighty-one patients with advanced hematologic cancers, including relapsed or refractory AML (n = 59) and heavily pretreated BPDCN (n = 4), have been enrolled. Patients received a single cycle of SL-401 via 15-minute IV infusion to determine the maximum tolerated dose (MTD) and assess antitumor activity. **Results:** A single cycle of SL-401 demonstrated single agent activity in relapsed or refractory AML patients, including 2 durable CRs of 8 and 25+ months duration and multiple cases of blast reductions. SL-401, when delivered at therapeutically relevant doses, was associated with > 3-fold greater median overall survival (OS) in AML patients who received 2+ prior lines of treatment relative to historical results. In addition, 3 heavily pre-treated patients with BPDCN, an uncommon malignancy that expresses high levels of IL-3R and is ultrasensitive to SL-401 (IC_{50} values in the femtomolar [10^{-15} M] range), had CRs, with durations of 5, 3+ and 1+ months. The MTD was 16.6 μg/kg/day; the dose-limiting toxicities of hypoalbuminemia and edema, which are manifestations of capillary leak, occurred at 22.1 μg/kg/day. Other ≥ Grade 3 adverse events included transient transaminase elevations. There was no treatment-related myelosuppression. **Conclusions**: SL-401 was well tolerated and demonstrated single agent activity in patients with relapsed or refractory AML and BPDCN. Based on these findings, single agent SL-401 given in multiple cycles will be advanced into pivotal studies of AML (3^{rd}-line) and BPDCN. Clinical trial information: NCT00397579.

7030 Poster Discussion Session (Board #22), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Exploratory analysis of the effect of ruxolitinib on bone marrow morphology in patients with myelofibrosis.

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Background: Myelofibrosis(MF) is characterized by splenomegaly, burdensome symptoms, progressive bone marrow (BM) fibrosis, and shortened survival. Ruxolitinib (Rux), an oral, FDA-approved JAK1/JAK2 inhibitor, has demonstrated improvements in spleen volume, symptoms, and survival in patients (pts) with MF. This study was conducted to explore possible effects of long-term Rux treatment on BM morphology in MF. **Methods:** Trephine biopsies were obtained at baseline, 24 (67 pts), and 48 (17 pts) months (mo) from the cohort of MF patients treated at MD Anderson Cancer Center who participated in a phase I/II trial of Rux (NCT00509899). The clinical outcomes from this trial have been published previously [Verstovsek, NEJM 2010]. Two of the authors (JT and HMK) independently evaluated the World Health Organization (WHO)-defined BM fibrosis grade (0-3). Reviewers were blinded to pts characteristics and outcomes and consensus decided discordant scores. For demonstrative purposes, WHO BM fibrosis grading was also determined for a control cohort of pts treated with hydroxyurea (HU) for 24 (31 pts) and 48 (20 pts) mo. Changes in BM fibrosis grade vs. baseline were calculated for 24 and 48 mo, and categorized as improvement, stabilization, and worsening for each patient. **Results:** A higher percentage of Rux-treated pts showed stabilization or improvement of BM fibrosis at both 24 and 48 mo than the HU-treated pts. Worsening was greater in the HU-treated cohort at both time points. **Conclusions:** This exploratory analysis of long-term exposure to Rux in MF provides the first indication that JAK inhibitor therapy may be able to meaningfully retard advancement of BM fibrosis. A comparable effect was not seen with long-term HU therapy. Additional research is needed to further elucidate these findings. Clinical trial information: NCT00509899.

Direction of changes in WHO-defined BM fibrosis grade versus baseline*	24 mo		48 mo	
	HU	Ruxolitinib	HU	Ruxolitinib
No. of pts	31	67	20	17
Stabilization	52%	57%	35%	53%
Improvement	10%	15%	0%	24%
No. of pts†	23	50	17	15
Worsening	52%	38%	76%	27%

* Not a formal comparison. †Pts with baseline BM fibrosis grade 3 were excluded from this calculation because they could only stabilize or improve.

7031 Poster Discussion Session (Board #23), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Phase II study of orally administered rigosertib (ON 01910.Na) in transfusion-dependent lower-risk myelodysplastic syndrome (MDS) patients.

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Background: Rigosertib, a novel small molecule inhibitor of PI3-Kinase and PLK pathways is currently evaluated (IV infusions) in a phase III trial in higher risk MDS patients who have failed hypomethylating agents. A previous phase I study found good bioavailability and activity of orally administered rigosertib in transfusion-dependent MDS patients (ASH 2011). Here we report preliminary results from an ongoing phase II study. **Methods:** This is a randomized, two-arm study of oral rigosertib (560 mg bid) administered either intermittently (2 out of 3 weeks) or continuously. Transfusion-dependent patients must have received at least 4 units RBC transfusions over 8 weeks before randomization, and can receive transfusions and erythrocyte stimulating agents (ESAs) while on study. **Results:** Twenty nine MDS patients (25 intermediate-1 and 4 low risk per IPSS classification) have been randomized as of December 17, 2012. Overall oral rigosertib was well tolerated except for a high incidence (5 of 9 patients) of grade 2+ urinary side effects (dysuria, hematuria, cystitis, and urinary urgency), in the continuous dosing arm. Accordingly, the protocol was amended to allow all patients to be treated with intermittent dosing, with option of dose interruption/reduction resulting in a much lower frequency of urinary side effects (4/20 patients with urinary grade 2+ toxicity). Fifteen patients (none of them with del5q cytogenetic) have been treated with intermittent dosing for at least 8 weeks. Seven (47%) patients achieved transfusion independence (no RBC transfusion for at least 8 consecutive weeks), which lasted 8 to 27 + weeks. Six of 7 responding patients were refractory to prior treatment with ESAs and 5 of these 7 patients received concomitant ESAs, suggesting an effect of rigosertib on ESA resistance. **Conclusions:** Preliminary results of this phase II study indicate that intermittent dosing of rigosertib administered orally is well tolerated and active in producing transfusion independence in approximately 50% transfusion dependent, lower risk MDS patients. The contributing role of rigosertib and ESAs in these transfusion responses is being investigated. Clinical trial information: NCT01584531.

7032 Poster Discussion Session (Board #24), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

The origin of GPI-AP deficient cells in MDS, MPD, and aplastic anemia and its significance in predicting leukemic transformation.

Jeffrey J. Pu, Jerry L. Spivak, Robert A. Brodsky, Alison Moliterno; Penn State Hershey Cancer Institute, Hershey, PA; Division of Hematology, Department of Medicine, Johns Hopkins University, Baltimore, MD; Johns Hopkins Medicine, Baltimore, MD

Background: PNH is a clonal disorder originating from a multipotent hematopoietic stem cell (HSC) acquiring a PIG-A gene mutation. PIG-A mutation lead to glycosylphosphatidylinositol-anchor protein (GPI-AP) deficiency, which contributes to many manifestations of PNH. About 25% of MDS and MPD, and 60% of AA also harbor small population of PNH-like cells. It was observed that 1) 10-20% AA harboring PNH-like cells eventually transform into PNH; but MDS and MPD seldom evolve to PNH; 2) AA harboring PNH-like cells may have a better response to immunosuppressive therapy; and 3) PIG-A mutation frequency significantly increased in some human cell lines with genomic instability. However, the clinical significances of these PNH-like cells in MDS, MPD, and AA are unclear. **Methods:** We prospectively recruit MDS, MPD, and AA patients. Peripheral blood flow cytometry is used to identify GPI-AP deficient blood cells, a proaerolysin-resistant CFC assay is used to select GPI-AP deficient progenitor cells, a novel T cell enrichment assay with proaerolysin selection is used to expand GPI-AP deficient T cells, and RT-PCR assay and DNA sequencing assay are used to identify and analyze particular gene expression deficiency in GPI-AP biosynthesis. **Results:** Our preliminary data shows that PNH-like cells in AA arise from multipotent HSC harboring PIG-A mutation; in MDS initiated at progenitor harboring PIG-A mutations and are transient; and in MPD caused from PIG-Y gene transcriptional silencing. Interestingly, the PIG-A mutation frequency in 4 MDS harboring PNH-like cells were 10~100 times higher than healthy controls. Furthermore, these 4 MDS and 3 MPD harboring PNH-like cells rapidly transformed into acute myelogenous leukemia. **Conclusions:** The origins and the clonality of PNH-like cells are different among MPD, MDS, and AA. This may explain why AA often evolves into PNH, but MPD and MDS seldom transform into PNH. PNH-like cell population in MPD and MDS is a marker of genomic instability and may predict a risk of leukemic transformation.

7033 Poster Discussion Session (Board #25), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Survival and cause of death in patients with refractory anemias.

Yue Zhang, Bonnie Gould Rothberg, Daniel Morgensztern; Yale School of Medicine, New Haven, CT

Background: Despite its common occurrence, there are few large population-based studies on low-grade myelodysplastic syndromes (MDS). We evaluated the outcomes for the two low-risk MDS subtypes. **Methods:** The Surveillance, Epidemiology and End Results (SEER) database was searched for patients with refractory anemia (RA) or RA with ringed sideroblasts (RARS), diagnosed between 2001 and 2009 with complete demographic information. Incidence rates were calculated from SEERStat 7.1. Overall survival (OS) and disease-specific survival (DSS) were calculated from diagnosis to death from any cause and death from MDS or acute leukemia, respectively. Univariate survival was estimated by the Kaplan-Meier method and curves compared by log rank. Univariate and multivariable Hazard ratios (HR) were calculated by Cox Proportional Hazards. **Results:** Among the 6,505 patients who met the inclusion criteria, there were 3,866 (59%) RA and 2,639 (41%) RARS. Age-adjusted incidence rates per 100,000 population for RA and RARS were 0.55 and 0.44 respectively. Medians OS for RA and RARS were 39 and 48 months respectively. Although RARS was associated with improved 5-year OS compared to RA (41.3% vs 37.7%; HR 0.86; 95% CI 0.81-0.92, $p < 0.0001$), there were no differences in 5-year DSS (74.2% vs 76.3%; HR 1.01, 95% CI 0.90-1.14, $p = 0.41$). Altogether, 2,112 deaths were accrued among RA patients and 1,352 among the RARS subclass. The number of deaths due to MDS or acute leukemia were 610 (28.8%) in RA and 457 (33.8%) in RARS. Acute leukemia was the cause of death in 190 (9.0%) RA patients and in 143 (10.6%) of RARS patients. Cardiovascular disease accounted for 25% of total deaths in RA and RARS. After adjusted for age, gender, race and year of diagnosis, RARS was associated with increased OS (HR 0.81; 0.76-0.87; $p < 0.0001$) but not DSS (HR 0.95; 0.84-1.07, $p = 0.41$). **Conclusions:** Both RA and RARS are indolent diseases with a high 5-year DSS and death occurring mostly from other causes, particularly cardiovascular disease. Although RARS was associated with better 5-year OS compared to RA, there were no differences in 5-year DSS.

7034 General Poster Session (Board #34B), Sun, 8:00 AM-11:45 AM

Costs of allogeneic hematopoietic cell transplantation using reduced intensity conditioning regimens.

Nandita Khera, Amy Emmert, Barry Storer, Brenda M. Sandmaier, Edwin Alyea, Stephanie Lee; Division of Hematology/ Oncology, Mayo Clinic in Arizona, Phoenix, AZ; Dana-Farber Cancer Institute, Boston, MA; Fred Hutchinson Cancer Research Center/University of Washington, Seattle, WA

Background: Reduced intensity (RIC) conditioning regimens have allowed older patients and those with comorbidities to receive hematopoietic cell transplantation (HCT). **Methods:** We analyzed medical costs from the beginning of conditioning to 100 days after HCT for 484 patients who underwent a RIC allogeneic HCT at Fred Hutchinson Cancer Research Center (FHCRC; n=147) and Dana Farber Cancer Institute (DFCI; n=337) from 1/2008 to 12/2010. Costs up to 2 years after HCT were analyzed for DFCI (n=311) as most patients receive their post-transplant care there. Multiple linear regression was used to analyze the association between clinical variables and costs. **Results:** Disease distribution and transplant characteristics were comparable between the two sites, though significant differences were seen in age distribution (88% FHCRC patients ≥ 50 years vs. 80% at DFCI, p=0.04) and pre-transplant performance scores (63% patients with Karnofsky score≥ 90 at FHCRC vs. 47% at DFCI; p=0.006). Median costs for first 100 days in 2010 $ at FHCRC and DFCI were $129 000 (range 31,000-352,000) and $96,000 (3,000-614,000) respectively, p=0.0002, but differences were not significant in multivariate analysis. Inpatient costs accounted for 42% of early costs at FHCRC and 87% at DFCI.Significant predictors for early costs included a diagnosis of lymphoma/ myeloma (17% decrease in costs; p=0.01), donors other than matched related (50 -100% increase; p<0.001), relapse (17% increase, p=0.04) and ≥ grade II acute GVHD (37% increase; p<0.001). Median costs between d100 and 2 years were $39,000 (0-976,000) at DFCI. 39% of the 2 year costs occurred after first 100 days. There was no association of late costs with pre-transplant variables, and only death was associated with higher costs (138% increase; p=0.005). **Conclusions:** After adjustment for pre and post HCT variables, the overall costs of the RIC allogeneic transplants were similar between the two institutions despite different management approaches (inpatient vs. outpatient conditioning) and accounting methodologies. Use of unrelated/ alternative donors, relapse and acute GVHD were predictors for higher early costs while only death was associated with higher late costs.

7035 General Poster Session (Board #34C), Sun, 8:00 AM-11:45 AM

Outcomes of hematopoietic stem cell transplant recipients admitted to the medical intensive care unit.

Duc Quang Tran, Amelia A. Langston, Edmund K. Waller, Melanie Simon, Charise Gleason, Daniela Casbourne, Micah Fisher, Jonathan L. Kaufman, Christopher Flowers, Sagar Lonial, Ajay K. Nooka; Emory University Winship Cancer Institute, Atlanta, GA; The Winship Cancer Institute of Emory University, Atlanta, GA; Emory University, Atlanta, GA; Emory University BMT Program, Atlanta, GA; Department of Medical Oncology, Winship Cancer Institute, Emory University, Atlanta, GA; Emory University School of Medicine, Atlanta, GA; Division of BMT, Emory University, Winship Cancer Institute - Hematology and Medical Oncology, Atlanta, GA

Background: Outcome results for hematopoietic stem cell transplant (HSCT) patients admitted to intensive care unit (ICU) and prognosis is infrequently reported during recent years, especially in view of increasing use of unrelated donors, increasing use of transplant maneuver in older patients using reduced intensity conditioning regimens and improvement in supportive care. We assessed our institutional survival outcomes and evaluated predictors of mortality in HSCT recipients admitted to ICU. **Methods**: Among the 390 HSCTs performed from March 2011 until July 2012, we retrospectively evaluated 34 HSCT patients admitted to ICU. 22 patients received mechanical ventilation (MV) or vasopressor support and were analyzed separately. All previously defined predictors of mortality were evaluated. SPSS version 20 was used for statistical analysis. **Results**: 9% of all HSCT patients were admitted to ICU. 65% of patients received allogeneic transplants. Major underlying hematological malignancies were AML/MDS (29%) and myeloma (24%). 41% were admitted for respiratory failure and 23.5% for sepsis. Median age was 55.5 (range: 27-76). Median length of ICU stay was 7 days (0-42) and median APACHE II score was 20 (9-39). 30 day and 60 day mortality rates are 47% and 62% among all patients; 54% and 68% among MV patients or receiving vasopressors. Predictors for day 30 mortality on univariate analysis among all patients were APACHE II score $\geq$26 ($p=0.05$). Predictors for day 60 mortality were APACHE II score $\geq$31 ($p=0.001$) and multiorgan failure ($p=0.009$). Among patients receiving MV or vasopressors, APACHE II score $\geq$31 is the only significant predictor of mortality ($p=0.011$). On multivariate analysis, APACHE II score $\geq$31 at day 30 hazards ratio (HR) 3.777 (95%CI 1.041-13.69; $p=0.043$) and at day 60 HR 3.789 (95%CI 1.07-13.45; $p=0.039$) are significant predictors of mortality. **Conclusions**: Significant predictors identified on multivariate analyses were APACHE II score $\geq$31 at day 30 and day 60. Interestingly, type of transplant is not a significant predictor of mortality. Future studies with larger patient samples and longer follow up are required for further understanding of prognosis in these patients.

7036 General Poster Session (Board #34D), Sun, 8:00 AM-11:45 AM

Cutaneous complications in hematopoietic cell transplant recipients: Impact of biopsy on patient management.

Oana Valeria Paun, Tycel Jovelle Phillips, PingFu Fu, Robert Novoa, Kord Honda, Kurt Quoc Lu, Hillard M. Lazarus; Case Western Reserve University, Cleveland, OH; University of Michigan, Ann Arbor, MI; Case Comprehensive Cancer Center, Cleveland, OH; University Hospitals Case Medical Center, Cleveland, OH; University Hospitals, Cleveland, OH

Background: Although skin biopsies are recommended for diagnostic purposes in hematopoietic cell transplant (HCT) recipients, their utility in directing management of post transplant cutaneous eruptions remains uncertain. Little evidence was found in support of this procedure either from a diagnostic or prognostic perspective. **Methods:** We retrospectively evaluated 351 consecutive HCT recipients transplanted at our institution between January 2005 and December 2011; 156 patients underwent 388 cutaneous biopsies. **Results:** The group that underwent cutaneous biopsy after transplantation and the group that was spared the procedure were homogenous with regards to age and gender. The pre-biopsy diagnosis and final diagnosis differed in 213 episodes (55%) as determined by histologic evaluation. Biopsy results led to a change in therapy in 61 of 388 (16%) biopsied rashes. With regards to therapy changes, 24 of 61 (39%) occurred in response to a clinical diagnosis of GVHD. In this situation the most frequently noted change was augmentation or addition of systemic immuno-suppression (19 of 24). Changes in systemic therapy occurred with similar frequencies with respect to concordance or discordance between clinical and histopathologic diagnosis ($p = 0.12$). We used classification and regression tree analysis to develop an algorithm to predict the biopsy yield as expressed by change of management. This is a non-parametric decision tree learning technique that produces a classification tree based on a categorical dependent variable, formed by a collection of rules based on variables in the modeling data set. **Conclusions:** Cutaneous biopsy findings often changed the clinical dermatologic diagnoses of HCT recipients; however, the impact of biopsy results on treatment decisions was less profound; altered diagnoses in patients who underwent biopsy often did not lead to therapy changes. Skin biopsies of post-transplant patients may not be mandatory for either diagnostic or therapeutic reasons, but in carefully chosen circumstances can yield extremely important data. A prospective study should be undertaken in order to evaluate current practice data and to validate our decision making analysis tree.

7037 General Poster Session (Board #34E), Sun, 8:00 AM-11:45 AM

Impact of oral mucositis on outcomes of multiple myeloma patients treated with high-dose melphalan conditioning and autologous stem cell transplantation (ASCT).

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Background: High-dose melphalan is the standard conditioning regimen for patients with multiple myeloma (MM) undergoing ASCT. However, this therapy is commonly associated with severe oral mucositis (OM). Low-level laser therapy (LLLT) has been reported as an effective method in preventing this complication. The aim of this study was to define the potential impact of OM on outcomes in patients with MM undergoing ASCT and receiving preventive LLLT. **Methods:** We describe a retrospective cohort of 79 consecutive patients with MM who received high-dose melphalan conditioning. All patients received prophylactic LLLT application performed daily from the beginning of the conditioning regimen up to day +2. The patients continued receiving LLLT in case of OM grade $\geq$ 2 until complete remission of the lesions. OM severity was assessed daily using WHO scale from the beginning of conditioning until hospital discharge. We examined the relationship between worst OM grade and clinical outcomes, including days with oral pain, days of total parenteral nutrition, days of LLLT and days with neutropenic fever. **Results:** Of 79 patients, 55 (69.62%) experienced OM grade 0-1, 16 (20.25%) experienced OM grade 2, 7 (8.86%) grade 3 and 1 (1.26%) grade 4. Patients with OM grade 0-2 had statistically fewer days of oral pain compared with grade 3-4 (0.88 and 6.25 days, respectively, $p = 0.0001$). The worst OM grade was also significantly ($p < 0.05$) associated with days of narcotic therapy and length of LLLT. Severe OM was not associated with febrile days or the use of parenteral nutrition. **Conclusions:** Severe OM is associated with worse clinical outcomes. In this transplantation setting, severe OM was not common as previously reported in literature, probably due to LLLT. Controlled randomized trials should be performed to confirm the real benefit of LLLT in this scenario as well as the pharmacogenomics and pharmacokinetic studies to better understand interpatient variability of melphalan exposure and toxicity.

7038 General Poster Session (Board #34F), Sun, 8:00 AM-11:45 AM

Comparison of allogeneic stem cell transplantations in chronic myeloid leukemia before and after the era of tyrosine kinase inhibitors.

Muhit Ozcan, Bengi Ozturk, Mehmet Ozen, Pervin Topcuoglu, Mutlu Arat, Onder Arslan, Osman Ilhan, Hamdi Akan, Meral Beksac, Nahide Konuk, Gunhan Gurman; Ankara University Faculty of Medicine, Department of Hematology, Ankara, Turkey; Department of Hematology, Ankara University Faculty of Medicine, Ankara, Turkey; Ankara University, Ankara, Turkey; Ankara University Faculty of Medicine, Department of Hematology, Istanbul, Turkey; Ankara University School of Medicine, Ankara, Turkey; Ankara University Faculty Of Medicine, Department of Hematology, Ankara, Turkey; Ankara University Faculty of Medicine Department of Hematology, Ankara, Turkey

Background: In this retrospective study we aimed to evaluate the rates and the clinical outcomes of allo-HSCT in CML following the advent of TKIs. **Methods:** We compared the transplantations (Txs) performed prior to 2002 (old era), the first year of TKIs, with the Txs during and after 2002 (new era). **Results:** Between 1989 and 2012 inour Tx unit a total of 189 allo-HSCTs were performed in 185 CML patients (second Tx for 4 patients). The ratio of Tx for CML among the whole Tx group decreased from 40 % to 12 % after 2002. The ratio also dropped to less than 5 % after 2008 and increased again to 15% in 2012. Time from diagnosis to Tx was longer in the old era than in the new era (9.2 months vs 15.4 months, $p<.0001$). The ratio of patients with advanced disease (accelerated or blastic phase) was higher in the new era. Although the progression free survival (PFS) was shorter in the new era than in the old era (median 13.8 months vs 37.1 months, $p=0.09$), overall survival, Tx outcomes and survival curves did not change. **Conclusions:** AlloHSCT rates sharply decreased after the TKIs, but a slight increase in recent years have been observed compatible with the TKI's failure in years. Despite the fact that patients who underwent allo HSCT in the new era had more challenging disease biologically, overall survival was not affected possibly due to post-Tx interventions such as use of TKI alone or with donor lymphocyte infusion.

Features	Prior to 2002 (n=128)	During and after 2002 (n=61)	P
Median age (range), years	34 (14-48)	34 (18-57)	0.4
Gender (M/F), n	73/55	35/26	0.9
Donor	32 (9-56)	32 (0-65)	0,8
Median age (range), years	72/50	31/50	0,5
Gender (M/F), n	128/0	54/7	<.0001
Related or unrelated, n			
TKIs use at pre-Tx	0	43 (70 %)	
Myeloablative/reduced IC	118/10	44/17	<.0001
Stem cell source	64/64/0	19/40/2	0.009
BM/PB/CB			
Immune-supression	120/4/4	45/15/1	<.0001
CsA-Mtx/CsA-MMF/other			
Disease status at pre-Tx	116/4/7/1	32/13/5/11	<.0001
CP1/[s]CP2/AP/BC			
Engraftment kinetics	16 (0-34)	16 (0-54)	0.8
Neutrophil (>0.5x10e9/L), d	15 (11-59)	14 (0-69)	0.3
Platelet (>20x10e9/L), d			
Tx response, CR (%)	86.7	91.8	0.2
Tx related mortality (%)	32.8	31.1	0,8
Median PFS	37.1	13.8	0.09
Median OS	Not reached	Not reached	0.3

7039 General Poster Session (Board #34G), Sun, 8:00 AM-11:45 AM

Comparison of four different strategies of stem cell mobilization in patients with multiple myeloma.

Jeffrey Michael Sivik, Sesilya Whaley, Joseph Mierski, William J. Castellani, Mitzi Lowe, Junjia Zhu, Melissa George, Witold B. Rybka, Giampaolo Talamo; Penn State Hershey Cancer Institute, Hershey, PA; Penn State Hershey Medical Center, Hershey, PA

Background: There is no consensus among institutions for the optimal strategy of peripheral blood stem cell (PBSC) collection for autologous stem cell transplantation (ASCT) in patients with multiple myeloma (MM). **Methods:** We retrospectively analysed the outcomes of PSBC collection in MM patients using the following mobilization regimens: cyclophosphamide 5,000 mg/m^2 + etoposide 1,000 mg/m^2 + G-CSF 5 mcg/Kg/day (Group A, n = 49); cyclophosphamide 2,000-3,000 mg/m^2+ G-CSF 5 mcg/Kg/day (Group B, n = 25); G-CSF 16 mcg/Kg/day (Group C, n = 21); G-CSF 16 mcg/kg/day + plerixafor 0.24 mg/Kg (Group D, n = 128). **Results:** The median number of PBSC collected was 28.1 (range, 2.1-134), 4.5 (0.1-39.7), 4.0 (0-7.3) and 8.4 (0.2-41.2) million CD34+/kg in groups A, B, C and D, respectively (p <0.001). The mean number of collection days was 1.3, 2.2, 2.4, and 1.3 in groups A, B, C, and D, respectively (p <0.001). Febrile neutropenia occurred in 16 (32.7%), 1 (4%), 0, and 0 patients in groups A, B, C, and D, respectively. One patient who received CTX 3 g/m^2 died of septic shock during the neutropenic phase. Failure to collect PBSC, defined as <2x10^6 CD34+ cells/Kg for a planned single ASCT or <4x10^6 for planned tandem ASCTs, was observed in 2/49 (4%), 5/25 (20%), 4/21 (19%), and 9/128 (7%) patients in groups A, B, C, and D respectively (p=0.037). **Conclusions:** Plerixafor + G-CSF provided the greatest benefit to risk ratio for PSBC collection in MM patients.

7040 General Poster Session (Board #34H), Sun, 8:00 AM-11:45 AM

Efficacy and cost of peripheral blood stem cell (PBSC) mobilization with low-dose cyclophosphamide (LD-CY) compared with plerixafor (P) in multiple myeloma (MM) patients (pts) treated with novel induction therapies.

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Background: Efficacy and cost effectiveness of P vs. LD-CY mobilization in MM pts treated with novel induction therapies is not known. **Methods:** We analyzed the mobilization outcomes of 107 consecutive pts who underwent a planned, single autograft within 1-year of starting induction therapy with novel agents (thalidomide, lenalidomide, bortezomib) between 2003-2012. Pts undergoing mobilization with LD-CY/G-CSF (1.5gm/m^2) (n=74) were compared against those receiving P/G-CSF (0.24mg/kg) (n=33). Efficacy of PBSC mobilization was assessed by evaluating peak peripheral blood (PB) CD34+ cell counts, CD34+ cell yield on day1 of collection, total CD34+ cell collection, and total number of apheresis sessions. Mobilization failure was defined as failure to collect $\geq 2 \times 10^6$ cells/kg body weight. Mobilization costs were calculated per patient in both groups. Centers for Medicare and Medicaid Services reimbursement rates and Red Book Average Wholesale Price were used for cost determination. **Results:** At baseline, the LD-CY and P cohorts were well balanced. Compared to LD-CY, P use was associated with higher median peak PB CD34+ cell count (68/μl vs. 36/μl, p=0.048), CD34+ yield on day 1 of collection (6.9 $\times 10^6$/kg vs. 2.4 $\times 10^6$/kg, p=0.001), and total CD34+ cell yield (11.6 $\times 10^6$/kg vs. 7$\times 10^6$/kg, p=0.001). Median numbers of apheresis sessions were 2 in each group (p=0.17). In pts with prior lenalidomide use, mobilization failure rate in the LD-CY group was higher compared to the P group (20% vs. 0%, p=0.01). P group had a higher number of pts collecting $\geq 10 \times 10^6$/kg CD34+ cells (60.6% vs. 31%, p=0.01). Rate of infectious complications, transfusion requirements and hospitalizations was similar in both groups. The average total cost of mobilization in the P group was significantly higher compared to the LD-CY group ($28,980 vs. $19,627, p-value<0.0001). **Conclusions:** Our data indicates that although associated with a significantly higher total mobilization cost, plerixafor produced a more robust PBSC mobilization, without any collection failures.

7041 General Poster Session (Board #35A), Sun, 8:00 AM-11:45 AM

Day 100 peripheral blood absolute monocyte/lymphocyte count prognostic score and survival in diffuse large B-cell lymphoma post-autologous peripheral blood hematopoietic stem cell transplantation.

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Background: Prognostic factors for diffuse large B-cell lymphoma (DLBCL) at day 100 post-autologous peripheral blood hematopoietic stem cell transplantation (APBHSCT) have not been evaluated. We previously reported that absolute monocyte (AMC)/lymphocyte count (ALC) prognostic score (AMLCPS) at diagnosis of DLBCL patients is a prognostic factor of survival, stratifying patients into three risk groups: low- (AMC$<$630/μL and ALC$>$1000/μL), intermediate- (AMC $\geq$ 630/μL or ALC $\leq$ 1000/μL) and high-risk (AMC $\geq$ 630/μL and ALC $\leq$ 1000/μL) (Leukemia 25: 1502-9, 2011). Therefore, we evaluated day 100 AMLCPS as a prognostic factor of survival by landmark analysis from day 100 post-APBHSCT in DLBCL patients. **Methods:** DLBCL patients that achieved complete response by day 100 post-APBHSCT qualified for the study. From 2000 to 2007, 134 consecutive DLBCL patients were evaluated. Overall survival (OS) and progression free survival (PFS) were calculated using Kaplan-Meier analysis. **Results:** The median follow up from day 100 for the cohort was 5.5 years (range: 0.17-12.17 years) and for living patients (N=93) was 6.9 years (range: 2.5-12.17 years). Day 100 AMLCPS was able to stratify patients into three risk groups low-, intermediate-, and high-risk for OS [low: median OS = not reached, 5-year survival rate = 94% (95%CI 83.3%-98.1%); intermediate: median OS = not reached, 5-year survival rate = 70% (95%CI 58.0%-79.8%); high: median OS = 2.2 years, 5-year survival rate = 13% (95%CI 3.4%-40.5%); p$<$0.0001] and PFS [low: median PFS = not reached, 5-year progression free rate = 87% (95%CI 74.5%-94.3%); intermediate: median PFS = 10.9 years, 5-year progression free rate = 67% (95%CI 55.4%-77.5%); high: median PFS = 1 year, 5-year progression free rate = 13% (95%CI 3.4%-40.5%); p$<$0.0001]. The day 100 AMLCPS was balanced in relation to the International Prognostic Index (IPI; p=0.22), infused CD34+ stem cells (p=0.92), and disease status pre-APBHSCT (complete remission versus partial response; p=0.11). **Conclusions:** The day 100 AMLCPS is a simple biomarker that can help identify DLBCL patients post-APBHSCT with poor clinical outcomes.

7042 General Poster Session (Board #35B), Sun, 8:00 AM-11:45 AM

Primary payer status and outcomes after autologous hematopoietic stem cell transplant: A national perspective.

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Background: With healthcare cost in rise, it is of interest to explore variation in healthcare delivery outcome with different payment source. This study was aimed to analyze relationship between payment source and outcome following autologous hematopoietic stem cell transplant (AutoHSCT) in a national database. **Methods:** We identified all hospitalizations with AutoHSCT (n=1,673) from Nationwide Inpatient Sample (NIS), Healthcare Cost and Utilization Project (HCUP), Agency for Healthcare Research and Quality 2010 database using the ICD 9 procedure codes 41.04 and 41.07. Based on sample weights an estimated 8,444 AutoHSCT procedures were performed nationwide in 2010. Patients were stratified on the basis of payer status: Medicare (27%), Medicaid (12%), private insurance (60%), and uninsured (0.8%). Multivariable logistic regression models were used to determine the association of primary payer status and outcomes. **Results:** Patients had a mean age of 54 (±13) years, 39% were women and 69% were whites. In-hospital mortality occurred in 1.1%, 2.9% and 3.3% of AutoHSCT patients with primary payer status of private insurance, Medicaid and Medicare respectively. AutoHSCT patients with primary payer status of Medicaid and Medicare had a statistically significant higher chance of in-hospital mortality compared to patients with private insurance (adjusted odds ratios and 95% confidence intervals, 2.68; 1.54-4.65; P <0.001 and 1.90; 1.21-2.99; P=0.005 respectively). Length of stay was longer for Medicare patients (20 ± 11 days) and Medicaid patients (20 ± 12 days) compared to private insurance (18 ± 8 days; P <0.001). Medicare and Medicaid patients also accrued higher hospital charges (USD 175,221 and USD 166,453), compared to private insurance patients (USD 157,120; P <0.001). **Conclusions:** In this national study Medicaid and Medicare patients had an independent risk for in-hospital mortality compared to private insurance patients. Medicaid and Medicare patients also had longer length of hospital stays and accrued higher hospital charges. This may mandate a closer look into the current resource utilization strategies to reduce such disparities among patients undergoing AutoHSCT.

7043 General Poster Session (Board #35C), Sun, 8:00 AM-11:45 AM

Incidence of engraftment fever post autologous transplant for lymphomas and analysis of risk factors.

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Background: Engraftment fever (EF) is a phenomenon observed in some patients undergoing autologous transplant (ASCT). We analyzed our data to evaluate the incidence and risk factors associated with EF. **Methods:** Seventy-nine patients underwent ASCT (53-Hodgkin's and 26- Non Hodgkin's) from August 2007 – January 2013. All except 5 received LACE (Lomustine, Ara-C, Cyclophosphamide and Etoposide) conditioning regimen. EF was defined as onset of fever with rising white cell count for which no infectious cause was ascertained. Patients of EF and non-EF groups were compared for the following variables to determine risk factors. These included histology, number of lines of chemotherapy regimens pre-transplant, complete remission (CR) at transplant, peripheral blood CD 34 count on day 1 of collection (PBCD34-D1), CD 34 cell dose collected and infused and number of days of stem cell collection. **Results:** The median age at transplant was 23.5 years with 57 males and 22 females. Time to neutrophil and platelet engraftment was 10 and 13 days respectively. EF was seen in 35 patients (44 %) at a median of 9 days. Short course of methylprednisolone (n=28) or hydrocortisone (n=3) was given to which all responded. On univariate analysis, PBCD34-D1 $>$ 50/uL (P = 0.037), CD 34 cell dose infused $>5.9x10^6$/kg (P=0.012),CD34 cell dose collected $>$ 7.2 x 10^6 /kg (P=0.032) , those receiving $\leq$ 2 lines of chemotherapy regimens before transplant (P=0.04), those who had $\leq$ 2 days of stem cell collection (P=0.002) and patients in CR at transplant (P = 0.015) were associated with risk of developing EF. On multivariate analysis, patients in CR at transplant and those who had $\leq$ 2 days of collection had higher risk of EF. **Conclusions:** The incidence of EF is high. Patients with lesser days of stem collection and those in CR at transplant have significant risk of developing EF.

7044 General Poster Session (Board #35D), Sun, 8:00 AM-11:45 AM

The impact of sarcopenia on transplant-related complications and number of days spent in the hospital in patients with lymphoma.

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Background: Sarcopenia, a state of abnormally low muscle mass, has been found to be associated with more treatment-related complications and shorter overall survival in patients with different cancers. Sarcopenia can be reliably assessed with routine computerized tomography (CT). The objectives of the study were to determine whether sarcopenia is associated with the number of complications and the number of days spent in the hospital in patients undergoing autologous hematopoietic stem cell transplantation (autoSCT) for lymphoma. **Methods:** Adult patients treated for non-Hodgkin's or Hodgkin's lymphoma with autoSCT between 2/2005 – 6/2/2012 at the University of Michigan (U-M) Bone Marrow Transplant (BMT) Program were eligible for inclusion if a CT of the abdomen was performed within 60 days prior to autoSCT. Total psoas area and lean psoas area were calculated for each patient with cross-sectional area and density measurements taken at the level of the fourth lumbar vertebra using algorithms programmed in the Analytic Morphomics Lab at U-M. All analyses were completed using Poisson regression models controlling for age, gender, body mass index, Hematopoeitic-Cell Transplant Co-morbidity Index (HCT-CI), and Karnofsky performance status (KPS). **Results:** Total and lean psoas area were calculated in the 121 patients who met inclusion criteria. Men with greater psoas muscle measures experienced fewer complications and spent fewer days in the hospital during the autoSCT admission compared to men who were sarcopenic (complications β = -0.206, p=0.001; hospital treatment days β = -0.043, p=0.029). Sarcopenia did not play a role in outcomes in women. A strong association existed between sarcopenia and re-admission days within 100 days following autoSCT among both men (β = -1.183, p<0.0001) and women (β = -0.805, p<0.0001). **Conclusions:** Muscle mass is independently associated with complication rates and duration of hospitalization in patients undergoing autoSCT for lymphoma. CT-determined psoas muscle mass may be a valuable addition to other indices used to guide optimal treatment selection and serve as a potentially modifiable host factor to improve transplant-related outcomes.

7045 General Poster Session (Board #35E), Sun, 8:00 AM-11:45 AM

MEDI-551, an anti-CD19 antibody active in chronic lymphocytic leukemia (CLL) patients previously treated with rituximab.

Mehdi Hamadani, Andres Forero, Thomas J. Kipps, Michelle A. Fanale, Antonio Cuneo, Jaime Perez de Oteyza, Douglas Gladstone, Trishna Goswami, Ramy A. Ibrahim, Meina Liang, Steven Eck, Nairouz Elgeioushi, Ronald Herbst, Bruce D. Cheson; Osborn Hematopoietic Malignancy and Transplant Program, West Virginia University, Morgantown, WV; University of Alabama at Birmingham, Birmingham, AL; UC San Diego Moores Cancer Center, La Jolla, CA; The University of Texas MD Anderson Cancer Center, Houston, TX; Università degli Studi Ferrara, Arcispedale Sant'Anna, Ferrara, Italy; Centro Integral Oncologico Clara Campal, Ona 10, Madrid, Spain; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD; MedImmune, LLC, Gaithersburg, MD; MedImmune, LLC, Hayword, CA; Georgetown University Medical Center, Washington, DC

Background: Anti-CD20 mAb therapy has provided survival advantage to patients (pts) with CLL; but pts invariably relapse after anti-CD20 therapy and new approaches are needed. The CLL cells of most pts express CD19, which are upregulated following anti-CD20 therapy. MEDI-551, an affinity-optimized anti-CD19 antibody, destroys malignant cells by Ab-dependent cellular cytotoxicity (ADCC) once bound to CD19. **Methods:** The activity and toxicity of single-agent MEDI-551 in CLL pts with prior rituximab administration was assessed in a phase 1/2, open-label, dose-escalation and expansion study (NCT00983619). Response was assessed using the 2008 Intl Working Group criteria. B-cell depletion was assessed with flow cytometry and confirmed with biomarker analyses (BAFF). Safety assessments included laboratory parameters and adverse events (AEs and serious AEs [SAEs]). **Results:** Of 91 pts with refractory B-cell malignancies included in the study, 26 had CLL. CLL pts had received a median of 6 prior therapies: 89% with chemotherapy, 27% with single-agent biologics. Within 3 cycles of MEDI-551 (3 mos), $>60\%$ of assessable pts achieved $CD20^+$ B-cell depletion to <20 cell/uL. Decreases in circulating $CD20^+$ and $CD22^+$B cells were associated with concomitant increases in serum BAFF concentrations. Of 20 pts evaluable for response, 4 achieved partial response and 13 had stable disease. Commonly reported AEs were generally grade 1/2 and included infusion reactions (62%), nausea (23%), pyrexia (23%), and neutropenia (23%). Six SAEs were noted in 3 pts: 1 had infusion reaction and general health deterioration, another had subarachnoid hemorrhage (SAH), and a third had dyspnea, pyrexia, and back pain. Only infusion reaction was considered treatment related. Two treatment-unrelated events of general health deterioration and SAH resulted in death. **Conclusions:** Single-agent activity with a manageable toxicity profile was seen in CLL pts treated in this phase 1/2 study of MEDI-551. An ongoing phase 2 study of MEDI-551 in combination with bendamustine in relapsed CLL patients (NCT01466153) is evaluating clinical response to MEDI-551 and chemotherapy. This study was sponsored by MedImmune, LLC.

7046 General Poster Session (Board #35F), Sun, 8:00 AM-11:45 AM

Management of chronic myeloid leukemia in chronic phase (CML-CP) by American Hematology-Oncology Physicians (AHOP's): Diagnostic and treatment preferences after first-line imatinib (2010-2012).

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Background: In CML-CP there is perceived complexity in risk stratification at diagnosis, and in testing for BCR-ABL kinase domain mutation (KD mut, including T315I) at relapse. We sought to understand AHOP practices in the context of NCCN and European LeukemiaNet guidelines. **Methods**: Between 2010 and 2012, we studied time dependent practice preferences of n=1,335 AHOP's using a proprietary, live, case-based market research tool. A core case scenario and variations based on available diagnostic & treatment options were constructed. Preference data were acquired using blinded audience response technology. All responses for each scenario were obtained contemporaneously prior to any display of summary respondent selections. All sources of research support were double blinded. AHOP's were presented with a scenario of 59-year old CML-CP patient, then indicated preferred management from up to 9 relevant available/emerging diagnostic or therapeutic options following relapse after 1st-line imatinib. **Results**: The majority of AHOP's in 2012 either did not calculate (52%), or were unfamiliar (21%) with Sokal or Hasford risk stratification score. Diagnostic preferences following relapse from 2010-12 are noted in Table (distribution over time, $p<0.0001$). If T315I was then detected in scenario, we noted marked differences in subsequent treatment preference in 2012 vs. 2011, respectively: decreased AlloBMT (16% vs. 32%); & increased 2nd-line dasatinib (26% vs. 14%) or bosutinib (12% vs. 8%) vs. nilotinib (8% vs. 20%) despite lack of efficacy for each in T315I. Preference increased slightly for ponatinib (16% vs. 14%), but not for omacetaxine (2% vs. 6%). **Conclusions**: Most AHOP's do not apply risk stratification. Increasing preference for KD mut panel testing at relapse conforms to guidelines, although not all AHOP's test. Heterogeneity in T315I treatment suggests uncertainty or unfamiliarity with newer agents, and evidence-based efforts are needed to improve awareness.

	2010	2011	2012
Mutation testing	**n=395**	**n=268**	**n=672**
Yes—KD mut panel	60%	65%	72%
Yes—T315I only	17%	15%	13%
None	9%	7%	15%
Refer to Center of Excellence, or Other	15%	13%	1%

7047 General Poster Session (Board #35G), Sun, 8:00 AM-11:45 AM

Association of prior epidemiologic exposures with cytogenetic risk in adult acute myeloid leukemia (AML).

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Background: In addition to secondary AML (sAML), important lifestyle and environmental exposures associated with increased risk of AML development have been identified in recent case-control studies including obesity (BMI>30kg/m^2), smoking, regular acetaminophen use, and rural/farm habitat. The association of these exposures with AML cytogenetic risk groups is unknown. We therefore evaluated relevant exposures in a cohort of 301 AML patients with confirmed central cytogenetics analysis diagnosed and treated at Mayo Clinic FL and AZ since 1995. **Methods:** Documented patient exposures were extracted from central electronic medical records, including: prior chemotherapy/radiation or hematologic malignancy, occupation, select medications, "toxins" (esp. benzene) and solid organ transplantation (SOT). Standard cytogenetic risk categories (including intermediate abnormal) were applied. The association of epidemiologic exposures with cytogenetic risk was evaluated on multivariable analysis using logistic regression models. **Results:** sAML was significantly associated with cytogenetic risk groups, as was prior SOT, healthcare occupation, farm habitat and toxin exposures [see Odds Ratios (OR), Table). In contrast, prior radiation for epithelial malignancies, smoking and BMI were not independently associated with specific cytogenetic risk categories. **Conclusions:** Specific epidemiologic exposures are significantly associated with AML cytogenetic risk categories suggesting a unique clinical phenotype. This supports a link to leukemogenesis and requires validation in a controlled prospective therapeutic study.

Exposures	N	Poor risk (OR)	P value	Intermediate abnormal risk (OR)	P value	Normal and good risk (OR)	P value
sAML	166	2.62	0.0002	1.09	NS	**0.40**	0.0002
Prior heme malignancy	147	2.33	0.001	0.95	NS	0.40	0.003
Radiation	41	0.82	NS	1.41	NS	0.97	NS
BMI	301	1.01	NS	1.16	NS	0.90	NS
Tobacco	169	0.85	NS	1.23	NS	0.96	NS
Health care worker	23	0.64	NS	6.36	<0.0001	0.23	0.01
Metformin	20	1.78	NS	1.73	NS	0.31	0.048
SOT	9	0.61	NS	3.20	0.098	0.53	NS
Farm habitat	14	2.74	0.078	0.86	NS	0.36	NS
Toxin	22	2.89	0.026	0.33	0.10	0.74	NS

7048 General Poster Session (Board #35H), Sun, 8:00 AM-11:45 AM

Analysis of the cardiovascular risk profile of Ph+ leukemia patients treated with ponatinib.

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Background: Coronary artery disease (CAD), peripheral arterial occlusive disease and cerebrovascular disease have been observed in pts treated with BCR-ABL tyrosine kinase inhibitors (TKIs). While uncommon, these events can be serious complications of BCR-ABL TKI therapy. **Methods:** The cardiovascular (CV) profile of ponatinib (45 mg/day) was evaluated in 449 pts with chronic myeloid leukemia (CML) or Ph+ acute lymphoblastic leukemia (Ph+ ALL) resistant or intolerant to prior TKIs in the phase 2 PACE trial. At analysis (23 July 2012), median follow-up was 12 (0.1-21) mos. Myocardial ischemic events including myocardial infarction (MI), CAD, and angina were analyzed. **Results:** Myocardial ischemic serious adverse events (SAEs) (14 MI, 5 CAD, 2 angina) were reported in 21/449 pts (5%). 10 of these 21 pts had active cardiac disease at entry characterized by prior MI (4 pts), coronary revascularization (4 pts), or documented CAD; 5 had MI reported on study. 5/21 pts had other cardiac disease at entry (eg, valvular or pericardial disease); 5 had MI on study. Thus, 10/14 MIs occurred in 15 pts with known cardiac disease. 6/21 pts had no history of cardiac disease, but 5/6 had ≥1 CAD risk factor; 4 MIs occurred in these pts, all had risk factors. Of 21 pts with myocardial ischemic SAEs (13 CP-CML, 6 AP-CML, 2 BP-CML/Ph+ALL), mean age was 67 (42-87), and median duration since diagnosis was 12 (1-20) yrs. They were heavily pretreated (67% TKI use ≥5 yrs) with multiple CAD risk factors at entry (71% ischemia, 57% hypertension, 38% hypercholesterolemia, 33% diabetes [62% BMI >25]); 81% had ≥2 risk factors, 95% had ≥1. Median time to onset and duration of SAE was 160 (9E402) and 7 (1E98) days, respectively. At analysis, 18/21 pts had the SAE reported as resolved (managed by dose interruption [50%] or no dose change [33%]), and 13/21 pts remained on study. Response rates for the subset of 21 pts with cardiac SAEs were major cytogenetic response 77% in CP-CML; major hematologic response 67% in AP-CML. **Conclusions:** In this uncontrolled study in heavily pretreated pts, these CV SAEs occurred mostly in pts with preexisting cardiac disease, and were primarily managed with satisfactory outcomes. Pts with preexisting CV co-morbidities should be monitored. Clinical trial information: NCT01207440.

7049 General Poster Session (Board #36A), Sun, 8:00 AM-11:45 AM

Frequency of rare cytogenetic abnormalities at relapse in acute myeloid leukemia (AML) with FLT3 internal tandem duplication (ITD) and normal karyotype at diagnosis: Evidence for genomic instability?

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Background: FLT3-ITD mutations are present in AML in 30% of patients, most commonly with a normal karyotype, and are associated with short disease-free survival. In vitro and in vivo studies of FLT3-ITD cell lines and patient samples have demonstrated DNA double-strand break repair by an alternative highly error-prone form of non-homologous end-joining (ALT NHEJ), resulting in illegitimate ligation of non-contiguous DNA breaks, causing DNA deletions and translocations that may contribute to disease progression. To look for clinical evidence of genomic instability, we reviewed cytogenetic changes at relapse. **Methods:** Charts of patients with cytogenetically normal AML with FLT3-ITD treated at the University of Maryland Greenebaum Cancer Center were reviewed along with metaphase analysis results at diagnosis and relapse. **Results:** Cytogenetic data were available from first and, when applicable, subsequent relapses for 12 patients with cytogenetically normal AML with FLT3-ITD who relapsed, including 5 following allogeneic hematopoietic stem cell transplantation (allo HSCT). Ten patients acquired cytogenetic changes, many of them rare translocations and inversions (Table). **Conclusions:** AML with FLT3-ITD and normal karyotype at diagnosis has a high frequency of rare cytogenetic abnormalities at relapse, providing clinical evidence for genomic instability. These data may support the potential therapeutic role of inhibitors of ALT NHEJ repair proteins, such as PARP1 and DNA ligase IIIa, in AML with FLT3-ITD.

Karyotypes at relapse (*after allo HSCT).
46,XY,t(2;14)(p23;q24)[2]/46,XY[18]
46,XX,t(4;4)(q21;q35)[7]/46,XX[13]
46,XX,t(5;13)(q31;q12)[20]*
46,XX,inv(9)(q22q32)[20]
46,XY,t(9;22)(q34;q11.2)[4]/46,XY[8]
46,XY,inv(10)(p11.2q21.2)[12]/46,XY[8]*
46,XY,t(10;13)(q10;q10)[9]/46,XY[9]//46,XX[2]*
47,XY,+21[10]/46,XY[10]*
46,X,t(X;10)(q13;q24),t(3;14)(p21;q11.2),t(12;17)(p12;q12)[15]//46,XY[5]*
45,XX,der(2)t(2;?)(q21;?),del(3)(q12),der(6)t(6;?)(p22;?),der(7)t(7;?)(p15;?),-17,-22,+mar[19]/46,XX[1]

7050 General Poster Session (Board #36B), Sun, 8:00 AM-11:45 AM

Rapid identification of drug-resistant BCR-ABL(+) leukemia.

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Background: Approximately 20% of patients with chronic myeloid leukemia and most patients with BCR-ABL-positive acute leukemia demonstrate resistance to imatinib mesylate resulting in treatment failure or suboptimal patient outcomes. We hypothesize that monitoring the development of cellular stress in BCR-ABL cells incubated with tyrosine kinase inhibitors (TKI) can be used as an early marker for determining the effects of the drugs on the cancer cells enabling rapid identification of drug-resistance and facilitating change to more effective therapies. **Methods:** The dielectric permittivities of non-leukemic peripheral blood mononuclear cells (PBMCs) and BCR-ABL cell lines known to be resistant (K562R and BaF3/T315I) or sensitive (K562 and HL60/BCR-ABL) to different TKIs were measured in the presence of imatinib (IMT), dasatinib (DAS), nilotinib (NIL), or ponatinib (PON) using the Z-Sense differential impedance sensing platform to record any changes in cellular stress. We also performed similar measurements on PBMCs from newly diagnosed CML patients exposed in vitro to the same TKIs. **Results:** Non-leukemic PBMCs showed no significant background levels when incubated with the following TKI concentrations: IMT (5 mg/mL), DAS (5 mg/mL), NIL (2.5 mg/mL), and PON (5 ng/mL). Normalized dielectric responses for all drug-resistant cell lines showed no change in value similar to control runs where no drugs were added. In contrast, all responses obtained for cell lines sensitive to these same TKIs were immediate and continuously decreased in value over time compared with resistant cell lines ($p<0.01$). All sensitivities were confirmed by MTT assay. Notably, the response of BaF3/T315I cells to PON was easily distinguished from the responses to IMT, DAS, and NIL. Of significance, all responses of BCR-ABL(+) patient blood to the four TKIs measured prior to commencing therapy were qualitatively similar to sensitive cell line measurements and subsequently confirmed to respond to IMT therapy. **Conclusions:** Drug-sensitive BCR-ABL(+) cells can be readily distinguished from drug-resistant cells without cell culturing in less than 60 minutes by monitoring the development of cellular stress in response to TKI drugs using differential impedance sensing.

7051 General Poster Session (Board #36C), Sun, 8:00 AM-11:45 AM

Effect of dose-optimized imatinib (IM) 800 mg on deep molecular responses (CMR 4.5) and prediction of survival: Results from the randomized CML-study IV.

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Background: Since complete molecular remission (CMR 4.5) defines a subgroup of patients who may stay in remission even after discontinuation of treatment, we analysed whether CMR 4.5 is reached faster with dose optimized IM 800 mg and whether the achievement of CMR 4.5 at specified points in time results in better survival than the achievement of less deep remissions. **Methods:** Confirmed CMR 4 and CMR 4.5 are defined as $\leq$ 0.01% BCR-ABL IS or $\geq$ 4 log reduction and $\leq$ 0.0032% BCR-ABL IS or $\geq$ 4.5 log reduction, respectively, from standardized baseline as determined by real-time PCR in 2 independent analyses. Details on CML-Study IV have been published (Hehlmann et al., JCO 2011). Cumulative incidences were estimated under consideration of competing risks. Landmark analyses were performed to evaluate the prognostic impact of different remissions at 4 years on survival. **Results:** Of 1551 randomized patients with newly diagnosed chronic phase CML 1525 were evaluable. Median age was 52 years, 88% were EUTOS low risk, 12% high risk. 113 patients were transplanted (73 in first chronic phase), 246 received 2nd generation TKI. 152 patients have died. After a median observation time of 67.5 months, 6-year OS was 88.2%.CMR 4.5 was reached after a median of about 76.1 months with IM 800 and 107.3 months with IM 400. EUTOS low-risk patients reached all remissions faster than high-risk patients. Independent of treatment approach CMR 4.5 at 4 years predicted OS significantly better than complete cytogenetic remission ($p=0.043$), but not significantly better than major molecular remission (MMR) or CMR4. After a median observation of 3.9 years 1 of 626 patients with CMR 4 has progressed. Only six of the 394 patients with CMR 4.5 have died after a median observation time of 3.0 years, no patient has progressed. An additional finding was that achieving MMR at 3 and at 6 months predicts faster achievement of CMR 4.5. **Conclusions:** We conclude that dose optimized IM 800 induces CMR 4.5 faster than IM 400 and that CMR 4.5 at 4 years is associated with a survival advantage. Dose optimized IM 800 may provide an improved therapeutic basis for treatment discontinuation in patients with CML. Clinical trial information: NCT00055874.

7052^ General Poster Session (Board #36D), Sun, 8:00 AM-11:45 AM

Nilotinib versus imatinib in patients (pts) with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP): ENESTnd 4-year (y) update.

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Background: In the 3-y follow-up (f/u) of ENESTnd, NIL demonstrated superior rates of molecular response and reduced progression to accelerated phase/blast crisis (AP/BC) vs IM. Here, we report results with a minimum f/u of 4 y. **Methods:** 846 adults with newly diagnosed Philadelphia chromosome–positive CML-CP were randomized to receive NIL 300 mg twice daily (BID; n = 282), NIL 400 mg BID (n = 281), or IM 400 mg once daily (QD; n = 283). **Results:** NIL continued to demonstrate higher rates of major molecular response (MMR; $\leq$ 0.1% BCR-ABL^{IS}), MR^4 ($\leq$ 0.01%^{IS}), and MR$^{4.5}$ ($\leq$ 0.0032%^{IS}) vs IM (Table). No new progressions have occurred on treatment on any arm since the 2-y analysis. NIL had significantly lower rates of progression to AP/BC on treatment (n = 2, 3, and 12 on NIL 300 mg BID, 400 mg BID, and IM, respectively) and when including f/u after discontinuation (n = 9, 6, and 19 on NIL 300 mg BID, 400 mg BID, and IM, respectively) and higher overall survival (OS) vs IM. By 4 y, half as many pts acquired new BCR-ABL mutations on study with NIL vs IM (n = 12, 11, and 22 on NIL 300 mg BID, 400 mg BID, and IM, respectively). Since the 3-y analysis, 2 new mutations (1 pt with T315I on NIL 300 mg BID; 1 pt with F317L on IM) were reported. Safety profiles of both drugs were consistent with previous ENESTnd analyses. By 4 y, peripheral arterial occlusive disease (PAOD) events were reported in 4 and 5 pts in the NIL 300 mg BID, and 400 mg BID arms, respectively. No pt in the IM arm had a PAOD event. **Conclusions:** ENESTnd 4-y data continue to demonstrate the superiority of NIL over IM for achieving deeper responses with lower risk of progression, supporting the use of NIL as frontline therapy in CML-CP. Clinical trial information: NCT00471497.

	NIL 300 mg BID (n = 282)	NIL 400 mg BID (n = 281)	IM 400 mg QD (n = 283)
Response by 4 y, % (P value vs IM)			
MMR	76 (< .0001)	73 (< .0001)	56
MR^4	56 (< .0001)	50 (< .0001)	32
MR$^{4.5}$	40 (< .0001)	37 (.0002)	23
4-y freedom from progression to AP/BC,[a] % (P value vs IM)			
On core treatment	99.3 (.0059)	98.7 (.0185)	95.2
On core or extension treatment or during f/u after discontinuation	96.7 (.0497)	97.8 (.0074)	93.1
4-y OS,[a] %			
All deaths	94.3 (.4636)	96.7 (.0498)	93.3
Pts with BCR-ABL mutations acquired on study, n			
Any	12	11	22
T315I	4	2	3

[a]Kaplan-Meier estimate.

7053^ General Poster Session (Board #36E), Sun, 8:00 AM-11:45 AM

Switching patients (pts) with chronic myeloid leukemia in chronic phase (CML-CP) with residual disease on long-term imatinib (IM) to nilotinib (NIL): ENESTcmr 24-mo follow-up.

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Background: The 12-mo results of ENESTcmr demonstrated that switching pts on IM with sustained BCR-ABL positivity to NIL leads to faster, deeper molecular responses (MRs)vs remaining on IM. These deeper molecular responses ($MR^{4.5}$ [BCR-ABL $\leq$ 0.0032%^{IS}] or greater) are a prerequisite to enter most treatment-free remission studies. Here, we report 24-mo f/u of ENESTcmr. **Methods:** Philadelphia chromosome–positive CML-CP pts (N = 207) who achieved a complete cytogenetic response, but had detectable BCR-ABL transcripts after $\geq$ 2 y on IM, were randomized to receive NIL 400 mg twice daily (BID; n = 104) or continue their IM dose (400/600 mg once daily [QD]; n = 103). **Results:** By 24 mo, significantly more pts achieved confirmed undetectable BCR-ABL (by RQ-PCR with $\geq$ 4.5 log sensitivity in 2 consecutive samples) with a switch to NIL vs continuing IM (22.1% vs 8.7%; P = .0087). The increase in the rate of undetectable BCR-ABL from mo 12 to 24 was higher for pts on NIL vs IM (9.6 vs 2.9 percentage points). In pts without $MR^{4.5}$ at baseline (BL), $MR^{4.5}$ was achieved by 24 mo in 42.9% vs 20.8% of pts (NIL vs IM; P = .0006). In pts without major molecular response (MMR; $\leq$ 0.1%^{IS}) at BL, $MR^{4.5}$ was achieved by 24 mo in 29.2% vs 3.6% of pts (P = .016). No progressions to accelerated phase/blast crisis or deaths occurred on study since the 12-mo f/u. Event-free survival at 24 mo was 96.6% vs 92.8% in the NIL and IM arms, respectively. Discontinuations due to adverse events occurred in 11.5% and 2.9% of pts in the NIL and IM arms. The NIL safety profile was consistent with prior switch studies. **Conclusions:** By 24 mo, significantly more pts achieved deeper responses ($MR^{4.5}$and undetectable BCR-ABL) with switch to NIL vs remaining on IM, and the difference between arms in these endpoints increased between 12 and 24 mo. Clinical trial information: NCT00760877.

	NIL 400 mg BID (n = 104)	IM 400 or 600 mg QD (n = 103)	P value
Confirmed undetectable BCR-ABL (ITT), %			
By 12 mo	12.5	5.8	.108
By 24 mo	22.1	8.7	.0087
MR by 24 mo (in pts without the response of interest at BL), %			
$MR^{4.5}$	(n = 94) 42.9	(n = 91) 20.8	.0006
Undetectable BCR-ABL	(n = 101) 31.7	(n = 100) 17.0	.0106
MR by 24 mo (in pts without MMR at BL), %			
MMR	(n = 24) 83.3	(n = 28) 53.6	.0342
$MR^{4.5}$	(n = 24) 29.2	(n = 28) 3.6	.016

7054^ General Poster Session (Board #36F), Sun, 8:00 AM-11:45 AM

Impact of early molecular response to nilotinib (NIL) or imatinib (IM) on the long-term outcomes of newly diagnosed patients (pts) with chronic myeloid leukemia in chronic phase (CML-CP): Landmark analysis of 4-year (y) data from ENESTnd.

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Background: ENESTnd demonstrated the superiority of NIL to IM in pts with newly diagnosed CML-CP, such as higher rates of molecular response (MR) and reduced risk of progression to accelerated phase (AP)/blast crisis (BC). This landmark analysis of ENESTnd is based on BCR-ABL transcript levels at 3 mo, with 4 y of follow-up. **Methods:** Rates of major MR (MMR; BCR-ABL$^{IS} \leq 0.1\%$), $MR^{4.5}$ (BCR-ABL$^{IS} \leq 0.0032\%$), progression to AP/BC, overall survival (OS), and progression-free survival (PFS) in pts in the NIL 300 mg twice daily (BID; n = 282) and IM 400 mg once daily (QD; n = 283) arms of ENESTnd were evaluated based on 3-mo BCR-ABL levels ($\leq 10\%$ vs $> 10\%$). **Results:** More pts treated with NIL than IM achieved BCR-ABL $\leq 10\%$ at 3 mo (91% vs 67%; Table). Other factors associated with MR at 3 mo included Sokal risk, spleen size, chromosomal abnormalities, white blood cell count, and median dose intensity (for NIL). On both arms, pts with BCR-ABL $\leq 10\%$ at 3 mo had significantly higher rates of MMR and $MR^{4.5}$and significantly improved PFS and OS than pts with BCR-ABL $> 10\%$ at 3 mo. Of the pts with BCR-ABL $> 10\%$ at 3 mo, 2 on NIL (8%) and 14 on IM (16%) progressed to AP/BC on study. Half of these progressions occurred between 3 and 6 mo. Analyses of outcomes based on BCR-ABL levels at 6 mo were similar to findings based on 3-mo data. **Conclusions:** BCR-ABL levels $\leq 10\%$ at 3 mo were associated with superior outcomes, including higher rates of $MR^{4.5}$ by 4 y and lower risk of disease progression. More pts treated with NIL than IM achieved this early level of MR. Clinical trial information: NCT00471497.

	NIL 300 mg BID (n = 258)[a]		IM 400 mg QD (n = 264)[a]	
	BCR-ABL level at 3 Mo		BCR-ABL level at 3 Mo	
	≤ 10%	> 10%	≤ 10%	> 10%
Pts, %	91	9	67	33
Median dose intensity during first 3 mo, mg/day	600	474	400	400
Sokal score, %				
Low	39	29	46	24
Intermediate	36	29	36	32
High	26	42	18	44
$MR^{4.5}$ by 4 y, %	47	4	34	5
P value	< .0001		< .0001	
4-y PFS, %	95	83	98	83
P value	.0061		< .0001	
4-y OS, %	97	87	99	84
P value	.0116		< .0001	
Pts with BCR-ABL > 10% at 3 mo, n	24		88	
Progression to AP/BC, %	8		16	
On study	4		8	
Between 3 and 6 mo				

[a]Pts with evaluable polymerase chain reaction samples at 3 mo.

7055 General Poster Session (Board #36G), Sun, 8:00 AM-11:45 AM

Arsenic trioxide: Pharmacokinetics in acute promyelocytic leukemia (APL) patients.

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Background: Arsenic (As) has significantly increased survival for APL patients. As and its metabolites' effects on cell proliferation, apoptosis, and methylation, especially long term, remain largely unknown. It is imperative to study the pharmacokinetics of As at therapeutic doses in order to limit untoward effects resulting from treatment. Arsenic trioxide (ATO), available as arsenous acid (iAs^{III}), is readily metabolized through sequential methyl group additions and electron reduction steps: $iAs^{III} \rightarrow MAs^{V} \rightarrow MAs^{III} \rightarrow DMAs^{V} \rightarrow DMAs^{III} \rightarrow TMAs^{V}O \rightarrow TMAs^{III}$. iAs^{III}, MAs^{III} and $DMAs^{III}$ are more biologically active and more toxic than pentavalent forms. The key enzyme involved is arsenic methyltransferase, and polymorphisms contribute to metabolic differences between individuals. **Methods:** Cancer patients not treated with ATO (controls) had one collection of blood and urine samples, while APL patients receiving therapeutic doses of ATO had collections immediately prior to and at 1, 2, 4, 6, and 24 hours, days 4, 8, 15, and 4 weeks after ATO-free interval. Total iAs ($iAs^{III}+iAs^{V}$), MAs ($MAs^{III}+MAs^{V}$) and DMAs ($DMAs^{III}+DMAs^{V}$) were measured in plasma using hydride generation cryotrapping atomic absorption spectrometry, a sensitive automated method of arsine detection. The same As species were measured in urine and in exfoliated bladder cells isolated from urine. **Results:** We report data on ten control patients and six treated patients (ATO 0.15 mg/kg/day). Initial average As concentrations in treated patients (0.051 ng/ml) were similar at baseline to the controls (0.046 ng/ml). We observed that iAs is quickly metabolized from a peak average plasma concentration of 32 ng As/ml to a trough of 10 ng As/ml within six hours from infusion, remaining unchanged for at least 24 hours. MAs and DMAs concentrations begin to increase at six hours, and continue to rise by day 4 to an average concentration of 8.5 and 10.4 ng As/ml respectively, followed by decline to baseline 4 weeks after final ATO infusion. **Conclusions:** Treatment with ATO leads to the formation of MAs and DMAs whose long term toxicity in APL patients is poorly understood. Studies involving analysis of As metabolites are needed to assess possible long term toxicities on non-targeted organs.

7056 General Poster Session (Board #36H), Sun, 8:00 AM-11:45 AM

Pharmacokinetics (PK) of ibrutinib in patients with chronic lymphocytic leukemia (CLL).

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Background: Ibrutinib is a first-in-class selective small molecular inhibitor of Bruton's tyrosine kinase (BTK) under development for the treatment of B-cell malignancies. Because of covalent binding to cys-481 of BTK, ibrutinib has a sustained pharmacodynamic (PD) effect. The aim of this study was to determine the PK of ibrutinib in patients (pts) with CLL. **Methods:** A Phase 1b/2 study (PCYC-1102-CA) of an oral dosing of single agent ibrutinib was conducted in pts with treatment-naïve (TN) or relapsed/refractory (R/R) CLL. Pts were enrolled into one of the following groups: R/R pts at 420 mg/day (n=27), TN pts at 420 mg/day (n=26), R/R pts at 840 mg/day (n=34), R/R high-risk pts at 420 mg/day (n=24), TN pts at 840 mg/day (n=5), and R/R pts at 420 mg/day for food-effect evaluation (n=16). One cycle was 28 days. Blood samples for PK assessment were obtained during the first cycle. PK parameters were calculated using non-compartmental analyses. **Results:** A total of 132 pts (98 males and 34 females) with CLL were treated across the 6 groups. Median ages for Groups 1 through 6 were 64, 71, 64, 68, 71, and 62 years, respectively. Ibrutinib exhibited rapid absorption (median Tmax of 2 h) and a mean elimination plasma half-life of approximately 6-9 hours. The AUCtau increased approximately proportional to doses from 420 to 840 mg/day. No accumulation of ibrutinib was apparent on Day 8. Ibrutinib exposure in males and females was similar. At 420 mg/day, pts $\geq$ 65 years old had AUC values that were ~30% higher than those of pts $<$ 65 years. In R/R pts, there were no substantive differences in systemic exposure to ibrutinib between the del 17p positive and del 17p negative pts. An increase in ibrutinib exposure ($<$2-fold) was observed when administration with high-fat breakfast was compared to administration following an overnight fast. In all cases, %CV of AUC ranged from 50 to 100%. **Conclusions:** Ibrutinib demonstrated rapid absorption and elimination and was well tolerated at doses of 420 and 840 mg/day. Lack of significant exposure differences with respect to age, gender, or 17p del status indicates that dose adjustment in these populations is not required. Because of a sustained PD effect ibrutinib can be dosed once daily despite a relatively rapid clearance. Clinical trial information: NCT01105247.

7057 General Poster Session (Board #37A), Sun, 8:00 AM-11:45 AM

Open label evaluation of ECG in patients with chronic lymphocytic leukemia (CLL) receiving ibrutinib monotherapy.

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Background: Ibrutinib is a first-in-class selective small molecule inhibitor of Bruton's tyrosine kinase (BTK) under development for the treatment of B-cell malignancies. The aim of this study was to characterize the possible effect of ibrutinib on ECG intervals in patients with CLL. **Methods:** A Phase Ib/II study (PCYC-1102-CA) of oral dosing of ibrutinib was conducted in patients with treatment-naïve (TN) or relapsed/refractory (R/R) CLL. Patients were enrolled into 6 groups treated with ibrutinib at 420 mg/day or 840 mg/day (n=132). One cycle was 28 days. ECG data were obtained along with the blood samples during Cycle 1. Additional ECG measurement was performed on Day 28 of Cycles 3, 6, 12, 18, and 24 and at the end of study. An interim ECG analysis was performed using the data from R/R patients at 420 mg/day (n=18), TN patients at 420 mg/day (n=20), and R/R patients at 840 mg/day (n=29). For ECG analysis, the pre-dose values on Cycle 1 Day 1 were used as the baseline for each post-dose time-point for all ECG parameters. The QT and RR values for each beat were used for both Fridericia's correction (QTcF) and Bazett's correction (QTcB). The relationship between plasma concentrations of ibrutinib and ΔQTcF (change-from-baseline QTcF) was investigated by a linear mixed-effects modeling approach. **Results:** Median ages for R/R 420 mg, TN 420 mg, and R/R 840 mg dose groups were 59, 71, and 62 years, respectively. There was no clinically significant change in heart rate (HR) relative to baseline observed in either dose groups or between R/R and TN populations. There was no evidence of PR interval prolongation above 240 msec. There were no treatment-related effects on QRS duration in any of the Treatment Groups. A total of 467 ΔQTcF measurements were included in the analysis. The population mean of baseline QTcF values was 402.0 msec with a SD of 15.2 msec. A concentration-dependent effect of ibrutinib on QTcF was not identified. **Conclusions:** Interim analyses of the data indicated that there was no evidence of clinically significant ECG findings or QTc prolongation with continuous daily dosing of ibrutinib at either the 420 mg or 840 mg dose in patients with TN or R/R CLL. Clinical trial information: NCT01105247.

7058 General Poster Session (Board #37B), Sun, 8:00 AM-11:45 AM

Phase I study of midostaurin and azacitidine in relapsed and elderly AML.

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Background: The Fms-like tyrosine kinase 3 (FLT3) receptor is expressed in 80% of AML and activating mutations are associated with an adverse prognosis. Midostaurin (mdn), an orally available agent, has been shown to inhibit FLT3 receptor signaling and induces cell cycle arrest and apoptosis of leukemic cells expressing both mutant and wild type FLT3 receptors. Preliminary data has shown modest single agent activity as well as safety and tolerablility of mdn in combination with standard induction chemotherapy. **Methods:** We conducted a phase I study of azacitidine (75 mg/m2 iv X 7days) with escalating doses of oral mdn (25 mg bid, 50 mg bid, and 75 mg bid) days 8-21 of a 28 day cycle in untreated elderly and relapsed AML. The protocol was IRB approved at participating institutions and all patients gave written informed consent. Dose limiting toxicities (DLTs) were defined as $>$ grade 3 non-heme toxicity during cycle 1 excluding grade 3 hepatotoxicity $<$ 7 days, grade 3/4 stomatitis or diarrhea that resolved by day 28, infections, and electrolyte abnormalities of any grade. Pharmacokinetics (pK) were obtained on day 8,15, and 21 before mdn dosing. **Results:** 17 pts (11 females and 6 males) ages 57-83 (median 73) were enrolled of whom 5 patients had prior intensive treatment for AML. All pts were FLT3 negative; 5 had normal cytogenetics and 12 had high risk cytogenetics. ECOG PS: 0 (4pts), 1 (11pts), 2 (2pts). No DLT were observed during escalation or in the expansion cohort of 75 mg bid. Responses were evaluable in 14/17 pts and included 2 CR, 1 PR, and 2 HI (clearing of peripheral blasts, platelet tx independence). Median survival from enrollment was 3.5 months (range 1-12 months). 4 pts remain on treatment (2- 9+ cycles). 3 pts died within 60 days (2 PD, 1 treatment-related). Non-infectious, non hematologic SAE's are listed on the table below. Plasma concentrations of mdn accumulated in the first week of treatment and declined thereafter despite continued dosing. **Conclusions:** The combination of azacitidine and midostaurin in safe and tolerable in elderly AML and should be further studied in FLT3 positive leukemia. Clinical trial information: NCT01093573.

Toxicity	Cycle1	Cycle 2	Cycle 3	Cycle 4
Hyponatremia	2		1	
Alb	1	1		
Nausea/vomiting		1		
Bowel perf		1	1	
Pain		1		1
Pneumonia	1		1	
Hepatotoxicity	1	1	1	
# pts	17	13	5	4

7059 General Poster Session (Board #37C), Sun, 8:00 AM-11:45 AM

Hematopoietic cell transplantation for refractory acute myeloid leukemia.

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Background: Hematopoietic cell transplantation (HCT) can be curative for patients with AML refractory to chemotherapy or re-induction after relapse. However, the role of HCT in this setting remains unclear. Our aim was to evaluate outcomes of HCT in these patients, and determine factors that may be predictive of complete remission (CR)/complete remission with incomplete count recovery (CRi) and overall survival (OS). **Methods:** Patients with relapsed AML who did not respond to re-induction or with primary induction failure (PIF) who received allogeneic HCT at University of Pittsburgh Cancer Institute 2000-2012 were identified. CR/CRi rates were calculated at day 30 and 100, and 3-year OS was determined using Kaplan Meier method. Cox proportional hazards regression was used to examine associations between factors of interest, and OS and CR/CRi. These included gender, age, relapse or PIF, 1° or 2° AML, cytogenetic risk, duration of CR1 (patients in relapse), performance status, number of induction cycles, circulating blasts, percentage of bone marrow (BM) blasts prior to HCT, matched unrelated or sibling donor, donor-recipient CMV status, and acute GVHD. **Results:** The study cohort consisted of 71 patients (median age 44 years, range 19-64) who underwent allogeneic HCT for refractory AML (relapse n=35, PIF n=36). At day 30, CR was 31% and CRi was 49%, for total 80% response rate. At day 100, 51% remained in CR/CRi. CR/CRi was associated with younger age (HR 1.26, $p<0.001$) and lower percentage BM blasts (HR 1.03, $p=0.026$). Three-year OS was 12.3% (5.6-21.8), and median OS was 0.57 years (0.35-0.75). Lower OS was associated with matched unrelated versus sibling donor (HR 1.74, 1.02-2.96) and older age ($p<0.06$). Of the 60 patients who were deceased, 38.6% died from progressive leukemia. **Conclusions:** Despite high CR/CRi rates after HCT for refractory AML, 3-year OS was low. Age and percentage BM blasts were significantly associated with CR/CRi. Only sibling donor was significantly associated with OS, though there was a trend for age. Though patients with refractory AML represent a high-risk group to undergo HCT, the high response rate through day 100 with subsequent disease-related mortality suggests a role for maintenance after HCT in this population.

7060 General Poster Session (Board #37D), Sun, 8:00 AM-11:45 AM

Chemokine receptors as novel targets of the oncogene Notch1 in acute lymphoblastic leukemia.

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Background: Malignant cells from different cancers express different profiles of chemokine receptors (CKR). Their presence may influence site-specific spread of tumor cells, by enabling them to respond to chemokine gradient, and may increase cell sensibility to chemokine mediated proliferative and anti-apoptotic stimuli. Notch ability to positively regulate CKR has been reported: stimulation of Pax5-/- pre-B cells with the Notch ligand Delta-1 results in induction of transcripts for CCR4, CCR8 and CXCR 6; the Delta-1-dependent regulation of Langerhans cell development includes induction of CCR6 expression resulting in the activation of chemotactic response to MIP-1a; Notch controls CCR7 signaling a regulator of CNS infiltration in T-acute lymphoblastic leukemia (T-ALL). **Methods:** This work aims to explore the correlation between the activation of the Notch oncogenic pathway in T-ALL and multiple myeloma (MM) cells and the aberrant expression CKR. Human T-ALL cell lines were treated with the Notch activation inhibitor, DAPT, or with a potent inhibitor of the Notch target, C-MYC, and evaluated the expression and functions of CCR9, CCR5, and CXCR4. **Results:** Treatment of human T-ALL and MM cell lines with pharmacologic inhibitors of Notch receptor activation produced a significant reduction of CCR9, CCR5 and CXCR4 expression, at both mRNA and protein levels. Results were confirmed by chemotaxis and survival assays. We identified the product of C-MYC gene as a possible mediator of Notch effect in regulating CKR networks in T-ALL and MM. **Conclusions:** These results suggest that Notch receptors play a previously unknown role in cancer progression and metastasis, by maintaining the expression levels of CKR. In conclusion, the identification of the potential axis Notch/CKR could have a prognostic value and provide the rationale for a tailored approach, since both Notch and CKR are targeted by emerging drugs.

7061 General Poster Session (Board #37E), Sun, 8:00 AM-11:45 AM

Outcome of pregnancy in women on imatinib for CML.

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Background: The use of imatinib (IM) now offers most patients with CML lengthy remissions and the hope of normal life expectancy. Majority of our CML patients are in the reproductive age group, and these improved survivals have resulted in issues relating to fertility and procreation. There is limited literature on the outcomes of pregnancy in women who continued IM during conception and through antenatal period. **Methods:** All women with CML who wished to conceive were counselled about the risks of pregnancy while on IM. They were given the choice of termination or stopping IM until delivery or continuing on IM with attendant risk to mother and baby. The records of all patients with CML treated with IM at our institute were retrospectively analysed over a period of 10 years. A total of 28 pregnancies in 25 women were documented. Only those women who were exposed to imatinib during conception and first trimester were included for this analysis. We report the outcome of 24 pregnancies in 22 women who had continued on IM in antenatal period. **Results:** Of the total of 24 pregnancies, 23 occurred in chronic phase and 1 in Blast phase. 21 of these conceptions occurred at IM dose of 400mg/ day, 1 at 600mg/ day and 2 at 800mg/ day. The median age at conception was 24.5 years (19-38). Mean time on IM at conception was 24.25 months (3-81). 19 patients (86.4%) were in CHR at conception and 11 of 22 patients (50%) attained complete cytogenetic response. The mean exposure to IM during pregnancy was 18.08 weeks (6-39 weeks).After explaining the pros and cons of continuation of pregnancy 6 women had stopped IM and 7 patients opted for termination of pregnancy. **Conclusions:** IM at higher dose appears to increase the risk of fetal loss. IM at standard dose of 400 mg does not appear to increase the incidence of congenital malformations or worsen foetal outcome.

Outcome of pregnancy (N = 24).	
Full term gestation with normal babies	8
Preterm deliveries	3 (2 babies died within 12 hours of birth – both exposed to IM dose 800) (1 live baby with cerebral palsy – IM dose 400)
Congenital anomalies	1 (Male, born at 24 weeks, death <24 hrs, Imperforate anus – IM dose 400)
Intrauterine deaths	1 (at 7 months – IM dose 600)
MTP	7
Spontaneous abortions	1 (IM dose 400) at 10 weeks
Ongoing	2
Lost to follow-up	1 (IM dose 400)

7062 General Poster Session (Board #37F), Sun, 8:00 AM-11:45 AM

Genetic and cytokine profiles associated with symptomatic stage of CLL.

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Background: Pathogenesis of symptomatic CLL involves genetic changes associated with the CLL clone and changes within the microenvironment which contribute to chemo-resistance. To further understand these processes we compared early stage CLL to symptomatic late stage CLL using gene expression profiling as well as serum cytokine profiling for a better insight of the genetic and microenvironment changes associated with the most severe forms of the disease. **Methods:** We obtained pretreatment blood samples from CLL patients (10 low stage and 14 high stage) at the time of diagnosis. Patients were classified as low stage (Rai stage 0/I/II) and high stage (Rai stage III/IV). Gene expression profiles were obtained on a subset of patients using the HG-U133A 2.0 Affymetrix platform and analyzed for differential gene expression profiles. Serum from a subset of patients was used to perform cytokine profiling using the Raybiotech Cytokine Array platform (AAH-CYT-G1000) that allows for simultaneous measurement of $>$100 different cytokines. **Results:** Comparison of low versus high stage CLL revealed a set of 21 differentially expressed genes. 15 genes were up regulated in the high stage versus low stage, while 6 genes were down regulated. GO Molecular function analysis revealed that 9 of the 21 genes are involved in transcription factor activity. Other genes up regulated in the high stage group include CSNK1- shown to be involved in Myc derived oncogenesis and SETD8- a histone lysine methyltransferase previously implicated in several cancers. Serum cytokine profiles showed 6 cytokines to be significantly different in high stage patients. Two chemokines SDF-1/CXCL12 and uPAR known to be involved in stem cell mobilization and homing are increased in the serum of high stage patients. IGFBP-2, BMP-4 and MCP-4 were lower among high stage patients. **Conclusions:** Our study revealed a novel group of transcription factors are associated with higher stage CLL. Cytokine profiling showed increased levels of SDF-1/CXCL12, a chemokine that plays a key role in mobilization and homing of hematopoietic stem and CLL cells in high stage patients. Our study identifies putative therapeutic targets including CSNK1, SDF-1 and SETD8 for patients with high stage CLL.

7063 General Poster Session (Board #37G), Sun, 8:00 AM-11:45 AM

Safety and durability of ponatinib in patients with Philadelphia chromosome-positive (Ph+) leukemia: Long-term follow-up of an ongoing phase I study.

Michael J. Mauro, Jorge E. Cortes, Hagop M. Kantarjian, Neil P. Shah, Dale Bixby, Ian Flinn, Thomas O'Hare, Simin Hu, Victor M. Rivera, Tim Clackson, Christopher D. Turner, Frank G. Haluska, Brian J. Druker, Michael W. N. Deininger, Moshe Talpaz; Oregon Health & Science University Knight Cancer Institute, Portland, OR; The University of Texas MD Anderson Cancer Center, Houston, TX; University of California, San Francisco, San Francisco, CA; Comprehensive Cancer Center, University of Michigan, Ann Arbor, MI; Sarah Cannon Research Institute, Nashville, TN; Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; ARIAD Pharmaceuticals, Inc., Cambridge, MA

Background: Ponatinib is a potent oral pan–BCR-ABL tyrosine kinase inhibitor (TKI) that is active against native and mutated forms of BCR-ABL. The safety and anti-leukemic activity of ponatinib in patients (pts) with chronic myeloid leukemia (CML) or Ph+ acute lymphoblastic leukemia (ALL) were evaluated in a phase I clinical trial. **Methods:** Pts (N=81) with resistant/refractory hematologic malignancies were enrolled in this ongoing, open-label, dose escalation, phase I study. Ponatinib was dosed once daily (2–60 mg). 65 pts had Ph+ leukemia and are included in the present analysis (data as of 9 Nov 2012). Median follow-up was 25 (0.5–44) mos. **Results:** The median age of pts was 55 yrs; median time since diagnosis was 6.5 yrs. Pts were heavily pretreated (94% had received ≥2 prior TKIs, 62% ≥3). 65% had baseline BCR-ABL mutations. 46% (67% chronic phase [CP] CML) of pts remained on study. Progression and adverse events (AEs) were the most common reasons for discontinuation (17% each). The most common treatment-related AEs were rash (42%), thrombocytopenia (34%), arthralgia (20%), and increased lipase (20%). Significant anti-leukemic activity was observed (Table). Responses (major cytogenetic response [MCyR] for CP-CML or major hematologic response [MaHR] for accelerated phase [AP] CML, blast phase [BP] CML, or Ph+ ALL) were observed against the following mutations detected in >1 pt at baseline: 14/19 T315I, 4/7 F317L, 2/4 G250E, 2/2 M244V, 2/2 M35IT, and 1/2 F359V. Among CP-CML pts, 73% with complete cytogenetic response (CCyR) and 63% with major molecular response (MMR) are estimated to maintain response at 2 yrs (Kaplan-Meier). Of 28 CP-CML pts with CCyR, 25 remained on study (19 with continuous CCyR); of 22 pts with MMR, 21 remained on study (15 with continuous MMR). Updated data will be presented. **Conclusions:** Significant and durable responses were observed in heavily pretreated CP-CML pts, regardless of mutation status, and ponatinib was generally well tolerated. Clinical trial information: NCT00660920.

	CP-CML N=43	AP-CML N=9	BP-CML N=8	Ph+ ALL N=5
MaHR, %	NA	44	25	40
MCyR, %	72	22	38	40
CCyR, %	65	22	13	20
MMR, %	51[a]	11	NA	NA

[a]14 (33%) CP-CML pts achieved MR^4; 8 (19%) achieved $MR^{4.5}$.

7064 General Poster Session (Board #37H), Sun, 8:00 AM-11:45 AM

Effect of obesity on overall survival in patients diagnosed with chronic myelomonocytic leukemia (CMML).

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Background: Obesity is a growing medical challenge that has strong association with many comorbid diseases. Body mass index (BMI) is used as one indicator for obesity. A few papers have linked hematological cancers with a worse prognosis if obesity was present. Aim: to study the influence of obesity clinical outcome in patients (pts) with CMML. **Methods:** A retrospective chart review of pts with CMML at Mayo Clinic Rochester between 1994–2011 was done. BMI was calculated at diagnosis or first time visit. Overweight was defined as BMI $\geq$25, while obesity as BMI $>$30. IRB approval was obtained. Comparison between medians was done using Wilcoxon test, while survival estimates were calculated using Kaplan-Meier estimates via JMP software v.9. **Results:** We found227 pts with a median follow-up of 311 days, 68% of which weremales. Median age was 71 years, hemoglobin 11 gm/dL, white blood cells (WBC) 12x 10^9/L, and platelets 90x 10^9/L. Obese pts had a median age of 68 (p=0.0058), hemoglobin 11 gm/dL (p=0.0018), WBC 13.5 x 10^9/L, platelets 115x10^9/L (p=0.012), PB blasts 0, bone marrow (BM) blasts 3.5% compared to non-obese pts (73, 10, 11, 78, 0, 3%, respectively). Diploid cytogenetics were similar in both groups (68% vs 64%, respectively, p=0.54). Leukemic transformation into acute myeloid leukemia (LT) was found in 13% vs 10% (p=0.83). Overall response (OR) was 24% and 23%, respectively (p=0.2), when limited to hypomethylating agents OR was 33% vs 27%, respectively (p=0.62). Median OS was found to be similar (571 day vs 569 days, respectively, p=0.56). When compared, overweight pts had similar outcome to non-overweight. Median LT was 11% vs 15% respectively, OR was 21% vs 28% respectively (p=0.5), and OS was 571 days vs 549 days respectively (p=0.21). On a multivariate analysis age, hemoglobin, platelets, BM blasts%, gender, and obesity (p=0.048) were of a significant value for OS. **Conclusions:** When compared, both obesity and overweight did not affect demographic characteristics, overall response, or transformation into AML. When comparing median overall survival, obesity was not a significant factor, possibly due to short follow-up. However, on multivariate analysis obesity did have a negative impact on overall survival.

7065 General Poster Session (Board #38A), Sun, 8:00 AM-11:45 AM

Treatment response monitoring in chronic phase CML (CP-CML) patients receiving tyrosine kinase inhibitor (TKI) therapy in US Oncology network.

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Background: To identify pts with TKI resistance in a timely manner, the National Comprehensive Cancer Network (NCCN) guidelines recommend monitoring pts at specific time points. We evaluated the relationship between NCCN guidelines and current treatment response monitoring patterns and outcomes of CP-CML pts in community practice. **Methods:** A retrospective longitudinal cohort study was conducted on newly diagnosed CP-CML pts initiating TKI therapy from Jan 1, 2008 to Dec 31, 2010. Data was extracted from the MSH/USON iKnowMed electronic health record database and chart reviews through Jul 31, 2012. Pts were stratified by presence of any cytogenetic monitoring by 12 mos or any molecular monitoring by 18 mos. **Results:** Of the 410 pts identified, 91% received imatinib and 9% received dasatinib/nilotinib. Median follow-up was 28 mos. Cytogenetic and molecular monitoring did not occur in 69% and 27% of pts, respectively. BCR-ABL mutation testing occurred in 10% of pts who were monitored for response. Pts $\geq$65 yrs old (vs $<$65 yrs, $p<0.01$), with public insurance (vs private insurance, $p<0.001$), or with Karnofsky Score $\leq$80 (vs $>$80, $p<0.05$) were less likely to have cytogenetic monitoring. Similar differences for age ($p<0.05$) and insurance ($p<0.001$) were seen for molecular monitoring. For pts with available monitoring results, 36% had complete cytogenetic response by 12 mos, and 59% had major molecular response by 18 mos. 4-yr overall survival (OS) rates were higher in pts with cytogenetic (98% vs. 89%, $P=0.0003$) or molecular (95% vs. 82%, $P\leq0.0001$) monitoring vs. those with no monitoring. **Conclusions:** In these CP-CML pts, 69% did not receive any cytogenetic monitoring by 12 mos and 27% did not receive any molecular monitoring by 18 mos. Obstacles related to monitoring may include age, payer status, and performance status. Pts that were monitored for cytogenetic and molecular responses had significantly higher OS rates at 4 yrs. Increasing the proportion of pts that are monitored according to NCCN guidelines in the community setting could improve patient outcomes.

7066 General Poster Session (Board #38B), Sun, 8:00 AM-11:45 AM

Post hoc analysis of sustained efficacy/tolerability of ≥12 cycles of omacetaxine mepesuccinate in chronic myeloid leukemia (CML).

Delphine Rea, Hagop M. Kantarjian, Meir Wetzler, Franck E. Nicolini, Jeffrey H. Lipton, Luke Paul Akard, Hanna Jean Khoury, Mauricette Michallet, Agnès Guerci-Bresler, Charles Chuah, Andrzej Hellmann, Laurence Legros, Krzysztof Warzocha, Purvish M. Parikh, Adam Craig, Jorge E. Cortes; Service des Maladies du Sang, Hôpital Saint-Louis, Paris, France; The University of Texas MD Anderson Cancer Center, Houston, TX; Roswell Park Cancer Institute, Buffalo, NY; Centre Hospitalier Lyon Sud, Pierre Bénite, France; Princess Margaret Hospital, Toronto, ON, Canada; Indiana Blood and Marrow Transplantation, Indianapolis, IN; Emory University School of Medicine, Atlanta, GA; Centre Hospitalier Universitaire, Brabois, Vandoeuvre-lès-Nancy, France; Singapore General Hospital, Duke-NUS Graduate Medical School, Singapore, Singapore; Medical University of Gdańsk, Gdańsk, Poland; Hôpital Archet, Nice, France; Institute of Hematology and Transfusion Medicine, Warsaw, Poland; Indian Cooperative Oncology Network, Mumbai, India; Formerly of Teva Pharmaceutical Industries Ltd., Menlo Park, CA

Background: Subcutaneous omacetaxine mepesuccinate (OMA), a first-in-class cephalotaxine, inhibits protein synthesis independent of Bcr-Abl signaling. It showed clinical activity in 2 phase II, open-label CML trials, 1 in patients with a *T315I Bcr-Abl* mutation failing imatinib, and 1 in patients failing ≥2 tyrosine kinase inhibitors (TKIs). **Methods:** This post hoc analysis pooled patients with chronic phase (CP) or accelerated phase (AP) from the 2 trials. 28-day cycles of OMA 1.25 mg/m^{2}BID were given ≤14 days for induction, ≤7 days as maintenance with dose delay/change as needed. Primary endpoints were major cytogenetic response (MCyR) for CP and complete hematologic response (CHR) for AP. Adverse events (AEs) were assessed. **Results:** Of 108 CP and 51 AP patients from the 2 trials, 31 (29%) CP and 7 (14%) AP patients received ≥12 cycles (Table). At baseline in the ≥12-cycle groups, most CP (median age 59 y) and AP patients (median age 67 y) had received hydroxyurea (17/31, 4/7) and ≥2 TKIs (22/31, 5/7), were not in CHR (22/31, 5/7), and were *T315I* positive (23/31, 3/7). As of March 31, 2012, 9 CP and 2 AP patients continued OMA treatment. Overall, mean days dosed per cycle were 6.1 for CP, 9.7 for AP; 5.3 and 8.9 at cycle 12. Grade 3/4 AEs occurred in 35/38 patients in this post hoc analysis, most in early cycles; 15/31 CP, 2/7 AP had grade ≥3 AEs first occurring at ≥12 cycles. Across all cycles, most common grade ≥3 AEs were thrombocytopenia (24/31 CP, 5/7 AP), anemia (16/31, 7/7), and neutropenia (17/31, 3/7).Nine patients receiving ≥12 cycles (5/31, 4/7) discontinued, most commonly due to disease progression (n=2). **Conclusions:** In this post hoc analysis of heavily pretreated CML-CP and CML-AP patients who had failed prior TKI therapy, efficacy was often durable for those who received OMA for ≥12 cycles. Most grade 3/4 AEs were hematologic and declined with time. Support: Teva BPP R and D, Inc. Clinical trial information: NCT00375219, NCT00462943.

7067 General Poster Session (Board #38C), Sun, 8:00 AM-11:45 AM

Do quality of life and physical function at diagnosis predict short-term outcomes during intensive chemotherapy in acute myeloid leukemia patients?

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Background: Intensive chemotherapy (IC) used to treat acute myeloid leukemia (AML) is associated with multiple short-term toxicities including mortality, particularly in older adults. Emerging data suggest that baseline quality of life (QOL) assessment and/or objective physical function tests may predict outcomes in oncology, although there are no data in AML patients. We investigated the association between baseline QOL and physical function with short-term treatment outcomes in adult and elderly AML patients. **Methods:** We conducted a prospective, longitudinal study of adult (age 18+) AML patients undergoing IC. Prior to starting IC, patients completed the EORTC QLQ-C30 and FACT-Fatigue in addition to physical function tests (grip strength, timed chair stands, and 2-minute walk test). Outcomes included 60-day mortality, intensive care unit (ICU) admission, and achievement of complete remission (CR). Univariate and multivariable logistic regression were performed to evaluate each outcome. **Results:** Of the 243 patients (median age 57.5 y), 56.7% were male and median Charlson comorbidity score was 0. 60-day mortality, ICU admission, and CR occurred in 9 (3.4%), 15 (6.2%), and 171 (70.4%), respectively. In univariate regressions, neither QOL nor physical function tests were predictive of 60-day mortality (all $P>0.05$), whereas cytogenetic risk group ($P=0.04$), ICU admission ($P=<0.001$), and remission status at 30 days ($P=0.006$) were. Fatigue was a significant predictor of ICU admission ($p=0.02$) whereas QOL and baseline physical function were not significant predictors. In univariate analyses, higher Charlson score was found to be a significant predictor of both ICU admission ($P=0.01$) and remission status at 30 days ($P=0.002$). Cytogenetic risk group was correlated with achievement of CR whereas neither QOL nor physical function were predictive (all $P>0.05$). Findings were similar when the subset of 96 elderly patients (age 60+) were examined. **Conclusions:** Baseline QOL and physical function tests in this prospective study were not associated with short-term mortality, ICU admission, or achievement of CR after the 1st cycle of chemotherapy.

7068 General Poster Session (Board #38D), Sun, 8:00 AM-11:45 AM

Results of omacetaxine plus low-dose cytarabine (LD-araC) in older patients with acute myeloid leukemia (AML).

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Background: Older patients with AML have poor tolerance to intensive chemotherapy and poor prognosis. Omacetaxine is active in AML and is part of standard combination chemotherapy in China under the name of homoharringtonine. **Methods:** The aim of the study was to evaluate the efficacy of low intensity therapy with omacetaxine and LD-ara C in newly diagnosed older patients (>/= 60 years) with AML or myelodysplastic syndrome (MDS). Older patients with AML not fit or who refuse intensive chemotherapy were eligible. Normal organ functions and performance status </= 2 were required. Other eligibility criteria were standard. Induction therapy consisted of omacetaxine 1.25 mg/m2 subcutaneously twice daily for 3 days and ara-C 20 mg subcutaneously twice daily for 7 days. Maintenance therapy was with the same induction schedule, repeated every 4-6 weeks for up to 2 years. Dose adjustments for prolonged myelosupression or severe non-hematologic toxicities were made by reducing the number of days of omacetaxine (-1 day by level) and cytarabine (-1 to 2 days by level). **Results:** 30 patients have been treated, with a median age of 71 years (range 64-81); 60% were age 70 years or older. AML post MDS in 20%; chromosome 5 and 7 abnormalities were present in 23%. Overall, 9 patients achieved CR (30%), 5 had CRp (17%) and 1 had PR (3%), for an overall response rate of 50%. Induction mortality was noted in 4 (Day 5, 27, 27, and 70 from start of therapy; 13%); resistant disease in 8 (27%); too early in 4 (13%). With the median follow-up time of 10 months the median survival is 9.3 months and the estimated 1-year survival rate 42%. No serious drug related adverse effects were observed with the combination. **Conclusions:** Low-intensity therapy with omacetaxine + LD-ara C shows promising activity and is safe in older patients with AML not fit for intensive chemotherapy. Clinical trial information: NCT01272245.

7069 General Poster Session (Board #38E), Sun, 8:00 AM-11:45 AM

Result of APL treatment associated with more experience of centers and more treatment as consolidation.

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Background: The first line therapy strategy remains controversial in acute promyelocytic leukemia (APL) patients. Arsenic trioxide (AS_2O_3) approved in relapsed or resistance patients and recently studies reveals benefits of AS_2O_3in first line therapy. Regardless of these, important challenges are early mortality during remission induction and post treatment relapse. **Methods:** Between 2000 and 2012, patients suffered APL whose was new case and confirmed by t(15;17) translocation with RT-PCR, enrolled in study. Until 2007, patients received 28 days AS_2O_3(0.15 mg/kg iv) as induction and after 28 days rest, treatment continued for 2 courses of consolidation therapy with the same dose and after 2007, two additional consolidation courses, one and two year after start treatment, was added for prevent post treatment relapse. At beginning of 2nd and 3th consolidation, consider CSF cytology and RT-PCR for detection of APL cells and weekly CNS prophylaxis by MTX and cytarabine, IT chemotherapy start if needed. Patients received no other treatment. **Results:** Totally 271 patients enrolled in study. Ninety six patients received 3 dose and 175 patients received 5 dose of AS_2O_3. Fifty four (20%) patients died during remission induction before achieve remission. In recent years, early mortality rate reduced below 10% compared with more than 24% in the early years. With median follow-up of 30 months, 170 (78.4%) patients among 217 patients (whose survived after successful induction therapy) were alive (mortality rate: 21.6%) and 2.5-year overall survival and leukemia free survival was 85% and 73% respectively. The cumulative incidence of relapse in group which received three courses of AS_2O_3 and group which received five courses of $AS_2O_3$was 41.5% and 12.6%, respectively (95%CI: 2.5-9.6, P-value=0.0001). **Conclusions:** Currently according recent studies, AS_2O_3 has been considered as first line therapy in APL patients but either early mortality or post treatment relapse remain challengeable factors which affect treatment result. Expedite the referral of patients and improvement of emergencies care can reduce early mortality. The next step might be in order to achieve best treatment strategy for reduce post treatment relapse.

7070 General Poster Session (Board #38F), Sun, 8:00 AM-11:45 AM

Preliminary safety and efficacy of IPI-145, a potent inhibitor of phosphoinositide-3-kinase-δ,γ, in patients with relapsed/refractory CLL.

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Background: Phosphoinositide-3-kinases (PI3Ks) are pivotal in cell signaling and regulate a variety of cellular functions relevant to oncogenesis. IPI-145, a potent oral inhibitor of the PI3KEδ and PI3K-γ isoforms, is in clinical development for patients (pts) with hematologic malignancies. Early results in pts with relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL) from an ongoing Phase I study are reported here. **Methods:** This dose-escalation study evaluates the safety, maximum tolerated dose (MTD), clinical activity, and pharmacokinetics (PK) of IPI-145. Expansion cohorts (EC) $<$ MTD are allowed. IPI-145 is given orally twice daily (BID) in 28-day cycles. Tumor response is based on modified IWCLL guidelines criteria. **Results:** 55 pts have been dosed with IPI-145. PK, available through 50 mg BID, are linear with continuous 24 hr inhibition of pAKT (Ser473) in primary pt CLL cells after a single dose of 25 mg. In the 16 pts with CLL (5 pts in dose escalation $<$ 25 mg BID and 11 pts in a 25 mg BID EC), the median [range] number of cycles was 2.7 [1–14] and 81% remain on study. Treatment-related adverse events (TRAEs) occurred in 10 (63%) pts with CLL, a similar incidence as seen in the total study population (56%). The most common $>$ Grade 3 TRAE in pts with CLL was neutropenia (25%). No $>$ Grade 3 ALT elevations occurred in pts with CLL. Among evaluable pts with CLL (n=11), 82% (n=9) had a PR or nodal response after 2 cycles of IPI-145, with a best response to date of 6 PR, 4 SD (all nodal responses), and 1 PD. **Conclusions:** IPI-145 appeared well tolerated and has shown clinical activity at the doses examined in pts with relapsed/refractory advanced CLL. The single agent MTD has not been determined and dose escalation continues. Updated safety and efficacy data from pts with CLL enrolled in dose escalation and ECs evaluating 25 mg BID and a higher dose ($<$MTD) of IPIE145 will be presented. Clinical trial information: NCT01476657.

7071 General Poster Session (Board #38G), Sun, 8:00 AM-11:45 AM

Quality of life (QOL) and physical function in one-year adult and elderly survivors of acute myeloid leukemia (AML).

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Background: The treatment of AML with intensive chemotherapy (IC) is associated with significant short-term toxicities. We previously showed similar impairments in QOL and physical function among younger (age 18-59) and older (age 60+) patients with AML at diagnosis, with similar recovery over 3 cycles of IC. We now comprehensively describe QOL and physical function recovery over 1 year from diagnosis. **Methods:** Younger and older AML patients undergoing IC without stem cell transplant were enrolled in a prospective, longitudinal study. Assessments were done at baseline (pre-IC) and at 7 time points over the next year. At each visit, patients completed the EORTC QLQ-C30 and the FACT-Fatigue to measure QOL and fatigue, respectively, in addition to 3 physical function tests (grip strength, 2-minute walk test (2MWT), and timed chair stands). Analyses involved multivariable linear regression analyses stratified by age group. **Results:** 243 patients were recruited (147 younger and 96 older, 56% male). Attrition was greater in older adults due to death or disease progression/relapse. Among patients remaining in remission after IC, global QOL and fatigue improved significantly over time ($p<0.001$ for both); trends were similar between older and younger patients. All 5 QOL domains improved or remained stable over time; the greatest improvements were seen in social function and role function and were similar in both age groups. Grip strength increased slightly over time ($p=0.04$) whereas both timed chair stands ($p<0.001$) and the 2MWT ($p<0.001$) had moderate to large improvements, with trends toward greater improvement in younger patients ($p=0.07$ and 0.09, respectively). Results were similar when missing data were imputed. **Conclusions:** Survivors of AML after successful conventional chemotherapy achieve significant improvements in QOL, fatigue, and physical function over time. The course of recovery is remarkably similar in younger and older AML patients, although significant attrition in older adults is a noteworthy limitation. These data suggest that appropriately selected older patients do well following IC for AML.

7072 General Poster Session (Board #38H), Sun, 8:00 AM-11:45 AM

Comparison of two major intergroup induction intensive regimens in Hispanic adolescent and young adults (AYA) with acute lymphocytic leukemia (ALL): The importance of a complete molecular response.

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Background: Novel intensive chemotherapy regimens impacted in the prognosis of adolescent and young adult pts with ALL. The application of pediatric inspired therapies demonstrated complete response reported to be > 80%, and long-term survival rates range from 30% to 45%. In the past, ALL treatments had been designed on the presence of risk factors as elevated WBC, time to complete remission or immunophenotype. Recently, MRD monitoring had risen as a risk predictor. Hypothesis: Complete response(CR) associated with a CMR has impact in disease-free survival. **Methods**: Between March> 2010 and November 2012, 101 adolescent and young adult pts were diagnosed and treated for (Ph)–negative ALL with the C10403 intergroup protocol (N=47) and the 2008 Spanish PETHEMA regimen (N=54). The residual disease status was assessed after induction by multiparametric flow cytometry (MRD <0.1%). **Results**: The median age of the pts was 17.56 years (range, 14-24); with 69 pts (68%) ≤ 18 year-old. 27 (26.7%) pts were WBC ≥ $50x10^9$/L, 63 pts (62%) B immunophenotype, cytogenetics was unknown in 69 pts. After the induction, the CR was achieved in 81% vs 79.6% pts (Int C10403 vs Pethema, respectively). The induction mortality rate was 0% vs 7%. Slow responders to induction chemotherapy were 23.81% and 28.8% respectively (p=0.591). A CMR (CR+MRD ≤0.1%) was seen on 70.21% vs 63.27%. The kaplan-meier 2-year disease free-survival rate calculated for CMR patients on C10403 was 35% vs 17% for the Pethema, which was statistically significant (p< 0.04). A multivariate analysis of pts characteristics in CMR could not identified risk factors for disease prognosis. **Conclusions**: Two different regimens C10403 vs Pethema, could not demonstrate a statistic difference in morphological CR. Lately,the addition of minimal residual disease ≤0.1% (MRD) in the analysis, demonstrated a plausible monitoring variable of response. We suggest that a CMR (CR +MRD at induction) could be a new standard variable to assess responses regardless of previous risk categories. Further validation may be mandatory.

7073 General Poster Session (Board #39A), Sun, 8:00 AM-11:45 AM

Omacetaxine mepesuccinate in chronic phase chronic myeloid leukemia (CML-CP): A post hoc analysis of myelosuppression.

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Background: Omacetaxine mepesuccinate (OMA) was active in 2 CML trials of patients with T315I Bcr-Abl mutations or failing ≥2 tyrosine kinase inhibitors. **Methods:** Hematologic events/recovery were pooled from the 2 trials. OMA 1.25 mg/m^{2}BID was given in 28-day cycles: ≤14 days induction, ≤7 days maintenance with dose delay/change as needed. **Results:** Of 108 patients, median exposure was 7.4 mos, with a median 3 cycle delays and 9 days dosing per patient. Of 91 patients receiving ≥2 cycles, 79 (87%) had ≥1 delay (366 delays in 729 cycles), most due to grade ≥3 thrombocytopenia. Median delay was longest early—peaking at 25 days in cycle 3. Predefined hematologic nadirs (see Table) were reached mostly in initial cycles and less after dose adjustments; 80 patients received blood products, 10 antibiotics. Most common lab grade 3/4 hematologic toxicities were thrombocytopenia (85%), neutropenia (81%), and anemia (62%). Grade 3/4 adverse events included 12 infections (6 treatment related, including 1 pneumonia, 1 sepsis) and 7 hemorrhages (1 related conjunctival, 1 postprocedural, 2 cerebral, 3 gastrointestinal [1 related]); 38 events were fatal (related: 1 pancytopenia, 2 sepsis, 2 unknown). There were 11 hematologic hospitalizations. **Conclusions:** In heavily pretreated CML-CP, myelosuppression was most common after initial OMA cycles, improved with dose adjustments, and rarely led to severe outcomes. Support: Teva BPP R&D, Inc. Clinical trial information: NCT00375219, NCT00462943.

	Cycles				
	1	2	3	4	10
Platelet sample, n pts	100	86	77	69	31
Mean (SD) d to nadir	20.1 (9.2)	22.5 (10.6)	18.8 (11.6)	17.5 (10.2)	13.0 (10.0)
Nadir <10x10^9/L, n (%)	14 (14)	14 (16)	8 (10)	4 (6)	1 (3)
Recovered, n (%)	11 (11)	13 (15)	5 (6)	3 (4)	0
Median d to recovery	5.5	5.5	16.0	9.5	–
Absolute neutrophil count sample, n pts	101	87	78	71	31
Mean (SD) d to nadir	21.0 (8.4)	21.8 (14.0)	18.8 (10.4)	17.1 (12.0)	14.0 (9.8)
Nadir <0.5x10^9/L, n (%)	35 (35)	33 (38)	21 (27)	8 (11)	1 (3)
Recovered, n (%)	31 (31)	30 (34)	18 (23)	6 (8)	0
Median d to recovery	7.0	7.0	7.0	11.0	–
Hemoglobin sample, n pts	102	89	80	71	31
Mean (SD) d to nadir	21.4 (9.5)	22.9 (13.9)	17.9 (10.8)	17.1 (12.3)	13.6 (13.4)
Nadir <80 g/L, n (%)	29 (28)	35 (39)	22 (28)	12 (17)	2 (6)
Recovered, n (%)	28 (27)	28 (31)	16 (20)	9 (13)	1 (3)
Median d to recovery	6.0	7.0	11.0	13.0	–

7074 General Poster Session (Board #39B), Sun, 8:00 AM-11:45 AM

Final report of phase I/II study of PR104, a hypoxia-activated pro-drug, in relapsed/refractory acute leukemia.

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Background: Hypoxia is prevalent in leukemia bone marrow (BM) microenvironment, suggesting its role as a therapeutic target. PR104 is a pro-drug activated by hypoxia-dependent reductases and by hypoxia-independent aldo-ketoreductase 1C3 (AKR1C3). **Methods:** Patients (pts) with relapsed/refractory AML (n=40) after 1 or 2 prior treatments; or ALL (n=10) after any number of prior treatments received PR104 as a 1-hr i.v. infusion q 2 weeks. Biomarkers for hypoxia and AKR1C3 were assessed. **Results:** Pts received PR104 at doses of 1.1 (n=6), 1.6 (n=1), 2.2 (n=1), 3 (n=20) and 4 gm/m2 (n=22) for a median of 1 cycle (range, 1 – 3 cycles). 17 pts had PR104 doses assigned using an adaptive method using toxicity-response trade-offs, patient age, and prior remission duration, and 33 pts were assigned doses by investigators for cohort expansion at 3 and 4gm/m^2. Most common treatment-related grade 3/4 adverse events included myelosupression (anemia 44%, neutropenia 56%, thrombocytopenia 52%), febrile neutropenia (22%), infection (22%) and enterocolitis (14%). 3 (14%) PR104-related deaths occurred at the 4 gm/m^2 dose level: hepatic failure (n=1), enterocolitis (n=1) and pneumonia (n=1). 49 of 50 pts were evaluable for response. No CRs were seen at doses $<$ 3 gm/m^2. 10 of 31 AML pts (32%, (0.19, 0.5)% CI) and 2 of 10 ALL pts (20%, (0.06,0.51)% CI) at 3 or 4 gm/m^2 had responses (CR, n=1; CRp, n=5; morphologic leukemia-free state (MLFS), n=6). In AML pts with 1 prior treatment, responses were seen in 7 of 21 pts (CR, n=1; CRp, n=3; MLFS, n=3). Median overall survival of all pts treated at 3 and 4 gm/m^2 was 72 days, and of pts who achieved CR/CRp/MLFS 143 days. 3 pts with AML (MLFS, n=2; CRp, n=1) and 1 with B-ALL (CRp, n=1) underwent allogeneic stem cell transplantation. Biomarker studies showed hypoxia in the BM; and levels of AKR1C3 in leukemic blasts did not correlate with responses (Benito et al., ASH 2012). **Conclusions:** PR104 administered at doses 3 to 4x the solid tumor MTD had moderate toxicity (most commonly myelosuppression and enterocolitis) in pts with relapsed/refractory AML and ALL. Evidence of activity supports continued evaluation of hypoxia-activated cytotoxins in acute leukemias. Clinical trial information: NCT01037556.

7075 General Poster Session (Board #39C), Sun, 8:00 AM-11:45 AM

Use of flow cytometry in acute promyelocytic leukemia.

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Background: Acute promyelocytic leukemia (APL) is a highly curable disease, with the majority of failures related to hemorrhagic complications. Hence, rapid diagnosis and early initiation of therapy can drastically prevent these complications and reduce mortality. The current diagnostic strategy utilizing fluorescent in situ hybridization (FISH) is often time-consuming and not readily available in some institutions. This is a review of our institutional experience with the use flow cytometry for diagnosis of APL. **Methods:** All cases with t(15;17) by FISH and karyotype between 2006 and 2012 were identified. A second group of consecutive cases of non-M3 acute myeloid leukemia (AML) and negative FISH and karyotype for t(15;17) was used for comparison. A total of 21 APL and 42 non-M3 AML cases were analyzed. **Results:** Both groups were comparable in regard to age, gender, white blood cell count, hemoglobin, blast count and lactate dehydrogenase level. The APL group had significantly higher prevalence of thrombocytopenia, disseminated intravascular coagulation and clinical bleeding at time of admission. Expression of CD11c was lacking in 92.3% (12/13) of APL and 14.6% (6/41) of non-M3 AML cases ($p<0.0001$). CD34 expression was lacking in 68.4% (13/19) of APL and 42.9% (18/42) of non-M3 AML cases ($p=0.06$). HLA-DR expression was lacking in 88.9% (16/18) of APL and 9.5% (4/42) of non-M3 AML cases ($p<0.0001$). Given that APL prevalence is 5% among all AML cases, lack of expression of CD11c, CD34 and HLA-DR have negative predictive values (NPVs) of 99.5%, 97.1% and 9933%, respectively. Among various immunophenotypic profiles, lack of expression of CD11c had the highest NPV (99.5%, $p<0.0001$) and simultaneous lack of expression of CD11c and HLA-DR had the highest specificity (95.1%, $p<0.0001$). **Conclusions:** Expression of CD11c reliably excludes the diagnosis of APL in the majority of AML cases. Flow cytometry has the potential of replacing FISH as the initial test to prompt initiating therapy in APL patients.

7076 General Poster Session (Board #39D), Sun, 8:00 AM-11:45 AM

High-dose cytarabine-mitoxantrone versus hyper-CVAD in adult acute lymphoblastic leukemia and Burkitt's lymphoma: A single center experience of two induction regimens.

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Background: This is a retrospective analysis of 111 newly diagnosed adult ALL patients treated between January 1994 and January 2012 at Westchester Medical Center. **Methods:** Patients received induction chemotherapy with either high dose mitoxantrone and high-dose Ara-c (HDAM, n=62) or Hyper-CVAD (n=49). The patient characteristics are summarized in the table. OS, CR duration and time to recurrence were estimated using the Kaplan-Meier product estimate methods and comparative study was conducted based on Log-rank test. Differences in CR rates by treatment and by prognostic factors were analyzed using Chi-squared test and Fisher's exact test. **Results:** The CR rate was 85% in the HDAM group and 84% in the HyperCVAD group. The median OS was 22.7 months (m), (95% CI 15.3-38.3 m) for the entire cohort, 21.4 m (95% CI 13.3 - 35.5 m) for HDAM arm and 26.8 m (95% CI 11.7 - 63.3 m) for HyperCVAD arm. The OS for patients with Philadelphia chromosome positive or t(4,11) was 13.2 m (95 % CI 9.5 – 26.8 m). In an analysis of the entire cohort for differences in CR rates based on prognostic factors, WBC $<$ 10,000 was the only favorable factor toward CR (p=0.049). Other prognostic factors including cytogenetics, cell type, age, LDH, were not statistically significant. **Conclusions:** HDAM and Hyper-CVAD appear to be comparable in CR induction and overall survival in this single institution retrospective analysis. These two regimens should be compared in a large multicenter randomized study.

Patient characteristics and treatment outcomes.

	HDAM arm	HyperCVAD arm	Entire cohort
Number	62	49	111
Median age (years)	38	41	39
Age < 35 years (%)	43.5	40.8	42.3
Male (%)	58.1	55.1	56.7
WBC median (*10^6 /L)	8100	7310	8050
WBC > 10,000 * 10^6 /L (%)	38.7	49	43.2
Platelet ≥ 20,000* 10^6 /L (%)	75.8	81.6	78.4
LDH ≥ 600 U/L (%)	48.4	55.1	51.4
Cytogenetics – t(9,22) and t(4,11) (%)	21.1	11.1	16.5
t(8,14) (%)	0	8.9	4.1
Others (%)	78.9	80	79.4
Histology Subtype Pre-B (%)	86.7	59.2	74.3
Burkitt (%)	0	14.3	6.4
T (%)	13.35	26.5	19.3
CR rates (%)	85.2	84.1	84.8
Resistant disease (%)	6.6	13.6	9.5
Toxic death (%)	8.2	2.3	5.7
Recurrence rate (%)	44.4	39.5 (NS) (p= 0.67)	42.4
Time to CR (days)	29	27 (NS)	29
Median OS (m)	21.4	26.8 (NS)(p=0.72)	22.7

7077 General Poster Session (Board #39E), Sun, 8:00 AM-11:45 AM

Results of a phase I trial of the proteasome inhibitor carfilzomib in patients with relapsed or refractory chronic lymphocytic leukemia (CLL) and small lymphocytic leukemia (SLL).

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Background: CLL is an incurable malignancy, and survival for patients (pts) with relapsed disease is limited. Carfilzomib (CFZ) has shown efficacy in multiple myeloma, and our group has shown significant in vitro activity in primary CLL cells. Therefore, we have undertaken a phase I trial of this agent in CLL. **Methods:** This is a single institution phase I trial of CFZ in pts with relapsed or refractory CLL. Primary endpoints were to determine maximal tolerated dose (MTD) and describe toxicity. Pts with CLL relapsed after at least one therapy were enrolled using a 3x3 design. CFZ was administered on the standard myeloma schedule. The first two doses were administered at 20 mg/m^2 with remainder given at doses starting at 27 mg/m^2 for dose level 1 with escalation to 56 mg/m^2. **Results:** 17 pts received at least 1 dose of CFZ. 12 pts completed at least 1 cycle of therapy, with the remaining 5 experiencing PD during cycle 1. The MTD was not reached, with 3 pts accrued to each dose level to the maximal dose tested without dose limiting toxicity. Most adverse events (AE) were grade (G) 1 or 2. G3/4 AE were quickly reversible and included G3 neutropenia (4 pts), G4 neutropenia (2), G3 febrile neutropenia (1), and G3 thrombocytopenia (3). G1/2 toxicities observed in $\geq$ 20% of pts included anemia (10), thrombocytopenia (7), and hypocalcemia (8). Median number of cycles was 3, with 9 pts achieving stable disease after 2 cycles. Of 3 pts enrolled at maximal dose level, 2 remain on therapy after 5 and 7 months, with 1 achieving a clinical partial response. Of 5 evaluable pts, at least 50% proteasome inhibition was seen in all at 1 hour, with minimal recovery at 24 hours. PK was best characterized by a two-compartment model. Maximum plasma concentrations across all dose levels ranged from 0.81 to 8.1 uM. Across the evaluated dose range, area under the curve increased in an apparent dose-proportional manner. **Conclusions:** Despite relatively limited efficacy in this study, CFZ has acceptable toxicity in CLL, with no MTD identified up to 56 mg/m^2. This suggests that CFZ may be better studied in CLL using a different schedule or in combination with other active agents. Clinical trial information: NCT01212380.

7078 General Poster Session (Board #39F), Sun, 8:00 AM-11:45 AM

The role of salvage induction chemotherapy after azacitidine (AZA) treatment failure.

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Background: Hypomethylating agents (HMA) such as AZA, are considered standard of care for patients (pts) with IPSS Int-2 or High-risk MDS. These agents are not curative. Many centers have used HMAs as a bridge to alloSCT in pts with MDS in an attempt to reduce tumor burden and prolong time to progression to AML. However, pts are at risk of AZA treatment failure, which may delay or prevent subsequent alloSCT. Recent data have demonstrated poor responses to intensive chemotherapy after AZA failure [ORR of 0% (0 of 4 pts) to 14% (3 of 22 pts) (J Clin Oncol 2011; Br J Haematol 2012)]. **Methods:** This retrospective analysis evaluates the outcomes of 18 pts with MDS, CMML and AML, who failed AZA therapy, and subsequently received induction chemotherapy at the Princess Margaret between July 2009 and December 2012. **Results:** Median age was 57.7 y (range, 19 - 75 y); only 1 pt was $>$ 70 y. 56% were male. Of the 18 pts, 83% were treated for MDS, 6% CMML-2, and 11% AML. IPSS was Int-2/High-risk in 16 pts and Int-1 risk in 2 pts. 83% of pts had been treated with AZA as first-line therapy. Two pts had received growth factors & 1 pt hydroxyurea prior to AZA. Median number of AZA cycles administered was 5.5 (range, 1 - 18) with 72% of pts receiving $<$ 6 cycles. Eleven (61%) pts had primary AZA failure, 5 (28%) secondary AZA failure, and 2 (11%) were taken off AZA to receive induction chemotherapy as an HLA-identical donor was found. At the time of induction chemotherapy, 15 pts had s/tAML, 2 RAEB-2 and 1 CMML-2. Cytogenetic risk was intermediate in 4 and poor in 11 pts, respectively. Karyotype analysis was not done or inconclusive in 3 pts. ORR was 44% and 37.5% in all pts and in AZA failures only, respectively. CR rate was 22% and 25%, CRi 27% and 12.5%, and MLFS 6% and 0% in all pts and in AZA failures only, respectively. Four pts died during induction. Four of 8 responders received an alloSCT, with the remaining 4 pts relapsing (3 while awaiting an alloSCT). Median F/U of all pts was 12.6 mos, with a median OS of 8.3 mos. **Conclusions:** Contrary to prior reports, salvage induction chemotherapy can yield responses in a significant number of pts who have failed AZA therapy. However, response duration and OS remain poor for AZA treatment failures. There is an unmet need for novel therapeutic agents in this group of patients.

7079 General Poster Session (Board #39G), Sun, 8:00 AM-11:45 AM

Plasma trough imatinib levels and molecular response in patients of chronic myeloid leukemia (CML): A single institution study from India.

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Background: One of the reasons proposed for suboptimal responses in Chronic Myeloid Leukemia (CML) patients receiving standard-dose Imatinib has been low blood levels of the drug. Our study aimed to determine the correlation between mean trough Imatinib plasma levels and molecular response in CML chronic phase patients at our centre. We also attempted to compare imatinib plasma levels in patients receiving Gleevec (Novartis) versus patients who were on the generic version of the drug. **Methods:** One hundred and thirty one (131) CML Chronic phase patients were included in this study. All patients had received 400 mg of imatinib for more than 2 year. Plasma Imatinib trough levels were estimated by high-performance liquid chromatography (HPLC). In order to estimate a threshold for plasma imatinib level that correlates with a favorable response, a receiver operating characteristic (ROC) curve was constructed. Patients were divided into two groups: those with Major Molecular Response (MMR) [bcr/abl : abl ratio $<1\%$ as assessed by RQ-PCR] or better (Responders) and those without MMR (bcr/abl : abl ratio $=/> 1\%$ as assessed by RQ-PCR) [Non Responders]. Imatinib plasma levels were also compared in patients who were on Gleevec versus those who were on the generic version of the drug. **Results:** The mean trough imatinib plasma level in the responders was significantly higher ($2.10 \pm 1.18 \mu$g/ml) than in the non responders ($1.31 \pm 0.72 \mu$g/ml) with p value of 0.001. The area under ROC curve was 0.733, with best sensitivity (51.85%) and specificity (89.42%) at a plasma threshold of 0.988 μg/ml. There was no significant difference between the mean trough plasma imatinib levels of the patients who were on Gleevec as compared to those who were on generic Imatinib (p value > 0.05). **Conclusions:** Plasma Imatinib trough levels were statistically similar in the Gleevec and generic Imatinib groups. These levels showed a statistically significant correlation with molecular response. Trough plasma imatinib levels may be a marker for suboptimal response to Imatinib and may identify patients in whom increase of drug dose or change to second generation tyrosine kinase inhibitors may be indicated.

7080 General Poster Session (Board #39H), Sun, 8:00 AM-11:45 AM

Phase I study of NRC-an-019, a tyrosine kinase inhibitor, in imatinib-resistant chronic myeloid leukemia (CML) in an Indian tertiary care hospital.

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Background: NRC-AN-019 is an orally administered tyrosine kinase inhibitor (TKI) of the Bcr-Abl protein-tyrosine kinase. The drug was given to patients as a ready-to-use liquid formulation. **Methods:** The primary objectives of the Phase-I study were to estimate the Dose Limiting Toxicity (DLT) and Maximum Tolerated Dose (MTD) of NRC-AN-019 and also to establish the safe dose for Phase II clinical trial. The secondary objectives were to study the pharmacokinetic properties and antileukemic activity of NRC-AN-019. Philadelphia positive CML patients in all phases, in the age group of 18-65 years were eligible. They had to be resistant or intolerant to Imatinib, with ECOG $\leq$ 2. Dosing was initiated at 50 mg/day and dose escalation was done in increments of 50 mg per each additional cohort. The maximum dose administered was 450 mg/day. The protocol-specific study duration was 30 days; patients continued to receive the study drug subsequently based on Investigator's decision. **Results:** A total of 30 patients were enrolled (3 at 50 mg, 4 at 100 mg, 3 at 150 mg, 3 at 200 mg, 4 at 250 mg, 4 at 300 mg, 3 at 350 mg, 3 at 400 mg, and 3 at 450 mg). DLT was not observed and MTD was not reached. The recommended Phase II-A dose is 300 mg/day, with a scope for escalation up to 450 mg/day. The maximum plasma concentration of NRC-AN-019 was 9,342 ng/mL and AUC was 1,262,191 ng.hr/mL. Common adverse events were skin rash, nausea, and vomiting. Hematological response was observed in 11 patients, cytogenetic response in 7 patients and molecular response in 5 patients. The maximum duration a patient has been on NRC-AN-019 is 863 days. **Conclusions:** Based on the Phase-I data, NRC-AN-019 showed considerable safety and response; it could be a potential treatment option for imatinib-resistant CML. Clinical trial information: CTRI/2009/091/000204.

7081 General Poster Session (Board #40A), Sun, 8:00 AM-11:45 AM

Clinical features and outcome of T-cell acute lymphoblastic leukemia in patients older than 9 years: A single center experience of 110 patients from AIIMS, New Delhi, India.

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Background: It is known that T cell acute lymphoblastic leukemias (ALL) have poorer outcomes than their B cell counterparts. Data on T-ALL in the age group of >9 years from India is minimal. **Methods:** This is a single institutional analysis of patients of above 9 years who were treated from January 2000 to December 2010. All patients who completed at least 4 weeks of induction therapy were analysed for various outcomes. **Results:** T-ALL formed 30% of all ALL in this age group. Of the 110 newly registered patients of T-ALL, the median age was 17 years (Range 10-50 years) with an M:F ratio of 5.9:1. Of this 62%, 30% and 18% patients belonged to 10-18, 19-30 and > 31 years age group respectively. Eighteen (19%) and 2 (2%) and 33 (30%) had CSF, testicular and other extramedullary sites involvement respectively. Twenty eight per cent had a total leucocyte count (TLC) of above $100x10^9$/L. Patients available for survival analysis were 104(94.5%). Complete remission (CR)rate was 68.2% and induction mortality was 14.4%. At a median follow up of 56.4 months 5 year leukemia free survival was 52.3% (median not attained). Twenty seven (38%) patients relapsed (median relapse time of 15.2 months, range 0.7 to 47.3 months), 55% during maintenance phase. The 5 year overall survival (OS) was 46.9% (median OS of 35.4 months). The 5 year OS of 10-18, 19-30 and > 31 years age groups were 42.8%, 71% and 16.6% respectively (p value not significant). Not attaining CR in 1^{st} induction, spontaneous tumor lysis syndrome and peripheral blood blast count of > 80% were significant poor prognostic factors for survival. **Conclusions:** This is one of the largest study of T-ALL outcomes in patients above 9 years from a single center from India. Attainment of CR in 1^{st} induction was the most important risk factor for survival. 5 year OS was 47%.

7082 General Poster Session (Board #40B), Sun, 8:00 AM-11:45 AM

Clinical features and outcome of B-cell acute lymphoblastic leukemia in patients older than 9 years: A single center experience of 241 cases from AIIMS, New Delhi, India.

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Background: Data on B cell Acute Lymphoblastic leukemia (ALL) in the poor prognostic age group of > 9 years from India is minimal. **Methods:** This is an analysis of patients of above 9 years that were diagnosed and treated from January 2000 to December 2010 at a single institute . All patients who completed at least 4 weeks of induction therapy were analysed for various outcomes. **Results:** Of the 241 newly registered patients, the median age was 19 years (Range 10-78 years) with an M:F ratio of 1.9:1. Out of this 47%, 25% & 28% patients belonged to 10-18, 19-30 & > 31 years age group respectively. Twenty seven (11.6%) and 5(2%) had CSF and testicular involvement respectively. Thirty nine per cent had a total leucocyte count (TLC) of above $30x10^9$/L. Philadelphia chromosome (Ph) positivity was seen in 27% and was equally distributed among the different age groups. Patients available for outcome analysis were 213(88.4%). Complete remission rate (CRR) was 66.6% and induction mortality was 26.3%.At a median follow up of 65.8 months 5 year leukemia free survival was 30.5%. Seventy eight (55%) patients relapsed (median relapse time of 13.5 months, range 1.7 to 53.4 months) , 55% during maintenance phase. The 5 year overall survival (OS) was 30.3% with a median OS of 15.8 months. The OS was similar in 10-18 and 19-30 age groups (5 year OS 35% vs. 27.5%, p=0.641) but it was significantly lower in >31 years (5year OS 21%, p=0.008). Apart from this, extramedullary disease, not attaining a CR in 1^{st} induction, albumin at presentation below 3.5gm% and TLC of $>100x10^9$/L were significant poor prognostic markers for survival. **Conclusions:** This is a large study of B-ALL outcomes in patients above 9 years from a single center in India. Patients above 30 years had a worse prognosis while the prognosis of 10-18 and 19-30 years age group were similar. Induction mortality was higher mainly because of advanced disease and poor performance status at presentation.

7083 General Poster Session (Board #40C), Sun, 8:00 AM-11:45 AM

Study of different mutations in chronic myeloid leukemia in India and their co-relation with drug resistance.

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Background: Emergence of ABL point mutations is the most frequent cause for imatinib resistance in CML. Aim of our study is to investigate two potential resistance mechanisms i.e.,mutations of BCR-ABL tyrosine kinase domain (TKD) and Additional Chromosomal Abnormalities during TKI treatment in CML. **Methods:** Karyotyping and BCR-ABL TKD mutation screening are performed in 100 imatinib resistant CML patients who were on imatinib at the time of loss of hematologic response, cytogenetic or molecular response. Imatinib–Resistance Mutation Analysis (Qualitative) were detected by Nested RTPCR and Sanger's Sequencing. In 100 cases, 34 received escalated imatinib, 34 nilotinib and another 32 dasatinib. **Results:** In 100 BCR-ABL positive imatinib, nilotinib and dasatinib resistant cases, 11 different BCR-ABL TKD mutations were detected. Analysis revealed no mutations-43 cases, M351T-12 cases, G250E-10 cases, F317L-8 cases, M244V-5 cases, E255K-4 cases, V379I-4 cases, F359V-3 cases, H396R-3 cases, Y253F-3 cases, E355G-3 cases, T315I-2 cases. 11 novel mutations (F317L, G250E, M244V, Y253F, E255K, M351T, F359V, H396R, V379I, E355G, T315I) conferring imatinib resistance, 10 nilotinib–resistant mutations (M244V, F359V, T315I, E355G, G250E) and 8 dasatinib-resistant mutations (H396R, F317L, H396R, T315I, M351T) were seen in our patient population. T315I was found more frequently in cases on dasatinib than on imatinib therapy. **Conclusions:** T315I which confers resistance to all TKIs was detected only in 2/100 patients who demonstrated loss of response in our population. As compared with other western studies, incidence of T315I mutation was very low in our study. In addition analysis of mutation patterns at baseline may help in stratifying patients for treatment. For cases with TKI resistance, mutation and ACA screening may play role in identifying patients with poorer prognosis. In our practice if nilotinib–resistant mutation was detected, dasatinib was preferred and for dasatinib-resistant mutation, nilotinib was preferred. We are planning for using bosutinib, panotinib and omacetaxine (SC route) in third line therapy in imatinib resistant different mutation positive chronic myeloid leukemia.

7084 General Poster Session (Board #40D), Sun, 8:00 AM-11:45 AM

Hypomethylating agents as first-line therapy in acute myeloid leukemia (AML).

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Background: Hypomethylating agents are used in older AML patients (pts) who are not considered candidates for standard induction therapy. However, data regarding their efficacy remains unclear. **Methods:** We retrospectively evaluated a cohort of 24 consecutive AML pts who were placed on hypomethylation therapy at diagnosis between October 2010 and June 2012 at Markey Cancer Center. **Results:** Baseline characteristics of the patients are described in table 1. Response rate (CR+PR) was 45.8%. Median number of infections were 1 (8 pts), 2 (5 pts), 3 (4 pts).Median hospital admissions required were 1 (10 pts), 2 (4 pts), 3 (5 pts), 4 or greater (2 pts). Average length of hospital stay was 10.3 days (0-37 days). Median units of packed red cell and platelet transfusions were 10 and 11 units (Range=0-64 and 0-78) respectively. After a median follow up of 145.5 days, 13 pts had died. Cause of death was AML (6 pts), infection and end organ failure (7pts).Median overall survival (OS) was 9.7 months (95%CI: 3.2-16.5 months). On multivariate analysis, blast count less than 30% was borderline significantly associated with better OS (P=0.05). However after addition of average hospital stay in the model only age (HR=1.3, CI=1.06- 1.67), gender (HR=11.5, CI=1.2, 110.5), and average hospital stay were significantly associated with OS (HR=1.2, CI = 1.04- 1.32). **Conclusions:** In this cohort of pts the median OS was 9.7 months. Older pts and those with longer average hospital stay had a higher mortality. Better selection of pts in a larger cohort who are likely to gain more benefit from these agents may impact outcomes.

Baseline characteristics.

	Median	(Min, Max)
Age (years)	69	(44, 82)
Blast %	39%	(20%, 85%)
WBC at presentation (k/ul)	3.7	(1.3, 387)
Hemoglobin at presentation (g/dl)	9.6	(6.0, 12.7)
Platelets at presentation (k/ul)	54.5	(11, 336)
Creatinine (mg/dl)	1.06	(0.51, 4.71)
	N	%
Male	13	54.2%
Comorbidity Index 0/1	15	62.5%
Blast presentation, < 30%	10	41.7%
Therapy		
Decitabine	17	70.8%
Decitabine + azacitidine	2	8.3%
Azacitidine	5	20.8%
Cytogenetics[a]		
Complex	12	50.0%
Intermediate	6	25.0%
Other	6	25.0%

[a]Complex=Deletion 7q, Complex; Intermediate= del(9)(q13q22), Normal; Other= Trisomy 10, Trisomy 8, Unknown.

7085 General Poster Session (Board #40E), Sun, 8:00 AM-11:45 AM

mTOR inhibition in MDR acute myeloid leukemia.

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Background: Signaling through the PI3K/PTEN/AKT/mTOR pathway is aberrantly activated in several human cancers, including Acute Myeloid Leukemia (AML) patients where it contributes to leukemic cell proliferation, survival and drug resistance. In leukemia patients treated with drugs such as anthracyclines, vinca alkaloids, chemo-resistance one of the major problems contributing to therapeutic failure, where all this drugs are modulated in their intracellular retention by a 170 kDa Phospho-glycoprotein, an mdr-1 gene product. The role of mTOR in various processes such as proliferation, growth, has been comprehensively described in many reviews, following its inhibition by rapamycin. Thus inhibition of mtor signaling in AML blasts could account for enhancing their sensitivity to cytotoxic agents. This study is to embrace the effect of Rapamycin, an allosteric mTOR inhibitor on MDR AML patients. **Methods:** We selected samples of 25 MDR AML patients isolated from bone marrow or peripheral blood and cultured in vitro. The effects of Rapamycin on fresh AML samples were analyzed by treating the cells with intermediate drug concentrations (100 nM) for 24 h, 48 h, 72 h, 96 h respectively followed by cytotoxicity assay (MTT assay). The effects of the drug on proliferation of cells were analyzed also by cell counting. **Results:** A marked reduction in cell viability at 96 h was detected in 25 samples treated with rapamycin. Out of the 25 analyzed samples, 16 were sensitive to the drug where it was observed that the leukemic cell count came down to almost 2% whereas 9 samples displayed various degree of resistance to the drug. Overall, these findings demonstrated that rapamycin has a cytotoxic activity against primary cells from AML patients with up-regulated mTOR signaling. **Conclusions:** We have evaluated the in vitro effects of Rapamycin on AML patient samples where reduced cell viability primary cells from AML patients were observed. However, further studies of the additional effects of rapamycin will be of the supreme importance, as they could help in designing more efficient curative protocols, for the treatment of acute leukemia patients.

7086 General Poster Session (Board #40F), Sun, 8:00 AM-11:45 AM

Variation in health-related quality of life (HRQOL) by line of therapy, age, and gender among patients with chronic lymphocytic leukemia.

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Background: The HRQOL of patients (pts) with chronic lymphocytic leukemia (CLL) has not been adequately delineated across patient, disease and treatment characteristics. We evaluated HRQOL of CLL pts undergoing treatment in the United States (US) by age, gender and line of therapy. **Methods:** Data were collected in Connect CLL, a prospective observational US registry. Physicians provided data on demographics, clinical characteristics and line of therapy at enrollment. HRQOL was self-reported by pts at enrollment using the Functional Assessment of Cancer Therapy-Leukemia, an instrument that yields a leukemia-specific total HRQOL score (FACT-Leu) and a cancer-specific total HRQOL score (FACT-G). Mean total scores were analyzed by line of therapy, age and gender. Statistical significance was ascertained by ANOVA using SAS 9.2. Multivariate analyses were conducted to assess the relative association of line of therapy, age and gender with HRQOL. **Results:** Among 1,252 pts enrolled from 161 geographically diverse centers (90% community, 8% academic, 2% veterans/military), pts were predominantly male (63%), white (89%) with mean age 69 yrs. Pts were categorized by line of therapy at enrollment: First 61%, Second 18%, Third 11%, Higher 9%; and by age group: <65 33%, 65-74 35%, 75+ 32%. Univariate analyses suggested that the total FACT-Leu score was significantly better in men than women (P=0.004); in pts aged 65-74 vs younger or older pts (P=0.033); and in pts initiating first-line treatment vs pts receiving subsequent treatments (P=0.0002). Similar results were found with the FACT-G score except that gender differences were not statistically significant. Multivariate analysis confirmed that line of therapy (P=0.007), gender (P<0.0001), and age group (P=0.039) were each associated with significant differences in the FACT-Leu total score. **Conclusions:** Results from the Connect CLL Registry indicate that HRQOL is better among pts initiating first-line therapy compared to pts initiating subsequent treatments, and that this remains true when age and gender are considered. Future analyses should determine how HRQOL may change over time relative to treatment and treatment response.

7087 General Poster Session (Board #40G), Sun, 8:00 AM-11:45 AM

Apoptosis induction mediated through PI3-kinase/AKT/mTOR pathway using anti-ROR1 monoclonal antibody in chronic lymphocytic leukemia cells.

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Background: The PI3K/AKT/mTOR is a central pathway activated in many types of cancer. Mammalian target of rapamycin (mTOR) is a serine/threonine protein kinase regulating cell growth, proliferation and survival. In CLL cells PI3K pathway is constitutively activated leading to AKT activation with subsequent phosphorylation of other downstream signaling molecules. ROR1 is a type I transmembrane RTK, overexpressed and constitutively phosphorylated in CLL. A unique anti-ROR1 mAb directed against CRD region of ROR1 was capable of inducing direct apoptosis as well as dephosphorylating the ROR1 molecule. Here, we investigated the apoptotic effect of the anti-ROR1 mAb and effects on the PI3K/AKT/mTOR pathway using primary CLL cells. **Methods:** Apoptosis was detected by the MTT assay and Annexin V/PI methods in a 24 h assay. Antibody untreated and treated cell lysates were prepared and subjected to Western blot analysis for identification of the signaling molecules involved in apoptosis induced by the ROR1 mAb. We analysed total and phosphorylated levels of the following signaling proteins: AKT, p-AKT, PI3K, p-PI3K, mTOR, p-mTOR, ERK, p-ERK, PKC and p-PKC. Phosphoproteins were measured before incubation with the mAb and after 20 min-24 h. **Results:** ROR1 detection on surface of the CLL cells was 80-85% and apoptotic frequency 45-50%. Western blot analysis showed decreased levels of p-AKT, p85 isoform of p-PI3K and p-mTOR in treated compared to untreated samples. No changes in the phosphorylation levels of ERK and PKC proteins were seen. **Conclusions:** Incubation of CLL cells with the anti-ROR1 mAb induced apoptosis of CLL cells. Apoptosis was preceded by dephosphorylation of PI3K, AKT and mTOR proteins indicating deactivation of these proteins by the ROR1 mAb. In untreated CLL cells no effect was noted. Furthermore no dephosphorylation of PKC or ERK was seen. We suggest that activation of mTOR might occur via the PI3K/AKT pathway and may be a survival signal in CLL cells associated with the aberrant expression of ROR1. Further studies are warranted to understand better the signaling pathways associated with ROR1 and the downstream signaling effects of ROR1 targeting drugs.

7088 General Poster Session (Board #40H), Sun, 8:00 AM-11:45 AM

Predictive factors associated with achievement of major cytogenetic response (MCyR) to omacetaxine mepesuccinate among patients with chronic phase chronic myeloid leukemia (CML-CP).

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Background: Omacetaxine mepesuccinate (OMA), a first-in-class cephalotaxine, is a protein synthesis inhibitor not dependent on Bcr-Abl signaling. OMA has shown clinical activity in CML patients resistant/intolerant to tyrosine kinase inhibitors (TKIs). This subanalysis of 2 phase 2 studies examines predictors of MCyR to OMA in patients failing ≥2 TKIs. **Methods:** OMA 1.25 mg/m^{2}BID was given in 28-day cycles: ≤14 days for induction, ≤7 days for maintenance. MCyR was defined as ≤35% Ph+ metaphases in bone marrow. A full logistic regression model with 11 baseline parameters was examined by Hosmer and Lemeshow Goodness-of-Fit test. **Results:** Of 81 patients (median age 59 y; range 26-83), 16 (20%) achieved MCyR. Mean (SD) baseline body surface area (BSA) was 1.90 kg/m^2(0.240). Median time since last TKI to start of study was 1.3 mo (range 0.2-28.0) and median time from diagnosis was 75.4 mo (range 7.9-234.3). The final model had 8 baseline predictors (goodness of fit of p=0.1473; Table). (Sex, 2 vs 3 TKIs, or status of any mutation were not in the final model.) Logistic regression analysis showed a significant association between MCyR and no hydroxyurea (HU) use at baseline (p=0.0118). Numerically higher MCyR rates occurred in patients with baseline CHR and BSA ≥1.94 kg/m^2. **Conclusions:** This small sample suggests that omacetaxine may be an important option for a range of patients, regardless of Bcr-Abl T315I mutation status. Prior HU may indicate more proliferative disease. Support: Teva BPP R&D, Inc. Clinical trial information: NCT00375219, NCT00462943.

Baseline	MCyR (%)	Ratio	95% CI	P value
Age <65 y	14/56 (25)	5.165	0.785-33.963	0.0875
≥65 y	2/25 (8)			
Complete hematologic response	9/24 (38)	4.243	0.975-18.457	0.0540
+	7/57 (12)			
–				
T315I mutation Absent/unknown	12/58 (21)	1.841	0.311-10.897	0.5012
Present	4/23 (17)			
BSA ≥1.94 kg/m^2	11/41 (27)	4.253	0.937-19.303	0.0607
<1.94 kg/m^2	5/40 (13)			
Imatinib response Yes	7/20 (35)	3.348	0.805-13.919	0.0965
No/unknown	9/61 (15)			
HU use No	12/38 (32)	7.785	1.577-38.436	0.0118
Yes	4/43 (9)			
Time since ≥1 mo	11/51 (22)	2.808	0.586-13.457	0.1966
prior TKI <1 mo	5/30 (17)			
Time since <75 mo	10/40 (25)	3.062	0.676-13.871	0.1465
CML diagnosis ≥75 mo	6/41 (15)			

7089 General Poster Session (Board #41A), Sun, 8:00 AM-11:45 AM

Prognostic impact of trisomy 8 cytogenetic abnormality in acute myelogenous leukemia: Analysis of a large cohort (N=2187) of newly diagnosed patients.

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Background: Trisomy 8 is grouped as intermediate risk in cytogenetic (CG) classifications of acute myelogenous leukemia (AML). In a multi-variate analysis of MRC data, trisomy 8 was associated with worse overall survival (OS). **Methods:** Between years 1993-2012, 2,187 patients (pts) with newly diagnosed AML presented at MD Anderson Cancer Center and 21 (10%) were with a trisomy 8 CG abnormality. The median age of trisomy 8 pts was 63 years (range, 17-89 years) and 59% were males. Sixty four (30%) had isolated trisomy 8, 45 (21%) had trisomy 8 +≤2 additional cytogenetic abnormalities and 102 (49%) had trisomy 8 + ≥3 additional abnormalities. Thirty three percent of pts with trisomy 8+≤2 additional abnormalities, had secondary AML compared to 21% of diploid CG (p=.007). Mutations in the FLT3 gene was seen in 9% and N or KRAS gene in 8%. **Results:** The overall remission rate (RR) was 47%, 53% and 43% among pts with trisomy 8 alone, trisomy 8+≤2 and trisomy 8+≥3 abnormalities respectively. Among pts <60 years of age and with trisomy 8 + ≤2 abnormalities, RR was 71% and the same was 77% for pts with diploid CG. For pts ≥ 60 years, the RRs were 26% and 57% respectively. Among pts ≥ 60 years and trisomy 8 with complex CG (≥3 additional abnormalities) the RR was 38% and that for patients with complex (non-trisomy 8) CG was 41%. Patients with trisomy 8 either alone or ≤2 additional abnormalities had a shorter OS (p= .04 and .05 respectively, median 10.8 and 8.6 months vs 16.5 months) compared to those with diploid CG. Event free survival was also shorter among patient with isolated trisomy 8 versus those with diploid CG (p=.008, median 2.9 versus 7.5 months). On the other hand, patients with trisomy 8+≥3 abnormalities had outcomes comparable to non-trisomy 8 CG group. **Conclusions:** Non-complex CG trisomy 8 is associated with worse clinical outcome in patients with AML than those with diploid CG and its inclusion in intermediate risk group may need reconsideration. The most adverse impact appears to be from lower RR among patients with trisomy 8+≤2 additional abnormalities and ≥60 years of age.

7090 General Poster Session (Board #41B), Sun, 8:00 AM-11:45 AM

Incidence and outcomes of chronic myeloid leukemia (CML) patients (pts) treated with second-generation tyrosine kinase inhibitors (TKI) who develop other chromosomal abnormalities (OCA).

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Background: Development of OCA has been reported among pts receiving imatinib as initial therapy for CML. Little is known about OCA development in CML pts treated with frontline 2nd generation TKI (dasatinib, nilotinib). **Methods:** OCA is defined as cytogenetic abnormality in non-Philadelphia chromosome positive clones as pts respond to TKI. Among pts treated with frontline dasatinib (n=99) or nilotinib (n=117), on parallel prospective single-arm phase II protocols at MDACC, 30 OCA ptswere identified, chronic (n=25) or accelerated phase (AP) (n=5). **Results:** 11 (11%) pts treated with dasatinib and 19 (16%) with nilotinib developed OCA; median follow-up 30 mo (range 0-71). Difference in OCA incidence with dasatinib and nilotinib was not statistically significant. At start of therapy, median age (years) of OCA pts was 53 (41-71) with dasatinib and 52 (37-82) with nilotinib, compared to those pts without OCA: 48 (18-83) with dasatinib and 49 (17-87) with nilotinib. Most common OCA was abnormality of chromosome 7 with 6 occurrences in 5 pts (1 pt with both inv(7) and +7) (inversion (n=1), 2 different translocations (n=2), deletions (n=2), and additions (n=1)). No pts developed trisomy 8 (historically most common OCA in imatinib-treated pts). Median time to first OCA: 9 mo (range 3-58) for all pts (12 mo (range 3-58) for dasatinib group and 9 mo (3-48) for nilotinib group). OCA disappeared spontaneously in 25 pts during follow-up. Outcomes for OCA versus non-OCA group (Table). For AP pts: 3/6 (50%) in dasatinib group and 2/17 (12%) in nilotinib group developed OCA. None of the OCA pts has developed AML or MDS. **Conclusions:** OCA is observed in 10-15% of pts receiving initial therapy with 2nd generation TKI. At median follow-up of 30 mo, occurrence of OCA confers no adverse impact on outcomes when compared to non-OCA pts treated with 2nd generation TKI and has not resulted in other hematologic disorders.

Outcomes in OCA group versus non-OCA group at 36 months (n=216).

	EFS (by IRIS) %	TFS %	OS %
OCA	100	100	100
Non OCA	93	97	99
P value	0.095	0.365	0.517

7091 General Poster Session (Board #41C), Sun, 8:00 AM-11:45 AM

Decreasing early mortality (30-day) in APL patients with use of streamlined treatment guidelines and support from core group of experts.

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Background: Recent evidence from population based studies in Brazil and US SEER data show that the early mortality (EM) in APL is around 30%. This is in contrast to observation in clinical trials where it is 5%. The common causes of death are hemorrhagic complications (HC), infection, differentiation syndrome (DS) and multi-organ failure. HC are unique to this condition due to DIC and HC are seen in upto 60% of patients. Hence, decreasing early deaths is a high priority at all leukemia treatment centers. We report our updated results showing that use of set of streamlined treatment guidelines along with support from experts decreases early deaths. **Methods:** At Georgia Regents University, between 7/2005 and 6/2009, 19 patients were diagnosed with APL. 7 patients (5 high-risk and 2 low-risk) died during induction resulting in an unusually high mortality rate of 37%. All patients who survived induction are still in remission at present. The high early death rate prompted us to develop a simple, 2 page treatment algorithm that focuses on quick diagnosis, prompt initiation of therapy, and proactive and aggressive management of all the major causes of death during induction. We also made our treatment protocol available to smaller treatment centers and helped the treating oncologists manage the patient during the first few days after diagnosis. **Results:** From 11/2010 to 12/2012, we treated 5 patients at GRU and helped manage 9 patients at 5 practices. Age range was 30-60 years. 4 patients were high-risk, 7 intermediate and three low-risk. There were no deaths during induction. Only 1 patient (8%) had HC and 4 had DS. **Conclusions:** While we recognize that this is a small cohort, our own experience and a similar approach pioneered by investigators in Brazil clearly shows this to be an effective model to decrease early deaths in APL. We believe our experience warrants large scale implementation of our protocol in an attempt to decrease early mortality in APL. We were awarded a 1.68 million grant by the Leukemia Lymphoma Society to implement this protocol in the states of Georgia and South Carolina with a catchment population of 15 million over a 3 year period.

7092 General Poster Session (Board #41D), Sun, 8:00 AM-11:45 AM

Phase I/II study of the combination of inotuzumab ozogamicin (CMC-544) with low-intensity chemotherapy in patients (pts) with acute lymphoblastic leukemia (ALL).

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Background: Older pts with ALL have a significantly worse outcome. This is primarily due to poor tolerance of intensive chemotherapy which results in ineffective delivery of induction-consolidation-maintenance chemotherapy. Addition of targeted non-myelosuppressive therapy to effective low-intensity chemotherapy might improve outcome. CD22 expression occurs in >90% of pts with ALL. Inotuzumab ozogamicin (IO) is a CD22 monoclonal antibody bound to a toxin, calecheamicin, and has shown single-agent activity in relapsed/refractory ALL (Kantarjian, Lancet Oncology 2012). **Methods:** Pts ≥60 years (yrs) with newly-diagnosed B-cell ALL were eligible. The chemotherapy was low-intensity hyper-CVAD (cyclophosphamide and dexamethasone at 50% dose reduction, no anthracycline, methotrexate at 75% dose reduction, ara-C at 0.5 g/m2 x 4 doses). Rituximab and intrathecal chemotherapy were given for first 4 courses. IO was given on day 3 of each of the first 4 courses. First 6 pts received 1.3 mg/m2 for cycle 1 followed by 0.8 mg/m2 for subsequent cycles; pts 7 onwards received 1.8 mg/m2 for cycle 1 followed by 1.3 mg/m2 for subsequent cycles. **Results:** Eleven pts (7 men, 4 women) have been treated so far. Median age is 70 yrs (range 60-79). Median follow-up is 8.2 months (mos). Grade 3-4 non-hematological toxicity included 2 pts with grade 3 LFT elevation. Seven pts had one or more infections. No dose-limiting toxicity was observed. Ten of 11 pts (91%) achieved complete remission (CR). All pts achieving CR have also achieved flow-cytometric MRD negative status and continue to be on study in CR anywhere from 1.0 to 12.4 mos. There have been no relapses. One patient did not achieve CR and died 2 mos later after receiving a salvage regimen. This is the only death on the study. Six-month disease-free and overall survival are 90% and 90%, respectively. **Conclusions:** Combination of IO with low-intensity chemotherapy is safe and shows very encouraging results (91% CR) in the frontline setting in elderly pts with ALL. These results appear to be better than those achieved with chemotherapy only approach and may become the new standard of care for frontline treatment of elderly pts with ALL. Clinical trial information: NCT01371630.

7093 General Poster Session (Board #41E), Sun, 8:00 AM-11:45 AM

Economic benefits of adequate molecular monitoring in patients with chronic myelogenous leukemia (CML).

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Background: Molecular monitoring every 3 months using quantitative polymerase chain reaction (qPCR) of BCR-ABL mRNA transcripts on International Scale is recommended by the National Comprehensive Cancer Network and the European LeukemiaNet for patients (pts) in chronic phase of CML. A previous study has shown an underutilization of qPCR in the community setting. This study assessed the impact of the frequency of molecular monitoring on hospitalization and medical costs among CML pts receiving 1st-line tyrosine kinase inhibitor (TKI) therapies. **Methods:** Two U.S. administrative claims databases were combined (01/2000-06/2012) to identify adult CML pts initiated on TKIs (imatinib, dasatinib, nilotinib). Pts were followed for 12 months from their first TKI prescription and categorized into 3 cohorts based on frequency of qPCR tests (i.e., 0, 1-2, and 3-4). Number of inpatient admissions and medical service costs (measured from a US payer perspective; adjusted to 2012 U.S. dollars) were compared between cohorts. Multivariate regression models adjusted for confounding factors (e.g., age, gender, CML complexity, TKI). **Results:** The study included 1,205 CML pts. Over the 12-month study period, 41.0% of the pts had no qPCR test, 31.9% had 1-2 tests, and 27.1 % had 3-4 tests. Compared to pts with no qPCR monitoring, those with 3-4 tests incurred 37% fewer CML-related (i.e., a primary CML diagnosis) inpatient admissions ($p=.017$) during the study period, leading to a \$4,000 ($p=.009$) reduction in CML-related inpatient costs and \$5,663 ($p=.005$) reduction in all-cause inpatient costs, accounting for the majority of the \$5,997 reduction in total medical service costs ($p=.049$). Pts with 1-2 tests a year showed smaller and statistically insignificant reductions from those with no test in the frequency of hospitalization and medical costs. **Conclusions:** Among CML pts who initiated 1st-line TKIs, pts with 3-4 qPCR tests a year incurred fewer inpatient admissions and lower medical service costs compared to pts with no test. These findings suggest that pts would benefit from regular qPCR testing and underscore the value of molecular monitoring in the delivery of quality care for Ph+ CML-CP pts on TKI therapies.

7094 General Poster Session (Board #41F), Sun, 8:00 AM-11:45 AM

Body mass index impact on acute myeloid leukemia (AML) outcomes.

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Background: Obesity is associated with comorbidities that could cause negative outcome upon delivering intensive care. In pediatric AML patients (pts), obesity was associated with more toxicity and worse prognosis. Here, we study Body-Mass Index (BMI) impact on clinical outcome of adult AML pts. **Methods**: A total of 180 adult pts with AML between 2003-2011 were enrolled. Retrospective data included demographics, labs, cytogenetics and outcome. LeukemiaNET Standardization (LNS), complete remission (CR), overall survival (OS) and relapse free survival (RFS) were obtained (Dohner E, Blood 2010). BMI of 25-30 was defined as overweight, while >30 as obesity. Fischer's and Wilcoxon tests were used for comparatives between groups, cox proportional hazards and logistic regression for associations for OS/RFS and CR, Kaplan-Meier test for OS and RFS estimates via JMP software V9.0. IRB approval was obtained according to Helsinki declaration. **Results**: The median age was 63 years, with 115 (64%) were men. Of 159 pts, karyotype was favorable, Intermediate I, II and adverse in 21 (13%), 76 (48%), 23 (%14) and 39 (25%) pts respectively. Median BMI was 28.2 (range 16.8-47.8). 48 (26%) had normal BMI, 62 (34%) were overweight, and 70 (38%) were obese. At diagnosis, BMI classes were not associated with age, sex, glucose, white blood count (WBC), platelets, blasts, ECOG status, LNS, FLT3/NPM1 status; nor treatment toxicities, CR rates, or relapse after CR. BMI classes were associated with presence of concomitant comorbidities ($p=0.047$) and glucose levels ($p=0.044$). In univariate analysis, overweight ($OR=1.8$, $p=0.16$) and obesity ($OR=1.9$, $p=0.13$) did not affect CR rates. On adjusting for age, sex, LNS, WBC and blast count at diagnosis, only overweight pts had a significant higher CR (76% vs 63%) rates ($OR=2.99$, $p=0.043$). OS and RFS were not associated with BMI in univariate ($p=0.51$) and multivariate ($p=0.32$) models. Median OS and RFS were not different across BMI subgroups ($p=0.52$ and 0.59). **Conclusions**: BMI subgroups showed no correlation with treatment toxicity, LNS, relapse rates, OS or RFS. This should encourage giving therapy to pts regardless of their BMI status. Overweight was associated with better CR rates despite increased concomitant morbidities.

7095 General Poster Session (Board #41G), Sun, 8:00 AM-11:45 AM

Inotuzumab ozogamicin (CMC-544) compared to chemotherapy in patients (pts) with relapsed/refractory (R/R) acute lymphoblastic leukemia (ALL): A retrospective comparison.

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Background: Modern multi-agent chemotherapy (CT) regimens result in complete remission (CR) rates of 80-90% and long-term survival rates of 40% in pts with ALL. The most common reason for treatment failure is relapse of the disease. Post-relapse therapies lead to second CR in 30-40% of pts with a 5-year survival of <10%. CD22 expression occurs in >90% of pts with ALL. Inotuzumab ozogamicin (IO) is a CD22 monoclonal antibody bound to a toxin, calecheamicin. We reported overall response rate of 57% with single-agent IO in R/R ALL (Kantarjian, Lancet Oncology 2012). **Methods:** We analyzed the outcomes of patients with R/R ALL treated with single-agent IO (n=90) vs. historical controls (n=292) treated with combination CT at our institution from 1990-2008. IO was dosed at 1.8 mg/m2 every 3-4 weeks (first 41 pts), and later weekly dosing (0.8 mg/m2 day 1, 0.5 mg/m2 on days 8 and 15, every 3-4 weeks). Fifty-percent of historical controls were treated with hyper-CVAD CT (n=147). **Results:** The median age in the IO cohort was 39.5 years (yrs) (range 4-84) and in the CT cohort was 37 yrs (range 14-81). Overall CR/CRp rate was 49% with IO vs. 29% with CT. In salvage 1, CR/CRp rate was significantly better with IO [66% vs. 40% with CT (p=0.007)]. When only hyper-CVAD-based regimens were included, the CR/CRp was not statistically different (66% with IO vs. 56% with hyper-CVAD, p=0.332). In salvage 1, the median overall survival (OS) was 9.2 months (mos) with IO vs. 6.2 mos with CT (p=0.06 compared with IO) vs. 7.9 mos with hyper-CVAD (p=0.48 compared with IO). In salvage 2, CR/CRp rate was better with IO vs. CT (44% vs. 16%, p=<0.001); OS was not different (4.3 mos vs. 2.5 mos, p=0.74). In salvage 3, CR/CRp rate was better with IO vs. CT (46% vs. 19%, p=0.03); OS was also better with IO vs. CT (6.6 mos vs. 2.6 mos, p=0.01). In salvage 4, CR/CRp rate was better with IO vs. CT (27% vs. 9%, p=0.01); OS was not statistically different (7.4 mos vs. 1.9 mos, p=0.09). **Conclusions:** In pts with R/R ALL, outcomes after single-agent IO are better than pts treated with CT alone. In addition, IO has fewer side effects than CT. IO has the potential to replace multi-agent CT as standard of care for treatment of pts with R/R ALL.

7096 General Poster Session (Board #41H), Sun, 8:00 AM-11:45 AM

Types, frequency, and adherence of molecular tests in chronic myelogenous leukemia at chronic phase (CML-CP) in the U.S. community setting.

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Background: The objective was to evaluate the types, frequency and adherence of molecular tests utilized in patients (pts) with CML-CP who initiated 1st-line TKI therapy in the community practice (prac) setting. **Methods:** A retrospective study of newly diagnosed CML-CP pts; initiating 1st-line TKI during 06/2007 and 03/2011, with ≥18-mo follow-up was conducted. Data was collected from iKnowMed, various local & national labs to evaluate whether qRT-PCR test results was reported in International Scale (IS) or not (non-IS). The proportion (prop) of pts tested for molecular response in 3-mo intervals was tallied. **Results:** The study identified 189 pts (mean age 57 yrs, 53% male), 15% had no cytogenetic (cyto, FISH included) or molecular test (MT) recorded during 1st-line TKI therapy. The median number of MT was 6 (range: 1-28). In 3-mo intervals, the prop of pts tested for cyto responses were: 0-3 mos (24%), 3-6 mos (21%), 6-9 mos (24%), 9-12 mos (22%), 12-15 mos (10%), and 15-18 mos (7%). The prop of pts had MT in the 3-mo intervals were: 34%, 47%, 54%, 47%, 51% , and 55%. Regional patterns show the Northeast (defined by U.S. census regions) had a higher prop of pts for MT at almost all of these intervals. The number of physicians seeing CML pts correlated with the prop of pts monitored at each interval. Of the 1,226 MT ordered, 25% were reported on IS, 9% were unknown and 69% were on non-IS (Data reported: 48% log reduction, 45% BRC-ABL%, 7% other). Labs in the Midwest report on IS most often (61%), followed by the Northeast, Western (29% for both), and the South (13%). As the prac size increased, so did the utilization of IS. **Conclusions:** A low prop of CML pts were monitored for cyto and molecular responses. Only a quarter of the MT results were reported in IS. These results suggest gaps in CML management that could be closed with effective educational programs stressing the importance of monitoring and using IS reporting labs.

7097 General Poster Session (Board #42A), Sun, 8:00 AM-11:45 AM

Safety of asparaginase *Erwinia chrysanthemi* in a compassionate-use trial: Subanalysis of the adolescent/young adult (AYA) and adult patient (Pt) population.

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Background: The AYA population is usually defined as pts aged 16 to 39 years. NCCN guidelines recommend that AYA patients with acute lymphoblastic leukemia (ALL) be treated with 'pediatric-inspired' protocols that includeL-asparaginase (L-ASP) as an integral component of their multiagent chemotherapy regimen. Hypersensitivity reaction is the most common toxicity associated with L-ASP treatment, occurring in 10%–30% of pts treated with *E coli*–derived L-ASP, necessitating its discontinuation. In those pts, it is recommended that L-ASP derived from *Erwinia chrysanthemi* (Erw) be initiated since it is immunologically distinct from *E coli*–derived L-ASP. **Methods:** A large compassionate-use trial in pts with ALL or lymphoblastic lymphoma who developed a hypersensitivity reaction (ie, grade $\geq$2) to an *E coli*–derived L-ASP was conducted to evaluate the safety of Erw. Pts were excluded if they had a history of pancreatitis, previous allergic reaction to Erw, or were pregnant. Adverse events (AEs) and/or case report forms were completed for 940 pts. The Erw safety information for the full study population was previously reported. Here, we report a safety analysis of pts aged $\geq$16 years with the majority being AYA (94%), a population in which little Erw safety information has been presented. **Results:** In this compassionate-use trial, 156 pts were aged $\geq$16 years. These pts were primarily male (67.9%), had nonrelapsed disease (70.5%), B-lineage ALL (71.2%), and received intramuscular Erw (85.9%). 71.8% completed their planned Erw course. Reasons for discontinuation included allergic reaction (3.2%), other AEs (9.6%), other reasons (6.4%), and unknown reasons (9%). Hypersensitivity occurred in 20 (12.8%); hyperglycemia, 9 (5.8%); pancreatitis, 6 (3.8%); thrombosis, 5 (3.2%); bleeding, 1 (1%). Grade 3/4 AEs with a $>$5% incidence included hyperglycemia (5.8%). There were 10 deaths: 4 disease progression, 3 infection, 1 coma, 1 renal impairment, 1 unknown. **Conclusions:** The safety profile of Erw in pts $\geq$16 years was consistent with the profile in the entire study population. This compassionate-use trial permitted the completion of L-ASP in 71.8% of AYA and adult pts. Clinical trial information: NCT00693602.

7098 General Poster Session (Board #42B), Sun, 8:00 AM-11:45 AM

Predictors of survival in patients with transformed chronic lymphocytic leukemia (TC).

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Background: Patients with CLL that develop Richter's syndrome (RS) have a very poor prognosis. Similarly, pts with CLL that have clinical and histological features (increased large cells/prolymphocytes in CLL tissue biopsy) of increased aggressiveness (defined as accelerated phase CLL, AP) have a poor prognosis. In order to identify prognostic factors in pts with AP and RS, collectively referred to as TC, we reviewed our center experience. **Methods:** Pts with TC and complete evaluation including biopsy and concomitant FDG/PET were included. Pts with de novo TC were excluded as their prognosis is substantially superior versus previously treated pts. Pts with N+ or M+ concurrent solid tumors were also excluded. Since FDG/PET-derived SUV reflects tumor proliferative rate, we used SUVmax≥10 to indicate high-risk disease (Falchi, Blood. 2012;120: abstr # 927). We identified factors associated with outcome and performed a multivariable model for OS. **Results:** One hundred eighty-three consecutive pts with TC (99 with AP and 84 with RS) were evaluated at MDACC between 2002 and 2012. Demographic and clinical characteristics were similar between pts with AP and pts with RS. 30% and 77% of pts with AP and RS, respectively had an SUVmax≥10. Approximately half of the pts were treated with intensive chemoimmunotherapy after the TC diagnosis. CR rates were 21% and 16% and overall response rates were 37% and 26% for pts with AP and RS, respectively. At the time of this analysis 144/183 pts have died, for a median OS of 9.6 months (7.9-14.7). Age ≥65, B symptoms, LDH, β2-microglobulin, del17p, SUVmax≥10, extensive disease by FDG/PET (SUVmax≥5 on both sides of the diaphragm), PS≥2 bulky disease and high Ki67 correlated with shorter OS. In multivariable analysis SUV uptake (max≥10), PS higher than 1 and bulky nodal disease (>5 cm) retained independent significance. **Conclusions:** Based on our experience, an SUVmax of 10 or higher, PS higher than 1 and bulky nodal disease (>5 cm) are the most important factors predicting outcome in pts with TC. A prognostic model for survival is being developed for pts with TC.

7099 General Poster Session (Board #42C), Sun, 8:00 AM-11:45 AM

Evolution of bosutinib (BOS) toxicity in patients (pts) with Ph+ leukemia after resistance/intolerance to prior therapy.

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Background: BOS is an oral dual Src/Abl tyrosine kinase inhibitor (TKI) approved for treatment of Ph+ CML following resistance/intolerance to prior therapy. Prior reports from this phase I/II trial indicated the BOS safety profile was primarily characterized by myelosuppression, gastrointestinal events, and rash. The current analysis compares the incidence of toxicity in Year 1 (Y1) for pts on treatment ≤1 y and within Y1 and Year 2 (Y2) for pts on treatment for >1 y. **Methods:** BOS 500 mg/d was evaluated in 3 cohorts: chronic phase (CP) CML after imatinib only (CP 2L cohort; n = 286); CP CML after imatinib + dasatinib and/or nilotinib (CP 3L cohort; n = 119); and accelerated/blast phase CML or ALL after prior TKI therapy (ADV cohort; n = 164). **Results:** The most common treatment-emergent adverse events (TEAEs) in each cohort occurred more frequently within Y1 than Y2 (Table). The incidence for grade 3/4 events followed a similar pattern. AEs were the most common reason for BOS discontinuation in Y1 (CP 2L, 53%; CP 3L, 32%; ADV, 41%). Of the pts whose primary reason for discontinuing BOS was an AE during the first 2 y, most did so during Y1 (CP 2L, n = 51/60 [85%]; CP 3L, n = 22/24 [92%]; ADV, n = 24/25 [96%]); the most common reasons during Y1 were thrombocytopenia (12%; 9%; 4%), increased ALT (6%; 4%; 2%), neutropenia (3%; 6%; 0%), diarrhea (4%; 3%; 0%), and vomiting (3%; 4%; 1%). Serious AEs were more common among pts who discontinued BOS ≤1 y versus on treatment >1 y in the CP 3L and ADV cohorts, but similar in the CP 2L cohort (Table). **Conclusions:** Discontinuation due to AEs was observed primarily in Y1. For pts on BOS for >1 y, the incidence of common TEAEs decreased substantially after Y1, suggesting BOS tolerability improves after long-term exposure. Clinical trial information: NCT00261846.

	CP 2L			CP 3L			ADV		
	BOS ≤1 y (n = 97)	BOS >1 y (n = 189)		BOS ≤1 y (n = 69)	BOS >1 y (n = 50)		BOS ≤1 y (n = 125)	BOS >1 y (n = 40)	
	Y1	Y1	Y2	Y1	Y1	Y2	Y1	Y1	Y2
TEAE, %									
Diarrhea	90	81	40	83	82	50	69	90	28
Nausea	41	45	12	51	36	18	42	58	15
Vomiting	40	31	7	41	32	8	41	43	8
Thrombocytopenia	34	28	19	28	36	20	34	30	18
Rash	29	33	12	23	24	12	22	53	13
Abdominal pain	24	21	8	19	16	14	16	30	8
Fatigue	23	19	10	25	16	14	19	10	10
Increased ALT	23	19	7	12	18	6	9	13	5
Anemia	22	14	13	15	12	8	36	35	18
Pyrexia	21	18	10	15	12	8	40	20	18
Headache	16	12	9	29	20	6	18	20	8
Serious AE, %	25	25	23	30	20	18	60	33	33

7100 General Poster Session (Board #42D), Sun, 8:00 AM-11:45 AM

Multivariate analysis of factors affecting overall survival, event free survival, and 60-day mortality among AML patients treated with CPX-351 or intensive chemotherapy.

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Background: CPX-351 encapsulates cytarabine (CYT) and daunorubicin (DNR) at a 5:1 molar ratio within liposomes, enabling preferential drug uptake within leukemic blasts and intracellular release, potentially enhancing efficacy in AML. A pair of randomized Phase IIb studies in newly diagnosed older patients (pts) and younger 1st relapse AML pts reported improved rates of morphologic leukemia-free state, CR + CRi, and significant improvements in survival among previously untreated high risk (secondary) pts and among poor-risk 1st relapse pts. This report presents the results of the multivariate analyses performed on all pts treated in both studies. **Methods:** Patients 60-75 yo with newly diagnosed AML and ≤ 65 yo with 1st relapse AML and ECOG PS= 0-2, S_{CR} < 2.0 mg/dL, total bilirubin < 2.0 mg/dL, ALT/AST <3x ULN, and LVEF ≥ 50% were eligible. Pts with APL, DNR exposure >368 mg/m^2, active CNS leukemia, and uncontrolled infections were excluded. Pts were randomized 2:1 to receive up to 2 inductions and 2 consolidations with CPX-351 (100 u/m^2; D 1, 3, 5) or CYT + DNR (7+3) for newly diagnosed pts or investigator's choice of salvage chemotherapy for relapsed pts. Allogeneic transplantation was permitted. Univariate and multivariate Cox and logistic regression were used to assess associations between baseline characteristics and overall (OS) and event-free survival (EFS) and 60-day mortality for all pts. The multivariate employed stepwise selection to identify statistically significant prognostic factors after accounting for potential treatment effects. **Results:** Patient characteristics including cytogenetics were well balanced. Significant negative prognostic factors affecting OS, EFS, and 60-day mortality included relapsed disease (Study 205 participation, HR=2.13, p<0.001), adverse cytogenetics (HR=1.52, p=0.024), and low (<3g/dL) serum albumin (HR=1.82, p=0.005). CPX-351 treatment was a significant positive factor in EFS (HR=0.62, p=0.006). **Conclusions:** This analysis identified and quantitated disease specific (adverse cytogenetics) and patient specific (albumin<3gm/dL) factors that can be used to better design future studies. Clinical trial information: NCT00788892 and NCT00822094.

7102 General Poster Session (Board #42F), Sun, 8:00 AM-11:45 AM

Outcomes of first-line treatment for chronic lymphocytic leukemia (CLL) with 17p deletion (del17p).

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Background: Patients (pts) with relapsed CLL bearing del17p are very high-risk for poor clinical outcomes. We summarize outcomes for first-line treatment of del17p CLL. **Methods**: We identified pts with CLL and del17p by FISH who received first-line treatment at MDACC between 1/04 and 12/12. Log-rank test and Cox regression were used for univariable and multivariable analyses. **Results**: Baseline characteristics are shown (Table). Median time from diagnosis to first treatment (TTFT) was 15 (11-19) mos; no association between % del17p positive cells at diagnosis and TTFT was noted (p=.45). With first-line therapy (Table), 19 pts (30%) achieved complete remission (CR), 2 (3%) nodular partial remission (nPR), 18 (30%) PR, and 24 (37%) were non-responders. Fourteen CR pts (78%) were minimal residual disease negative by flow cytometry. The median time-to-treatment failure (TTF) was 14 (10-18) mos (43 events); the median follow-up was 33 (1-89) mos. Univariable analyses showed age >65 yrs (p=.04), complex karyotype (p=.02), lack of response to therapy (p<.001) and >50% cells positive for del17p by FISH (p=0.009) associated with shorter TTF. The multivariable model showed karyotype (p=.005) and quality of response (p<.001) independently associated with TTF. Median Overall Survival (OS) was 63 (43-83) mos (48 deaths). Fifteen pts (23%) developed Richter Syndrome (RS) after a median of 12 (1-27) mos; 8 deaths (29%) were related to RS. Univariable analysis showed that only lack of response was associated with a shorter OS (p=.001). **Conclusions**: Del17p CLL is high-risk for first-line therapy; better response to therapy was observed in young patients with low % del17p positive cells by FISH who received FCR. New strategies and agents must aim at both improving response and maintaining remission, particularly in pts with complex karyotype.

Characteristics (N=63)	n	CR/nPR (%)	ORR (%)
Age > 65 y	25	8*	44*
< 65 y	38	50	74
Rai III-IV	27	33	59
0-II	36	33	64
B2M > 4 mg/L	43	33	60
< 4	20	35	65
IGVH (n=58)	.	.	.
UM	47	34	60
M	11	36	64
Del17p FISH >50%	45	22*	56
<50%	18	61	78
Karyotype (n=54)	.	.	.
Complex w del17p	20	15	55
Complex w/o del17p	9	56	56
< 3 abn w del17p	6	50	83
< 3 abn w/o del17p	19	42	68
FCR	49	43*	71*
Rituximab/lenalidomide	14	0	29

*p < 0.05 (Chi-square)

7103 General Poster Session (Board #42G), Sun, 8:00 AM-11:45 AM

Autoimmune disorders in patients with B-cell chronic lymphocytic leukemia.

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Background: B-cell chronic lymphocytic leukemia (CLL) results from the accumulation and proliferation of malignant B cells with a predisposition for autoreactivity and autoimmune disease, particularly hematologic disorders such as autoimmune hemolytic anemia (AIHA) and immune thrombocytopenic purpura (ITP). We sought to define the prevalence of autoimmune conditions and associated prognostic factors in our CLL cohort. **Methods:** We retrospectively reviewed the electronic medical records (EMR) of CLL patients at Duke University Medical Center (DUMC) and Durham VA Medical Center (DVAMC) for known diagnoses of autoimmune conditions, or clinical descriptions matching those disorders. Laboratory data confirming the diagnoses (e.g., Coombs test for AIHA) were verified directly in our EMR. IGVH mutation status, CD38 and ZAP-70 expression were previously determined. **Results:** We found 92 CLL patients with autoimmune disorders (21.4% prevalence), with higher numbers of both hematologic (58, 11.1%) and non-hematologic(42, 8.1%) conditions than previously published data [Barcellini et al. *Haematologica* (2006) 91:1689], although one series did show 9.7% of CLL patients with hematologic phenomena [Hamblin et al. *J Clin Path* (1986) 39:713-6]. CLL patients with AIHA and/or ITP had significantly shorter treatment-free survival [2.1 years (1-3.3)] and overall survival [11.9 years (9.6-15.8)] than those without [6.2 years (5.2-7.3) and 18.0 years (14.0-22.6), respectively]. 52% of CLL patients with autoimmunity had mutated IGVH (41/79 known results), 18% were CD38 positive (16/89) and 49% were ZAP-70 positive(39/80). In CLL patients without autoimmune disorders, the prevalence of mutated IGVH, and CD38 and ZAP-70 positivity were similar at 60% (219/364), 25% (99/395), and 47% (176/377), respectively. **Conclusions:** There is a higher prevalence of both hematologic and non-hematologic autoimmune disorders in our CLL cohort than previously reported. CLL patients with hematologic autoimmune disorders had shorter time to treatment and survival, compared to those without. There was no difference in frequency of mutated IGVH, CD38 or ZAP-70 expression between those patients with autoimmune conditions and those without.

7104 General Poster Session (Board #42H), Sun, 8:00 AM-11:45 AM

Use of flow cytometry during induction chemotherapy to determine outcomes in acute myeloid leukemia.

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Background: The use of MRD to predict outcome in AML is controversial. We sought to determine concordance between FC and BM biopsy morphology on day 14 (D14BM) and CR bone marrow (CRBM) specimens and whether MRD detected by FC predicted for inferior outcomes. **Methods**: We performed a retrospective analysis of adult AML patients treated between 2005 and 2010 with standard induction chemotherapy. Based upon BM morphology and FC, patients were designated as BM+FC+, BM+FC-, BM-FC+, or BM-FC-. Outcomes assessed included induction failure, RFS and OS. Results were adjusted for age at diagnosis, NCCN risk classification, and secondary AML status. **Results:** Of 287 evaluable patients, 74 had D14 BM and FC results and 98 had CR BM and FC results. Using BM morphology as the gold standard, discordance rates for the presence and absence of disease for the D14 BM by FC were 29% and 23% respectively. Multivariate analysis revealed that patients categorized as BM-FC+ at D14 were more likely to experience induction failure (HR 8.62, CI 0.36-208) and had lower RFS and OS (HR 1.47, 1.95 CI 0.40-5.41, 0.52-7.36 respectively). Analysis of the CR BM samples showed similar results. **Conclusions:** In this retrospective study there was a high discordance rate between FC and BM morphology on D14 BM and CR BM. While there was a trend toward inferior patient outcomes when disease was detected by FC but not morphology, this was not statistically significant. Limitations of our study include the retrospective nature of the analysis, paucity of patient samples that had a FC evaluation, lack of data to see if positive FC at D14 or CR changed clinician therapy choices and interpretation bias by pathologists as a result of access to FC results during BM morphology interpretation. Larger prospective studies are needed to evaluate whether MRD detected by FC as early as D14 during AML therapy affects clinical outcomes.

7105 General Poster Session (Board #43A), Sun, 8:00 AM-11:45 AM

Congestive heart failure (CHF) in acute myeloid leukemia patients during induction.

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Background: Leukemia induction treatment is associated with significant morbidity and mortality. Myocardial stunning may be a result of chemotherapy as well as cytokines released from lysis of tumor cells leading to drop in ejection fraction (EF). When CHF is associated with sepsis, it may result in increased mortality. We report the incidence of CHF in leukemia patients undergoing induction. **Methods:** We performed a retrospective chart review on patients diagnosed with AML including acute promyelocytic leukemia (APL), who received chemotherapy between December 1, 2004 and December 31, 2012 at Georgia Regents University. Baseline and follow up EFs were recorded by echocardiogram or nuclear medicine scan. We evaluated patients who had a drop in EF after the first or subsequent inductions. We excluded patients who had a delayed drop in EF. **Results:** 217 consecutive patients with AML with normal ejection fraction at diagnosis were evaluated. 18 patients (8.2%) demonstrated a decrease in EF. This included 14 patients with AML and 4 with APL. 15 patients received one cycle of induction, 2 received re-induction and 1 was treated for relapsed disease. 2 patients did not receive anthracyclines(ACs). Median age of patients with CHF was 57 years (range 29-75). The median drop in EF was 23% (10-45%). Median days from the start of treatment to the observed drop were 25 (5-109). 6 patients are alive with median survival of 175 days. Overall, 5 out of 18 patients recovered their cardiac function with a median survival in these patients of 1,173 days. In 13 patients without recovery in EF survival was only 71 days. **Conclusions:** Chemotherapy by itself and cytokines released from treatment may result in reversible drop in EF in some patients and a persistent drop in the others. Re-induction is essential in a significant proportion of patients and ACs are commonly used that puts them at an increased risk for CHF. We propose that repeat cardiac evaluation, especially in patients getting re-induced, is necessary for identifying patients with cardiac abnormalities to prevent further cardiac injury and increased mortality.

7106 General Poster Session (Board #43B), Sun, 8:00 AM-11:45 AM

Influence of BMI on outcomes of high-dose cytarabine and mitoxantrone induction therapy for AML.

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Background: Acute Myeloid Leukemia (AML) affects thousands of Americans every year. With approximately 35.7% of the U.S. adult population being obese, it is important to understand how a patient's BMI can affect their outcome with AML treatment. This study evaluates a high-dose cytarabine and mitoxantrone induction regimen, and the results are examined to determine the effect of BMI on outcome, in terms of induction response and survival. **Methods:** Eighty nine patients were treated with a High Dose Cytarabine and Mitoxantrone regimen from 2008-2012. Two doses of cytarabine 3 gm/m^2 were given 12 hours apart followed by one dose of mitoxantrone 30 mg/m^2on days 1 and 5. All patients were dosed based on their actual body weight. Before treatment began, the BMI for each of the patients was recorded. The outcome data was collected and analyzed. **Results:** Of the 89 patients, 22 patients were normal, 33 overweight, and 34 obese. The BMI readings are based on the definitions established by the WHO. The overall CR rate for all 89 patients was 65%. The CRR for normal patients was 77%, 55% for overweight patients, and 68% for obese patients. 62 (70%) patients remain alive: 73% of normal patients, 58% of overweight, and 79% of obese. 17 of patients never achieved remission, even after multiple induction courses: 2 (9%) in the normal group, 10 (30%) in the overweight group, and 5 (15%) in the obese group. Of the responders, 35% of normal patients had a relapse, 30% in the overweight group, and 21% in the obese group with median relapse free survival of 8 months, 10 months and 6 months, respectively. **Conclusions:** Patients with a healthier BMI were more likely to respond to induction therapy with high-dose cytarabine and mitoxantrone. However, there was no difference in relapses amongst the groups. Patients who did not respond initially were unlikely to respond to other treatments. Therefore, using actual weight to determine dosing in AML induction therapy is the appropriate strategy.

7107 General Poster Session (Board #43C), Sun, 8:00 AM-11:45 AM

Evaluating oncogenic pathway dysregulation in adolescents and young adults with acute myeloid leukemia.

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Background: Adolescent and young adults (AYAs) with Acute Myeloid Leukemia (AML) have been shown to have better outcomes with induction chemotherapy when compared to older young adults (OYAs). Multiple psychosocial, treatment, and host-related factors unique to AYAs have been identified but the contribution of disease biology to these outcomes has not yet been fully characterized. The purpose of this study was to evaluate disease biology as it relates to age-specific differences in outcomes for AYAs with AML. **Methods:** Clinically annotated, microarray data from 425 patients with newly diagnosed AML from two publicly available datasets: GSE1159; and GSE12417 were analyzed. Age-specific cohorts (AYAs $\leq$ 30 years; n = 58 and OYAs $>$30 but $\leq$ 60 years; n=276) were prospectively identified. Patients in GSE1159 were treated according to protocols of the Dutch–Belgian Hematology–Oncology Cooperative group and included 111 patients who ultimately underwent stem-cell transplantation. Patients in GSE12417 were treated per the AMLCG-1999 protocol. Gene expression analysis was conducted by applying previously defined and tested signature profiles reflecting deregulation of oncogenic signaling pathways and altered tumor environment. All statistical analysis was performed using S-plus and survival analysis by Cox proportional-hazards regression was used to assess differences in overall survival (OS) between age-specified study cohorts and a one-sided p-value $\leq$ 0.05 was considered statistically significant. **Results:** AYA patients had a significantly better OS (median survival 24.1 months vs. 13.0 months in OYAs; *p=0.0285*), but there was no difference in Event Free Survival (*p=0.23)*. Analysis of oncogenic pathways revealed that AYA patients likely had better OS because of lower TNF (*p=0.03*) and higher myc (*p=0.02*) pathway activation. **Conclusions:** AML arising in AYAs may represent a distinct biologic entity characterized by unique patterns of deregulated signaling pathways that contributes to OS. We hope these findings will enable clinically meaningful adjustments of treatment strategies in the AYA AML patient population.

7108 General Poster Session (Board #43D), Sun, 8:00 AM-11:45 AM

The effect of BMI on systemic toxicity in AML patients receiving chemotherapy.

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Background: There are about 15,000 new cases of acute myeloid leukemia (AML) every year in the US, and about 9,000 will die annually from this disease. Because approximately 69.2% of adults in the US are overweight or obese, it is important to examine whether body mass index (BMI) can affect treatment outcomes. While there has been a study of survival based on BMI, there have been no studies to examine the effect of BMI on systemic toxicity with induction chemotherapy. **Methods:** 91 patients with AML were treated with a high-dose cytarabine and mitoxantrone regimen from 2008-2012. Prior to receiving induction chemotherapy, each patient's BMI was recorded. All patients in this study were treated with doses based on actual weight. Two doses of cytarabine 3 gm/m^2 were given 12 hours apart followed by one dose of mitoxantrone 30 mg/m^2on days 1 and 5. The lowest platelet and hemoglobin after each induction treatment was recorded, along with the number of red blood cell (RBC) and platelet transfusions. Systemic toxicity was further examined by presence of infection and/or bleeding. **Results:** The BMI groups are based on the World Health Organization classifications. Of the 91 AML patients in this study, 2 were underweight, 35 were normal weight, 29 were overweight, 16 were obese, and 9 were morbidly obese. The mean number of platelet transfusions for the underweight group was 8.5, 10.6 for normal weight, 13.8 for overweight, 12.1 for obese, and 5.0 for the morbidly obese group. The mean number of RBC transfusions for the underweight group was 6.0, 9.1 for normal weight, 11.2 for overweight, 9.1 for obese, and 9.2 for the morbidly obese group. The rates of infection by positive cultures were the following: 51% of normal, 58% of overweight, and 68% of obese patients. Rates of infection by imaging were 37% of normal, 31% of overweight, and 26% of morbidly obese patients. The percentage of patients bleeding after induction was 20% in the normal weight group, 31% for overweight, 12.5% of obese, and 33% of morbidly obese patients. **Conclusions:** The results of this study show that there is no difference in toxicity amongst the different BMI groups. The data demonstrates the importance of dosing chemotherapy on actual, rather than ideal, body weight.

7109 General Poster Session (Board #43E), Sun, 8:00 AM-11:45 AM

Updated results from a randomized phase II dose-ranging study of the JAK2-selective inhibitor SAR302503 in patients with myelofibrosis (MF).

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Background: We previously reported results of treating MF patients with 3 cycles of 300, 400, or 500 mg of SAR302503 (NCT01420770; *Blood* 2012;120:21 Abs 2837). This is a report of efficacy and safety after 6 cycles. **Methods:** Patients ≥18 years of age with intermediate-2 or high-risk MF and splenomegaly were eligible. SAR302503 is administered orally, once a day in consecutive 4-week cycles until disease progression or unacceptable toxicity. Spleen response (≥35% reduction in spleen volume vs baseline) was assessed by MRI/CT (blinded independent central review). **Results:** 31 patients were enrolled (n=10 in the 300 and 400 mg groups; n=11 to 500 mg). Risk status was balanced in all but the 300 mg group (70% high-risk). Most patients were *JAK2*V617F positive (90%) and blood transfusion independent (81%). Spleen response rates at the end of cycle (EOC) 6 (secondary end point) were 30% (3/10) in the 300 mg group, 60% (6/10) with 400 mg, and 55% (6/11) with 500 mg compared with EOC 3 rates of 30%, 50%, and 64%, respectively. One patient on 500 mg who had a spleen response at EOC 3 (39% reduction), but not at EOC 6 (25% reduction) had dose reductions to 200 mg due to anemia. Median number of cycles was 13 (range, 2–17) and 24 patients have been on treatment >12 months. SAR302503 reduced baseline constitutional symptoms at the EOC 3, with the greatest responses for night sweats in 14/15 patients (93%), itching 10/14 (71%), early satiety and abdominal pain, each in 10/18 (56%). Most common adverse events were anemia and diarrhea, with grade 3–4 rates of 58% and 13%, respectively. The rate of grade 3–4 thrombocytopenia was 16%. There was no grade 3–4 neutropenia. The diarrhea rate tended to decrease after the first 2 treatment cycles. There have been no reports of withdrawal syndrome after stopping SAR302503. Median *JAK2*V617F allele burden was 93% at baseline, 87% at the EOC 3, and 78% at EOC 6 in 19/26 patients who had available samples. The expression of 22 of 97 cytokines was significantly regulated (≥1.5 fold difference; $p<0.05$) after cycle 1. **Conclusions:** In this Phase II trial, continued treatment with SAR302503 was associated with clinically meaningful reductions in splenomegaly. Symptom data will be updated. Clinical trial information: NCT01420770.

7110 General Poster Session (Board #43F), Sun, 8:00 AM-11:45 AM

Modulation of plasma cytokines and its association with clinical response to treatment with the JAK2-selective inhibitor SAR302503 in myelofibrosis (MF).

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Background: Abnormal cytokine expression may represent an inflammatory response that contributes to the clinical phenotype of MF. Some constitutional symptoms (eg. fever, fatigue, pruritus, cachexia) are thought to be caused by elevated cytokines. In phase I/II studies, SAR302503 reduced splenomegaly and constitutional symptoms in patients with MF. Here, we report the effects of SAR302503 on the expression of 97 cytokines in MF patients enrolled in a Phase II study (NCT01420770) and the relationship to clinical response (spleen size), pharmacokinetic (PK) exposure, and body weight changes. **Methods:** Thirty-one patients were randomized to receive 300, 400, or 500 mg of SAR302503 orally, once daily, continuously in 4-week cycles. Plasma cytokines were measured at baseline and at the end of 4, 8, and 12 weeks of treatment using a microsphere-based immuno-multiplex assay (Rules Based Medicine). **Results:** Complete sample sets were available for 29/31 patients. A total of 28 cytokines predominantly involved in immune/inflammation pathways were regulated $\geq$1.5-fold (ANOVA $P<0.05$) and of these, 19 were regulated at all time points, indicating rapid and sustained modulation by JAK2 inhibition. At 4 weeks, 16 cytokines were down-regulated, including TNFα, IL-1RA, and IL-18, and 6 were up-regulated, including leptin, EPO, and adiponectin. Hierarchical clustering of the 22 regulated cytokines enriched patients into spleen responder ($\geq$35% reduction in spleen volume by MRI) and non-responder groups, suggesting a link between cytokine modulation and clinical response. Moderate correlations ($P<0.05$) with spleen volume reduction at the end of week 12 were seen for a subset of regulated cytokines, including adiponectin and TNFα. Levels of the majority of the regulated cytokines tended to correlate with steady state PK exposure at week 4. A positive association with weight changes at week 24 were observed for leptin and adiponectin at week 4 ($P<0.05$). **Conclusions:** This analysis shows that SAR302503 treatment modulated the expression of circulating cytokines in MF patients in association with changes in clinical activity, PK exposure, and symptom improvement (weight gain). Clinical trial information: NCT01420770.

7111 General Poster Session (Board #43G), Sun, 8:00 AM-11:45 AM

Identification of pSTAT5 gene signature in hematologic malignancy.

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Background: The JAK/STAT pathway is an important signaling pathway downstream of multiple cytokine and growth factor receptors. Receptor-associated JAKs are activated following receptor-ligand binding. Activated JAKs phosphorylate STAT proteins, which then dimerize and translocate to the nucleus where they modulate the expression of target genes. Dysregulated JAK/STAT signaling has been implicated in the pathogenesis of multiple human malignancies. Activating mutations in JAK2 and the associated activation of STAT5 in myeloproliferative neoplasia is one example of the involvement of this pathway in human cancer. Additionally, overactivated JAK/STAT signaling has been suggested as a survival mechanism in several human cancers. Given the importance of JAK/STAT dysregulation in human diseases, it is important to identify patients with an overactivated JAK/STAT pathway for possible treatment with JAK inhibitors. Thus, we developed a gene signature assay to detect overactivated JAK/STAT5 signaling. **Methods:** The cancer cell line encyclopedia (CCLE) and associated gene-expression data were used to correlate the activation status of STAT5 with the induction of a set of STAT5 target genes. First, we used 27 tumor cell lines of hematologic lineage, with predetermined phosphorylated STAT5 (pSTAT5) status, to derive STAT5 activation gene signatures. Next, the putative gene signatures were validated against a different set of 13 hematologic tumor cell lines. **Results:** With this approach, a collection of 7 target genes were identified (*PIM1*, *CISH*, *SOCS2*, *ID1*, *LCN2*, *EPOR*, and *EGR1*) whose expression significantly correlated with pSTAT5 status in the 40 hematologic tumor cell lines ($P < .0001$), either together or in specific subsets of 4 and 6 genes (Table). **Conclusions:** These 4-, 6-, and 7-gene signatures can be used to stratify or select for a patient population with activated JAK/STAT5 signaling that could potentially benefit from treatments targeting the JAK/STAT5 signaling pathway.

Correlation of genes with pSTAT5 status in the 40 hematologic tumor cell lines.

4-gene signature	6-gene signature	7-gene signature
PIM 1	PIM 1	PIM 1
CISH	CISH	CISH
SOCS2	SOCS2	SOCS2
ID1	ID1	ID1
	LCN2	LCN2
	EPOR	EPOR
		EGR1
P < .0001	P < .0001	P < .0001

7112 General Poster Session (Board #43H), Sun, 8:00 AM-11:45 AM

Characterization of Philadelphia-negative myeloproliferative neoplasm patients with chromosome 12 abnormalities.

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Background: Chromosome 12 (Chr 12) abnormalities have been reported as infrequent events in myelofibrosis (MF). Structural abnormalities at 12q13-15 and 12q24 have been reported in primary MF (PMF), and understanding genes at these loci, such as *Hmga2* and *Lnk* may help in the treatment of Philadelphia-negative (Ph-neg) myeloproliferative neoplasms (MPN). We sought to better characterize Ph-neg MPN patients (pts) with Chr 12 aberrations. **Methods:** We queried a database of pts with any Ph-neg MPN who were referred to MD Anderson Cancer Center from 1985 to 2012. We identified pts with Chr 12 abnormalities and reviewed available clinical information. We compared characteristics and outcomes of pts who had Chr 12 abnormalities with pts who had no Chr 12 abnormality. **Results:** Of 1,787 pts with Ph-neg MPN, 36 pts (2%) were found to have a Chr 12 abnormality. Of these, 31 (86%) had MF, 1 (3%) had polycythemia vera (PV), 3 (8%) had hypereosinophilic syndrome, and 1 (3%) had unspecified MPN. Fourteen pts (39%) had successive biopsies demonstrating evolving cytogenetic abnormalities. The percentage of pts with MF was significantly higher among patients with Chr 12 abnormalities (86% vs. 54%, p-value < 0.001). A larger fraction of MF pts with Chr 12 abnormalities had post-PV MF (PPMF) (31% vs. 14%, p-value < 0.001). Age, JAK2 status, and incidence and rate of leukemic transformation from MF were not significantly different between the two groups. Of the 31 Chr 12 pts with MF, 12 (39%) had an abnormality at 12q13, 8 (26%) at 12q24, 6 (19%) had trisomy 12, 5 (16%) at 12q15, and 6 (19%) had another Chr 12 abnormality. Four pts (13%) had a structural abnormality at >1 site along the long arm of Chr 12. Survival of Chr 12 MF pts as a whole or subdivided by chromosomal abnormality was not significantly different than MF pts without Chr 12 abnormalities. **Conclusions:** Our investigation into pts with Ph-neg MPN harboring Chr 12 abnormalities is the largest of its kind, and shows 3% of MF pts possessed some type of Chr 12 abnormality, most frequently at 12q13. We found that Chr 12 Ph-neg MPN pts were more likely to have MF and PPMF. Further investigation into the functional significance of these structural abnormalities is warranted.

7113 General Poster Session (Board #44A), Sun, 8:00 AM-11:45 AM

Evidence for selective benefit of sequential treatment with azanucleosides in patients with myelodysplastic syndromes (MDS).

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Background: Azanucleosides (AZN) remain the mainstay of therapy in myelodysplastic syndrome (MDS). Sequential use of AZNs is common practice given the limited alternatives. The only published experience described 14 patients showing a 28% response with decitabine (DAC) after failure or lack of response to azacitidine (AZA). To investigate the potential benefit of this approach,we reviewed cases of sequential AZN treatment. **Methods:** Patients who received treatment with both AZNs were identified through the Moffitt Cancer Center MDS database. Two groups were identified; group one who received DAC after AZA failure and group 2, who received AZA after DAC failure. The primary objective was to estimate overall response rates according to the International Working Group (IWG) 2006 criteria. The Kaplan–Meier method was used to estimate median OS. **Results:** A total of 39 MDS patients were identified who received treatment with both AZNs. Complete records were available in 31 patients, including 21 patients in group 1 (DAC after AZA) and 10 patients in group 2 (AZA after DAC). The Table summarizes baseline characteristics and response rates. The median OS for Group 1 from diagnosis was 48 months and for group 2 was 100 months (p=0.7). **Conclusions:** Sequential use of AZNs after failure of first line may be an effective alternative outside the context of clinical trials. Response rate is higher in patients who receive AZA after DAC. Sequential use of HMA should be considered in context of randomized clinical trial of novel agent as the control arm.

		Group 1 (DAC after AZA) (n=21)	Group 2 (AZA after DAC) (n=10)
WHO subtype	RA	3 (14%)	1 (10%)
	RARS	4 (19%)	1 (10%)
	RCMD	2 (10%)	2 (20%)
	RAEB	11 (52%)	6 (60%)
	Del 5q	1 (5%)	0
IPSS at diagnosis	Low	4 (19%)	1 (10%)
	Int-1	10 (48%)	0
	Int-2	4 (19%)	7 (70%)
	High	2 (10%)	2 (20%)
	missing	1 (5%)	0
IPSS prior AZA	Low	4(19%)	4 (40%)
	Int-1	5 (24%)	5 (50%)
	Int-2	5 (24%)	1 (10%)
	High	2 (10%)	
	Missing	5 (24%)	
IPSS prior DAC	Low	1 (5%)	5 (50%)
	Int-1	2 (10%)	3 (30%)
	Int-2	8 (38%)	2 (20%)
	High	2 (10%)	
	Missing	8 (38%)	
Response rate (IWG criteria)	CR	AZA DAC	DAC AZA
	mCR	2 (10%)	2(20%) 2(20%)
	HI	4(20%) 1(5%)	4(40%) 4(40%)
	SD	7(33%) 3(14%)	2(20%)
	PD	1(5%) 14(67%)	2(20%)
	Missing	6(28%) 3(14%)	2(20%) 2(20%)

7114 General Poster Session (Board #44B), Sun, 8:00 AM-11:45 AM

Pregnancy outcome in chronic myeloid leukemia patients on imatinib therapy.

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Background: Now that imatinib is being used to treat thousands of chronic myeloid leukemia (CML) patients for more than 10 year it is highly probable that many patients will get pregnant during its use. Company warns against any such use. But the fact remains that there is need for planned pregnancies in indicated cases. So we selected few cases both male and female for such pregnancies by interrupting treatment and following the pregnancy closely. Their outcome was studied so that we have an idea about what best could be suggested in such instance. **Methods:** From November 2002 to May 2010, 634 patients with CML in any stage of the disease were treated with imatinib at our tertiary cancer research institute. We selected 22 (12 females and 10 males) cases of pregnancies by interrupting treatment. We reported 9 accidental pregnancies and 13 planned pregnancies involving 22 patients who or their wives conceived while receiving imatinib for the treatment of CML. **Results:** Among 22 pregnancies there were 3 spontaneous abortions and 4 elective abortions. In case of 7 female patients, 3 and 4 were male and female babies respectably and in case of six male patients 4 and 4 were male and female babies. Two babies were with congenital anomaly such as one Hypospandium and one Mild-Hydrocephalus (in case of unplanned pregnancies and imatinib exposure during the first trimester of organogenesis). **Conclusions:** In conclusion, exposure to Imatinib during pregnancy might result in an increased risk of serious fetal abnormalities or spontaneous abortions. Women of childbearing potential should use adequate contraception while using Imatinib. We can suggest that planned pregnancy during therapy should be encouraged but imatinib therapy in unplanned pregnancy can cause spontaneous abortion or minor congenital anomaly.

7115 General Poster Session (Board #44C), Sun, 8:00 AM-11:45 AM

Clinical implications of discrepancy in the diagnosis of primary myelofibrosis between referral and tertiary center.

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Background: Primary Myelofibrosis (PMF) is a stem cell-derived clonal disorder with broad disease spectrum and the diagnosis is based on a combination of clinicopathological criteria. The aim of the study is to evaluate the frequency of diagnostic discrepancies between the referring center and a tertiary center and the impact in clinical outcomes in patients with PMF. **Methods:** 560 patients (pts) with Primary Myelofibrosis (PMF) referred to MD Anderson Cancer Center from January 2007 to December 2011 were evaluated. **Results:** 70 (12.5%) pts were discordant and 490 (87.5%) were non-discordant. The median age was 67 years (range, 32-88): 39 (56%) discordant versus 326 (67%) non-discordant pts were older than 65 years ($p<0.075$). Cytogenetics in the discordant group were favorable in 40 (57%) and unfavorable in 27 (39%) and in the non-discordant group 309 (63%) and 162 (33%) respectively ($p<0.36$). The DIPSS-plus score in the discordant group was low in 3 (4%), intermediate-1 in 11(16%), intermediate-2 in 27 (39%), and high in 26 (37%), and in the non-discordant group 12 (2%), 63(13%), 251 (51%) and 161 (33%) respectively ($p < 0.33$). *JAK2V617F* was positive in 46 (66%) cases of discordant group and in 381 (78%) of the non-discordant group ($p<0.027$). Peripheral blasts >1% were present in 378 (77%) non-discordant and in 36 (51%) discordant cases ($p<0.001$). The referring diagnosis for discordant cases were MPN unclassified in 18(26%), PV in 12 (17%), ET in 7 (10%), CML in 5 (7%), MDS/MPN unclassified in 15 (21%), *BCR-ABL* negative CML in 2 (32%), CMML in 2 (3%) and MDS in 8 (11%) cases. The median OS in the non-discordant group versus discordant group after the appropriate diagnosis were 44.6 and 36.6 months respectively ($p<0.069$). **Conclusions:** The results confirm that the diagnosis of PMF is complex. The rate of discrepancy is high confirming the need for complete evaluation in a tertiary center. The presence of peripheral blasts and *JAK2* mutation appear to helped in making proper diagnosis before referral.

7116 General Poster Session (Board #44D), Sun, 8:00 AM-11:45 AM

A phase II study of mocetinostat, an oral isotype-selective histone deacetylase (HDAC) inhibitor, in combination with 5-azacitidine in patients with myelodysplastic syndrome (MDS).

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Background: Mocetinostat (MGCD0103) is an orally available, isotype-selective, non-hydroxamate HDAC inhibitor targeting HDACs 1,2, 3 and 11 with single agent activity in AML and both Hodgkin's and non-Hodgkin's lymphomas. Preclinical evaluation demonstrating in vitro and in vivo synergy and antileukemic activity with demethylating agents, including 5-azacitidine (AZA), prompted clinical evaluation of mocetinostat + AZA in MDS and AML. **Methods:** This open-label, Phase II trial enrolled patients with MDS or AML. Patients received AZA (75 mg/m^{2}SC; days 1-7 every 28 days) and mocetinostat (90-110 mg 3x/wk starting on AZA day 5). Anticancer activity, safety and pharmacokinetics and pharmacodynamics were evaluated. We report here on the MDS cohort. **Results:** Twenty patients with MDS were enrolled. Eight patients had received prior therapy for MDS including decitabine (n=1), lenalidomide (n=3), tipifarnib (n=2) and cytarabine (n=2). Median age was 70.5 yrs (range 41-81). Disease control rate (defined as CR + marrow-CR + PR + SD) was 80% (16/20). Ten patients (50%) had baseline marrow blast counts ≥10% (protocol-defined high risk). Responses in high-risk patients included 5 (50%) with CR + marrow-CR and 2 (20%) with SD. Six patients (30%) had an on-treatment marrow blast count of 0. These included 3 patients in the high-risk category, with baseline blast counts of 11%-15%. CR was observed in one patient, a 74-yr-old male with previously untreated RAEB. In this patient, marrow blasts fell from a baseline of 11% to 0% following 1 cycle of treatment; CR with normalization of all cell lines was achieved by late Cycle 3. He remained on study for 1 yr. Most drug-related AEs in the study were grade 1 or 2. The most common drug-related grade 3/4 events were nausea (15%), vomiting, fatigue, anemia, thrombocytopenia and febrile neutropenia (10% each). There was one death (5%), due to pneumonia that was not felt by the investigator to be drug related. **Conclusions:** The combination of mocetinostat and 5-azacitidine in patients with MDS demonstrated an acceptable safety profile and encouraging evidence of clinical benefit. Further clinical studies are warranted. Clinical trial information: NCT00324220.

7117 General Poster Session (Board #44E), Sun, 8:00 AM-11:45 AM

Cytidine deaminase status as a predictive marker in patients with hematologic malignancies treated with azacytidine or cytarabine.

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Background: Cytarabine and azacytidine are mainstays for treating haematological malignancies. As most nucleosidic analogs, both azacytidine and cytarabine are metabolized in the liver by an exclusive enzymatic step driven by cytidine deaminase (CDA). CDA is highly polymorphic and dysregulations have been repeatedly associated with poor clinical outcome with gemcitabine. **Methods:** We have used a test to determine, on a phenotype basis, CDA status in patients. This test was used prospectively in a subset of 39 adult patients (16F, 23M, mean age 77 years), all treated for various haematological malignancies (i.e., CML, AML, lymphomas, myelodysplastic syndromes) with either aza-cytidine or a cytarabine-containing regimen. Response and treatment-related toxicities were monitored following current standards. In addition, impact of CDA status on azacytidine tolerance was evaluated in mice with or without CDA deficiency, as a proof of concept for the actual implication of metabolic deregulations in the toxicities observed in patients. **Results:** In patients, mean CDA activity was 3.7 +/-2.8 U/mg (min: 1, max: 14.8 U/mg). Ten out of 39 patients (i.e., 25%) showed low CDA activities and were considered as PM. Conversely, 8 patients (i.e., 20%) displayed CDA activities particurlary elevated (i.e., $>$ 6U/mg) and were considered as UM patients. Of note, PM patients all showed severe toxicities, including two toxic-deaths. Conversely, UM patients showed little efficacy when treated with either azacytidine or cytarabine. In mice with CDA-deficiency, standard azacytidine led to profound and long-lasting neutropenia, as compared with normal mice. Drug monitoring confirmed that individuals with low CDA activity and toxicities showed higher concentrations of azacytidine as compared with normal individuals. **Conclusions:** Overall this pilot study strongly suggests that CDA status could be a relevant marker for predicting clinical outcome in patients treated with either azacytidine or cytarabine. CDA status could be further used as a covariate to tailor drug dosage so as to ensure an optimal efficacy/toxicity balance in patients with haematological malignancies.

7118 General Poster Session (Board #44F), Sun, 8:00 AM-11:45 AM

Exploring educational gaps in myelodysplastic syndromes in medical students and internal medicine residents: A dual-institution survey.

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Background: Myelodysplastic syndromes (MDS) are a heterogeneous and poorly understood group of disorders. Prior studies have focused on patient and provider understanding of these disorders; however, no study to our knowledge has been conducted to explore educational gaps of medical students and medicine residents. The hypothesis of this work is that MDS are poorly understood by trainees, but this could be improved after education. **Methods:** A nine question survey pertaining to definition, diagnosis, risk assessment and survival in MDS was sent to medical students and medicine residents a week prior to a lecture on MDS. At Duke, the lecture was a senior resident talk; at Rush, it was a medicine grand rounds by a hematology attending. The survey was resent to the initial groups 15 days after the lectures, but only those who attended the lecture were invited to take it. **Results:** At Duke, the response rate was 141 out of 255 (55%); at Rush, it was 65 out of 414 (16%). Responses for the questions were similar at both institutions with no statistical difference in the percent of correct responses by institution. 83.7% said that anemia was not a normal consequence of aging. 82.4% acknowledged that a bone marrow biopsy is required to diagnose MDS. 57.6% said anemia was the most common hematologic manifestation of MDS. 40.4% said that a hemoglobin of <10 should be referred to hematology. 36.1% said the bone marrow in MDS is hypercellular. 17.6% said MDS transforms to AML in 30% of cases. 11.2% identified MDS as a cause of macrocytic anemia. Only 11.1% identified MDS as a malignancy, and 5.5% identified the average survival of high-risk IPSS stage MDS as 0.4 years. In post-lecture surveys ($n= 23$), knowledge largely improved. However, given low number of responses, this reached statistical significance in only four of nine questions. **Conclusions:** MDS are poorly understood by both medical students and residents, especially in regard to the definition as a malignancy, prognosis, and risk of AML evolution. We propose that educational efforts aimed at early trainees would improve these knowledge deficits, in addition to the medical care of patients with MDS. The study is limited by the post-survey completion rate.

7119 General Poster Session (Board #44G), Sun, 8:00 AM-11:45 AM

Use of the SFMA as a measure of overall functionality in patients undergoing hematopoietic stem cell transplantation (HSCT).

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Background: The 6 minute walk test (6MW) has been used in research as a measure of overall functionality and has been related to prognosis and quality of life (QOL) in cancer patients. For some clinics, the use of other functional tests may be a timely and space saving option. The selective functional movement assessment (SFMA) is a short, systematic evaluation of 7 fundamental movement patterns which can be conducted in patient rooms. The SFMA can make clinicians aware of deficient, painful movement patterns that may indicate impairment and motor control deficits. The SFMA may help identify functional impairments for pre- and peri-transplant interventions in patients undergoing HSCT. **Methods:** Patients were assessed prior to HSCT. A composite score (range: 19-38) was given to patients based SFMA performance. A lower score represented improved movement profiles. 6MW was tested by standardized protocol on an established route. Pearson correlations were calculated to evaluate the relationship between 6MW and SFMA. **Results:** We evaluated 32 patients (10 autologous, 11 myeloablative allogeneic, 11 reduced intensity allogeneic). One patient was unable to complete all portions of the SFMA due to physical limitations; all patients completed the 6MW. The mean SFMA composite score was 24.9$\pm$ 3. $\geq$50% of patients exhibited deficient movement patterns during forward flexion and deep squat. Other patterns that showed a high level of deficiency ($>$ 30% of all patients) were back extension, single leg stance, shoulder mobility, and cervical rotation. The mean 6MW was 477$\pm$ 94 m. There was a moderate negative correlation between 6MW and SFMA composite score ($r = -0.46$, $p < 0.001$), implying that a shorter 6MW was associated with more deficient movements. **Conclusions:** The SFMA could be useful for quantifying overall functionality in settings where the 6MW is not ideal. The SFMA may also be useful for identification of functional issues that may be addressed before or during HSCT by interventions to limit disability and maintain QOL. Further research should evaluate the SFMA results pre to post transplant to assess changes in fundamental movement deficits. The use of the SFMA's prognostic ability should also be evaluated.

7120 General Poster Session (Board #44H), Sun, 8:00 AM-11:45 AM

Detection of the NRAS Q61R mutation in Erdheim-Chester disease.

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Background: There is a high frequency of activating mutations in proteins of the Ras/Raf/MEK/ERK pathway in melanoma and other solid tumors. The *BRAF* V600E mutation has been found recently to be highly prevalent in ECD, a rare non-Langerhans cell histiocytosis with poor prognosis, as well as Langerhans cell histiocytosis (LCH). Treatment of patients with ECD and the *BRAF* V600E mutation with vemurafenib has been associated with unprecedented and dramatic response in a few cases. **Methods:** We present a 66 year-old man evaluated for several months of cognitive and motor decline. He was found to have multifocal enhancing lesions in the cerebral meninges, multiple masses in the abdomen and sacrum, and abnormal nuclear uptake in the long bones of the legs. **Results:** Biopsy of a renal mass demonstrated a foamy CD68+/CD1a- histiocytic infiltrate, consistent with ECD. Interrogation of tumor tissue with the Sequenom MassArray system demonstrated absence of the *BRAF* V600E mutation but presence of the NRAS Q61R mutation. **Conclusions:** This is, to our knowledge, the first report of an activating NRAS mutation in ECD. The finding of an oncogenic NRAS mutation in ECD further supports the hypothesis that this disease is driven by activation of the Ras/Raf/MEK/ERK pathway. Further investigation into the role of this pathway in ECD and LCH is warranted and may open new opportunities for targeted therapies for these disorders.

7121 General Poster Session (Board #45A), Sun, 8:00 AM-11:45 AM

Long-term follow-up of autologous hematopoietic stem cell transplantation for stage II/III breast cancer.

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Background: In the 1980s and 1990s, adjuvant chemotherapy with high-dose chemotherapy (HDC) and autologous stem cell transplantation (ASCT) was utilized for the treatment of high-risk breast cancer. Previous studies showed that ASCT significantly reduced the risk of relapse in these patients, but failed to provide evidence of improved overall survival when compared with standard therapy in randomized trials. Due to the mortality, morbidity, and cost associated with ASCT and lack of a clear overall survival benefit, the use of HDC with ASCT for high-risk breast cancer was halted. In this retrospective, observation study, we analyzed the toxicity and efficacy of ASCT in high-risk breast cancer at a large community hospital. **Methods:** The study population consisted of 57 women diagnosed with high-risk primary breast cancer who underwent treatment with HDC followed by ASCT from 1991-1999. Women receiving treatment for metastatic breast cancer were excluded. The medical records of the study population were retrospectively reviewed, with particular attention to long-term toxicities and efficacy. **Results:** Fifty seven patients were evaluated: 54 with ductal and/or lobular breast cancer and 3 with inflammatory breast cancer. Median age was 44 years (29- 61). Twenty six patients (46%) were alive at time of review. Twelve patients (21%) experienced a recurrence of their breast cancer. Four patients (7%) developed secondary malignancies. Two patients (4%) experienced cardiac toxicities. Estrogen/progesterone receptor-positive breast cancers accounted for 42% of recurrences, 100% of secondary malignancies, and 50% of cardiac toxicities. HER-2/neu status analysis revealed amplification in 17% of breast cancer recurrences, but in no cases of secondary malignancy or cardiac toxicity. **Conclusions:** High-dose chemotherapy and ASCT can be effective in reducing long-term recurrences in women with high-risk, Stage II/III breast cancer. This treatment, however, carries an associated risk of secondary malignancies and cardiac toxicities. Estrogen/progesterone receptor-positive breast cancer appears to have a greater association with disease recurrence and secondary malignancies.

7122 General Poster Session (Board #45B), Sun, 8:00 AM-11:45 AM

A 36-month analysis of treatment patterns and outcomes in patients with lower-risk myelodysplastic syndromes from a prospective observational study.

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Background: Many patients (pts) with lower-risk myelodysplastic syndromes (MDS) require chronic red blood cell transfusions for symptomatic anemia, which can result in iron overload. We present a 36-month interim analysis of a 5-year US registry that prospectively collected data on clinical events and survival in chelated vs non-chelated, transfused, lower-risk MDS pts. **Methods:** This multicenter, non-interventional registry enrolled 600 pts ≥18 yr old with lower-risk MDS (WHO, FAB, and/or IPSS risk stratification criteria) and transfusional iron overload (serum ferritin ≥1,000 ng/mL and/or ≥20 packed red blood cell units and/or ≥6 units every 12 wks). The chelated group included pts who had received any chelation. **Results:** Median age was 76 yr (range, 21–99), 57.8% were male, and risk status was 38.6% IPSS low risk and 61.4% IPSS INT-1 risk. Baseline demographics and IPSS risk status were similar between groups, although transfusion burden trended higher in chelated pts. As of April 30, 2012, 169 pts continued on the registry, and 431 discontinued (345 died, 57.5%; 61 lost to follow-up, 10.2%; and 25 other, 4.2%). In all, 264 pts (44%) received chelation therapy; 200 had ≥6 mos chelation. Overall survival (OS) and time to acute myeloid leukemia (AML) transformation were significantly longer, and the percentage of deaths was significantly lower, in chelated ≥6 mos vs non-chelated pts ($P<0.0001$, $P=0.011$ [median not reached in either group], $P=0.0002$, respectively. AML transformations appeared to be lower in chelated ≥6 mos pts (not significant [NS]). At baseline in non-chelated vs chelated ≥6 mos pts, there was a higher prevalence of vascular, cardiac, endocrine, and ophthalmologic disorders; this trend continued at 36 mos. Most frequent causes of death were MDS/AML, cardiac events, and infection. Use of MDS therapy was lower among non-chelated pts (non-chelated, 88.4%; ≥6 mos chelation, 93.5%; NS). **Conclusions:** At 36 mos,chelated pts had significantly longer OS and time to AML, as well as significantly fewer deaths. Trends toward fewer AML transformations and fewer vascular, cardiac, endocrine, and ophthalmologic disorders were observed in chelated pts.

7123 General Poster Session (Board #45C), Sun, 8:00 AM-11:45 AM

Defining parameters that can guide public cord blood units (CBUs) in Korea.

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Background: It is well recognized that TNC and CD34 define a superior Cord blood unit (CBU). According to "the Law of Korean CB Banking and Research", only 40% of collected CBUs meet the criteria. To improve a rate of banking, we analyzed the characteristics of CBUs and assessed predictive factors for numbers of TNC and CD34+ in collected CBUs. **Methods:** 2004 to 2012, CBUs donated to the Daegu Fatima Hospital Public CB Bank (n = 1074) were analyzed. The associations between TNC, CD34+ and variables including body weight (BW), GA, delivery type, gender, collecting volumes (CV) were analyzed by logistic regression analysis. **Results:** In our study cohort (n = 1074, male;553, female;521, all Koreans), the median value of TNC, numbers of CD34+, GA, BW and CV were 10.6úI10^{8} /unit (6.0-35.1), 3.41úI10^{6}/unit (0.8-27.0), 39 weeks (36-42 weeks), 3310g (1660-4600g) and 75.4ml (35-179ml) respectively. In univariate analysis, maternal /donor (M/D) characteristics that were associated with high TNC (> 10úI10^{8}) included higher GA(GA > 39 weeks) [OR 2.02 (95% CI 1.54-2.66 p < 0.001)], normal delivery [OR 3.05 (95% CI 2.21-4.22 p < 0.001)], female [OR 1.46 (95% CI 1.15-1.86 p=0.001)], BW > 3310g [OR 2.05 (95% CI 1.60-2.60 p < 0.001)] and CV> 75ml [OR 6.99 (95% CI 5.34-9.14 p < 0.001)].In multivariate analysis of TNC, CV > 75ml [OR 7.91 (95% CI 5.92-10.56 p < 0.001)] was the best predictor of followed by female [OR 1.73 (95% CI 1.30-2.30 p < 0.001)], BW > 3310g [OR 1.70 (95% CI 1.27-2.26 p < 0.001)] and GA > 39 weeks [OR 1.45 (95% CI 1.04-2.04 p = 0.03)]. In univariate analysis, M/D characteristics that were associated with high numbers of CD34+ (>3x10^{6}) included normal delivery [OR 2.09 (95% CI 1.49-2.93 p < 0.001)], BW > 3310g [OR 1.94 (95% CI 1.52-2.47 p < 0.001)] and CV > 75ml [OR 3.22 (95% CI 2.51-4.14 p < 0.001)]. In multivariate analysis of CD34+, CV > 75ml [OR 3.13 (95% CI 2.43-4.05 p < 0.001)] and BW > 3310 [OR 1.84 (95% CI 1.41-2.40 p < 0.001)] were significant predictors. **Conclusions:** M/D characteristics were associated with CV which is the best predictor followed by BW for both TNC and CD34+ in collected Korean CBUs. These associations could be used to prioritize donations, collections, optimizing and financial modeling in Korean CB banks.

7124 General Poster Session (Board #45D), Sun, 8:00 AM-11:45 AM

Ofatumumab in combination with high-dose methylprednisolone for the treatment of patients with relapsed or refractory chronic lymphocytic leukemia.

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Background: We performed a phase II, single-arm, clinical trial evaluating ofatumumab in combination with HDMP for the treatment of patients with relapsed or refractory CLL. **Methods:** Patients received ofatumumab at the dose of 1,000 mg weekly (half the conventional dose) for 12 weeks, without monthly maintenance doses. The HDMP dose was 1,000 mg/m^{2}for 3 days of each of 3 monthly cycles. Prophylactic medications included acyclovir, bactrim, fluconazole, and allopurinol. **Results:** 21 patients were enrolled at a single center. The median age was 63 years (range 46–76). The median number of prior therapies was 3. 24% had unfavorable cytogenetics (Del 17p or Del 11q) and 76% had CLL cells that expressed unmutated IgVH genes or high levels of ZAP-70. 24% were fludarabine-refractory. Treatment was well tolerated. The majority of adverse events were grade 1 or 2, including insomnia, anxiety, fatigue, and infusion reactions. There were no grade 4 toxicities.19% of patients had grade 3 neutropenia, and 5% had grade 3 thrombocytopenia. Other grade 3 toxicities were hyperglycemia (71%), non-melanoma skin cancer and other skin lesions (19%), as well as acute coronary syndrome, atrial fibrillation, renal calculi, pneumonia, and hypocalcemia (1 patient each). Responses were assessed two months after completion of therapy. The overall response rate was 81% (17/21) with 5% CR (1/21), 10% nodular PR (2/21), 67% PR (14/21), 14% SD (3/21), and 5% PD. The median follow-up time was 12 months (range 5-23). The median progression-free survival (PFS) time was 9.1 months (95%CI: 7.5-NA) and the median treatment-free survival (TFS) was 11.5 months (95%CI: 10.0-NA). Patients with Del 17p or Del 11q had a significantly lower overall response rate (p-value <0.001, fisher's exact test). **Conclusions:** The combination of HDMP and ofatumumab is an effective, tolerable, non-myelosuppressive treatment regimen. We observed a higher ORR and longer PFS than those previously reported with single agent mAb. This regimen may be useful for patients who are unable to tolerate more aggressive, myelosuppressive therapies, or have not responded to other treatments.

7125 General Poster Session (Board #45E), Sun, 8:00 AM-11:45 AM

Epidemiologic study of myelodysplastic syndromes in a racially diverse inner-city population.

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Background: The International Prognostic Scoring System (IPSS) and the revised IPSS (IPSS-R) are used to assess prognosis after diagnosis of myelodysplastic syndromes (MDS). They are based on cytogenetics, bone marrow (BM) blasts, and number and degree of cytopenias. This retrospective analysis examined racial disparities in the presentation and survival of MDS patients (pts) in Bronx, NY. **Methods:** MDS pts treated at the Einstein/Montefiore system between 1997-2011 were included. Diagnosis was confirmed by review of BM biopsy. Demographics, cytogenetics (for 135/161 pts), blood counts, and BM blasts at diagnosis were collected. The Kaplan-Meier method was used for median survival estimates. The two-sample t-test and chi-square analysis were used to compare clinical variables between groups. **Results:** 161 pts with MDS were identified. Mean length of follow-up was 3.66 years (yrs). There were significant differences between mean age at diagnosis between Hispanics and African-Americans (66.5 vs 72.3 yrs, $p<0.05$) and Hispanics and whites (66.5 vs 73.1 yrs, $p<0.05$). There was also significantly increased thrombocytopenia at diagnosis in Hispanics ($p<0.05$, when compared to non-Hispanics). Median survival decreased with higher risk among IPSS groups, however, the intermediate risk group in IPSS-R had a longer median survival (9 yrs) than all other risk groups. **Conclusions:** The cohort used to validate prognostic risk with IPSS and IPSS-R was primarily Caucasian. In our minority rich inner-city population, Hispanics presented with MDS earlier and with more thrombocytopenia. IPSS was a stronger predictor of survival than IPSS-R as the IPSS-R intermediate risk group had better survival than lower risk groups. Larger studies should be conducted to assess the applicability of IPSS-R in minority rich populations.

	Total	Hispanic	African-American	White
# Pts	161	49	54	58
Mean age	70.6	66.5	72.3	73.1
Median survival (yrs)	6.2	8.6	6.2	3.7
Thrombocytopenia				
Plts<100	70	27	18	25
Plts>100	91	22	36	33
Pts analyzed with IPSS	135	Median survival	Median survival (Greenburg et al.)	
IPSS				
Low	65	8.6	5.7	
INT-1	46	4.4	3.5	
INT-2	21	0.9	1.2	
High	3	0.6	0.4	
PSS-R				
Very low	27	8.6	8.8	
Low	54	6.7	5.3	
Intermediate	27	9.0	3.0	
High	10	2.7	1.6	
Very high	17	0.8	0.8	

7126 General Poster Session (Board #45F), Sun, 8:00 AM-11:45 AM

Application of the French prognostic score (FPS) to assess overall survival (OS) in a U.S.-based cohort of patients (pts) treated with azacitidine (Aza).

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Background: In pts with IPSS high-risk myelodysplastic syndrome (HR-MDS), Aza prolonged OS. The FPS was developed for Aza-treated HR-MDS pts based on 4 baseline clinical criteria: Performance status, karyotype, presence of circulating blasts, and RBC transfusion dependency (TD) (Itzykson et al, Blood 2011). The FPS discriminated 3 risk groups [low-risk [LR), intermediate-risk (IR), and high-risk (HR), with significantly different median OS at 32, 15, and 6 months (M), respectively. We sought to validate the FPS in a U.S.-based cohort. **Methods:** The North American Leukemia Intergroup Trial E1905 randomized 150 pts with MDS, CMML, and AML with dysplastic changes to Aza 50 mg/m^2/day (d) for 10 d +/- entinostat (Ent) 4 mg/m^2/d on d3 and d10. OS was defined as time from registration to death from any cause, with follow-up censored at last contact. Kaplan-Meier estimates were used for survival distribution. **Results:** The FPS could be determined for 115 pts. Median follow-up was 48.5 M. The median OS was significantly different between the HR, IR, and LR FPS groups in the 115 pts (9.7, 14.7, 25.3 M, respectively, log Rank test P=0.017), and for pts in Aza arm (n=55) (7.8, 19.3, 26.4 M, respectively, P=0.008), but not for patients in the Aza+Ent arm (n=60) (12.5, 12.4, 24.1 M, respectively, P=0.21). Using multivariate Cox model with WBC count, hemoglobin, disease type, and platelet TD, the prognostic effect of HR vs. LR FPS groups remained significant for the entire cohort (P=0.046) and for the Aza arm (P=0.037). No significant differences in response rates were observed. **Conclusions:** The FPS warrants further evaluation as a baseline prognostic tool that can define a subgroup of pts with lower probabilities of achieving survival benefit from Aza therapy. Such pts might be considered from alternative therapeutic interventions.

7127 General Poster Session (Board #45G), Sun, 8:00 AM-11:45 AM

Trends and outcomes of severe sepsis in hematopoietic stem cell transplant recipients.

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Background: Sepsis is common in hematopoietic stem cell transplant (HSCT) patients due to deficient immune system in the early part of the transplant and in patients with graft versus host disease (GVHD). There is very limited data on outcomes and trends of severe sepsis (SS) in these groups of patients. **Methods:** Using the Nationwide Inpatient Sample 2000-2008, patients older than 18 years, discharged with SS were identified using ICD-9-CM codes. Status of HSCT was identified using ICD-9-CM codes 41.0x. We also identified subsequent hospital admissions using ICD-9-CM codes V42.81-82 and 996.85 and GVHD using 279.5x. Hospital mortality was the primary outcome studied. Chi square test was used for comparison. Logistic regression model was constructed to examine the independent effect of HSCT on mortality in patients with SS. We adjusted for age, gender, race, insurance, hospital characteristics, Charlson's co-morbidity index and severity of sepsis using number of organ failures. **Results:** Of the 291,182 admissions with HSCT from 2000 to 2008, 7.5% had SS. The rate of SS was 5 times higher in HSCT when compared to non transplant group. In engraftment period, allogenic transplant had higher rates of SS when compared to autologous (13.2% vs. 5.2%, $p<0.001$). During engraftment, in-hospital mortality with SS was higher in allogenic transplant (55.1%) compared to autologous group (30.1%) (mortality in non-transplant was 32.9%). On adjusted analysis, compared to non transplant group, the odds of mortality was 4.69 times (95%CI 2.85-7.69) higher in allogenic transplants while it was similar in autologous group. In subsequent admissions, the odds of mortality were 2.38 times (95%CI 2.10-2.69) higher in GVHD and 1.45 times higher (95%CI 1.28-1.65) in non-GVHD patients when compared to the non-transplant group. The in-hospital mortality in HSCT decreased from the year 2000 to 2004 but has not changed ever since, while in the non-transplant group the mortality has continued to decrease. **Conclusions:** Higher mortality is observed in allogenic transplant patients and in those developing GVHD when compared to non-transplant patients. The mortality due to SS in HSCT patients has not changed since 2004 and may warrant more aggressive interventions.

7128 General Poster Session (Board #45H), Sun, 8:00 AM-11:45 AM

Derivation and validation of the SEER-Medicare MDS risk score (SMMRS).

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Background: The Surveillance Epidemiology and End Results (SEER) program has been collecting data on myelodysplastic syndromes (MDS) since 2001. These data, when linked to Medicare claims (SEER-Medicare), are an outstanding resource for MDS-related outcomes research. Unfortunately, in terms of prognostic factors at diagnosis, only morphologic subtype is available, and in about half of the registry cases, this is unclassifiable (MDS-U). We aimed to devise a prognostic risk score for use in the SEER-Medicare dataset, and compare it to the standard International Prognostic Scoring System (IPSS) using a granular MDS patient database at our institution (the DFCI/MDS CRIS). **Methods:** Borrowing from several validated MDS risk scoring systems, a set of candidate predictors that could be determined from claims was pre-specified. Cox proportional hazards models were then built for overall survival, using the 2001-2007 SEER-Medicare MDS dataset (n=9820). Different categorizations of each predictor were tested so that the final model would achieve the best predictive performance. The model was then validated independently using DFCI/MDS CRIS patient data (n=328). C-statistics were calculated to compare the performance of the new scoring system (SMMRS) with the IPSS. **Results:** The final model included cytopenias, MDS morphologic category, age at diagnosis, hospitalization at diagnosis, red cell or platelet transfusion dependence, and Charlson comorbidity score. The C-statistic for the final model in SEER-Medicare was 0.688. The table shows how the SMMRS performed in the DF/MDS CRIS database compared to, and in combination with, the IPSS. When the analyses were restricted to DF/MDS CRIS patients 65 or older (n=164), similar results were observed. **Conclusions:** Although missing some important clinical characteristics (eg, cytogenetics), the SMMRS can risk-stratify SEER-Medicare MDS patients with a precision similar to that of the IPSS. The SMMRS thus promises to make the large SEER-Medicare dataset much more useful for MDS clinical research.

Scoring system	C-statistics (95% CI)	Difference from SMMRS (95% CI)
SMMRS	0.626 (0.582, 0.671)	-
IPSS	0.634 (0.590, 0.679)	0.031 (-0.054, 0.069)
SMMRS + IPSS	0.667 (0.626, 0.708)	0.040 (0.005, 0.076)

TPS7129 General Poster Session (Board #46A), Sun, 8:00 AM-11:45 AM

EPIC: A phase III randomized, open-label study of ponatinib versus imatinib in adult patients with newly diagnosed chronic myeloid leukemia in chronic phase.

Jeffrey H. Lipton, Michael W. N. Deininger, Stephanie Lustgarten, Christopher D. Turner, Victor M. Rivera, Tim Clackson, Michele Baccarani, Jorge E. Cortes, Francois Guilhot, Andreas Hochhaus, Timothy P. Hughes, Hagop M. Kantarjian, Neil P. Shah, Moshe Talpaz, Frank G. Haluska; Princess Margaret Hospital, Toronto, ON, Canada; Oregon Health & Science University Knight Cancer Institute, Portland, OR; ARIAD Pharmaceuticals, Inc., Cambridge, MA; Institute of Hematology, Bologna, Italy; The University of Texas MD Anderson Cancer Center, Houston, TX; CIC Inserm 0802, Centre Hospitalier Universitaire de Poitiers, Poitiers, France; Universitätsklinikum Jena, Jena, Germany; Centre for Cancer Biology, SA Pathology, University of Adelaide, Adelaide, Australia; University of California, San Francisco, San Francisco, CA; Comprehensive Cancer Center, University of Michigan, Ann Arbor, MI

Background: The hallmark genetic abnormality of chronic myeloid leukemia (CML), known as the Philadelphia chromosome, generates the BCR-ABL fusion gene; expression of BCR-ABL in hematopoietic stem cells gives rise to CML. Ponatinib is a potent oral pan–BCR-ABL tyrosine kinase inhibitor (TKI) that is active against native and mutated forms of BCR-ABL, including the T315I gatekeeper mutant. Results from the phase 1 and phase 2 studies of ponatinib demonstrated that ponatinib is generally well tolerated and has substantial anti-leukemic activity in patients with CML who are resistant or intolerant to prior TKI therapy, regardless of baseline mutation status. In addition, multivariate analyses suggest that ponatinib has greater activity in younger patients who are less heavily pretreated and have a shorter time since diagnosis. The phase 3 EPIC (Evaluation of Ponatinib vs Imatinib in CML) study is testing the hypothesis that ponatinib is an effective treatment for newly diagnosed chronic phase (CP) CML patients when compared with standard imatinib therapy. **Methods:** EPIC is a multicenter, international, phase 3, two-arm, open-label trial of ponatinib (45 mg once daily) versus imatinib (400 mg once daily) in patients with newly diagnosed CP-CML. Patients $\geq$18 years of age with CP-CML (diagnosed within 6 months prior to study entry) and adequate renal, hepatic, and pancreatic function are eligible for enrollment. Enrolled patients are assigned to receive ponatinib or imatinib in a 1:1 fashion, stratified by Sokal Risk score (low vs intermediate vs high). The primary efficacy endpoint for this trial is major molecular response (MMR) rate at 12 months. Secondary endpoints include MMR rate at 5 years, BCR-ABL^{IS}$<$10% rate at 3 months, CCyR rate at 12 months, progression-free survival, overall survival, and safety. A sample size consisting of 480 patients will provide 90% power to detect a 15% absolute increase in MMR rate at 12 months using an unstratified Fisher exact 2-sided test at an alpha level of 0.05. Assuming a 10% dropout rate, approximately 528 patients will be enrolled. The first patient was enrolled in August 2012. Clinical trial information: NCT01650805.

TPS7130 General Poster Session (Board #46B), Sun, 8:00 AM-11:45 AM

Randomized, multicenter, open-label, phase III study of the BTK inhibitor ibrutinib versus chlorambucil in patients 65 years or older with treatment-naive CLL/SLL (RESONATE-2, PCYC-1115-CA).

Jan Andreas Burger, Paolo Ghia, Aaron Polliack, Constantine Tam, Deepali Suri, Fong Clow, Silvija Kraljevic, Danelle Frances James, Thomas J. Kipps; The University of Texas MD Anderson Cancer Center, Houston, TX; Università Vita-Salute San Raffaele and Istituto Scientifico San Raffaele, Milano, Italy; Hadassah University Hospital and Hebrew University Medical School, Jerusalem, Israel; Peter MacCallum Cancer Center, Melbourne, Australia; Pharmacyclics, Inc., Sunnyvale, CA; Pharmacyclics, Sunnyvale, CA; Pharmacyclics Switzerland, Schaffhausen, Switzerland; UC San Diego Moores Cancer Center, La Jolla, CA

Background: There is an unmet need for safer and more effective therapies for CLL patients who are older/have comorbidites. Ibrutinib, a small molecule inhibitor of BTK, has demonstrated single-agent activity in CLL in the Ph 1b/2 study, PCYC-1102-CA. Treatment-naïve (TN) patients aged >= 65 yrs (n=31) experienced an estimated PFS and OS of 96% at 26 months; ORRs per iwCLL were: 10% CR, 58% PR, and 13% PR with lymphocytosis (Byrd, ASH 2012). AEs were generally Grade 1/2, most commonly diarrhea. Incidence of Grade 3/4 hematologic toxicities was low. These findings support a phase III study of ibrutinib in older patients with treatment-naïve CLL/SLL. **Methods:** The ongoing study is a randomized, multicenter, open label Ph 3 study comparing safety and efficacy of ibrutinib vs. chlorambucil in TN patients aged >= 65 yrs with CLL/SLL. Approximately 272 patients will be randomized in 1:1 ratio to receive either chlorambucil or ibrutinib, stratified for ECOG PS and Rai stage. Oral chlorambucil will be administered at 0.5 mg/kg on Days 1 and 15 of each 28-day cycle, for up to 12 cycles. Ibrutinib 420 mg q.d. will continue until PD or unacceptable toxicity. Key incl. criteria include age >= 65 yrs, active disease requiring treatment per iwCLL, measurable nodal disease by CT, ECOG performance status 0-2, and adequate organ function (ANC $\geq$1,000/μL, platelets $\geq$50,000/μL, creatinine clearance $\geq$30 mL/min). Key excl. criteria include Richter's transformation, del(17p13.1) or previous treatment for CLL/SLL. The primary endpoint of the study is PFS, assessed by Independent Review Committee (IRC). Secondary endpoints include ORR, MRD-negative CRs, fatigue by FACIT-F, hematological improvement, safety, and tolerability. Subjects who relapse on PCYC-1115 will be enrolled on PCYC-1116 for long term follow up. Second line therapy is investigator choice; ibrutinib will be made available for patients who experience IRC-confirmed PD $\leq$12 months of completing chlorambucil therapy, if they meet the treatment criteria. Approximately 85 sites will enroll patients in North America, Europe, Israel, Australia/New Zealand and China. Enrollment began in Q1 2013. Clinical trial information: NCT01722487.

TPS7131 General Poster Session (Board #46C), Sun, 8:00 AM-11:45 AM

A phase III, randomized, controlled study evaluating the efficacy and safety of idelalisib (GS-1101) in combination with ofatumumab for previously treated chronic lymphocytic leukemia (CLL).

Ian Flinn, Eva Kimby, Finbarr E. Cotter, Francis J. Giles, Ann Janssens, Elisa Jacobsen Pulczynski, Loic Ysebeart, Andrzej Pluta, Jose Antonio Garcia Marco, Kerry Taylor, Carolyn Owen, David Michael Johnson, Maria Aiello, Roger D. Dansey, Ronald L. Dubowy, Jeffrey Alan Jones; Sarah Cannon Research Institute, Nashville, TN; Karolinska Institute at Huddinge University Hospital, Stockholm, Sweden; Barts Cancer Institute, London, United Kingdom; HRB Clinical Research Facility, National University of Ireland and Trinity College Dublin, Dublin, Ireland; University Hospitals Leuven, Leuven, Belgium; Aarhus University Hospital, Aarhus, Denmark; Service d'Hématologie CHU Purpan, Toulouse, France; Podkarpackie Oncology Center Hospital, Brzozow, Poland; Hospital Puerta de Hierro de Majadahonda, Madrid, Spain; Haematology and Oncology Clinics of Australasia, Brisbane, Australia; Tom Baker Cancer Centre, Calgary, AB, Canada; Gilead Sciences, Inc., Seattle, WA; The Ohio State University, Columbus, OH

Background: PI3K-delta is critical for activation, proliferation and survival of B cells and plays a role in homing and retention in lymphoid tissues. PI3Kδ signaling is hyperactive in many B-cell malignancies. Idelalisib is a first-in-class, selective, oral inhibitor of PI3Kδ that reduces proliferation, enhances apoptosis, and inhibits homing and retention of malignant B cells in lymphoid tissues (Lannutti et al, 2011). Ofatumumab (O) is an anti-CD20 monoclonal antibody approved for the treatment of pts with CLL refractory to fludarabine and alemtuzumab. Phase 1 studies demonstrated that idelalisib, as monotherapy or combined with O, is highly active in pts with heavily pretreated CLL: pts experienced profound and rapid regression of lymphadenopathy, reductions in disease-associated chemokines, and durable clinical benefit with an acceptable safety profile (Furman et al, 2012). **Methods:** This study will enroll 210 pts with CLL previously treated with a purine analog and/or bendamustine, with measurable lymphadenopathy who require treatment for CLL and have disease that is not refractory to ofatumumab, and are expected to benefit from a change in therapy because of CLL progression $<$24 months since completion of their last prior treatment. Pts are randomized in a 2:1 ratio (Arm A:Arm B). In Arm A, pts receive idelalisib at 150 mg BID continuously in combination with 12 infusions of O at 1000 mg over ~24 weeks (weekly x 8 then monthly x 4). In Arm B, pts receive 12 infusions of O at 2,000 mg over ~24 weeks. Stratification factors address IGHV mutational status, del(17p)/p53 mutation status, and refractory vs relapsed disease. The primary study endpoint is PFS. Secondary endpoints include ORR, lymph node response rate, CR rate, and OS. This is an event-driven trial and primary endpoint evaluation will be based on independent central review. For the primary efficacy analysis, the difference in PFS between the treatment arms will be assessed in the ITT analysis set using Kaplan-Meier methods and the stratified log-rank test. The study opened for enrollment in Dec 2012. Clinical trial information: NCT01659021.

TPS7132 General Poster Session (Board #46D), Sun, 8:00 AM-11:45 AM

A phase II, dose-optimization trial of autologous T cells genetically engineered to express anti-CD19 chimeric antigen receptor (CART-19) in patients with relapsed or refractory (r/r) CD19+ chronic lymphocytic leukemia (CLL).

David L. Porter, Noelle V. Frey, Alison W. Loren, Bruce Levine, Michael Kalos, Holly McConville, Joan Gilmore, Anne Chew, Angela Shen, Charlene So, Michele Sharr, Patricia Ann Wood, Carl H. June; Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA; Novartis Pharmaceuticals Corp, East Hanover, NJ

Background: The poor prognosis and lack of effective treatment options for patients with r/r CLL highlight the need for novel therapies in this setting. CD19 is a promising anticancer target because it is broadly expressed on normal and malignant B cells through several stages of maturation but absent on pluripotent stem cells. CART-19 (CTL019) therapy involves adoptive transfer of autologous T cells genetically modified via lentiviral transduction to express chimeric antigen receptors (CAR) designed to target CD19+ cells. CART-19 cells express a CD19 antigen recognition domain combined with intracellular signaling domains, CD137 (4-1BB) and CD3-zeta, which mediate cytolytic T-cell activity. In patients with r/r CLL, CART-19 therapy showed potent antileukemic activity with long-term persistence of transduced cells at doses from 1.4×10^7 to 1.1×10^9 CART-19 cells. As of August 2012, 3 of 8 evaluable CLL patients achieved CR (two $>$ 24 months and one $>$ 5 months) and remain in CR with detectable CART-19 cells. Two patients had PR lasting 3 and 5 months, and 3 patients did not respond (Porter et al. *NEJM.* 2011; Kalos et al. *Sci Transl Med.* 2011; Porter et al. ASH 2012). Here, we describe a study to determine the optimal dose of CART-19 cells (NCT01747486). **Methods:** Adults with relapsed or persistent CLL or SLL after $\geq$ 2 previous therapies will undergo leukapheresis to obtain T cells, which will be stimulated, expanded, and lentivirus transduced ex vivo to express the CD19/4-1BB/CD3-zeta CAR. Patients will undergo lymphodepletion chemotherapy prior to infusion of CART-19 cells. In stage I of the II-stage trial, 30 patients will be randomized 1:1 and receive either $1\text{-}5 \times 10^8$ or $1\text{-}5 \times 10^7$ CART-19 T cells. The optimal dose in stage I will be selected based on clinical responses, feasibility, and tolerability. In stage II, 8 additional patients will be enrolled into the selected dose cohort. Study objectives are to determine the efficacy (CR rate within 3 months) and safety (CTCAE v 4.0) of each dose, in vivo CART-19 expansion, and manufacturing feasibility. Three patients have been enrolled as of January 2013. Clinical trial information: NCT01747486.

TPS7133 General Poster Session (Board #46E), Sun, 8:00 AM-11:45 AM

A phase III, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of idelalisib (GS-1101) in combination with bendamustine and rituximab for previously treated chronic lymphocytic leukemia (CLL).

Herbert Aaron Eradat, Steven E. Coutre, Jacqueline Claudia Barrientos, Kanti Roop Rai, Charles Michael Farber, Peter Hillmen, Jeff Porter Sharman, Paolo Ghia, Bertrand Coiffier, Jan Andrzej Walewski, Zwi N. Berneman, Susan Mary O'Brien, Jennifer R. Brown, Sissy Peterman, Roger D. Dansey, Thomas Michael Jahn, Paula Cramer, Michael J. Hallek; David Geffen School of Medicine at University of California, Los Angeles, Los Angeles, CA; Stanford Cancer Institute, Stanford, CA; Hofstra North Shore-LIJ School of Medicine, Hyde Park, NY; Morristown Memorial Hospital, Carol G. Simon Cancer Center, Morristown, NJ; St James's University Hospital, Leeds, United Kingdom; Willamette Valley Cancer Institute/US Oncology Research, Springfield, OR; Università Vita-Salute San Raffaele and Istituto Scientifico San Raffaele, Milano, Italy; Hospices Civils de Lyon Sud, Pierre-Bénite, France; Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland; Antwerp University Hospital, Edegem, Belgium; The University of Texas MD Anderson Cancer Center, Houston, TX; Dana-Farber Cancer Institute, Boston, MA; Gilead Sciences, Inc., Seattle, WA; University of Cologne, Cologne, Germany

Background: PI3K-delta is critical for the activation, proliferation and survival of B cells and plays a role in homing and retention of B cells in lymphoid tissues. PI3Kδ signaling is hyperactive in many B-cell malignancies. Idelalisib is a first-in-class, selective, oral inhibitor of PI3Kδ that reduces proliferation, enhances apoptosis, and alters trafficking of malignant B cells in lymphoid tissues (Lannutti, 2011). Phase 1 trials demonstrated that idelalisib is highly active in heavily pretreated pts with CLL as a single agent or in combination with rituximab (R), bendamustine (B), or BR: pts experienced reductions in disease-associated chemokines, profound and rapid reductions in lymphadenopathy, and durable clinical benefit with an acceptable safety profile (Coutre et al, 2012; Sharman et al, 2011). **Methods:** Study will enroll 390 pts with previously treated CLL who have measurable lymphadenopathy, have received prior therapy containing a purine analog or B and an anti-CD20 monoclonal antibody, are not refractory to B, have experienced CLL progression within 36 months from the completion of the last prior therapy, and are currently sufficiently fit to receive cytotoxic therapy. Pts are randomized in a 1:1 ratio to Arm A or B. On Arm A, subjects receive idelalisib continuously at 150 mg BID + R at 375 mg/m^2 (1st dose) and then 500 mg/m^2 every 4 weeks for 6 cycles + B at 70 mg/m^2 on Days 1 and 2 of each 4-week cycle for 6 cycles. On Arm B, subjects receive placebo instead of idelalisib. Stratification factors address IGHV mutational status, del(17p)/p53 mutation status, and refractory vs relapsed disease. The primary endpoint is PFS and key secondary endpoints include ORR, lymph node response rate, CR rate, and OS. This is an event-driven trial and primary endpoint evaluation will be based on independent central review. For the primary efficacy analysis, the difference in PFS between the treatment arms will be assessed in the ITT analysis set. The study was initiated in June 2012 and a data monitoring committee has begun regular review of data. Clinical trial information: NCT01569295.