8000 **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

CALGB 50401: A randomized trial of lenalidomide alone versus lenalidomide plus rituximab in patients with recurrent follicular lymphoma.

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Background: Lenalidomide (L) and rituximab (R) are active as single agents in follicular (FL) and other B-cell lymphomas, although combination strategies have not been previously assessed in a randomized fashion. **Methods:** CALGB 50401 is a randomized phase II study, initially designed to evaluate 3 regimens: R alone (375 mg/m2 weekly x 4), L alone (15 mg cycle 1, then escalated to 20 mg cycles 2-12, administered days 1-21 q 28 days x 12 cycles) or the combination of L+ R (other 2 arms combined). The R alone arm was discontinued due to slow accrual with 3 enrolled subjects. Eligibility included recurrent FL, prior therapy with rituximab alone or in combination, and TTP of $\geq$ 6 months from last rituximab dose. Prophylactic ASA or LMW heparin was recommended for patients at high risk for thrombosis. **Results:** Of 94 pts registered to L or LR, 89 (45 L and 44 LR) received at least one dose and had adequate data for analysis. Baseline characteristics include median age 63 (range 34-85) and 60% with intermediate- or high-risk FLIPI. Grade 3-4 adverse events (AE) were most commonly neutropenia (16% L,19% LR), fatigue (9% L, 14% LR) and thrombosis (16% - 7 pts L, 4% - 2 pts LR, p=0.158), and overall were seen in 49% (L) and 52% (LR) with 9% grade 4 in each arm. The full regimen was completed in 33% (L) and 59% (LR) of patients, with the difference due to more progressions or non-responders in the L group. In both arms about 19% of subjects discontinued therapy early due to AEs and dose intensity was over 80%. Objective response rates are L - 49% (13% CR) and LR - 75% (32% CR). With a median follow-up of 1.5 years (range 0.1- 3.6 years), median EFS is 1.2 years (L) and 2.0 years (LR), p=0.0063, log-rank test. **Conclusions:** Lenalidomide + rituximab is more active than lenalidomide alone in patients with recurrent FL with similar toxicity. A trend toward lower thrombosis risk with LR may relate to greater anti-tumor efficacy. The LR regimen warrants further study in FL including as a backbone for addition of novel agents in relapsed and frontline settings.

8001 **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

A phase III randomized intergroup trial (S0016) comparing CHOP plus rituximab with CHOP plus iodine-131-tositumomab for front-line treatment of follicular lymphoma: Results of subset analyses and a comparison of prognostic models.

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Background: Advanced follicular lymphomas (FL) are considered incurable with chemotherapy and there is no consensus on the best treatment. Outcomes are variable, but can be partially predicted by defined prognostic factors. SWOG and CALGB compared the safety and efficacy of 2 immunochemotherapy regimens in a Phase III trial enrolling 554 patients between 3/1/2001 and 9/15/2008. **Methods:** Patients were eligible if they had bulky stage II, III or IV FL and had not received prior therapy. Patients randomized to CHOP-R received 6 cycles of CHOP every 21 days + 6 doses of rituximab. Patients randomized to CHOP-RIT received 6 cycles of CHOP, followed by consolidative radioimmunotherapy with tositumomab/ iodine I-131 tositumomab. A Cox proportional hazards multi-variable regression analysis assessed the prognostic impact of age, stage, LDH, LN size and number, performance status, hemoglobin, β2 microglobulin, BM involvement, and B symptoms. The prognostic value of 3 multi-variable models were compared. **Results:** Outcomes were outstanding with either CHOP-R or CHOP-RIT (2 yr PFS: 76% vs 80% [p =0.11]; 2 yr OS: 97% vs 93% [p =0.08], respectively). Subset analyses so far have not identified any subgroups clearly benefitting to a greater degree from CHOP-R or CHOP-RIT in terms of both PFS and OS. Cox multivariable regression analysis identified serum-β2M, LDH level, and FLIPI index as the strongest prognostic factors associated with worse PFS and OS. **Conclusions:** Both regimens produced outstanding PFS and OS, and no statistically significant differences between them were observed. FLIPI, FLIPI2, and LDH + β2M models were all strong predictors of patient outcomes. A combination of LDH + β2M was as good as the FLIPI index, and was simpler to apply. (Supported in part by NCI grants CA32102 and CA38926 from the NCI and GlaxoSmithKline.)

	PFS		OS	
Parameter	HR (95% CI)	p	HR (95% CI)	p
LDH	1.59 (1.17-2.17)	.003	2.46 (1.49-4.07)	.0004
Serum-β2M	1.70 (1.27-2.28)	.0004	2.22 (1.31-3.76)	.003
β2M and LDH	2.25 (1.51-3.31)	<.0001	3.96 (2.02-7.78)	<.0001
FLIPI	2.28 (1.54-3.35)	<.0001	3.65 (1.82-7.18)	.0002

8002 **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

ABVD (8 cycles) versus BEACOPP (4 escalated cycles => 4 baseline) in stage III-IV high-risk Hodgkin lymphoma (HL): First results of EORTC 20012 Intergroup randomized phase III clinical trial.

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Background: Escalated BEACOPP and derivatives achieved superior time to treatment failure (FFTF) over COPP/ABVD, resulting in higher overall survival (OS) for advanced HL. However, later clinical trials have failed to confirm OS superiority over ABVD. **Methods:** Eligibility criteria: clinical stage III/IV HL, International prognostic score (IPS) $\geq$ 3, age$<$60. We compared ABVD (8 cycles) vs. BEACOPP (escalated 4 cycles $\geq$ baseline 4), without irradiation. Randomization was stratified for institution and IPS. Primary endpoint was EFS, defined as treatment discontinuation, no complete response (CR) after 8 cycles, progression, relapse or death. Additional endpoints were CR, progression free survival (PFS), OS, quality of life and secondary malignancies. Outcomes were reviewed by study coordinators to ensure consistency across pts. **Results:** From 2002-2010, 549 pts were randomized (ABVD 275, BEACOPP 274): stage IV 74%, PS 0, 1, 2: 34, 48 and 17%, B-symptoms 81%, median age 35.2y, males 75%. IPS was 4 or higher for 59% of pts. Histology reviewed no HL in 4 cases. CR was 83% in both arms. With a median follow-up of 3.8 yrs, EFS at 4 yrs was 63.7% vs. 69.3% (HR = 0.86, 95%CI=0.64 to 1.15, p=0.312). PFS at 4 yrs was 72.8% vs. 83.4% (HR = 0.58, 95%CI=0.39 to 0.85, p=0.005). OS at 4 yrs was 86.7 vs. 90.3 (HR = 0.71, 95%CI=0.42 to 1.21, p=0.208). Toxic deaths occurred in 6 and 5 pts, with early discontinuation (prior to cycle 5) in 12 & 26 pts, respectively. There were 5 crossovers to BEACOPP and 10 to ABVD. Second malignancies occurred in 8 ABVD and 10 BEACOPP pts (myelodysplasia/leukemia 2 and 4, lung 2 and 1, NHL 3 and 2, other 1 and 3); cumulative incidence curves did not differ significantly. **Conclusions:** The primary endpoint (EFS) was similar between treatment arms. However, more progressions/relapses were observed with ABVD, while early discontinuations were more frequent with BEACOPP. Nevertheless, even in this high-risk group, OS was not improved with BEACOPP. Additional considerations (treatment burden and cost, fertility issues, long term relapses and immediate and late morbidity) may guide physician/patient decisions toward ABVD or BEACOPP.

8003 **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

Plasma viral DNA as a marker of tumor response in EBV(+) Hodgkin lymphoma in a phase III study (E2496).

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Background: Epstein-Barr virus (EBV) is associated with Hodgkin lymphoma (HL) and can be detected by in situ hybridization (ISH) of viral nucleic acid (EBER) in tumor cells. Studies have suggested a correlation in HL between plasma EBV DNA and EBER ISH. We previously studied the DNase sensitivity of plasma EBV DNA and found plasma EBV of patients with EBV(+) HL was not protected from DNase digestion, consistent with tumor-derived DNA, while plasma EBV of patients with HIV without EBV(+) tumors was protected from DNase digestion, consistent with virion DNA. We sought to determine whether plasma EBV could serve as a surrogate for EBER ISH and whether reappearance of plasma EBV predicts treatment failure. **Methods:** Specimens from a Cancer Cooperative Intergroup Trial (E2496/Stanford V versus ABVD for HL) were used to compare pretreatment plasma EBV DNA copy number, assessed by real-time quantitative PCR, with EBV status by EBER ISH. An ROC analysis was performed using patients with both pretreatment plasma EBV and EBER results (n=121), identifying a cutoff of 60 viral copies/100 μL plasma (95% concordance, 92% sensitivity, 96% specificity for EBV status by EBER). Using this cutoff, pretreatment plasma specimens (n=274) were designated EBV(+) (n=54) or EBV(-) (n=220), as were serial follow-up specimens. Cox proportional hazard models were constructed to evaluate plasma EBV as a prognostic factor for failure-free survival (FFS). FFS was estimated by the Kaplan-Meier method. **Results:** Pretreatment EBV(+) plasma was associated with treatment failure with a hazard ratio of 2.1 (95% CI 1.2-3.6, p=0.01) after adjusting for International Prognostic Score, treatment arm, and histology. Of the EBV(+) patients with follow-up specimens (n=45), patients with EBV(+) plasma beyond 1 month of therapy (n=9) had inferior FFS compared to those who cleared their plasma of EBV (n=36), (3-year FFS 44% versus 69%, respectively; log rank p=0.03). **Conclusions:** HL patients with EBV(+) plasma at baseline have inferior FFS compared to others. Among patients with EBV(+) plasma at baseline, those in whom plasma EBV persists or reappears after initiation of therapy have inferior FFS. Such patients may benefit from experimental or intensified therapies.

8004 **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

High-dose chemotherapy followed by allogeneic stem cell transplantation in high-risk relapsed and refractory aggressive non-Hodgkin lymphoma: Results of a prospective study of the German high-grade non-Hodgkin lymphoma study group.

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Background: The role of allogeneic stem cell transplantation (alloSCT) in high-risk aggressive NHL is poorly defined; the role of graft-versus-lymphoma effect is unclear. Reduced intensity conditioning has shown limited efficacy in patients with refractory disease. **Methods:** Patients with primary refractory disease, early relapse (<12 months) or relapse after autologous SCT of aggressive B-cell (n=61) or T-cell (n=23) NHL were enrolled from June 2004 to March 2009. Myeloablative conditioning (fludarabine 125mg/m^2, busulfan 12mg/kg, cyclophosphamide 120 mg/kg) was followed by alloSCT from related (n=24) or unrelated (n=60) donors. 57/84 patients received a 10 HLA-loci compatible graft. **Results:** Overall survival at 3 years was 42% (95% CI, 31% to 52%), progression-free survival (PFS) was 40% (95% CI 29% to 50%). Non-relapse mortality (NRM) was 12% at 100 days and 35% at one year. Graft-versus-host disease (GVHD) and infection were the predominant causes of NRM. Relapse rate was 30% with latest relapse at day +327. Patients with an HLA fully compatible donor (plus ATG with unrelated donors) (n=40) had the best outcome (NRM at 1y 10.4 vs 57.2%, PFS at 3y 64.7% vs 31.8%, $p < 0.0001$). GVHD > grade I correlated with improved PFS (HR 0.45, p=0.0088). Patients with refractory disease or early relapse (n=60) experienced PFS at 3y of 33%. **Conclusions:** Lymphoma-debulking (high-dose) chemotherapy followed by alloSCT shows excellent results in heavily pretreated patients with early relapse or primary refractory aggressive lymphoma. There was evidence of graft-versus-lymphoma activity in this setting. For patients with a fully matched (10/10) related or unrelated donor the results compare favorably to autoSCT or alloSCT following reduced-intensity conditioning.

8005 **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

A pooled analysis of 1,144 patients with HIV-associated lymphoma: Assessment of lymphoma-, HIV-, and treatment-specific factors on clinical outcomes.

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Background: Non-Hodgkin Lymphoma (NHL) remains the most common malignancy in patients with HIV. Outcomes have significantly improved over the last decade, but there is no accepted consensus regarding the optimal initial therapeutic approach. Our objective was to assess the effects of clinical factors on response and survival. **Methods:** We performed a systematic review to search for prospective clinical phase II or III trials that assessed therapeutic interventions for HIV-associated NHL and assembled individual patient data from 16 trials published between 2000 and 2011 including 1144 patients (median N=62/trial, range 17-195). Treatment factors included type of chemotherapy (CHOP, N=642; EPOCH, N=178; CDE, N=191; intensive regimens, N=155) and rituximab use (N=542). Endpoints included complete response (CR), progression-free survival (PFS), and overall survival (OS). We used logistic regression and Cox proportional hazard models adjusted for age, sex, age-adjusted International Prognostic Index (IPI), baseline CD4 count, baseline HIV viral load, use of concurrent antiretroviral therapy, and histology. Odds ratios (OR) $>$ 1 for CR denote improved CR, and hazard ratios (HR) $<$ 1 indicate reduced risk of progression or death. **Results:** Among the lymphoma- and HIV-specific covariates evaluated, only a higher IPI score was associated with inferior CR rate, PFS and OS ($p<0.001$). Rituximab was associated with a higher CR rate (OR 1.75; $p=0.017$), better PFS (HR 0.39, $p<0.001$) and OS (HR 0.39, $p<0.001$); patients with a higher baseline CD4 count benefited more from rituximab (HR for OS 0.57 if baseline CD4 count $\geq$100/ul vs. $<$100/ul; $p<0.001$). For all histologies, initial therapy with the EPOCH regimen resulted in a better CR rate (OR 1.78, $p=0.039$), PFS (HR 0.61, $p=0.032$) and OS (HR 0.47, $p<0.001$) when compared to CHOP. **Conclusions:** In this pooled analysis including 1144 patients with HIV-associated NHL, the addition of rituximab to chemotherapy was associated with significantly improved CR rate, PFS, and OS, specifically for patients with a baseline CD4 count $\geq$100/uL. Treatment with infusional EPOCH was also more effective than CHOP.

8006 **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

R-CVP versus R-CHOP versus R-FM as first-line therapy for advanced-stage follicular lymphoma: Final results of FOLL05 trial from the Fondazione Italiana Linfomi (FIL).

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Background: The optimal chemotherapy regimen for patients with advanced, active follicular lymphoma (FL) has not been established yet. We conducted a randomized trial comparing R-CVP with R-CHOP and R-FM. **Methods:** Previously untreated patients with advanced FL were randomly assigned to receive 8 doses of rituximab associated to 8 cycles of CVP, or 6 cycles of CHOP or FM (fludarabine 25 mg/m2 day 1-3, mitoxantrone 10 mg/m2 day 1). No maintenance therapy was allowed. The principal study end point was Time to Treatment Failure (TTF). Events in TTF were failure of induction therapy, progressive or relapse disease and death from any causes. In order to show a hazard ratio between each experimental arms and standard arm of 0.53 we planned to accrue 534 patients (178 per arm) with 4 years of accrual and 1 year of follow-up. Statistical tests were two-sided with an alpha error of 0.05, adjusted by Bonferroni for multiple arm comparison, and power of 90%. **Results:** Between March 2006 and September 2010, 534 patients were enrolled; 30 were subsequently excluded due to violation of inclusion criteria. Median patient age was 56 years (range 30-75), 63% of patients had stage IV disease, 37% had 3-5 FLIPI and 27% 3-5 FLIPI2 scores. At the end of induction treatment the overall response rate (CR+ PR) for the whole group was 91% ($p=0.247$). After a median follow-up of 34 months 208 events for TTF were recorded; 3-year TTF was 46%, 64% and 61% for patients treated with R-CVP, R-CHOP and R-FM respectively (R-CHOP *vs* R-CVP $p=0.007$; R-FM *vs* R-CVP $p=0.021$; R-FM *vs* R-CHOP $p=0.969$). The 3-year overall survival rate (OS) was 98%, 95% and 93% for R-CVP, R-CHOP and R-FM group, respectively (P=NS). Patients treated with R-FM had a higher rate of g III-IV neutropenia (64% *vs* 28% R-CVP, $p<0.001$; and *vs* 50% R-CHOP, $p=0.015$). During follow-up second malignancies were registered as late events in 23 patients (2%, 3% and 8% in R-CVP, R-CHOP and R-FM, respectively). **Conclusions:** This trial showed that R-CVP was associated with an inferior 3-year TTF and PFS compared with R-FM and R-CHOP. OS was similar among study arms but R-FM showed a higher rate of secondary tumors.

8007 **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

A subgroup analysis of small lymphocytic and marginal zone lymphomas in the Eastern Cooperative Oncology Group protocol E4402 (RESORT): A randomized phase III study comparing two different rituximab dosing strategies for low tumor burden indolent non-Hodgkin lymphoma.

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Background: Management of low tumor burden (LTB) indolent lymphoma in the rituximab (R) era is uncertain. We hypothesized that R could delay the need for chemotherapy and that maintenance R (MR) would be superior to R retreatment (RR) at progression. E4402 is a randomized phase III study comparing MR and RR for previously untreated, LTB (by GELF criteria) small lymphocytic lymphoma (SLL), marginal zone lymphoma (MZL) and FL. Results for the FL subset was previously presented (*Kahl, et al. Blood 2011; 118(21): LBA 6*); we now report outcomes for the non-FL patients (pt). **Methods:** Pt received R 375 mg/m^2 weekly x 4, with responders randomized to MR (1 dose R q 3 mo) or RR (R q wk x 4 at progression), each continued until treatment failure. The primary endpoint, time to treatment failure (TTTF), was defined as progression within 6 mo of last R, no response to RR, initiation of alternative therapy, or inability to complete protocol therapy. Pt were evaluated q 3 mo, with CT scans q 6 mo. Secondary endpoints: time to first cytotoxic therapy (TTCT), quality of life (QOL) and safety. **Results:** From 11/03 to 9/08,137 non-FL pt were enrolled. Complete or partial response was achieved in 57 (41%), who were randomized to MR (n=32) or RR (n=25). 136 pt were stage III-IV (1 IE), and all had PS 0-1; for MR vs RR, median age 66 vs 64, and M:F 47:53% vs. 28:72%, respectively. The mean no. of R doses/pt (incl. 4 induction doses) was 17.9 (range 5- 30) for MR and 5.8 (range 4-12) for RR. With a median follow-up of 4.3 yr, TTTF was 3.74 yr for MR vs. 1.07 yr for RR (p=.0002; HR 4.95). At 3 yr, 100% of MR vs. 70% of RR pt (p=.0002) remained free of cytotoxic therapy. Grade 3-4 toxicities occurred in 2 MR pt, 1 neutropenia and 1 encephalopathy. **Conclusions:** A planned subgroup analysis of non-FL pt showed significant benefit in TTTF and TTTC for MR but with 2 grade 4 toxicities. This differs from the FL pt in this trial, for whom response to induction was higher (70 vs. 41%; p<.0001) and where no TTTF benefit was observed with MR. LTB non-follicular indolent lymphoma pt who achieve a CR or PR to induction R benefit from MR therapy.

8009 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

Phase I/II study of carfilzomib plus melphalan-prednisone (CMP) in elderly patients with de novo multiple myeloma.

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Background: Melphalan-prednisone + thalidomide (MPT) or bortezomib (MPV) are approved in frontline MM patients (pts) >65 years. Both regimens demonstrated significant benefit over MP alone in terms of PFS and OS but this benefit could be hampered by the risk of peripheral neuropathy (PN). Carfilzomib (Cfz) is a novel proteasome inhibitor that has demonstrated promising activity and favorable toxicity profile, with low rates of PN. This phase I/II study was designed to determine the maximum tolerated dose (MTD) of CMP, to assess safety and evaluate efficacy of this combination in newly diagnosed MM >65. **Methods:** In Phase I, Cfz was the only escalating agent starting at 20 mg/m2 (level 1) with maximal planned dose 36 mg/m2 (level 3), given IV on days 1, 2, 8, 9, 22, 23, 29, 30 for nine 42-day cycles. Oral melphalan 9 mg/m^2 and prednisone 60mg/m^2 were given on days 1 to 4, for all dose levels. Based on toxicity assessment, the study was amended to add dose level 4 (Cfz 45 mg/m2). MTD determination was based on occurrence of Dose limiting toxicities (DLTs) during the first cycle only. DLTs were defined as any grade 4 hematologic toxicity or preventing administration of 2 or more of the 8 Cfz doses of the first treatment cycle except grade 4 thrombocytopenia without bleeding or grade 4 neutropenia lasting $\leq$ 7 days; or grade $\geq$ 3 febrile neutropenia; or any other grade $\geq$ 3 nonhematologic toxicity. **Results:** As of January 20th 2012, 24 pts have been enrolled in the phase I: 6 pts at level 1 (Cfz 20), 6 at level 2 (Cfz 27), 6 at level 3 (Cfz 36), and 6 at level 4 (Cfz 45). There were 2 DLTs at level 4 (fever and hypotension not related to sepsis) and the MTD was considered to be 36 mg/m^2. Then, 16 additional pts were included in the phase II at level 3. Overall, 40 pts have been enrolled into the phase I/II study and 26 pts are evaluable for response. The ORR was 92% including 42% at least VGPR. These results compare favorably to those achieved with MPV, MPT, MPR or lenalidomide-dex (ORR 71, 76, 80 and 85%, respectively) in the same population. **Conclusions:** Frontline carfilzomib (36 mg/m2) + MP is a tolerable and very effective combination in elderly MM pts. Treatment is ongoing, with updated toxicity and efficacy data to be presented at the meeting.

8010 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

A phase I/II trial of cyclophosphamide, carfilzomib, thalidomide, and dexamethasone (CYCLONE) in patients with newly diagnosed multiple myeloma.

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Background: Carfilzomib is a proteasome inhibitor that irreversibly binds its target with favorable toxicity profile that has shown significant activity in relapsed multiple myeloma (MM). Here we used carfilzomib as the center of a 4 drug induction regimen designed for MM patients pre stem cell transplant (SCT). **Methods:** We conducted a phase I safety run in 6 patients with no DLT observed before expanding to phase II. The phase II regimen is shown below. Treatment was for 4 cycles with expected SCT post induction. For the phase II portion of this trial, the primary endpoint is the proportion of patients who have $\geq$ very good partial response to treatment. All patients received herpes zoster prophylaxis and ASA daily. **Results:** Twenty seven patients were enrolled. Median age was 65 (range 27-74). ORR for evaluable patients (n=17) at phase II dosing is 100%: CR 35%, VGPR 48%, PR 18% after 4 cycles of CYCLONE. Grade 3 toxicity was reported in 52% of patients and 14% experienced a grade 4 toxicity. Grade 3/4 toxicities occurring in $>$5% of patients included fatigue, neutropenia, lymphopenia, thromboembolism, myopathy. Toxicities of any grade seen in $>$20% of patients included fatigue, constipation, lethargy, thrombocytopenia, somnolence, creatinine increased, malaise. Four patients (20%) developed grade 1 sensory neuropathy; no higher grade or painful neuropathy was evident. All patients are alive. All patients advancing to SCT successfully collected stem cells. One patient with t(4;14) disease who was not transplanted has progressed. 94% remain progression free. **Conclusions:** The 4 drug CYCLONE regimen has remarkable efficacy (83% $\geq$VGPR) and manageable toxicity in newly diagnosed patients with multiple myeloma. Especially notable was the low incidence of neuropathy and depth of response (CR 35%) after only 4 cycles. Given the relative lack of toxicity an extension of this regimen at higher doses of carfilzomib (20/45mg/m^2) has been initiated.

Agent	Dose level	Route	Day	Cycle length
Carfilzomib	20 mg/m^2 cycle 1 27mg/m^2 $\geq$ cycle 2	IV	1, 2, 8, 9, 15, 16	28 days
Thalidomide	100 mg	Orally	1-28	28 days
Cyclophosphamide	300 mg/m^2	Orally	1,8,15	28 days
Dexamethasone	40 mg	Orally	1,8,15,22	28 days

8011 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

Stringent complete response (sCR) in patients (pts) with newly diagnosed multiple myeloma (NDMM) treated with carfilzomib (CFZ), lenalidomide (LEN), and dexamethasone (DEX).

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Background: Combination treatment (tx) with CFZ, LEN, and DEX (CRd) is well tolerated and highly active in NDMM. In a phase 1/2 study, CRd provided rapid reduction of disease by 68% after cycle (C) 1 and 94% ≥partial response (PR) at a median of 8C, including 65% ≥very good PR and 53% ≥near CR (nCR), which improved to 79% ≥nCR after C12 (ASH 2011, Abstr 631). Here, we examine the clinical significance of the response rates with longer follow-up. **Methods:** Pts with NDMM were treated in 28-day (d) C with CFZ 20–36 mg/m^2 IV (d1, 2, 8, 9, 15, 16), LEN 25 mg PO (d1–21) and DEX 40/20 mg PO weekly (C1–4/5–8). After C4, autologous stem cell transplant (ASCT) candidates achieving ≥PR could collect stem cells but then continued CRd with the option to proceed to ASCT. After C8, pts received CRd maintenance, using the last tolerated doses, with LEN/DEX at the same schedule but a modified CFZ schedule (d1, 2, 15, 16). Response was assessed by IMWG criteria plus nCR. **Results:** As of Nov 30, 2011, median follow-up was 14 mo (range 4–25) with 33/53 (62%) pts achieving ≥nCR and 42% sCR. After a median of 13C (range 1–25), 36 pts completed C8 and continued CRd maintenance, 64% achieving sCR. 20/22 pts in CR evaluated for minimal residual disease (MRD) by multiparameter flow cytometry had no MRD. Progression-free survival (PFS) rate was 97% at 12 and 92% at 24 mo. All pts who achieved sCR have maintained response for a median of 9 mo (range 1–20). Extended CRd tx was well tolerated. During CRd maintenance, the most common toxicities (all grades) were lymphopenia (30%), leukopenia (26%), and fatigue (25%), and peripheral neuropathy remained limited (11%, all G1/2). There were no tx discontinuations due to toxicity during maintenance and limited dose modifications (CFZ 19%, LEN 28%, DEX 31%). **Conclusions:** CRd is highly active in NDMM, providing rapid and deep responses. Extended tx was well tolerated and resulted in improved depth of response with a high sCR rate and a significant proportion of pts without evidence of MRD. Responses were durable with very promising PFS. All pts who achieved sCR remained on CRd with sustained sCR. These results compare favorably to other frontline regimens.

8012 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

PANORAMA 2: A phase II study of panobinostat in combination with bortezomib and dexamethasone in patients with relapsed and bortezomib-refractory multiple myeloma.

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Background: Patients (pts) with multiple myeloma (MM) refractory to bortezomib (BTZ) and an immunomodulatory drug have limited treatment options and a poor prognosis. In a phase I study of pts with relapsed or relapsed/refractory MM treated with panobinostat (PAN) + BTZ, clinical responses were observed overall and in pts with BTZ-refractory disease. We report results in PANORAMA 2, a trial in relapsed and BTZ-refractory pts. **Methods:** PANORAMA 2 is a single-arm, phase II study of PAN + BTZ + dexamethasone (Dex) in pts with relapsed and BTZ-refractory MM. Treatment phase 1 (TP1) consists of eight 3-week cycles of oral PAN + intravenous BTZ + oral Dex. Pts demonstrating clinical benefit enter treatment phase 2 (TP2) which consists of four 6-week cycles of PAN + BTZ + Dex. The primary endpoint is overall response (≥ partial response [PR]) in TP1. **Results:** Fifty-five pts with BTZ-refractory MM were enrolled with 10 pts ongoing and 28 in follow-up. The median age was 61 years (range 41-88 years). Pts were heavily pretreated: the median number of prior regimens was 4 (range 2-11), and most pts (64%) received prior autologous stem cell transplant. Twenty-seven (49%) and 36 (65%) pts had BTZ and Dex in their most recent prior line of therapy, respectively. Eighteen pts achieved ≥ PR for an overall response rate of 33% (1 near complete response and 17 PR), and 13 pts achieved MR for a clinical benefit rate of 56%. Three pts achieved a VGPR. Eighteen pts completed TP1 and entered TP2, and 2 have completed ≥ 12 cycles. Common adverse events (AEs) of any grade included thrombocytopenia (66%), fatigue (64%), diarrhea (62%), nausea (58%), dyspnea (40%), anemia (38%), decreased appetite (36%), and dizziness (36%). Common grade 3/4 AEs included thrombocytopenia (58%), fatigue (17%), anemia (15%), pneumonia (15%), neutropenia (13%), and diarrhea (13%). Only 1 pt (2%) experienced grade 3/4 peripheral neuropathy. **Conclusions:** PAN synergizes with BTZ in recapturing responses in heavily pretreated, BTZ-refractory MM pts. The combination of PAN and BTZ is a promising treatment for pts with BTZ-refractory MM that is generally well tolerated, with several pts receiving therapy long term.

8013 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

Phase I trial of obatoclax mesylate in combination with bortezomib for treatment of relapsed multiple myeloma.

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Background: Obatoclax mesylate (GX15-070MS) is a BH3 mimetic that inhibits Bcl-2 protein family members including MCL-1, a dominant target in myeloma (MM). Obatoclax (OBX) inhibited viability of 14 MM cell lines (mean IC_{50} 215 nM) and primary MM samples while exhibiting pre clinical synergy with bortezomib (BTZ). Sensitivity correlated with basal levels of Mcl-1 and Bcl-$_{XL,}$ but not Bcl2, Bim, Bax or Bak expression. **Methods:** We report a phase I trial of OBX in combination with BTZ. Eligibility required measureable disease, $>$ 1 prior MM therapy, $\leq$10 cycles of prior BTZ and did not progress on prior BTZ therapy, creatinine $\leq$2 ULN. Starting dose level 1 was OBX 14 mg/m^2 24-hour continuous iv. infusion days 1, 8, 15 of a 21-day cycle. BTZ given at 1.3mg/m^2 iv. days 1, 4, 8 and 11. After protocol amendment OBX level 1 dosing was 30 mg/m^2, level 2 was 40 mg/m^2 IV both by continuous 3 hour infusion days 1, 8 and 15 on a 21 day schedule. Pre med. with famotidine was required. **Results:** Eleven patients were accrued, median age 62 (range: 46-77), median time from diagnosis was 4.7 years. Median of 2.5 cycles (range: 1-10). Median follow-up for patients still alive is 11.6 months (range: 0.9-35.5). At dose level 1, there were 2 DLTs. After amendment 8 patients were accrued (3 hour infusion): 4 at amended dose level 1 and 4 at dose level 2. All patients are now off treatment. 10 patients are evaluable for response: 2 patients at original dose level 1 (2 PR), 3 patients at dose level 1 (2 PR, 1 MR), no patients at dose level 2 responded: overall PR of 40%, clinical benefit response in 50% (95% CI: 19-81%). 6 patients had disease progression and 2 patients died. 4 DLTs were seen: at original dose level 1 grade 4 thrombocytopenia and delay of therapy $>$ 15 days. At dose level 2, 1 patient had grade 3 somnolence, a 2nd patient grade 3 euphoria and grade 4 thrombocytopenia. No DLTs were seen at amended dose level 1. Common adverse events of any grade included GI, hematologic and neurologic e.g. euphoria, decreased level of consciousness, psychosis, speech. **Conclusions:** In summary MTD is OBX 30mg/m^2 by 3 hour iv infusion once weekly, BTZ 1.3 mg/m^2 days 1,4,8, and 11. Major toxicities were central neurologic and hematologic. This P2C consortium study was supported by NCI N01-CM62205.

8014 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

Bendamustine, bortezomib, and dexamethasone (BVD) in elderly patients with relapsed/refractory multiple myeloma (RRMM): The Intergroupe Francophone du Myélome (IFM) 2009-01 protocol.

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Background: Bortezomib (V) plus dexamethasone (D) is a treatment of choice of RRMM. In small series, the addition of an alkylator was beneficial. Bendamustine (B) showed a high activity in advanced MM. The IFM 2009-01 trial evaluates the combination of B, V and D in elderly pts with MM progressive on or after 1st line therapy. **Methods:** We conducted a phase 2 trial combining B 70 mg/m^2 D1-8, V 1.3 mg/m^2 D1-8-15-22 and D 20 mg D1-8-15-22 every 28 days. 4 cycles were administered. In responders (PR or better), 2 additional cycles were provided followed by a maintenance phase with 6 cycles given every 2 months. Inclusion criteria were progression on or after 1 prior line of therapy, measurable disease, PS ECOG <3, ANC $> 1.5x10^9$/l, platelets $> 100x10^9$/l, creatinine < 250 mcmol/l, AST and ALT < 3xULN. Pts with prior exposure to bortezomib were excluded. Response was evaluated according to IMWG criteria. Primary end point was response at end of cycle 4, secondary objectives overall response rate (ORR), progression-free survival (PFS), overall survival (OS) and toxicity. **Results:** The present analysis was restricted to the first 4 cycles. From 03/2010 to 07/2011, 73 pts were included, median age 75.8 years (range 66-86). Median time from diagnosis to inclusion was 29 months. All pts received only 1 prior therapy: MP in 12, MP-thalidomide in 44, lenalidomide-dexamethasone (LD) in 14, other in 3. 42 pts (57.5%) were responders at end of cycle 4 [CR: 8 (10.9%), VGPR: 9 (12.3%), PR: 25 (34.2%), SD: 10 (13.6%), progression: 11 (15%), early discontinuation: 10 (13.6%)]. 6pts/10 were in PR and 1pt/10 in VGPR at time of discontinuation. ORR was 67.1% (49/73 pts). 11 pts died (MM: 6, sepsis: 4, renal failure: 1). Adverse events grade 3-4 were neutropenia: 16 pts, thrombocytopenia: 7 pts, sepsis: 12 pts, gastro-intestinal: 8 pts, anaphylaxis: 1 pt. 2 pts had DVT. Peripheral neuropathy grade>1 occurred in 9 pts, all grade 2. Treatment was stopped in 20 pts (lack of efficacy: 11, toxicity: 9). **Conclusions:** These results compare favorably with those achieved with VD or LD. The triplet BVD combination is very effective and tolerable in elderly pts with MM in 1st progression.

8015 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

Efficacy and side-effect profile of long-term bisphosphonate therapy in patients (pts) with multiple myeloma (MM): MRC myeloma IX study results.

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Background: Bisphosphonates (BPs) are recommended in pts with osteolytic lesions from MM. However, data on the long-term efficacy and safety of BPs beyond 2 y is somewhat limited. The MRC Myeloma IX study has already revealed significant overall survival (OS) and progression-free survival (PFS) benefits for zoledronic acid (ZOL) over clodronate (CLO) in MM pts (N = 1960) initiating chemotherapy (Morgan GJ, et al. *Lancet.* 2010). We now report the efficacy and safety of BP therapy with long-term follow-up. **Methods:** Newly diagnosed MM pts were randomized to ZOL (4 mg IV q 21-28 days) or CLO (1600 mg/day PO) plus antimyeloma therapy. BPs continued at least until disease progression. PFS and OS were estimated using Kaplan-Meier methodology. Hazard ratios (HRs) were calculated using stratified Cox models. Adverse events (AEs) were monitored continuously and analyzed using cumulative incidence functions. **Results:** At a median follow-up of 5.8 y in 1960 evaluable pts, ZOL improved PFS (HR = 0.88; $P = .01$) and OS (HR = 0.88; $P = .03$) vs CLO. Both BPs were generally well tolerated, and acute renal failure events were similar between groups (ZOL 5.2% vs CLO 5.8% at 2 y, with incidence plateaued thereafter). Overall incidence of confirmed osteonecrosis of the jaw (ONJ) has remained low (ZOL 3.7% vs CLO 0.5%; $P < .0001$). ONJ incidence was lower among pts receiving thalidomide-containing regimens (1.4%) vs no thalidomide (2.76%; $P = .041$). Events were generally low-grade, most occurred between 8 and 30 mo (median time to ONJ = 23.7 mo), and cumulative incidence plateaued at ~36 mo. Ten pts had data on ONJ recovery: complete recovery in 4 pts, improvement in 2 pts, no change in 3 pts in the ZOL group; and no change in 1 CLO pt. Dental surgery or trauma preceded ONJ in 6 ZOL pts. **Conclusions:** ZOL provided sustained PFS and OS improvements vs CLO during long-term therapy in the MRC Myeloma IX study. Overall incidence of AEs was similar between groups, with no notable changes during long-term therapy. ONJ incidence remained low during long-term (> 2.5 y) therapy and was reduced in pts receiving thalidomide (possibly because of anticytokine effects of this agent).

Pomalidomide (POM) with or without low-dose dexamethasone (LoDEX) in patients (pts) with relapsed/refractory multiple myeloma (RRMM): Outcomes in pts refractory to lenalidomide (LEN) and/or bortezomib (BORT).

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Background: Response and survival outcomesare poor in pts with RRMM who are refractory to BORT and immunomodulatory drugs. POM+LoDEX has demonstrated activity in pts with advanced multiple myeloma who have received multiple lines of therapy. This analysis evaluates outcomes in pts with disease refractory to LEN, BORT, or both, as well in pts with disease refractory to both LEN and BORT who had received prior transplant. **Methods:** In the MM-002 phase II trial, pts received POM (4 mg/day on days 1–21 of each 28-day cycle) alone (n=108) or in combination with LoDEX (40 mg/week) (n=113). Refractory disease was defined as documented progression during treatment or within 60 days of the last dose of treatment. Response rates were assessed using European Group for Bone Marrow Transplantation (EBMT) criteria by independent adjudication committee. **Results:** Patients who received POM+LoDEX were refractory to LEN (77%), BORT (73%), or both (61%). Forty-two percent were refractory to both LEN and BORT and had received prior transplant. Overall, 20% of pts achieved ≥ PR, median PFS was 3.5 months, and 1-year survival rate was 59%. Response rates and duration were comparable in pts with disease refractory to LEN, BORT, or both, and in pts who had received prior transplant (response rate 25-34%, median duration of response 5.7-7 months). Survival outcomes were similar across the groups (median PFS 3.8-4.6 months; 1-year survival rate 60-67%). **Conclusions:** POM, given at 4 mg/day on days 1–21 of each 28-day cycle in combination with LoDEX, 40 mg/week, is effective in pts with RRMM refractory to LEN, BORT, or both, and including those with prior transplant. These results suggest a lack of cross-resistance between POM and LEN, and confirm activity not only in BORT-refractory pts but also those for whom transplant has failed.

	Refractory to:			
	LEN n=87	BORT n=82	LEN and BORT n=69	LEN and BORT with prior transplant n=47
POM+LoDEX				
≥ PR, %	25	29	28	34
≥ MR, %	41	46	46	53
Median duration of response, months*	7	5.8	6.2	5.7
Median PFS, months	3.8	3.8	3.8	4.6
1-year survival rate, %	65	60	61	67

* In patients achieving ≥PR.

8017 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

Phase I study of twice-weekly dosing of the investigational oral proteasome inhibitor MLN9708 in patients (pts) with relapsed and/or refractory multiple myeloma (MM).

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Background: MLN9708 is the first oral proteasome inhibitor to enter clinical investigation in MM. This study (NCT00932698) assessed safety, MTD, and response rate with twice-weekly oral MLN9708 in pts with relapsed and/or refractory MM, and characterized plasma pharmacokinetics (PK) and blood pharmacodynamics. **Methods:** Pts aged ≥18 yrs with measurable MM received MLN9708 on d 1, 4, 8, and 11 of 21-d cycles. In the dose-escalation phase, pts required ≥2 prior therapies (including bortezomib, thalidomide/lenalidomide, and corticosteroids). At the MTD (2.0 mg/m^2), pts were enrolled to relapsed and refractory [RR], bortezomib-relapsed [VR], proteasome-inhibitor [PI] naïve, and carfilzomib [CZ] expansion cohorts. **Results:** 57 pts (53% M) were enrolled, 37 to the expansion cohorts (16 RR, 14 VR, 6 PI naïve, 1 CZ). Median age was 65 yrs (range 50-86). Median number of prior lines of therapy was 4 (range 1-28); 88%, 84%, 61%, and 5% had prior bortezomib, lenalidomide, thalidomide, and carfilzomib, respectively. Pts have received a median of 3 cycles (range 1-24) to date (data cut-off Dec 1, 2011); 7 (12%) have received ≥13 cycles. Drug-related AEs were seen in 89% of pts, including fatigue (46%), thrombocytopenia (40%), and nausea (30%); 63% had drug-related grade ≥3 AEs, including thrombocytopenia (33%), neutropenia (14%), fatigue (9%), and rash (7%). Only 6 (11%) pts had drug-related peripheral neuropathy (PN; no grade ≥3). 7 pts discontinued due to AEs. 2 pts died on study, due to PD and an unrelated cardiac disorder. Of 46 response-evaluable pts, 6 have achieved ≥PR, with 1 sCR (PI naïve cohort) and 5 PRs (2 in dose-escalation, 1 in RR, 2 in VR cohorts), and 1 VR pt has achieved MR, with duration of disease control of up to 18.6 mo. PK analyses showed MLN2238 (biologically active hydrolysis product) has linear plasma PK (0.8-2.23 mg/m^2), T_{max} of 0.5-1.25 hr, and terminal half-life of 4-6 d. A dose-dependent increase in whole blood 20S proteasome inhibition was observed. **Conclusions:** Current data suggest MLN9708 has clinical activity in heavily pretreated MM pts, with durable responses/disease control, and is generally well tolerated with infrequent low-grade PN.

8018^ **Clinical Science Symposium, Mon, 11:30 AM-1:00 PM**

Phase II, randomized, double blind, placebo-controlled study comparing siltuximab plus bortezomib versus bortezomib alone in pts with relapsed/refractory multiple myeloma.

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Background: Preclinical studies of siltuximab (S), a chimeric anti-IL-6 mAb, in combination with bortezomib (B) indicate an additive to synergistic effect in multiple myeloma (MM) cell lines. This randomized study evaluated the safety and efficacy of S+B compared with placebo (plc)+B in pts with relapsed/refractory MM after 1−3 prior tx lines, measurable disease but no prior B exposure. **Methods:** 286 pts were randomized 1:1 to S+B: B+plc. S 6 mg/kg or plc was given IV q2w. B 1.3 mg/m^2 was given IV on d 1, 4, 8, 11, 22, 25, 29, 32 for a max of 4 of 42-d cycles and then reduced to q1w for 35-d cycles. B was stopped for pts with PD/intolerability, and high dose oral dexamethasone (dex) 40 mg could then be started qd on d 1−4, 9−12, 17−20 for a max of 4 of 28-d cycles and on d 1−4 of subsequent cycles until PD, while S/plc continued. Primary endpoint was PFS by EBMT criteria censored at the start of dex/subsequent tx. Secondary endpoints included overall response rate (ORR), OS, and safety before dex. **Results:** 142 and 144 pts received S+B and B+plc, respectively. Baseline demographics and disease characteristics were well balanced across S+B and B+plc, except for age (median 64 vs. 61 yrs) and myeloma type (IgG 65 vs. 71%, IgA 27 vs. 20%). Median tx duration was 5.1 mo in both grps. Median PFS was 8.1 mo in S+B and 7.6 mo in B+plc (HR 0.869, p = 0.345). ORR (CR+PR) was 55% in pts on S+B and 47% on B+plc (p = 0.213); CR rates were 11 and 7% (p = 0.342), respectively. With 24.5 mo median follow up, median OS was 30.8 mo for S+B and 36.9 mo for B+plc (HR 1.353 for S+B, p = 0.103). Fewer pts on S+B than B+plc moved to dex (23 vs. 31%) and had subsequent SCT (5 vs. 11%). Gr ≥3 AEs occurred in 91% on S+B and 74% on B+plc. Common gr ≥3 AEs in S+B were neutropenia (49%), thrombocytopenia (48%), leukopenia (14%). SAEs occurred in 29% on S+B and 24% on B+plc. Death occurred within 30 d of last study agent administration pre-dex in 8% on S+B and 5% on B+plc. **Conclusions:** The combination of S+B had higher response rates but did not prolong survival compared with B+plc. A negative survival trend heavily influenced by differences in dex and SCT rescue was noted. S+B appears to be generally well tolerated but had a higher incidence of hematologic AEs.

8019 **Clinical Science Symposium, Mon, 11:30 AM-1:00 PM**

Daratumumab, a CD38 mab, for the treatment of relapsed/refractory multiple myeloma patients: Preliminary efficacy data from a multicenter phase I/II study.

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Background: Daratumumab (HuMax-CD38) is a human CD38 monoclonal antibody with broad-spectrum killing activity; it effectively kills CD38-expressing tumor cells via antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC) and apoptosis. From an ongoing first-in-human (FIH) dose-escalation study (ClinicalTrials.gov CT00574288), it has been shown that daratumumab has an acceptable safety profile (Gimsing: ASH 2011 abstract 1873). The objectives of this FIH study are to establish the safety profile and MTD. In addition efficacy is evaluated. **Methods:** Pts $\geq$18 years and previously diagnosed with MM requiring systemic therapy and considered relapsed or refractory (RR) to at least two different prior lines of therapy and not eligible for salvage ASCT were enrolled. The design of this study encompasses an accelerated dose-escalation based on a classical 3+3 design. Daratumumab is administrated over a 9 wk period encompassing 2 pre-doses and 7 full-doses. The doses range from 0.005 mg/kg to 24 mg/kg. The decision to dose escalate is based on recommendation by an external Independent Data Monitoring Committee. Evaluation of efficacy data was according to Rajkumar (Blood 2011;117: 4691-5). The results presented in this abstract are based on preliminary data analyzed before database lock. **Results:** Data from 23 pts including the 4 mg/kg group are collected. Preliminary efficacy evaluation is based on best paraprotein response as reflected by change in serum and/or urine M-component. For groups $\leq$ 1 mg/kg, 3/17 pts achieved a reduction in serum M-component (12%, 14%, 19%), in the 2 mg/kg group, 1/3 pts had a reduction in urine M-component (55%), and in the 4 mg/kg group, 3/3 pts had a reduction in the serum M-component of 49%, 55, and 64%, respectively. In the 4 mg/kg group a marked reduction in the percentage of plasma cells in the bone marrow was seen in all pts (80%, 89%, and 97%). The toxicity was manageable. **Conclusions:** Daratumumab treatment resulted in reductions in M-component and bone marrow plasma cells in pts with RR MM. Toxicity has been manageable. Additional data will be presented at the meeting.

8020 **Clinical Science Symposium, Mon, 11:30 AM-1:00 PM**

A randomized phase II study of elotuzumab with lenalidomide and low-dose dexamethasone in patients with relapsed/refractory multiple myeloma.

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Background: Elotuzumab (Elo) is a humanized monoclonal IgG1 antibody targeting CS1, a cell surface glycoprotein. CS1 is highly expressed on >95% of multiple myeloma (MM) cells, with lower expression on natural killer cells and little to no expression on normal tissues. A phase 1 trial of Elo plus lenalidomide and low-dose dexamethasone (Elo/Len/Dex) demonstrated an 82% objective response rate (ORR) in patients (pts) with relapsed/refractory (RR) MM (Lonial et al. J Clin Oncol, in press). **Methods:** In this phase 2 study, previously treated pts with MM were randomized to Elo 10 or 20 mg/kg IV (days 1, 8, 15, and 22 every 28-days in first 2 cycles and days 1 and 15 of subsequent cycles), Len 25 mg PO (days 1-21) and Dex 40 mg PO weekly. Prophylaxis for infusion-related reactions (IRs) was administered prior to each Elo infusion. Treatment continued until disease progression or unacceptable toxicity. The primary objective was to assess efficacy (ORR ≥partial response [PR]) according to IMWG criteria. **Results:** Among73 pts (median age 63 years; range, 39-82), 55% had received ≥2 prior therapies, 60% had received prior bortezomib, and 62% prior thalidomide. ORR was 82% for all pts including 48% ≥ very good PR (VGPR). The ORRs were 92% in the 10 mg/kg group (n=36) and 73% in the 20 mg/kg group (n=37). Median time to best response was 2.2 months (range, 0.7-17.5). After a median follow-up of 14.1 months, median progression-free survival (PFS) has not been reached, with PFS rates of 75% (10 mg/kg) and 65% (20 mg/kg). Elo/Len/Dex also showed encouraging activity in pts with high-risk cytogenetics (ORR 80%) and/or Stage 2-3 MM (ORR 81%). The most common grade 3/4 toxicities were neutropenia (16%), lymphopenia (16%), and thrombocytopenia (16%). Investigator-designated IRs were reported in 12% of pts (all grades); 1 pt (1.4%) had grade 3 IR (rash). **Conclusions:** Elo/Len/Dex was generally well tolerated and resulted in a high ORR, and PFS not reached after 14.1 months of median follow-up in pts with RR MM. Updated results will be presented at the meeting. Two phase 3 trials of 10 mg/kg Elo/Len/Dex are ongoing in newly diagnosed MM (ELOQUENT1; CA204-006; NCT01335399) and RR MM (ELOQUENT2; CA204-004; NCT01239797).

8021 **Poster Discussion Session (Board #1), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM**

R-CHOP14 compared to R-CHOP21 in elderly patients with diffuse large B-cell lymphoma (DLBCL): Final analysis of the LNH03-6B GELA study.

Richard Delarue, Herve Tilly, Gilles A. Salles, Catherine Thieblemont, Nicolas Mounier, Thierry Jo Molina, Corinne Haioun, Andre Bosly; Hôpital Necker, Paris, France; Centre Henri Becquerel, Rouen, France; Hospices Civils de Lyon and Universite de Lyon, Pierre-Bénite, France; Saint-Louis Hospital, Paris, France; CHU l'Archet, Nice, France; Hotel Dieu, Paris, France; CHU Henri Mondor-Chenevier, Creteil, France; UCL Mont-Godinne, Yvoir, Belgium

Background: In 2000, the GELA established a new standard for elderly patients with DLBCL, demonstrating survival advantage of R-CHOP21 over CHOP21. Based on RICOVER-60 results, the DSHNHL proposed R-CHOP14 as a standard. Comparison between both regimens is lacking. We report the results of the final analysis of the randomized phase III trial LNH03-6B, with a median follow-up of 56 months. **Methods:** Pts between 60 and 80 years old with DLBCL and aaIPI≥1 were eligible. They were randomized between R-CHOP14 and R-CHOP21 for 8 cycles. G-CSF prophylaxis was given according to physician decision. Primary objective was to evaluate the efficacy of R-CHOP14 compared to R-CHOP21 as measured by the EFS. **Results:** 602 pts were randomized, 600 were evaluable, 304 with R-CHOP14 and 296 with R-CHOP21. Median age was 70 years. Pts characteristics were similar between the two arms. Percentage of pts with baseline IPI3-5 was 72% in R-CHOP14 arm and 78% in R-CHOP21 arm. Median interval between 2 cycles was 14 d in R-CHOP14 arm and 21 d in R-CHOP21 arm. In R-CHOP14 arms, 89% of cycles were administered with G-CSF. Median dose-intensity for R-CHOP14 arm was 88% for cyclophosphamide and doxorubicin. There was no difference in median dose-intensity according to G-CSF administration at first cycle. Response rate (CR+CRu) was 71% in R-CHOP14 arm and 74% in R-CHOP21 arm (p=0.42). The 3-y EFS was 56% in R-CHOP14 arm and 60% in R-CHOP21 (HR 1.04; CI95% 0.82-1.31; p=0.79). Moreover, there is no difference between both arms regarding 3-y PFS (60% vs. 62%; HR 0.99; CI95% 0.78-1.26; p=0.90), DFS (72% vs. 67%; HR 0.80; CI95% 0.58-1.10; p=0.80) and OS (69% vs. 72%; HR 0.96; CI95% 0.73-1.26; p=0.75). Finally, percentage of patients with at least one serious adverse event (R-CHOP14: 51%; R-CHOP21: 47%) and rate of toxic death (4.6% and 4.7% respectively) were similar. **Conclusions:** Results of the final analysis of LNH03-6B demonstrate similar efficacy and safety profile between R-CHOP14 and R-CHOP21.

8022 **Poster Discussion Session (Board #2), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM**

Role of radiotherapy for elderly DLBCL patients in the rituximab (R) era: Final results of the RICOVER-60-no-rx study of the DSHNHL.

Gerhard Held, Niels Murawski, Marita Ziepert, Viola Poeschel, Carsten Zwick, Marcel Reiser, Sibylla Wilhelm, Tobias Gaska, Michael Heike, Joerg Schubert, Norbert Schmitz, Markus Loeffler, Christian Ruebe, Michael Pfreundschuh, German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL); Saarland University Hospital, Homburg, Germany; Institute for Medical Informatics, Statistics and Epidemiology, Leipzig University, Leipzig, Germany; University Hospital, Cologne, Germany; Hospital Karlsruhe, Karlsruhe, Germany; St. Marien Hospital, Siegen, Germany; Hospital Dortmund, Dortmund, Germany; Asklepios Hospital St. Georg, Hamburg, Germany

Background: 117/306 (38%) of the total of 1,222 elderly (61-80 y) DLBCL pts. treated in RICOVER-60 with 6xR-CHOP-14+2R were assigned to receive additional radiotherapy (Rx) to bulky disease (Pfreundschuh et al., *Lancet Oncol. 2008*). To study the relevance of Rx to bulky disease (Bx), 166 pts. were prospectively treated without Rx in the R-CHOP-14-noRx amendment of RICOVER-60. **Methods:** The outcome of 166 R-CHOP-14-noRx patients was compared with the 306 patients who had received 6xR-CHOP-14+2R plus radiotherapy to Bx (≥7.5 cm) in RICOVER-60. Methods: The outcome of 166 R-CHOP-14-noRx patients was compared with the 306 patients who had received 6xR-CHOP-14+2R plus radiotherapy to Bx (≥7.5 cm) in RICOVER-60. **Results:** 164/166 R-CHOP-noRx patients are evaluable (median observation: 39 mos). Patients in R-CHOP-noRx were older (71 vs. 69 y.; median; p=0.018), more frequently in advanced stages (60% vs. 50%; p=0.037), and with extranodal involvement (63% vs. 53%; p=0.024), while Bx was more frequent in R-CHOP-14-Rx (38% vs. 29%; p=0.038). Overall response to therapy, EFS and OS were similar in the two studies adjusting for the prognostic imbalances between the cohorts. Patients with Bx who received received additional radiotherapy to Bx in R-CHOP-14-Rx had a better 3-year EFS (80% vs. 54%; p=0.001), a better PFS (88% vs. 62%; p<0.001), and a better OS (90% vs. 65%; p=0.001) compared to R-CHOP-14-noRx. This was due the worse outcome of pts. with Bx in R-CHOP-14-noRx not achieving CR or CRu after 6xR-CHOP, since there was no difference in 3-year EFS in patients with Bx in CR or CRu after 6xR-CHOP-14 with and without additional radiotherapy (3-year EFS and PFS: 84% vs. 75%; p=0.430); OS 87% vs. 79%; p=0.839). **Conclusions:** In the R era, radiotherapy to bulky disease does not improve the outcome of elderly pts. in CR/CRu after completion of R-CHOP-14 immunochemotherapy, but appears to be beneficial for pts. with Bx not achieving CR/Cru. By restricting Bx radiotherapy to patients not achieving a CR/CRu, 43% of the patients with Bx could be spared radiotherapy. Supported by Deutsche Krebshilfe.

8023 Poster Discussion Session (Board #3), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

A multicenter phase II study of bendamustine with rituximab in patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL).

Michinori Ogura, Kiyoshi Ando, Nozomi Niitsu, Seok Jin Kim, Ken Ohmachi, Naoki Takahashi, Toshiki Uchida, Naoto Takahashi, Naokuni Uike, Hyeon Seok Eom, Yee Soo Chae, Takashi Terauchi, Ukihide Tateishi, Mitsuaki Tatsumi, Won Seog Kim, Cheolwon Suh, Kensei Tobinai, Japanese and Korean Bendamustine Lymphoma Study Group; Department of Hematology and Oncology, Nagoya Daini Red Cross Hospital, Aichi, Japan; Department of Hematology and Oncology, Tokai University Hospital, Kanagawa, Japan; Department of Hematology, Saitama Medical University International Medical Center, Saitama, Japan; Hematology-Oncology, Samsung Medical Center, Seoul, South Korea; Department of Hematology, Akita University Hospital, Akita, Japan; Hematology, National Kyusyu Cancer Center, Fukuoka, Japan; Hematology-Oncology Clinic, Center for Specific Organs Cancer, National Cancer Center, Gyeonggi-do, South Korea; Hematology-Oncology Department, Kyungpook National University Hospital, Daegu, South Korea; Cancer Screening Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, Japan; Department of Radiology, Yokohama City University Hospital, Kanagawa, Japan; Diagnostic and Interventional Radiology, Osaka University Hospital, Osaka, Japan; Department of Oncology, Asan Medical Center, Seoul, South Korea; Department of Hematology, and Hematopoietic Stem Cell Transplantation, National Cancer Center Hospital, Tokyo, Japan

Background: Effective salvage therapies are needed in patients (pts) with relapsed/refractory DLBCL after R-CHOP. Therapy with bendamustine plus rituximab (B-R) was well tolerated and effective in the preceding phase I study in relapsed/refractory aggressive B-cell non-Hodgkin lymphoma, including DLBCL. This phase II study assessed the efficacy and safety of B-R in pts with relapsed/refractory DLBCL. **Methods:** Pts with histologically confirmed DLBCL (excluding transformed disease) and 1-3 prior therapies received rituximab 375 mg/m^2 IV on day 1 and bendamustine 120 mg/m^2 IV on days 2 and 3 of each 21-day cycle, for up to 6 cycles. Recovery of neutrophil count to $\geq$1,000/mm^3 and platelet count to $\geq$75,000/mm^3 were required prior to the start of each cycle; treatment delays $>$2 weeks resulted in discontinuation. The primary endpoint was overall response rate (ORR); secondary endpoints included complete response (CR) rate, progression-free survival (PFS), and safety. **Results:** A total of 63 pts were enrolled; data from 59 pts were available. Median age was 67 (range, 36-75) years with 37 pts over 65 years. The majority of pts (64.4%) had 1 prior therapy; 57 pts (96.6%) were previously treated with rituximab-containing combination chemotherapy and 8 (13.6%) had prior auto-PBSCT. Pts received a median of 4 (range, 1-6) treatment cycles. Sixteen (27.1%) pts completed 6 treatment cycles; most common reasons for early discontinuation were disease progression (n=15) and failure to meet criteria to start the next cycle (n=13). Among 59 pts evaluable for response, ORR was 62.7% with a 37.3% CR rate. The median PFS was 200 days (95% CI, 109-410). Most common grade 3/4 adverse events (AEs) included CD4 lymphocytes decreased (66.1%), neutropenia (54.2%), and thrombocytopenia (10.2%). Four (6.8%) pts discontinued due to serious AEs (cytomegalovirus infection, infection, pneumonia, and pneumonia/respiratory failure). **Conclusions:** B-R demonstrated promising activity in pts with relapsed/refractory DLBCL. Toxicity was primarily hematologic and generally manageable. These results suggest that B-R is a promising salvage regimen for pts with relapsed/refractory DLBCL after R-CHOP.

8024 Poster Discussion Session (Board #4), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Evidence for rituximab (R) underdosing in subpopulations of elderly patients with DLBC: Results of the RICOVER-60 study of the DSHNHL.

Michael Pfreundschuh, Carsten Mueller, Samira Zeynalova, Gerhard Held, Viola Poeschel, Carsten Zwick, Marcel Reiser, Eva Lengfelder, Hjalmar B. Steinhauer, Christina Limmroth, Norbert Schmitz, Niels Murawski, German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL); Saarland University Hospital, Homburg, Germany; University Hospital, Cologne, Germany; Institute for Medical Informatics, Statistics and Epidemiology, Leipzig University, Leipzig, Germany; University Hospital, Mannheim, Germany; Carl-Thiem-Hosptital (CTK), Cottbus, Germany; University Hospital Grosshadern, Munich, Germany; Asklepios Hospital St. Georg, Hamburg, Germany

Background: Gender and weight independently influence R clearance and R serum elimination half life (Mueller et al., Blood 2012). To investigate whether the differences in R pharmacokinetics translate into different outcomes, we analyzed elderly patients (pts) with different R pharmacokinetics treated in the RICOVER-60 study. **Methods:** 1222 elderly pts. (61-80 y) were randomized to receive 6 or 8 cycles of CHOP-14 with or without R given on days 1, 15, 29, 43, 57, 71, 85, and 99. For this study, subgroup analyses were performed for pts with faster R clearance: elderly male (vs. female) pts and elderly weighty (upper quartile: >77kg) vs. slim (lower quartile: ≤60 kg) female pts. **Results:** Elderly females had a slower R clearance (8.21 ml/h vs. 12.68 ml/h; p=0.003) and a prolonged R half life compared to men ($t_{1/2\beta}$=30.7 vs. $t_{1/2\beta}$=24.7 d; p=0.003). Female pts had a higher 3-year PFS (68% vs. 61%; p=0.062) and OS (74% vs. 68% p=0.086). The differences in outcome were due to a greater outcome improvement by the addition of R in females: the difference in 3-year PFS between female and male pts was 5.1% (p=0.448) in pts. receiving CHOP-14 only and 7.7% (p=0.053) when R was added. In a multivariate analysis the relative risk for progression in male compared to female patients was not significantly elevated after CHOP-14 (1.1; p=0.348), but was significantly higher after R-CHOP-14 (1.6; p=0.004). With respect to weight, addition of R resulted in a significantly improved 3-year PFS (74% vs. 49%; p=0.006) in female pts with a body weight within the lower quartile (≤60 kg) who have an R serum half life of >38.1 days, while there was no improvement by the addition of R (72% vs. 71%; p=0.816) in female pts. with a body weight within the upper quartile (>77kg), who have a serum half life of <29.3 days. **Conclusions:** The reduced benefit of adding R to CHOP in elderly DLBCL pts. with a shorter rituximab serum half life (and hence lower serum levels) suggests that the respective subpopulations (males and weighty females) are underdosed when R is dosed based on body surface area at 375 mg/m^2. Ongoing studies of the DSHNHL investigate whether higher R doses for pts with a shorter R serum half life can improve the outcome of the respective pts.

8025 **Poster Discussion Session (Board #5), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM**

Outcome of elderly DLBCL patients with 6xCHOP-14 and 8 rituximab (R) applications given over an extended period (SMARTE-R-CHOP-14 trial of the DSHNHL).

Niels Murawski, Gerhard Held, Samira Zeynalova, Carsten Mueller, Viola Poeschel, Andreas Viardot, Mathias Haenel, Ulrich Keller, Marcel Reiser, Marita Ziepert, Norbert Schmitz, Michael Pfreundschuh, German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL); Saarland University Hospital, Homburg, Germany; Institute for Medical Informatics, Statistics and Epidemiology, Leipzig University, Leipzig, Germany; University Hospital, Cologne, Germany; University Hospital Ulm, Ulm, Germany; Chemnitz Hospital, Chemnitz, Germany; Klinikum Rechts der Isar, Technical University Munich, Munich, Germany; Asklepios Hospital St. Georg, Hamburg, Germany

Background: 6xCHOP-14 with 8xR given over an extended period improved 3-year EFS (67% vs. 54%; p=0.030) and OS (80% vs. 67%, p=0.034) of poor-prognosis patients (IPI=3-5) in the SMARTE-R trial compared to the RICOVER-60 trial where patients received 8xR every 2 weeks. Because we had recently shown (Mueller et al., Blood 2012) that elderly male patients have a faster R clearance (12.68 ml/h vs. 8.21 ml/h; p=0.003) and shorter serum elimination half life ($t_{1/2ß}$=24.7 vs. $t_{1/2ß}$=30.7 days; p=0.003) than females, we analyzed whether these differences translated into different outcomes by comparing the results achieved by elderly female and male patients in the RICOVER-60 and SMARTE-R trials. **Methods:** In SMARTE-R, 189 evaluable elderly (61-80 y) pts. with DLBCL received 6 cycles of 2-weekly CHOP-14 combined with 8xR on days -4, -1, 10, 29, 57, 99, 155, and 239. The primary endpoint was event-free survival (EFS). 306 pts treated within the RICOVER-60 trial with 6xCHOP-14 + 8 R given on days 1, 15, 29, 43, 57, 71, 85 and 99 served as controls. **Results:** The 3-year EFS of 51 poor-prognosis male patients in SMARTE-R was 67% compared to 47% of 66 poor-prognosis male patients treated in RICOVER-60 (p=0.037); the respective figures were 71% vs. 53% (p=0.051) for PFS and 80% vs. 60% (p=0.027) for OS. In contrast, female poor-risk patients had only a small benefit from the extended rituximab exposure in SMARTE-R (n=48) compared to RICOVER-60 (n=57): 67% vs. 61% (p=0.354) for EFS; 71% vs. 67% (p=0.489) for PFS; and 80% vs. 76% (p=0.528) for OS. **Conclusions:** Elderly male patients with poor-prognosis DLBCL who have a faster R clearance and shorter R serum elimination half life than female patients, benefit significantly from the longer R exposure in SMARTE-R with a gain of 20% in 3-year OS, while the outcome of female patients was only slightly improved. Even though R maintenance has failed to demonstrate any benefit in the primary treatment of DLBCL to date, these results underline the importance of a minimum exposure time of R in order to exploit its full therapeutic potential in DLBCL. Supported by Deutsche Krebshilfe.

8026 Poster Discussion Session (Board #6), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Multicenter, phase II study of bendamustine in refractory or relapsed T-cell lymphoma: The BENTLY trial.

Remy Gressin, Gandhi Laurent Damaj, Kamal Bouabdallah, Guillaume Cartron, B Choufi, Emmanuel Gyan, Arnaud Jaccard, Sophie Park, Jean-Marc Schiano De Colella, Laurent Voillat, Bertrand Joly, Steven Le Gouill, Alain Saad, Laurence Sanhes, Marie-Pierre Moles-Moreau, Michael Bubenheim, Marie C. Bene, Antoine Martin, Jean pierre Marolleau, Thierry Lamy; University Hospital Grenoble, Grenoble, France; Centre Hospitalier Universitaire Amiens Sud, Amiens, France; Department of Hemagology, Hôpital du Haut Lévêque, Centre François Magendie, Pessac, France; University Hospital Montpellier, Montpellier, France; Hématologie, CH Boulogne, Boulogne, France; University Hospital Tours, Tours, France; Hématologie Clinique et Thérapie Cellulaire, Limoges, France; CHU Cochin, Paris, France; Institut Paoli-Calmettes, Marseille, France; Hematology, Hopital de Chalons sur Saone, Chalons sur Saone, France; Centre Hospitalier Sud Francilien, Corbeil-Essonnes, France; University Hospital Nantes, Nantes, France; Hematology/Oncology, Hopital de Beziers, Beziers, France; Hematology, Hopital de Perpignan, Perpignan, France; Hematology, University Hospital Angers, Angers, France; Biostatistics Department, Rouen University Hospital-Charles Nicolle, Rouen, France; Immunology Laboratory, CHU de Brabois and Nancy University, Vandoeuvre les Nancy, France; Pathology, University hospital Avicenne, Bobigny, France; CHU Amiens, Amiens, France; CHU Pontchaillou, Rennes, France

Background: T-cell lymphomas have a poor prognosis with few options of effective treatment. This study determined the efficacy and safety of bendamustine as a single agent in the treatment of refractory or relapsed T-cell lymphomas. **Methods:** Patients with histologically confirmed peripheral T-cell lymphoma (PTCL) or cutaneous T-cell lymphoma (CTCL), who had previously received at least one line of chemotherapy were selected. Bendamustine was administered IV at the dosage of 120 mg/m^2 on days 1 and 2 every 3 weeks, for 6 cycles. Treatment response was assessed using the IWC for non-Hodgkin's lymphoma. The primary end point was overall response rate (ORR). Secondary end points were duration of response (DoR), progression-free survival (PFS), and overall survival (OS), NCT00959686. **Results:** Twenty two female and 38 male were included. The median age was 66 years with more 1/4 of them $>$ 75. Histology was predominantly angio-immunoblastic lymphadenopathy (n=32) and PTCL-nos (n=23). The median previous line of chemotherapy was 1 (1-3). Nearly one half (45%) of the patients was refractory to the last previous chemotherapy and the median duration of the best previous response was 6.6 (1.5-67) months. The disease was disseminated in the majority of case (87%) and the international prognostic index (IPI) was high (3–5) in 68% of the patients. Twenty patients (33%) received less than 3 cycles of bendamustine. The major reason for early discontinuation was disease progression. In the Intent-To-Treat (ITT) population, the best ORR was 50%, including complete response (CR) in 28% and partial response (PR) in 22 %. Bendamustine showed a consistency in the efficacy as a function of major disease characteristics. The median values for DoR, PFS and OS were 3.5, 4 and 6 months respectively. The most frequent grade 3/4 AEs were neutropenia (30%), thrombocytopenia (24%) and infections (20%). **Conclusions:** Bendamustine is active in high risk refractory and relapsed T-cell lymphoma with manageable toxicity.

8027 **Poster Discussion Session (Board #7), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM**

Retreatment with brentuximab vedotin in CD30-positive hematologic malignancies: A phase II study.

Nancy Bartlett, Pauline Brice, Robert W. Chen, Michelle A. Fanale, Ajay K. Gopal, Jeffrey Matous, Joseph David Rosenblatt, Laurie E. Grove, Andres Forero-Torres; Washington University, Siteman Cancer Center, St. Louis, MO; Hospital Saint-Louis, Paris, France; City of Hope, Duarte, CA; University of Texas M. D. Anderson Cancer Center, Houston, TX; University of Washington/Fred Hutchinson Cancer Research Center, Seattle, WA; Colorado Blood Cancer Institute, Denver, CO; University of Miami Sylvester Comprehensive Cancer Center, Miami, FL; Seattle Genetics, Inc., Bothell, WA; University of Alabama at Birmingham, Birmingham, AL

Background: Brentuximab vedotin comprises an anti-CD30 antibody conjugated by a protease-cleavable linker to a microtubule-disrupting agent, MMAE. In pivotal phase 2 studies in patients (pts) with relapsed/refractory Hodgkin lymphoma (HL) or systemic anaplastic large cell lymphoma (sALCL), objective response rates were 75% and 86% and median durations of response were 6.7 and 12.6 mo, respectively. A phase 2 study was initiated to investigate if pts who have previously responded to brentuximab vedotin could achieve another remission with retreatment (ClinicalTrials.gov #NCT00947856). **Methods:** Pts had a CD30-positive hematologic malignancy, achieved an objective response (per Cheson 2007) with prior brentuximab vedotin treatment, and experienced relapse after discontinuing treatment. Brentuximab vedotin was administered IV 1.8 mg/kg every 21 days; antitumor activity was assessed by the investigator. **Results:** 14 HL pts and 8 sALCL (5 ALK-negative) pts were enrolled (median age 34 yr, range 16–72). Pts had received a median of 4 prior chemotherapy regimens (range 2–12). Median time since the previous brentuximab vedotin treatment was 6.9 mo (range 1–44). Median number of retreatment cycles was 7 (range 1+ to 32+). Adverse events (AEs) in >25% of pts were nausea (41%), fatigue (36%), peripheral sensory neuropathy (36%), and diarrhea (27%). The most common Grade 3/4 AEs were anemia, fatigue, and hyperglycemia (3 pts each). Of the 11 pts who had pre-existing peripheral neuropathy, 3 (27%) had worsening with retreatment. Best clinical responses in pts with HL were 3 CR, 5 PR, 3 SD, 3 PD. Among pts with sALCL, 5 achieved a CR, 1 had PD, and 2 were not yet evaluated. Of the 8 pts with CR in retreatment, previous best responses to brentuximab vedotin treatment were 4 PR and 4 CR. Median duration of retreatment response was 10.8 mo (range 0+ to 10.8), and in pts who achieved CR, the median duration of response was not reached (range 0+ to 10.5 mo); 11 pts remain on retreatment. **Conclusions:** Retreatment with brentuximab vedotin was generally well tolerated. Objective responses were observed (13 of 20; 65%) in this heavily pretreated population. Enrollment to the phase 2 retreatment study is ongoing.

8028 Poster Discussion Session (Board #8), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Everolimus (EVE) for relapsed/refractory classical Hodgkin lymphoma (cHL): Open-label, single-arm, phase II study.

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Background: Effective treatment for relapsed/refractory cHL is lacking. The oral mammalian target of rapamycin inhibitor EVE showed promising efficacy and acceptable toxicity in cHL. We conducted a study to confirm EVE safety and efficacy in relapsed/refractory cHL. **Methods:** In this multicenter, open-label, 2-step, phase 2 study, adults with cHL that progressed after high-dose chemotherapy with autologous hematopoietic stem cell transplant (AHSCT) or a gemcitabine-, vinorelbine-, or vinblastine-containing regimen received EVE 10 mg/d until disease progression or unacceptable toxicity. Response was assessed every 12 wk via integrated positron emission tomography/computed tomography (CT) with contrast or CT with contrast. Primary endpoint was overall response rate (ORR) per modified response criteria for malignant lymphoma. Adverse events (AEs) were assessed during, and for ≥4 wk after, EVE treatment. **Results:** 55 patients were enrolled. Of the 38 currently evaluable patients, 37% were men, median age was 32.5 y, 53% were pretreated with AHSCT, and 95% were pretreated with gemcitabine, vinorelbine, or vinblastine; 71% had disease progression during previous therapies or discontinued previous treatment due to progression. 23 patients discontinued treatment, most commonly due to disease progression (n = 11). ORR was 37% (Table). Median progression-free survival (PFS) was 7.2 mo. The most common hematologic AEs were thrombocytopenia (39%) and anemia (24%); the most common nonhematologic AEs were fatigue (47%), cough (29%), dyspnea (26%), headache (21%), and rash (21%). Grade 3/4 AEs, most commonly thrombocytopenia (18%), were observed in 45% of patients. **Conclusions:** EVE showed a favorable ORR and median PFS in the first 38 evaluable patients with highly pretreated, relapsed/refractory cHL. The AE profile was consistent with that previously observed for EVE. These preliminary results confirm those of an earlier study and support further evaluation of EVE in cHL.

Best overall response, n (%)	EVE 10 mg/d N=38
ORR	14 (36.8)
Complete response*	1 (2.6)
Partial response	13 (34.2)
Stable disease	10 (26.3)
Progressive disease	5 (13.2)
Unknown	9 (23.7)

*Defined as resolution of all adenopathy.

8029 Poster Discussion Session (Board #9), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

A multicenter phase II study of vorinostat in patients (pts) with relapsed or refractory indolent B-cell non-Hodgkin lymphoma (B-NHL) or mantle cell lymphoma (MCL).

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Background: Most pts with indolent B-NHL relapse even after rituximab-containing chemotherapy. Vorinostat is an orally active histone deacetylase (HDAC) inhibitor, and is under investigation as monotherapy or in combination regimens in various hematologic malignancies. It has been reported that the histone acetyltransferase genes (EP300 and CREBBP) are frequently mutated in NHL, suggesting the potential usefulness of HDAC inhibitors in its treatment. **Methods:** We conducted a phase 2 study to investigate the efficacy, safety and tolerability of vorinostat in pts with indolent B-NHL or MCL with the overall response rate (ORR) against follicular lymphoma (FL) as the primary endpoint. The primary hypothesis was to demonstrate the efficacy in FL pts as measured by the ORR. Assuming the true ORR with vorinostat of 50% and without vorinostat of less than 25%, 39 pts will provide 90% power to demonstrate an ORR$>$25%. Vorinostat was administered at the dose of 200 mg BID for 14 consecutive days in a 21-day cycle. The ORR and PFS were determined by an independent review panel in the Full Analysis Set (FAS) population. **Results:** A total of 56 pts with a median age of 60 years (range: 33 - 75) were enrolled, and 50 of them (39 with FL, 11 with other subtypes of indolent B-NHL or MCL) were included in the FAS population. The number of prior therapeutic regimens was 2 (range: 1 - 4) and 41 pts have previously received rituximab-based regimens.. The percentages of pts with FLIPI at low risk, intermediate risk and high risk were 41%, 39%, and 21%, respectively. The ORR in 39 pts with FL was 49% (95% CI: 32, 65), and the pre-specified statistical success criterion was met. The median PFS in 39 pts with FL was 17.5 months (range: 2, 22+), especially the median PFS in 19 responders with FL has not yet been reached. The major toxicities were hematologic and gastrointestinal ones, which were reversible and manageable. Grade 3/4 infection was observed in 2%. **Conclusions:** This phase 2 study demonstrated that oral vorinostat is an agent with sustained antitumor activity in pts with relapsed or refractory indolent B-NHL, with acceptable safety profiles, warranting further investigations.

8030 Poster Discussion Session (Board #10), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Interim analysis of the largest prospective trial to date in adult CD20-positive post-transplant lymphoproliferative disorder (PTLD): Introducing risk-stratified sequential treatment (RSST).

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Background: The prospective, multicenter international phase II PTLD-1 trial of sequential treatment (ST, 4 cycles of weekly rituximab followed by 4 cycles of CHOP-21 + G-CSF) in adult CD20-positive PTLD demonstrated excellent efficacy (90% overall response rate, ORR) and safety (11% treatment-related mortality, TRM). As the response to rituximab predicted overall survival (OS), the trial was amended in 2007 introducing risk-stratified sequential treatment (RSST) according to the response to rituximab (NCT00590447). **Methods:** Following rituximab on days 1, 8, 15 and 22, RSST consisted of 4 3-weekly courses of rituximab monotherapy for patients (pts) in complete remission (CR, low risk) while all others (high risk) received 4 cycles of R-CHOP-21 + G-CSF. Key exclusion criteria were CNS involvement, HIV infection, severe organ dysfunction not related to PTLD, and ECOG $>$ 2. Primary endpoint was ORR. This is an analysis of the first 91 patients treated with RSST. **Results:** 79/91 pts had monomorphic, 12 polymorphic PTLD. 41/91 pts were kidney, 27 liver, 12 heart, 7 lung or heart+lung, 3 heart+kidney and 1 kidney+pancreas transplant recipients. Median age at diagnosis was 60 years (range 20-82). 73/91 pts had late PTLD and 39/85 PTLDs were EBV-associated. 1 pt died before initiation of treatment; 5 pts discontinued treatment after 4 cycles rituximab. TRM of RSST was 7/90 (8%) including 5 deaths with unknown remission status. ORR was thus 74/80 (93%, 95%CI: 84-97%; CR: 62/80 [78%]). 24/90 pts (27%) achieved CR with 4 cycles of rituximab. After a median follow up of $>$3 years, relapse rate in low risk pts was not increased by rituximab consolidation in RSST compared to CHOP consolidation in ST (3/23 vs. 5/14, p=0.104]). In patients in PD after rituximab, R-CHOP was more effective than CHOP in achieving CR (15/23 vs. 3/11, p=0.038). OS at 3 years was higher with RSST (70%, 95% CI: 60-82%) compared to ST (61%, 95%CI 49-72%) but this difference was not significant. **Conclusions:** With RSST 27% of pts were classified as low risk and achieved durable tumor control without chemotherapy while R-CHOP seems more efficient than CHOP in in high risk patients.

8031 Poster Discussion Session (Board #11), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

CNS-directed chemotherapy including high-dose chemotherapy with autologous stem cell transplantation (HD-ASCT) for CNS relapse of aggressive lymphomas: Final analysis of a phase II study.

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Background: The outcome of patients with CNS relapse of aggressive lymphoma (secondary CNS lymphoma, SCNSL) is poor with no standard therapy established thus far. Here we present the final analysis of a prospective multicenter phase II study using an intensive induction regimen followed by high-dose chemotherapy and autologous stem-cell transplantation. **Methods:** Adult immunocompetent patients ≤65 years with SCNSL were eligible. Induction chemotherapy consisted of two cycles MTX/IFO (methotrexate 4g/m^2 iv. d1, ifosfamide 2g/m^2 iv. d3-5 and i.th. liposomal cytarabine 50mg d6) and one cycle AraC/TT (cytarabine 3g/m^2 d1-2, thiotepa 40mg/m2 iv. d^2 and i.th. liposomal cytarabine 50mg d3). Then, patients without progression received high-dose chemotherapy with carmustine 400mg/m2 iv. d -5, thiotepa 2x5mg/kg iv. d -4 to -3 and etoposide 150mg/m^2 iv. d -5 to -3 followed by ASCT d0. **Results:** Thirty eligible patients (median age 58 years) were enrolled. Three patients had T-cell and 27 aggressive B-cell lymphoma. Pre-treatment was CHOP-like in 29 patients, including rituximab in 26. CNS relapse occurred after a median of 8.5 (3-80) months and was intracerebral in 23 and meningeal in13 patients (combined in 7); 6 had concomitant systemic lymphoma. After induction therapy CNS response was found in 22 (73%) patients (8xCR, 14xPR), 3 patients had SD, 4 patients PD and 1 patient no response evaluation. HD-ASCT was performed in 24 patients; resulting in 15 CR (63%), 2 PR (8%) and 7 PD (29%). Myelotoxicity was the most frequent WHO grade 3-4 adverse event with infections in 8/30 pts on MTX/IFO (27%), 5/23 (22%) on AraC/TT and 11/20(55%) on HD-ASCT. One patient died due to septic diverticulitis and one developed persisting fecal incontinence. The median follow up was 21 months. The median PFS was 12.1 months (95% CI 6.4-17.7) in all patients and 30.4 (95%CI 2.5-58.3) months after HD-ASCT, the median overall survival was 27.4 months and not reached, respectively. **Conclusions:** This first prospective study on SCNSL demonstrates that lasting remissions can be achieved with CNS-directed HD-ASCT in a large proportion of patients and probably cure in some.

8032 Poster Discussion Session (Board #12), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Phase Ib trial of AVL-292, a covalent inhibitor of Bruton's tyrosine kinase (Btk), in chronic lymphocytic leukemia (CLL) and B-non-Hodgkin lymphoma (B-NHL).

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Background: Btk supports activation, survival, and proliferation of malignant B cells in CLL and B-NHL. AVL-292 is an oral, potent ($IC_{50} < 0.5$nM), selective small molecule covalent inhibitor of Btk. **Methods:** Patients (pts) with previously treated CLL or B-NHL were administered AVL-292 in escalating cohorts of 125, 250, or 400 mg po QD using a 3+3 design in continuous 28 day cycles until progressive disease (PD) or toxicity. Key objectives were safety, DLT, MTD, PK, and Btk occupancy. Plasma AVL-292 levels were assessed by LC-MS-MS. Btk occupancy by AVL-292 was assessed by covalent probe assay in peripheral blood mononuclear cells. **Results:** 12 pts have enrolled (3 each at 125 and 250 mg and 6 at 400 mg: 5M/7F; median age 68 years, range 45-79; median 2.5 prior therapies, range 1-10) including 8 CLL (2 with 17p-, 2 with 11q22-, 2 with both 17p-/11q22-; 2 mutated *IGHV*, 5 unmutated *IGHV*, 1 missing) and 4 B-NHL (1 diffuse large B cell lymphoma (DLBCL); 1 follicular (FL); 2 marginal zone (MZL)). Median time on treatment is 65 days, range 28-158. Ten of 12 pts continue on treatment: 1 pt (DLBCL) discontinued for PD after 1 cycle and 1 pt (FL) for DLT (Gr 4 plts; 400 mg QD). No other DLTs or grade 4 adverse events (AEs) have occurred and MTD has not been reached. Most frequent AEs reported include transient diarrhea, rash/skin infection, URI, nausea, and fatigue. Gr 3 AEs include 1 atrial fibrillation (not drug related) and 1 ANC low (probably drug related). To date, 8 of 8 CLL patients have stable disease (SD) with median 28% decrease from baseline lymph node measurement (range 3-40% decrease). Six of 8 pts with CLL experienced increased ALC in cycle 1: median increase 89.5% (range 50-212%). Two of 4 NHL pts have SD (both MZL), 1 PD (DLBCL), and 1 not evaluable due to DLT (FL). Full Btk occupancy was achieved with dose levels $\geq$ 250 mg. Multiple dose PK exposure (AUC_{last}) was linear with no accumulation from Day 1 to 15. **Conclusions:** AVL-292 was well tolerated from 125-400 mg po QD and early efficacy analysis in CLL and B-NHL shows 10/11 efficacy evaluable pts with SD. Full Btk occupancy was achieved with $\geq$ 250 mg QD and PK was predictable with no accumulation. Dose escalation is ongoing and MTD cohort expansion is planned.

8033 Poster Discussion Session (Board #13), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Oral weekly MLN9708, an investigational proteasome inhibitor, in combination with lenalidomide and dexamethasone in patients (pts) with previously untreated multiple myeloma (MM): A phase I/II study.

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Background: MLN9708 is an oral, reversible 20S proteasome inhibitor. The feasibility of combining a proteasome inhibitor with an immunomodulatory drug and a steroid in previously untreated MM has been demonstrated with the RVD regimen. This is the first study of MLN9708 in combination with lenalidomide and dexamethasone (NCT01217957). Here we report the phase (Ph) 1 MTD and preliminary Ph 2 results. **Methods:** Pts with previously untreated MM, aged ≥18 yrs with measurable disease received oral MLN9708 (phase 1: 1.68–3.95 mg/m^2) days 1, 8, and 15, lenalidomide 25 mg days 1–21, and dexamethasone 40 mg days 1, 8, 15, and 22, for up to twelve 28-day cycles. Primary objectives were determination of safety, MTD, and recommended phase 2 dose (RP2D) (Ph 1), and CR+VGPR rate (Ph 2). **Results:** At data cut-off (Dec 1, 2011), 29 pts had been enrolled (15 Ph 1, 14 Ph 2). Median age was 64 yrs (range 40–82); 69% ISS stage II/III. In Ph 1, the MLN9708 MTD was determined as 2.97 mg/m^2 and the RP2D as 2.23 mg/m^2; for Ph 2, the RP2D was converted to a 4.0 mg fixed dose based on population PK results. Ph 1 pts have received a median of 6 treatment cycles (range 1–11), 8 received ≥6 cycles; 6 stopped to receive ASCT, 7 are ongoing. Ph 2 pts received a median of 1 (range 1–2), all are ongoing. Grade ≥3 hematologic toxicity was reversible and included anemia (n=2) and thrombocytopenia (n=1). Grade ≥3 nonhematologic toxicity included erythematous rash, syncope, and vomiting (2 pts each). All-grade drug-related peripheral neuropathy was seen in 6 pts (21%), including grade 2 with pain in 2 (both Ph 1 at doses above the MTD). Two pts discontinued due to AE; there were 5 pts who had serious drug-related AE (all Ph 1). Of 19 response-evaluable pts (Ph 1 + Ph 2), all achieved ≥PR, including 5 CR (1 sCR), 4 VGPR, and 10 PR; all remain in response with duration of confirmed response of up to 9.5 months. Of 4 response-evaluable Ph 2 pts, 1 has achieved VGPR and 3 PR to date. **Conclusions:** Oral MLN9708 plus lenalidomide and dexamethasone appears well tolerated with manageable toxicity. These data show antitumor activity at the RP2D in pts with previously untreated MM, with ≥PR in all pts to date.

8034 Poster Discussion Session (Board #14), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Weekly dosing of the investigational oral proteasome inhibitor MLN9708 in patients (pts) with relapsed/refractory multiple myeloma (MM): A phase I study.

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Background: Phase 1 studies are evaluating IV and oral dosing of the reversible proteasome inhibitor MLN9708 in multiple tumor types. We report the safety, MTD, pharmacokinetics (PK), pharmacodynamics, and preliminary responses with weekly oral MLN9708 in pts with relapsed/refractory MM (NCT00963820). **Methods:** Pts aged ≥18 yrs received MLN9708 on d 1, 8, and 15 of 28-d cycles. In the dose-escalation phase, pts required ≥2 prior therapies (including bortezomib, thalidomide/lenalidomide, and corticosteroids). At the MTD, pts were to be enrolled to relapsed and refractory (RR), bortezomib-relapsed (VR), proteasome inhibitor (PI) naïve, and carfilzomib (CZ) expansion cohorts. **Results:** 36 pts have been enrolled to date (data cut-off: Dec 1, 2011), 32 in the dose-escalation phase (0.24–3.95 mg/m^2) and 8 to expansion cohorts (2 RR, 5 VR, 1 PI naïve; RR and VR cohorts each include 2 pts from MTD dose-escalation cohort). Median age was 64.5 yrs (range 40–79), 53% were male, and median number of prior lines of therapy was 3.5 (range 1-13), including 92%, 92%, 56%, and 8% who had prior bortezomib, lenalidomide, thalidomide, and carfilzomib, respectively. Pts have received a median of 2 cycles (range 1–11); 5 pts remain on treatment. Among 24 DLT-evaluable pts, 3 DLTs were seen: 2 at 3.95 mg/m^2 (1 grade 3 rash, 1 grade 3 GI AEs) and 1 at 2.97 mg/m^2 (grade 3 GI AEs). The MTD was determined as 2.97 mg/m^2. Overall, 69% of pts had drug-related AEs, and 28% had related grade ≥3 AEs, including thrombocytopenia (17%), diarrhea (11%), nausea, neutropenia, and fatigue (each 8%). Only 3 (8%) pts had drug-related peripheral neuropathy (PN; no grade ≥3). 2 pts discontinued due to AEs. In 18 response-evaluable pts, 1 had a VGPR at 3.95 mg/m^2, 1 had a PR at 2.97 mg/m^2, and 8 have achieved SD durable for up to 9.5 mos. PK analyses showed linear plasma PK (0.8–3.95 mg/m^2), T_{max} of 0.5-2 hr, and terminal half-life of 7 d for MLN2238 (biologically active hydrolysis product). There was a trend for a dose-dependent increase in whole blood 20S proteasome inhibition. **Conclusions:** Current data suggest weekly oral MLN9708 is generally well tolerated with infrequent PN, and shows early signs of antitumor activity.

8035 Poster Discussion Session (Board #15), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Response rates to single-agent carfilzomib in patients refractory or intolerant to both bortezomib and immunomodulators in trial PX-171-003-A1.

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Background: Patients (pts) with relapsed and refractory multiple myeloma (RR MM) who are refractory or intolerant to both bortezomib (BTZ) and immunomodulators (IMiDs; thalidomide [Thal] or lenalidomide [Len]) (ie, "double-refractory/intolerant"), have few therapeutic options and a poor prognosis. Carfilzomib (CFZ), a next generation proteasome inhibitor (PI), has shown durable single-agent activity in clinical studies including 003-A1, an open-label, single-arm phase 2b trial in RR MM. The present analysis describes clinical activity in pts from 003-A1 with double-refractory/intolerant disease and in other groups of clinical interest including pts with disease refractory to all 5 approved classes of anti-MM tx (alkylators, anthracyclines, corticosteroids, IMiDs, and PIs) in clinical use ("refractory to all approved tx"). **Methods:** Pts from 003-A1 with double-refractory/intolerant disease were analyzed, as were pts with disease refractory to all approved tx. CFZ was given on days 1, 2, 8, 9, 15, 16 of 28-day cycles (C), (20 mg/m^2 in C1; 27 mg/m^2 in C2–12). Primary endpoint was overall response rate (ORR). Secondary endpoints included duration of response (DOR), overall survival, and safety. **Results:** The study ORR was 22.9% with median DOR of 7.8 mo (N=266). 228 pts (86%) with double-refractory/intolerant disease had ORRs of 20.6% and a median DOR of 7.4 mo. **Conclusions:** Single-agent CFZ demonstrated clinically meaningful, durable responses in pts with double-refractory/intolerant MM or disease refractory to all 5 approved classes of tx. The ORRs across groups of clinical interest were generally consistent with results for the entire study population. These results are notable for a next-generation PI and demonstrate the activity of single-agent CFZ in pts with advanced stage MM.

Refractory status	n	ORR (≥PR), %	DOR, mo
Refractory/intolerant to BTZ and (≥1 IMiD)	228	20.6	7.4
To BTZ in any prior regimen	194	16.5	7.8
To Thal in any prior regimen	118	17.8	5.6
To Len in any prior regimen	221	22.2	7.8
Refractory to all approved tx	44	20.5	7.8

8036 Poster Discussion Session (Board #16), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Clarithromycin, pomalidomide, and dexamethasone (ClaPD) in relapsed or refractory multiple myeloma.

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Background: Clarithromycin has been shown to enhance anti-myeloma activity of lenalidomide+dexamethasone in the upfront treatment of multiple myeloma (MM). Pomalidomide is an immunomodulatory agent effective in relapsed/refractory MM (RRMM). We hypothesized that clarithromycin may similarly enhance pomalidomide + dexamethasone in RRMM. We now report updated results from a phase 2 trial of ClaPD in RRMM. **Methods:** 73 patients with RRMM were enrolled in a single-institution phase 2 study of ClaPD. All subjects had ≥ 3 prior lines of therapy, one of which must have included lenalidomide. ClaPD is clarithromycin 500mg twice daily; dexamethasone 40mg weekly; and pomalidomide 4mg for days 1-21 of a 28-day cycle. All patients had VTE prophylaxis with aspirin. Monthly disease response evaluation included immunoelectrophoresis and free light chain analysis; bone marrow biopsy with skeletal imaging was used to confirm MM responses. Treatment continued as tolerated until disease progression. **Results:** The 66 patients who completed ≥ 1 cycle of ClaPD are reported. Median number of cycles was 6 (range 1-17). Responses were progressive disease: 10%, stable disease: 21%, minimal response: 12%, partial response: 33%, very good partial response: 18%, stringent complete remission: 5%, for an overall response rate (ORR) of 56% and ≥VGPR rate of 23%. Median time to PR was 1.25 cycles (range 1-8). Median PFS was 5 months. Response and PFS were not different in patients refractory to lenalidomide (85%), bortezomib (82%), or double-refractory patients (76%). After a median follow up of 12 months,28 pts (42%) remain on study without progression and 56pts (85%) are alive. Two pts withdrew due to toxicity (1 Grade 3 fatigue, 1 Grade 4 muscular weakness). One patient withdrew consent. **Conclusions:** ClaPD is highly effective for heavily pre-treated RRMM, particularly in lenalidomide-refractory disesase and compares favorably to previously published Phase 2 data of Pom/Dex (ORR 56% vs 40% - Lacy et. al JCO 2009) without excess toxicity. Response to ClaPD is rapid, well tolerated, and sustained over 7 months in most subjects. These data support the clinical efficacy of pomalidomide based regimens in RRMM.

8037 Poster Discussion Session (Board #17), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Connect MM: The multiple myeloma (MM) disease registry—Incidence of second primary malignancies (SPM).

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Background: Advances in the treatment of MM have greatly improved clinical outcomes for patients (pts). SPM occurrence has been observed in early and late stage MM as well as with increasing age. US SEER Cancer Registry reports a background incidence rate of SPM 2.1/100 person-yrs (PY) among persons ≥ 65 yrs of age. However, incidence of SPM in MM pts and the relationship to therapy still warrants further exploration. **Methods:** Connect MM is a US-based observational registry designed to characterize pts with newly diagnosed MM from 266 US sites. Initiated in Sep 2009, patient data were collected at baseline and each subsequent quarter with a standardized form. On Dec 14, 2011, Connect MM reached full enrollment at 1,500 pts. **Results:** As of Jan 13, 2012, preliminary retrospective SPM data is available for 1015 pts. Median age was 67 yrs, 56.8% male, and median follow-up was 10.6 mo (0.03-24.9 mo). 12 pts (7 male) with median age of 68.5 yrs developed SPM. Median time to SPM was 8.5 mo (0.8-17.7 mo) after treatment initiation. 11 invasive SPM were observed - 4 hematological (heme): 1 AML, 1 MDS, 1 CMML and 1 DLBCL, and 7 solid: 2 melanoma skin, 1 bronchus, 1 breast, 1 prostate, 1 tonsil, and 1 gastric carcinoid. Also, 1 pt had non-melanoma skin cancer (NMSC), and 1 pt with invasive skin cancer also had NMSC. Of the 4 pts developing heme SPM, 3 had bortezomib (BORT), 1 had thalidomide (THAL), 1 had lenalidomide (LEN), 2 had melphalan (MEL), and all 4 pts had steroids. Of the 7 pts who developed solid tumor SPM, 5 had BORT, 5 had LEN, 2 had doxorubicin, 1 had MEL, 5 had steroids, 1 had irradiation, and 1 had not received MM treatment. 2 pts with prior history of invasive malignancy developed solid tumor SPM (1 pt also developed NMSC).1 pt who received irradiation developed NMSC. Early overall incidence of invasive SPM was 1.21/100 PY (95% CI 0.60, 2.16) for all pts and 1.20/100 PY (95% CI 0.44,2.62) for pts ≥ 65 yrs of age. **Conclusions:** This preliminary analysis shows that SPM occurred at an expected rate in this disease specific registry of patients with NDMM and appeared to occur irrespective of MM treatment administered. Incidence rates of SPM may increase over time as patients receive transplantation and alkylators. Prospective observation will continue.

8038 Poster Discussion Session (Board #18), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Risk factors for development of second primary malignancies (SPM) after autologous stem cell transplant (ASCT) for multiple myeloma.

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Background: Studies from the CALGB and IFM have suggested an increased incidence of SPM post ASCT in patients on lenalidomide maintenance. Patients with MM as well as patients post ASCT are inherently at higher risk of SPM. Therefore, assessment of risk factors associated with SPM would be useful in therapeutic decisions re preASCT therapy and post ASCTmaintenance. **Methods:** We conducted a retrospective cohort study of 841 consecutive MM patients who underwent at least one ASCT at City of Hope from 1989 to 2009. Sixty cases with 70 SPMs were identified. A nested case-control study was also conducted to understand the role of therapeutic exposures associated with SPMs. Controls were MM patients post ASCT matched by year of HCT ($\pm$5 years). **Results:** The median length of follow up was 3.3 yrs. (range 0.3-19.9). Median age at ASCT was 56 yrs (range 18-77). 62% had received a single autologous HCT, 27% tandem autologous HCT, 11% had received multiple HCTs (72 had a second allogeneic HCT)). The overall cumulative incidence of any SPM was 7.4% at 5 years and 15.9% at 10 years; the cumulative incidence of SPMs for patients $>$55 years approached 21.9% at 10 years. The cumulative incidence of MDS/AML was 1.8% and of solid tumors was 13.0%. Factors examined included age, race, sex, number and individual therapeutic exposures (pre-ASCT, conditioning, and post-ASCT), disease status at ASCT. Multivariate Cox regression analysis revealed non-Hispanic whites (RR=2.4, 95% CI, 1.2-4.6, p=0.01) and older age ($>$55) at diagnosis of MM (RR=2.3, 95% CI, 1.3-4.1, p=0.004) to be associated with an increased risk of developing SPMs. Only cumulative thalidomide exposure (both pre-ASCT and post-ASCT) demonstrated a trend toward a positive association (OR=3.5, 95% CI, 0.6-19.4, p=0.15). Six patients (3 cases and 3 controls) were exposed to lenalidomide prior to development of SPM (OR=1.0, 95% CI, 0.14-7.10). **Conclusions:** This single institution analysis identified non-hispanic whites and older age to be associated with increased risk of developing SPM in pts post ASCT for MM. The trend towards increased risk with thalidomide exposure may be suggestive of a class effect from IMIDs that is not restricted to lenalidomide alone.

8039 Poster Discussion Session (Board #19), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Second cancer risk 40 years after cure for Hodgkin lymphoma.

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Background: During the last decades Hodgkin Lymphoma (HL) treatment changed towards less toxic chemotherapy schemes and smaller radiation fields. The impact of these changes on second cancer (SC) risk is still unknown. **Methods:** We calculated standardized incidence ratios (SIR), comparing SC risk after HL treatment with expected risk, based on cancer incidence in the general population, and compared SC risk between treatment modalities, accounting for competing events, in a large Dutch cohort comprising 3,390 5-years HL survivors, aged 15-51 years at HL treatment and diagnosed between 1965-2000. **Results:** The median follow-up was 18.2 years; 23% of the patients was followed ≥25 years. During follow-up 734 SCs and 92 third cancers (TC) occurred. The SIR for any SC was 4.5 (95% confidence interval (95%CI) 4.1-4.9). SC risk was still elevated after 35 years of follow-up (SIR 3.9; 95%CI 2.5-5.8) and cumulative incidence (CI) reached 47.1% (95%CI 43.6-50.5) at 40 years follow-up. For TCs the SIR was 5.5 (95%CI 4.4-6.9); the 20-year CI was 22.3% (95%CI 17.8-27.2). Risks of NHL and leukemia strongly decreased in more recent treatment periods (P-trend <0.001). The CI of solid tumors (ST) between 5-19 years after HL treatment did not differ for patients treated between 1965-1979, 1980-1989 or 1990-2000 ($P=0.21$; 19-year CI 9.1%, 11.6% and 11.4%, respectively). Radiotherapy (RT) above the diaphragm increased risk of STs above the diaphragm (hazard ratio (HR) 2.4, $P<0.001$), while subdiaphragmatic RT was associated with a 1.7-fold increased HR of a subdiaphragmatic ST ($P=0.001$). An incomplete mantle field was associated with significantly lower breast cancer (BC) risk (hazard ratio (HR) 0.4, 95%CI 0.2-0.8). A cumulative procarbazine dose >4.2 g/m^2 yielded a 1.3-fold increased HR (95%CI 1.0-1.7) for non-breast STs and a 2-fold (95%CI 1.2-3.1) increased HR for gastrointestinal STs, but was associated with a strongly decreased BC risk (HR 0.3, 95%CI 0.2-0.6). **Conclusions:** SC risk after HL has decreased with treatment changes over the last decades, due to strongly decreasing risk of leukemia and NHL. Smaller radiation fields and procarbazine doses >4.2 g/m^2 are associated with lower breast cancer risk, while high procarbazine doses increase risk of gastrointestinal STs.

8040 Poster Discussion Session (Board #20), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Impact of t (11;14) on the outcome of autologous hematopoietic cell transplantation (Auto-HCT) in multiple myeloma.

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Background: Approximately 15-20% of patients with multiple myeloma (MM) present with t(11;14)(q13; q32) involving *IgH* and *CCND1-XT* genes. In this study, we report the impact of the t(11;14) on the outcome of patients with MM. **Methods:** We performed a retrospective chart review on patients with MM who underwent high-dose chemotherapy followed by auto-HCT at the M.D. Anderson Cancer Center between 2/2000 and 8/2010, and had conventional cytogenetic (CC) or fluorescent in situ hybridization (FISH) results available before transplant. The primary objective was to compare the progression free survival (PFS) and overall survival (OS) of patients with t(11;14) to patients without chromosomal abnormalities. **Results:** CC or FISH studies were available for 1239 patients: 863 normal, 28 with t(11;14), 348 with other abnormalities. Concurrent high-risk abnormalities on CC or FISH were seen in 15/28 patients with t(11;14): del(13q) in 11 , del(17p) in 3, and t(14;16)(q32;q23) in 1. Induction treatment in patients with t(11;14) was: bortezomib + dexamethasone +/- thalidomide/lenalidomide : 15 (53%), thalidomide or lenalidomide + dexamethasone: 11 (39%), others 2 (8%); they received auto-HCT after a median of one line (1-7) of therapy. Median follow up in surviving patients was 39 months. There was no significant difference in median time from diagnosis to auto-HCT from diagnosis (6.9 vs. 7.7 months, p=1.0), disease status at auto HCT (>PR1: 82 vs. 76%, <PR1: 7 vs. 11%, relapsed 10 vs. 13%), complete remission (CR: 21% vs. 32%; p=0.30), very good partial remission (VGPR: 29% vs. 21%; p=0.23) or overall response (75% vs. 85%; p=0.18) between patients with t(11;14) and normal karyotype. Median PFS in patients with t(11;14) and normal karyotype was 15.7 months and 35.9 months, respectively (p=0.017). Median OS in patients with t(11;14) and normal karyotype was 51.4 months and 88.4 months, respectively (p=0.03). There was no difference in PFS (p=0.25) or OS (p=0.71) in patients with t(11;14), with or without other high-risk chromosomal abnormalities. **Conclusions:** In this large single center study with a long follow up, we demonstrated that t(11;14) in MM is associated with a shorter PFS and OS in the context of auto-HCT.

8041 Poster Discussion Session (Board #21), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Metronomic therapy for heavily pretreated relapsed/refractory multiple myeloma (RRMM).

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Background: RRMM represents a true challenge in MM therapy. Based on the effectiveness of metronomic therapy in solid tumors, we developed a treatment of metronomically scheduled therapy (MT) for RRMM (Hollmig, ASH 2004). We are now updating our experience with a median follow up of 25.6 months. **Methods:** We identified 187 patients treated with MT from 03/2004 to 11/2011. **Results:** The median age was 61 years (range 36-83); the median number of prior therapies was 14 (range 1-51). 79% of patients had prior HDT, 99% had a prior exposure to bortezomib, 98% to an IMiD, and 95% to their combination . The median number of completed MT cycles was 1 (range 1-5). 63% of patients had a response of MR or better (6% CR ,7% VGPR, 36% PR, 16% MR). The median overall (OS) and progression free (PFS) survivals were 11.3 and 3.7 months respectively. 91 of 187 patients had gene expression profiling (GEP) prior to initiation of MT, of which 53% were high risk according to the 70-gene (GEP70) risk model. OS was affected by elevated CRP ($>$ 8mg/L, HR$=$1.71, p$=$0.009) and cytogenetic abnormalities within 6 months of initiation of MT (HR$=$2.45, p$<$0.001). For the 91 patients with GEP data available, OS was correlated with elevated CRP $>$ 8mg/L (HR$=$2.11, p$=$0.009) and GEP70 high-risk (HR$=$2.65, p$<$0.001), which also showed a trend towards shorter PFS. Hematological toxicity grading was difficult as 69% of patients presented with grade $>=$3 thrombocytopenia within 90 days prior to starting MT. Grade 4 leucopenia , anemia thrombocytopenia due to MT occurred in 74%, 17%, 89% of patients respectively. Incidence of grade 4 neutropenic fever was 1%. Grade 4 or worse incidence of all non-hematological toxicities was below 9%. Most patients were treated in the outpatient setting (95%) and secondary admissions due to regimen toxicity occurred in 20%. **Conclusions:** MT is an effective salvage treatment in RRMM, with a high ORR and a favorable toxicity profile.

MT regimen.

Agent	Days	Dosage
Bortezomib	1,4,7,10,13,16	1 mg/m^2
Thalidomide	1-16	200 mg
Dexamethasone	1,4,7,10,13,16	20-40 mg
Doxorubicin hydrochloride	1-16	3 mg/m^2 IV continuous infusion
Cisplatin	1-16	1.5-3 mg/m^2 IV continuous infusion
Rapamycin	1-16	3mg on day 1 , 1mg days 2-16

8042 Poster Discussion Session (Board #22), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Detection of the MYD88 L265P mutation in Waldenström's macroglobulinemia using a highly sensitive allele-specific PCR assay.

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Background: Waldenström's macroglobulinemia (WM) is a B-cell malignancy characterized by bone marrow (BM) infiltration with lymphoplasmacytic cells and production of an IgM paraprotein. By whole genome sequencing, we recently identified a somatic mutation (L265P) in the MYD88 gene in 27/30 (90%) WM patients (Treon et al, ASH 2011). To expand this finding for possible diagnostic testing, we developed an allele-specific PCR assay for MYD88 L265P and evaluated this assay in a large cohort of WM patients. **Methods:** An allele-specific PCR assay was developed with a threshold of detection of 0.125% for MYD88 L265P. DNA from bone marrow aspirates from 99 patients with the clinicopathological diagnosis of WM was used for assessment of MYD88 L265P expression by both allele-specific PCR and Sanger sequencing. Findings were correlated with clinical parameters using ANOVA. **Results:** We observed that 85/99 (86%) WM patients were positive for MYD88 L265P using the allele-specific PCR assay. Of the 85 allele-specific PCR positive patients, 81 demonstrated a detectable mutation peak by Sanger sequencing. All 14 allele-specific PCR negative patients remained negative by Sanger sequencing. By the allele-specific PCR assay, MYD88 L265P positive patients showed greater bone marrow involvement, higher serum IgM and lower serum IgA and IgG levels versus MYD88 L265P negative patients ($p<0.008$). **Conclusions:** MYD88 L265P is highly expressed in BM samples of WM patients using an allele-specific PCR assay, and is associated with greater bone marrow disease burden and serum IgM levels. Use of allele-specific PCR provides a simple and sensitive diagnostic tool for detection of the MYD88 L265P mutation.

8043 Poster Discussion Session (Board #23), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Long-term results of the phase II trial of the oral mTOR inhibitor everolimus (RAD001) in relapsed or refractory Waldenstrom macroglobulinemia.

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Background: The mammalian target of rapamycin (mTOR) signal pathway controls cell proliferation and survival. The trial's goal was to determine the anti-tumor activity and safety of single-agent everolimus (TORC1 inhibitor) in patients with relapsed/refractory Waldenstrom macroglobulinemia (WM). **Methods:** Eligible patients had measurable disease (IgM monoclonal protein >1000 mg/dL with >10% marrow involvement or nodal masses >2 cm), a platelet count ≥75,000 x 10^6/L, a neutrophil count ≥1,000 x 10^6/L. Patients received everolimus 10 mg PO daily. Tumor response was assessed after cycles 2 and 6 and then every 3 cycles until progression. **Results:** 60 pts were treated. The median age was 64 years (range, 43-85). The median number of prior therapies was 3 (range, 1-11). All but two patients (97%) had received prior rituximab based therapy and 64% of patients had received prior alkylator based therapies. The overall response rate (complete response CR+ partial response PR+ minimal response MR) was 73% (95% CI: 60-84%), with a PR of 50% and 23% MR. The median time to progression (TTP), progression-free survival (PFS), and overall survival (OS) for the entire study population is 28 months (mos), (95% CI: 18-not reached (NR)), 22 mos (95% CI: 12 0-NR), and 55 mos (95% CI: 55-NR), respectively. The estimated PFS at 12 and 24 months is 62% (95%CI: 51-75%), and 48% (95%CI: 37-63%), respectively. The 30 patients who achieved a PR responded after a median of 2 months (range, 1-26) of treatment. The median duration of response (DR) for these patients has not yet been reached and 19 of these patients remain in response after a median follow up of 31 months (range, 3-54). All but two patients had a decrease in their serum IgM. Grade 3 or higher related toxicities were observed in 67% of patients. The most common were hematological toxicities with cytopenias. Pulmonary toxicity occurred in 5% of patients. Dose reductions due to toxicity occurred in 63% of patients. **Conclusions:** Everolimus has high single-agent activity with an overall response rate of 73% and manageable toxicity in patients with relapsed WM, and offers a potential new therapeutic strategy for this patient population.

8044 General Poster Session (Board #32A), Mon, 1:15 PM-5:15 PM

Survival with splenectomy in splenic marginal zone lymphoma: Analysis of the Surveillance, Epidemiology and End Results (SEER) database.

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Background: The role of splenectomy as the primary therapy for splenic marginal zone lymphoma has been questioned. We studied relative survival in SMZL and the impact of splenectomy on lymphoma-specific survival (LSS). **Methods:** SMZL cases (diagnosed in 1993-2008) were derived from the SEER database. Age, sex and race-matched actuarial survival data were summarized. Factors predictive of splenectomy were studied using logistic regression with a subsequent propensity score (PS)-weighted survival analysis. **Results:** 1071 patients were identified with a median age of 69 years (range, 25-96) and a median follow up of 33 months. 53% were women and 92% were white. 70% of the lymphomas were stage III/IV with B symptoms recorded in 22.3%. 54% of patients underwent splenectomy. The significant factors predictive of surgery included younger age ($p<10^{-14}$), stage I/II ($p<10^{-15}$), B-symptoms ($p=0.003$), no prior malignancy ($p=0.002$), with significantly lower rates in black patients (OR 0.41, 95%CI 0.21-0.80, $p=0.008$), on the Pacific Coast (OR 0.62, 95%CI 0.47-0.81, $p=0.0004$) and with decreasing rates over time ($p=0.0002$). The actuarial 5-year relative survival was 82.8% (95%CI 77.9-86.7%) with no difference by sex ($p=0.79$), race or stage. 54% of deaths were related to SMZL with the estimated LSS of 80.8% (95%CI 78-84%). Splenectomy was not associated with improved LSS in propensity score-stratified log-rank test ($p=0.60$) or in the PS-weighted Cox model (HR=0.93, 95%CI 0.62-1.38, $p=0.70$). Advancing age (HR 1.05, 95%CI 1.03-1.07, $p<10^{-8}$) and presence of B-symptoms (HR=1.98, 95%CI 1.30-3.01, $p=0.002$) were significantly predictive of death from SMZL, with no evidence of improvement in LSS over the years (HR=0.97, 95%CI=0.91-1.03, $p=0.34$). There was also no detectable impact of splenectomy on survival in patients who ultimately died of SMZL ($p=0.83$). **Conclusions:** In this cohort, the largest studied to date, splenectomy did not demonstrate a survival benefit in SMZL. Patients continue to have decreased survival despite advances in other indolent B-cell lymphomas. The role of splenectomy versus chemoimmunotherapy remains to be determined.

8045 General Poster Session (Board #32B), Mon, 1:15 PM-5:15 PM

Survival outcomes in marginal zone lymphomas in the rituximab era: Analysis of the Surveillance, Epidemiology, and End Results (SEER) database.

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Background: Despite prognostic models developed for marginal zone lymphoma (MZL), the impact of different characteristics and treatments on survival in the population is largely unknown. We studied survival of MZL patients included in the SEER database. **Methods:** Records of MZL adult cases diagnosed between 1989-2008 were studied using descriptive methods and analysis of overall (OS) and lymphoma-specific (LSS) survival based on Kaplan-Meier function, stratified log-rank tests and Cox proportional hazard models. **Results:** 13,957 patients with MZL were identified and classified as splenic (SMZL; n=1,111, 8%), nodal (NMZL; n=4,101, 29%) or extranodal MALT-type MZL (MALT; n=8,745, 63%). The median age was 68 years, 74% of patients were white and 55% were women. Median follow-up was 40 months. MALT was more common in non-Caucasians ($p<10^{-27}$). B-symptoms were more common in SMZL ($p<10^{-5}$). Both LSS and OS were significantly better for MALT ($p<10^{-60}$) with no difference between SMZL and NZML (p=0.30). 10-year LSS estimates were 67% for SMZL, 67% for NMZL, 84% for MALT. There was evidence for improved LSS since 2000 in MALT (HR 0.69, 95% CI 0.59-0.82, p=0.0003) and NMZL (HR 0.64, 95% CI 0.54-0.77, $p<10^{-5}$), but not for SMZL (HR 0.85, 95% CI 0.56-1.28, p=0.43). Similar results were found for OS. There were differences in survival in MALT subtypes depending on primary site ($p<10^{-12}$; Table). **Conclusions:** In the rituximab era, survival has improved for MALT and NMZL, but not for SMZL, possibly due to disparate treatment paradigms. The prognosis of MALT is different depending on primary site of involvement.

Site	n	5-year OS (%)	95% CI
Skin	664	87.1	83.5-90.0
Thyroid	179	85.8	78.0-90.9
Ocular	1,108	82.4	79.4-85.0
Salivary	719	82.4	78.7-85.5
Connective tissue	190	81.7	73.9-87.4
Breast	277	78.9	72.2-84.2
Gastric	3,207	72.1	70.3-73.9
Lung	737	72.1	67.9-75.9
Bowel	791	71.1	67.2-74.7
Other	392	72.7	67.0-77.7

8046 General Poster Session (Board #32C), Mon, 1:15 PM-5:15 PM

Early determination of treatment sensitivity in HIV-related Hodgkin lymphoma by FDG-PET/CT after two cycles of ABVD chemotherapy: A European Cooperative Study Group on AIDS and Tumors (GECAT) study.

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Background: The high prognostic value of FDG-PET/CT performed after 2 cycles of chemotherapy for HIV negative Hodgkin lymphoma (HL) is well known. However, experience with PET in HIV-related HL needs to be further studied as nodal FDG uptake can be observed in various opportunistic infections and AIDS-related conditions. **Methods:** A total of 45 consecutive HL patients (pts) were enrolled in 10 centers from the GECAT. There were 42 males and 3 females. Median age was 46 yo, range [26;64]. Median CD4 count was 391/mm^3, range [33;1191]. Viral load was negative in 38 pts (84%) and uncontrolled in 5 pts (11%). Forthy three pts (96%) received concomitant HAART. HL was staged III-IV in 25 pts. International Prognostic Index scored 3-5 in 24 pts. All PET studies were performed after 2 ABVD cycles. They were scored, blinded to treatment outcome, according to the 5-point Deauville visual scale. It was considered as negative when scored 1-3 (i.e tumor FDG uptake less or equal than liver uptake) and positive when scored 4-5 (i.e. more than liver uptake or new lesions). Chemotherapy was not modified : 4-8 cycles of ABVD, as initially planned. **Results:** Overall, 35 pts (78%) achieved a CR after the end of treatment. Three pts received Involved Field Radiation Therapy. At a median follow-up of 18 months, 3 pts relapsed and 2 of them died from HL. The 2 yr OS and PFS were estimated at 94 and 90%, respectively. PET after 2 cycles of ABVD was negative in 40 pts (89%) and positive in 5 pts (11%). Patients with negative PET had a significantly better outcome than those with positive PET in term of 2 yr PFS (94% vs 60%, P=0.005), and 2 yr OS (100% vs 60%, P=0.0002). The negative predictive value was estimated at 97% and specificity at 93%. All patients who were PET-negative after the 2nd cycle stayed PET-negative after the 4th cycle and entered a durable CR. **Conclusions:** This largest study in HIV-positive HL showed that interim PET could play a central role in driving risk-tailored treatment. In further studies, de-escalation strategies should be tested for patients responding after 2 cycles of ABVD and those not reponding should be managed with intensive salvage strategies.

8047 General Poster Session (Board #32D), Mon, 1:15 PM-5:15 PM

The utility of serum lactate dehydrogenase (LDH) in the follow-up of patients with diffuse large B-cell lymphoma (DLBCL).

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Background: The prognostic significance of high serum LDH is well established for both indolent and aggressive lymphomas at diagnosis. The performance characteristics of LDH in predicting relapse after treatment in patients (pts) with DLBCL has not been well studied. The determination of utility of LDH monitoring in pts with DLBCL would have widespread practice implications. **Methods:** We searched the Nebraska Lymphoma Study Group database to identify pts with DLBCL who were treated with a rituximab-based regimen, from 2000 to 2010, and sustained a complete response (CR). For the pts who relapsed (RP), after sustaining a CR, we collected the LDH level at relapse and the LDH level 3 months prior (considered baseline). For pts who never relapsed (NR), we collected the last 2 LDH levels at follow-up; levels had to be at least 3 months apart. The relative increase of LDH was compared, to baseline, among RP vs. NR. **Results:** We identified 129 pts, 15 pts were excluded from the analysis as their LDH results were not available, 27 relapsed and 87 didn't. Median age of pts was 57 years. Only 9/27 RP (33%) had increase in LDH above upper limit of normal (ULN) at relapse. The mean increase in LDH at relapse was 1.2 fold above the ULN for RP vs. 0.83 for NR ($p=0.59$). The mean increase in LDH, from baseline, was 1.1 fold in NR vs. 1.3 in RP ($p=0.3$). The likelihood ratio (LR) of relapse was 4.65 for pts who had 1.5 fold increase in LDH above baseline (1.5xLDH) vs. those who didn't ($p=0.03$). The sensitivity, specificity, positive and negative predictive values of 1.5xLDH for detecting relapse, compared to clinical and imaging findings were 0.18, 0.95, 0.55, and 0.79 respectively. Also, 1.5xLDH at relapse was significantly associated with the presence of fever ($LR=5.74$; $p=0.03$) but not with other symptoms including drenching night sweats, anemia, or new/progressive lymphadenopathy. **Conclusions:** A 1.5 fold increase in LDH, over a period of 3 months, is associated with increased likelihood of relapse from DLBCL. Modest elevations in LDH (<1.5 fold of baseline) doesn't seem to be associated with relapse. LDH, when elevated at least 1.5 fold of baseline, is a specific (i.e. 56%), but not a sensitive (i.e. 19%) marker, for relapse of DLBCL.

8048 General Poster Session (Board #32E), Mon, 1:15 PM-5:15 PM

Association of low expression of VEGF121 soluble isoform with prognostic impact and survival in patients with activated B-cell-like (ABC-like) diffuse large B-cell lymphoma (DLBCL) from the CORAL trial.

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Background: Gene expression profiling (GEP) has demonstrated that survival of DLBCL is influenced by the origin of the tumor cells (COO), germinal center-like (GC-like) vs ABC-like (Alizadeh et al. 2000), but also by the tumor microenvironment, particularly the angiogenesis (Lenz et al., 2008). To further understand the prognostic impact of these tumoral characteristics, we analysed the prognostic impact of COO and the expression of biomarkers involved in angiogenesis, in a selected population of 36 patients with relapsed/refractory DLBCL included in CORAL (Gisselbrecht, ASCO 2011). **Methods:** Expression of 5 biomarkers including VEGF (isoforms 121, 165, and 189), and their receptors (VEGFR-1 and R-2) was assessed by quantitative qRT-PCR after total RNA extraction and cDNA synthesis of tumor samples. COO was determined by GEP, and progression free- (PFS) and overall- (OS) survivals were analysed. **Results:** In the study population, VEGF121 expression below the median was associated to a better outcome, with 4 year-PFS at 63% *vs* 33% (p=.053), and a 4-year-OS at 79% *vs* 37% (p = 0.032), respectively. VEGF-165 -189, VEGF-R1, -R2 did not have any significant impact. Eighteen patients were predicted as ABC-like DLBCL and 18 as GCB-like DLBCL. In patients with ABC-like DLBCL, low VEGF121 level was associated to a significantly better survival than in those with high VEGF121 level: 4-year OS at 100% *vs* 36% (p=.011). The type of induction treatment, R-ICE or R-DHAP, did not influence the outcome. The differences in outcome according to VEGF isoforms were not significant among CGB patients. **Conclusions:** Our data suggest that angiogenesis plays a central role in ABC-like DLBCL. VEGF121 seemed to be a key player in this context and should be proposed as a target in the treatment of patients with ABC-like DLBCL.

8049 General Poster Session (Board #32F), Mon, 1:15 PM-5:15 PM

Transformation of follicular lymphoma in the era of immunochemotherapy: A population-based study from British Columbia.

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Background: Several published series have established that the risk of transformation of follicular lymphoma (FL) to aggressive lymphoma is approximately 3% /year (15%-20% at 5 years). The addition of rituximab (R) to chemotherapy (immuno-chemotherapy) has significantly improved the outcome of patients with FL. The impact of immuno-chemotherapy on the risk of transformation remains unknown. We assessed whether the introduction of immuno-chemotherapy has altered this risk. **Methods:** We examined the Lymphoid Cancer Database of the British Columbia Cancer Agency for FL patients treated with immuno-chemotherapy. Inclusion criteria: FL grades 1-3A by WHO criteria; only patients requiring treatment at diagnosis were included. Exclusion criteria: FL grade 3B or composite histology (FL and DLBCL) at diagnosis; pts who received anthracycline-based chemotherapy; and HIV positivity. The diagnosis of transformation was confirmed by biopsy when possible (n=19; 79%) but patients who were considered to have transformed based on pre-defined clinical assessment (n=5; 21%) were also included in the analysis. **Results:** We identified 261 pts with FL grade 1-3A requiring treatment at diagnosis, who received immuno-chemotherapy; median f/u 47 months (0.2-116), median age, 61 y (34-86). Treatment: 243 (93%), R-CVP of which 145 (59%) also received maintenance R; 9 (4%), R-Fludarabine combination. 24 pts developed transformed aggressive lymphoma. The risk of transformation for the entire group was approximately 2% per year or 10% at 5 years. However, pts treated with maintenance R (n=151) had a lower risk of transformation compared to pts who only received R-chemo at induction (n= 110), 8% vs 20% at 5 years respectively, (P= 0.003). The post-transformation outcome remains poor with a median survival of 6 months. **Conclusions:** We and other groups have demonstrated that the risk of transformation from FL to aggressive lymphoma is approximately 15% to 20% by 5 years. Our study suggests that the introduction of immuno-chemotherapy has reduced this risk to less than 10%. This effect is particularly apparent when patients receive maintenance R. The outcome for patients who develop transformation remains poor.

8050 General Poster Session (Board #32G), Mon, 1:15 PM-5:15 PM

Long-term follow-up results of a phase I/II study of concurrent chemoradiotherapy for localized nasal NK/T-cell lymphoma (NKTCL): JCOG0211.

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Background: Concurrent chemoradiotherapy has been regarded as one of the standard management for localized nasal NKTCL. However, its long-term efficacy and toxicity is not known. **Methods:** The JCOG0211 trial is a phase I/II study of concurrent chemoradiotherapy consisting of radiotherapy (RT) of 50 Gy and 3 cycles of DeVIC (carboplatin, etoposide, ifosfamide, dexamethasone) for newly diagnosed, localized nasal NKTCL (JCO 2009). Patients (Pts) with newly diagnosed, localized diseases (IE & contiguous IIE with cervical node involvement) who were 20-69 yrs of age with PS 0-2 were eligible. 3-D conformal RT planning with a wide margin (+ 2 cm to the gross tumor, the entire nasal cavity and the nasopharynx) and a 2-step cone down were required. 33 pts were enrolled in the study, 27 of whom were treated with RT and a 2/3-dose of DeVIC, which was selected as the recommended phase II dose in the preceding phase I portion of the trial. All pts completed RT without any protocol violations. Long-term follow-up results on overall survival (OS), progression-free survival (PFS) and toxicity were evaluated. **Results:** The median follow-up was 69 months (range, 62-96). The pt (N=33) characteristics were as follows: median age 54 yrs (range, 21-68); stage IIE 33%; B symptom (+) 36%; elevated serum LDH 21%. %5-yr OS and PFS were 73% (95%CI, 54-85%) and 67% (95%CI, 48-80%), respectively. 11 pts (33%) experienced disease recurrence. Two achieved a 2nd CR by salvage chemotherapies followed by allogeneic stem cell transplantation, and the remaining 9 pts died of disease. There was no observed death and disease progression after 34 and 31 months, respectively. One pt experienced Grade 3 irregular menstruation for 3 years. No other Grade 3 or 4 late non-RT-associated adverse events (AEs) were observed. One pt received plastic surgery due to Grade 4 RT dermatitis. No other Grade 3 or greater RT-associated late AEs were encountered. **Conclusions:** Both survival benefit and disease control from concurrent chemoradiotherapy with RT and DeVIC are maintained during a 5-yr follow-up, indicating the excellent efficacy of this approach as a first-line therapy for localized nasal NKTCL. Long-term toxicity is acceptable.

8051 General Poster Session (Board #32H), Mon, 1:15 PM-5:15 PM

Efficacy of alemtuzumab (ALZ) in combination with dose-adjusted EPOCH (DA-EPOCH) in untreated nodal peripheral T-cell lymphoma (PTCL).

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Background: The survival of patients (pts) with PTCL (excluding ALCL) is disappointing following anthracycline-based therapy and novel approaches are needed. In diffuse large B-cell lymphoma, the addition of anti-CD20 therapy to CHOP has significantly improved outcome and we investigated if in PTCL, adding ALZ – which targets CD52, expressed on most PTCLs – was feasible and improved outcome. **Methods:** This was a single-center phase I/II trial of ALZ, in combination with DA-EPOCH in patients with treatment-naïve CD52+ PTCL. The MTD of 30 mg ALZ was combined with DA-EPOCH for phase II evaluation resulting in an intention-to-treat population (ITTP) of 30 pts. **Results:** Patient (n=30) characteristics: median (range) age 50 (17-77); M:F 1:1; Stage III/IV 27 (90%); IPI ≥2 22 (73%). Histologies: ATLL 11 (37%), PTCL NOS 6 (20%), AITL 5 (16%), Hepatosplenic 3 (10%), Peripheral T NK cell 2 (7%), Other 3 (10%). At 67 months median follow-up, 11 patients were alive, 10 disease-free. Median overall (OS) and event-free survivals (EFS) were 15.4 and 6.7 months respectively. Outcome was substantially better for pts with 'nodal' (AITL, PTCL-NOS, Other) compared to 'non-nodal' (ATLL and 'extranodal' histologies) PTCL subtypes. 3-year OS for the two groups was 58.3% and 27.8% respectively (p=0.082); 3-yrs EFS was 50% (median 27.0 months) and 22.2% (median: 5 months) respectively (p=0.041). Half of the 'nodal' PTCL pts had sustained long-term complete remissions demonstrated by a plateau in the EFS curve at 27 months. There were 3 treatment related deaths: 2 from neutropenic sepsis; 1 from toxoplasma. Other toxicities included CMV and BK virus reactivation in 53% and 30% respectively. Febrile neutropenia was seen in 20% and grade 4 thrombocytopenia in 12 % of cycles. **Conclusions:** Although it has significant infectious toxicity, ALZ 30mg and DA-EPOCHin untreated PTCL is feasible and associated with a long-term favorable outcome in nodal but not extranodal or leukemic PTCL. A phase III study of ALZ 30mg with anthracycline-based therapy is ongoing and we await the results with interest.

8052 General Poster Session (Board #33A), Mon, 1:15 PM-5:15 PM

Radioimmunotherapy efficiency and safety in consolidation and relapse treatment of aggressive B-cell non-Hodgkin lymphoma: An updated analysis of 230 patients of the international RIT-network.

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Background: In aggressive lymphoma, few reliable clinical data about the use of radioimmunotherapy exist. Pts. with DLBCL registered in the international RIT-Network (RIT-NT) were analyzed with regard to Indication, line of therapy and outcome. **Methods:** The RIT-NT recruited 1111 pts. between Dec. 2006 and 2010. It is a web-based registry that collects observational data from RIT-treated patients with malignant lymphoma. 232 pts. with DLBCL registered in the database were evaluated in the analysis. **Results:** 232 pts with DLBCL are registered, 17 pts were excluded. Histologic subtypes: 190 DLBCL, 15 primary mediastinal, 9 large cell anaplastic, 1 intravascular. Median age was 62 years (range 17-88), 27% of pts >70 years old. Stage I 16pts, II 54 pts, III 60 pts, IV 68 pts; 6 extranodal involvement, for 11 pts. stage is not documented. 187 pts had 1-3 previous chemotherapies (Ctx), 21 pts 4-6 previous Ctx, 1 pts had 7 previous Ctx, for 6 pts. previous Ctx is not documented. 15 pts. had previous RIT and 24 pts a stem cell transplantation prior to RIT. 6 pts had bone marrow infiltration prior to RIT, 3 with more than 25%. 87 pts had RIT as first line (8 pts. conditioning, 68 pts consolidation, 1 primary therapy, 10 other), and 84 pts received RIT in relapse (2d to 8 th. line therapy) (2 pts. conditioning, 31 pts consolidation, 26 recurrence, 19 therapy refractory, 6 other). Grade IV° hematotoxicity occured for neutrophils and platelets, grade III° for hemoglobin after RIT. Median time to recovery of blood count was 81 days (range 0-600 days). ORR was 63,3 %; CR 54,4%; PR 8,8%, SD 0,9%, PD 23,7%, N.D. 12%. CR rate first line was 76,3 %, for relapse 44,3%. Mean overall survival (OS) in first line was 26,5 months 14,3 months for pts. treated in relapse or refractory disease. **Conclusions:** Most pts. with DLBCL in the RIT-N received RIT as consolidation after first line therapy with excellent CR rates and OS compared to published data from risk groups . In relapsed DLBCL RIT is a safe and feasible treatment leading to satisfactory response rates with low toxicity. A prospective randomized phase III trial in front line DLBCL is currently planned (ZEST).

8053 General Poster Session (Board #33B), Mon, 1:15 PM-5:15 PM

LR-CD: Lenalidomide combination therapy for untreated low-grade B-cell NHL.

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Background: Lenalidomide (LEN) is an immunomodulatory agent that has shown significant single-agent anti-lymphoma activity in patients with relapsed disease and in combination may enhance the efficacy of rituximab by various mechanisms. There is limited data on the role of LEN in combination regimens for treatment-naïve patients. This phase II single arm trial was designed to evaluate tumor response, toxicity (AE) and survival with a combination of LEN, rituximab, cyclophosphamide (CTX) and dexamethasone (DEX) (LR-CD) in symptomatic untreated patients with low grade B-cell non-Hodgkin lymphoma. **Methods:** Eligibility required age ≥18, ECOG PS ≤2, confirmed diagnosis of low-grade B-cell lymphoma (FL1-2, SLL, MZL or LPL/WM), measurable nodes ≥2cm or IgM ≥400mg/dL(LPL/WM), ANC ≥1400/mm^3, platelets ≥100,000/mm^3, creatinine ≤2mg/dL, signed informed consent and in need of therapy. Treatment consisted of IV rituximab 375mg/m^2 D1, oral LEN 20mg D1-21, CTX 250mg/m^2 D1, 8, 15, DEX 40mg D1, 8, 15, 22 and ASA 325 mg daily in a 28 day cycle. Treatment continued 2 cycles beyond best response (max 12). Toxicity was assessed by NCI CTCAE v3.0. **Results:** 28 patients have enrolled at Mayo Clinic with 25 evaluable for toxicity and 21 for response: Median age 65(43-83), 72% male, FL 24%, MZL 28%, LPL/WM 38%, and SLL 4%. Median number of cycles given was 5. Overall response in 21 patients with response data is 95% (95% CI 76-100%) with 19% CR (95% CI 5-42%), and 76% PR (confirmed and unconfirmed, 95% CI 53-92%). The ORR in 8 patients with LPL/WM with response data was 88%, all PR (95% CI 47-100%). At a median f/u of 14.7 months 96% are alive without progression. 1 death (unrelated) occurred 7.7 months after completing 12 cycles of treatment. The most common grade ≥3 AEs were neutropenia (37.5%), leukopenia (16.7%), anemia (12.5%) and fatigue (12.5%). **Conclusions:** The combination LR-CD with the novel agent LEN is feasible, well tolerated and produces high response rates in symptomatic patients with low grade B-cell NHL. Toxicities are manageable and similar to reported data of single agent LEN.

8054 General Poster Session (Board #33C), Mon, 1:15 PM-5:15 PM

Final results of phase I/II trial of vorinostat in combination with cyclophosphamide, etoposide, prednisone, and rituximab (R-CVEP) for elderly patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL).

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Background: Standard treatment of relapsed/refractory DLBCL in elderly patients who are not candidates for autologous stem cell transplantation (auSCT) has not been established. Cyclophosphamide (C), etoposide (E), prednisone (P) and procarbazine (CEPP) has been used by many clinicians based on limited data (Blood 76: 1293-98, 1990). Vorinostat (V) is a histone deacetylase inhibitor that is approved for relapsed cutaneous T-cell lymphoma and has activity in B-cell lymphomas. This trial defined the maximum tolerated dose (MTD) of V added to standard therapy and determined the response rate of this combination. **Methods:** Patients ≥age 60 with relapsed/refractory DLBCL not candidates for auSCT were enrolled on R-CVEP (R 375mg/m^2 IV, d1; C 600mg/m^2 d1 and 8, E 70mg/m^2 IV d1, 140mg/m^2 d2 and 3; V PO and Pred 60mg/m^2 PO d1-10) every 28 days for 6 cycles. In the phase I component V was administered at doses of 300mg/d or 400mg/d for 10 days. The phase I was a 3 + 3 design and the phase II a two stage design requiring 8/20 complete responses (CR) for expansion. Assessment of response utilized end-of-treatment positron emission tomography (PET) (JCO 25: 579-86, 2007). Quality of life (QOL) was measured with the FACT-Lym v.4. **Results:** 27 pts. were enrolled. 1 died before treatment. For 26 pts: median age 76 yrs. (69-88), 14 females and 12 males, baseline PS (ECOG) 1 (0-2). Median follow-up for survivors: 9.2 mo. Phase I: 6 pts. at 300mg/d (no dose-limiting toxicity-DLT), 6 pts. at 400mg/d (2 grade 3 neutropenia = DLT). MTD 300mg/d x 10d. For 20 pts. at V 300mg/m^2 (6 phase I + 14 phase II): 2 off study for toxicity, 1 withdrew consent, 6 CR (30%), 5 partial response (PR) (25%), 6 progressed (30%). Phenotypic overall responses (OR): germinal center (GC) 4/8 (2 CR), non-GC 6/10 (3 CR), transformed CLL 1/2 (1 CR). Median progression-free survival: 10 mo. QOL results will be presented. **Conclusions:** OR rate for V added to conventional chemotherapy and R was 55% (CR 30%, PR 25%) in relapsed/refractory DLBCL in elderly pts. not candidates for auSCT. This could provide a baseline for comparison with future clinical trials in this understudied population.

8055 General Poster Session (Board #33D), Mon, 1:15 PM-5:15 PM

Association of prior rituximab exposure among patients undergoing autologous stem cell transplantation for relapsed/refractory diffuse large B-cell lymphoma with inferior outcomes in males compared with females.

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Background: The combination of rituximab with CHOP remains the standard upfront therapy of patients (pts) with advanced diffuse large B-cell lymphoma (DLBCL). Gender disparity in survival of pts with DLBCL appears to be significantly modified by the use of rituximab in both upfront (Ngo, 2008; Pfreundschuh, 2009; Riihijarvi, 2010) and post-transplant maintenance (CORAL trial) settings. The presence of interaction between gender and prior rituximab exposure remains unknown in pts with relapsed/refractory DLBCL undergoing autologous stem cell transplantation (ASCT). **Methods:** We conducted a retrospective cohort study of 320 consecutive pts who underwent ASCT for relapsed/refractory DLBCL at our center from 01/1998 to 12/2010. Relapse-free survival (RFS) and overall survival (OS) were estimated by Kaplan-Meier method and by Cox proportional hazards regression analysis in SAS 9.1 (Cary, NC). **Results:** Among all pts (median age=54 yrs (IQR, 45-61); 92% Caucasians) 210 (66%) were males and 110 (34%) were females. 85 pts (27%) received more than two prior chemotherapy regimens. 174 pts (55%) had pre-ASCT exposure to rituximab as a part of induction or salvage regimens. Preparative regimen for ASCT uniformly consisted of Bu/Cy/VP-16. In the stratified univariate analysis of pts treated with rituximab prior to the ASCT, male pts had inferior RFS ($p=0.02$; hazard ratio [HR]=1.86, 95% CI, 1.09-3.18) and OS ($p=0.03$; HR=1.94, 95% CI, 1.05-3.58). In pts who did not receive rituximab prior to the ASCT, no difference in RFS or OS according to gender was observed (all $p>0.4$). Gender disparity among rituximab recipients was even more evident for both RFS ($p=0.004$; HR=2.22, 95% CI, 1.28-3.83) and OS ($p=0.005$; HR=2.42, 95% CI, 1.3-4.5) in the multivariable analyses controlling for age at transplant, number of prior chemotherapies, and pre-ASCT disease response. **Conclusions:** Our data support an emerging concern that male patients with DLBCL have inferior outcomes when treated with rituximab. The present study has extended this observation to pts with relapsed/refractory DLBCL treated with ASCT.

8056 General Poster Session (Board #33E), Mon, 1:15 PM-5:15 PM

Effect of short-duration chemoimmunotherapy plus radioimmunotherapy on response rates in relapsed follicular lymphoma: A U.K. NCRI Lymphoma Group Study, CR UK/07/038.

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Background: Radioimmunotherapy (RIT) and rituximab (R) maintenance have been investigated after chemotherapy (CT) or R-CT in first line treatment of follicular lymphoma (FL), but less is known about the efficacy of RIT after R-CT in relapsed FL. This phase II study was conducted to examine efficacy and safety of abbreviated R-CT followed by ^{90}Y Ibritumomab tiuxetan in patients with recurrent FL. **Methods:** Patients (pts) had FL, at 1st or 2nd relapse after response to R-CT or CT alone. All had WHO/ECOG performance status $\leq$2, and adequate bone marrow (BM), kidney, liver and cardiac function. BM involvement by lymphoma had to be $<$25% prior to infusion of ^{90}Y Ibritumomab tiuxetan, but could be higher at study entry. Pts received 3 cycles of either R-CHOP or R-CVP, followed by ^{90}Y Ibritumomab tiuxetan (15MBq/Kg, maximum 1200 MBq). No maintenance R was given. **Results:** 52 pts were enrolled from 6/2008 to 7/2010. Median age was 62 years (range 31-87). 46% had high FLIPI score at entry, 31% intermediate. 80% were at 1st recurrence. Median duration of best prior remission was 27.7 months. 65% pts had previously received R and 25% doxorubicin. 71% pts had R-CHOP and 29% R-CVP, prior to RIT. Overall response rate (ORR) after 3 cycles R-CT was 94% (CR/CRu 10%) and after RIT ORR 96% (CR/CRu 28%). Grade 3/4 thrombocytopenia occurred in 58% pts (median duration 16 days): 3/52 pts after R-CT and 27/52 after RIT. Grade 3/4 neutropenia occurred in 62% pts: 15/52 pts after R-CT and 27/52 after RIT. 5 pts had a total 8 grade 3 infections, only 1 attributable to RIT. 6 pts required platelets and 4 red cell transfusions. 1 pt developed myelodysplasia 10 months after ^{90}Y Ibritumomab tiuxetan, but no other second malignancy was recorded. PFS was 31.4 months (95% CI 15.8 - not reached). There was no difference in PFS according to FLIPI score at entry or reinduction CT (R-CHOP vs R-CVP). Pts with CR/CRu following RIT showed a trend to improved PFS compared to those with PR (12 month PFS 90% versus 63%, p=0.06). **Conclusions:** Abbreviated R-CT and consolidation with ^{90}Y Ibritumomab tiuxetan is an option for pts with recurrent FL, with responses of comparable duration to those seen after a full course R-CHOP.

8057 General Poster Session (Board #33F), Mon, 1:15 PM-5:15 PM

Phase I study cohort evaluating an optimized administration schedule of SAR3419, an anti-CD19 DM4-loaded antibody drug conjugate (ADC), in patients (pts) with CD19 positive relapsed/refractory b-cell non-Hodgkin's lymphoma (NCT00796731).

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Background: The recommended dose (RD) of SAR3419 administered intravenously every 3 weeks (q3w) for 6 cycles is 160 mg/m2 and is 55 mg/m2 when administered weekly (q1w) for 8-12 doses. Reversible corneal deposits were dose limiting (DLT) in the q3w schedule. The q1w schedule was well tolerated and active. However, based on the occurrence of late/cumulative adverse events (AE) at the RD supported by pharmacokinetic (PK) analyses showing ADC plasma accumulation after 4 weekly doses, an optimized schedule consisting of 4 weekly doses followed by 4 bi-weekly doses at the RD was tested. **Methods:** The q1w study was extended to treat 25 pts with the optimized schedule for 8 to 12 doses. **Results:** Twenty-one pts were evaluable. Main histologies were diffuse large B-cell (DLBCL) (9; 43%) and follicular (6; 29%). Median number of prior regimens was 2 [1-8], 6 pts received prior autologous transplantation and 95% of pts were Ann Arbor stage III-IV at study entry. Median number of doses received was 8 as planned with a median relative dose intensity of 1.0 [0.8-1.0]. Most frequent AEs were asthenia (1 pt with grade 3) and gastrointestinal disorders in 7 pts each. No AE fulfilled the defined DLT criteria. Reversible grade 1 blurred vision/corneal event occurred in 1 pt. Grade 3-4 haematological toxicities were minor consisting of non complicated neutropenia in 4 pts, thrombocytopenia in 2 pts and anemia in 1 pt with no transfusion support. Six (29%) pts, among them 3 with DLBCL, achieved an objective response including 3 CRu (1 in a pt refractory to last regimen). In addition, 9 (43%) pts had stable disease. Response duration was [8-35+] weeks, 5 pts still responding at the cut-off date. **Conclusions:** The optimized administration schedule shows an improved safety profile compared to prior tested schedules. The clinical efficacy is preserved essentially in aggressive lymphoma. The optimized schedule is being assessed in 2 phase II studies evaluating SAR3419 either as a single agent or in combination with rituximab in pts with DLBCL histology.

8058 General Poster Session (Board #33G), Mon, 1:15 PM-5:15 PM

Hodgkin's disease and HIV infection (HD-HIV): Prognostic factors in 596 patients (pts) within the group of European Cooperation on AIDS and Tumors (GECAT).

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Background: Hodgkin's disease (HD) is the most common non-AIDS defining tumour diagnosed in HIV setting. The introduction of highly active antiretroviral therapy (HAART) has opened a new prospective in the treatment of pts with HD-HIV as the better control of the underlying HIV infection allows the use of more aggressive chemotherapy regimens, including high dose chemotherapy. However, up to now prognostic factors on overall survival (OS) or time to treatment failure (TTF) have not yet been identified. **Methods:** In order to identify prognostic factors, we analyzed data on 596 pts with HD-HIV diagnosed and treated in 90 different Institution of 6 European countries from October 1983 to March 2010. All factors were analyzed for OS and TTF. **Results:** 86% of pts were male and the median CD4 cell count was 224/dl (range 3-1274); 52% of pts had mixed cellularity subtype, stages III-IV were diagnosed in 72% of cases and 55% of pts had extranodal involvement (bone marrow 35%, spleen 21%, liver 14%). The table summarizes the results of multivariate analysis. **Conclusions:** We identified a new "European Score" for HD-HIV able to predict different outcomes in these patients. This score should be considered for future prospective studies.

Factors	Overall survival	Time to treatment failure
IPS < 2	1	1
IPS > 2	2.33 (1.61-3.39) p<0.0001	1.57 (1.09-2.26) p=0.02
CD4 > 200	1	1
CD4 < 200	1.63 (1.16-2.29) p=0.005	1.43 (1.02-2.01) p=0.04
European Score		
0	1	1
1	2.06 (1.40 - 3.02)	1.64 (1.17 - 2.30)
2	3.08 (2.13 - 4.45) p<0.001	2.31 (1.66 - 3.20) p<0.001

8059 General Poster Session (Board #33H), Mon, 1:15 PM-5:15 PM

High affinity CD3 RECRUIT TandAb for T cell-mediated lysis of $CD19^+$ tumor B cells.

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Background: CD19 is expressed from early B cell development to the differentiation into plasma cells and is an attractive target for B cell malignancies either lacking CD20 expression or refractory to anti-CD20 antibody therapies. T cells are potent tumor killing effector cells that are not recruited by native antibodies. The CD3 RECRUIT-TandAb AFM11, a human bispecific tetravalent antibody with two binding sites for both CD3 and CD19, is a novel therapeutic for the treatment of NHL that harnesses the cytotoxic nature of T cells. **Methods:** A bispecific anti-CD19/anti-CD3 tetravalent TandAb with humanized and affinity matured variable domains was constructed. The TandAb's binding, T-cell mediated cytotoxic activity, and cytokine release were characterized in a panel of in vitro assays. In vivo efficacy was evaluated in a murine NOD/scid xenograft model reconstituted with human PBMC. **Results:** AFM11 mediates highly potent target tumor cell lysis in cytotoxicity assays: EC_{50} values are low to sub-picomolar range in a panel of $CD19^+$ cell lines and primary B-CLL tumor cells. The cytotoxic activity of tetravalent AFM11 is superior to that of alternative bivalent antibody formats possessing only a single binding site for both CD19 and CD3. High affinity binding of AFM11 to CD19, and more so to CD3 (low to sub-nanomolar Kd), is essential for efficacious T cell recruitment. The high affinity bivalent binding of AFM11 to CD3 does not trigger T cell activation in the absence of $CD19^+$ target cells in functional in vitro assays. AFM11 activates T cells only in the presence of its targets and mediates lysis while sparing antigen-negative bystanders. AFM11 induces down-modulation of the CD3/TCR complex in the absence of target cells and at high concentrations. Also, AFM11-treated T cells can be re-engaged for target cell lysis. These features of AFM11-induced T cell activation may contribute additional safety with no compromise of efficacy. Finally, AFM11 demonstrates a robust dose-dependent inhibition of subcutaneous Raji tumors in mice. **Conclusions:** AFM11 is a novel highly efficacious drug candidate for the treatment of B cell malignancies with an advantageous safety profile.

8060 General Poster Session (Board #34A), Mon, 1:15 PM-5:15 PM

Characteristics and outcomes of extranodal NK/t-cell lymphoma (ENKL): A North American (NA) multi-institutional experience.

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Background: ENKL is a rare and aggressive subtype of peripheral T-cell lymphoma. Due to its geographic predilection there is a paucity of data on clinical experiences from non-Asian countries. The purpose of this study was to analyze characteristics and outcomes of patients (pts) with ENKL identified from major academic centers in NA. **Methods:** Pts with newly diagnosed CD56+ ENKL were retrospectively identified. Analyses included disease characteristics, ethnicity, therapy, and outcomes. **Results:** 115 pts (63.5% Caucasian, 20% Asian, 16.5% other) were identified across 10 centers diagnosed between 5/1990-5/2011 (Era 1: pre-2000, n=16; Era 2: 2000-2005, n=45; Era 3: post-2005, n=54). Median age was 52 years (19-88). 75 (65%) had stage I/II disease and were treated with combined modality therapy (CMT) n=48, chemotherapy (CT) n=14 or radiotherapy (RT) n=14. 40 pts had stage III/IV disease and were treated with CT (n=23), CMT (n=12) or RT (n=5). CT regimens used alone or in CMT were either anthracycline-based (n=68) or other (n=29). 63% of stage I/II pts and 40% with stage III/IV achieved complete remission (CR). 30 pts underwent a stem cell transplant (SCT); 14 in first CR and 16 at progression/relapse (autologous, n=21; allogeneic, n=9). Pts with stage I/II disease had a better progression-free survival (PFS) and overall survival (OS) compared with stage III/IV (12 vs 5.2 months ($p=0.003$) and 41.5 vs 8.9 months ($p<0.0001$), respectively). For all stages, treatment with CMT compared with CT or RT alone was also associated with better PFS and OS, 18.0 vs 3.9 months ($p<0.0001$), and 41.5 vs 10.2 months ($p=0.002$) respectively. Non-anthracycline-based regimens were associated with better PFS ($p=0.001$) and OS ($p=0.045$). No survival differences were seen between Asian and non-Asian pts. **Conclusions:** This series represents one of the largest experiences of ENKL in NA. Our data are consistent with Asian studies in: 1) majority of pts present with early stage disease; 2) overall poor outcome; 3) superiority of CMT and non-anthracycline regimens. Advances in understanding biology and international collaborative efforts are required to improve outcome in this rare entity.

8061 General Poster Session (Board #34B), Mon, 1:15 PM-5:15 PM

Determinants of and outcomes associated with chemoimmunotherapy dose density in elderly subjects with diffuse large B-cell lymphoma (DLBCL).

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Background: RCHOP is the standard first line therapy for DLBCL but elderly patients often receive suboptimal doses. Relative dose intensity (RDI) less than 70-90% has previously been associated with inferior survival in CHOP treated patients. We now investigate the clinical determinants of immunochemotherapy dose delivery and comparative effectiveness of dose intensity on lymphoma-specific outcomes in persons over the age of 60. **Methods:** SPORE MER (Molecular Epidemiology Resource) is a prospectively accrued observational study in which University of Iowa and Mayo Clinic patients with a diagnosis of Non Hodgkins lymphoma have been enrolled since 2003. We reviewed data from the Iowa patients along with medical records from DLBCL patients over the age of 60 treated with anthracycline based chemo immunotherapy consecutively enrolled up through to December 2009. Statistical tests of associations between RDI and clinicopathologic factors, as well as survival outcomes, were performed. **Results:** We identified 92 patients over the age of 60. The median age was 70. 47 subjects experienced at least 1 dose reduction, 26 subjects had dose delays, and 20 subjects were unable to complete therapy. RDI ranged from 0.30-1.70 (median 0.92) for doxorubicin and from 0.29-1.70 (median 0.97) for cyclophosphamide. 24 and 19% of subjects received $< 80\%$ of RDI for dox and cy respectively. Age ($p < 0.001$ for both dox and cy) and performance status ($p = 0.04$ for dox) but not number of medications, ACE27 co-morbidity score, body surface area, nor need for acute care visits were associated with decreased RDI. Adjusted for IPI, RDI did NOT have a significant effect on event-free or lymphoma-specific survival. **Conclusions:** Among clinical variables, age is the dominant variable associated with delivery dose intensity for chemotherapy in elderly patients treated for DLBCL; and among elderly patients receiving chemo immunotherapy, we did not find an association between dose intensity and lymphoma-specific outcomes.

	Doxorubicin		Cyclophosphamide	
	Correlation	p value	Correlation	p value
Age at Rx	-0.348	.0007	-0.358	.0006
BMI	0.097	.359	0.205	.055
# of meds	0.050	.636	-0.007	.942
LVEF	0.096	.458	0.011	.933

8062 General Poster Session (Board #34C), Mon, 1:15 PM-5:15 PM

Biweekly regimen of nonpegylated liposomal doxorubicin with cyclophosphamide, vincristine, and prednisone plus rituximab (R-COMP-14) as primary treatment for diffuse large B-cell lymphoma (DLBCL): Long-term follow-up of a phase II study.

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Background: To evaluate the efficacy and toxicity of dose-dense biweekly schedule of (R-COMP-14) in patients newly diagnosed of agrressive diffuse B cell lymphomas (DLBCL). **Methods:** In this single-arm, open-label, multicenter trial, 60 pts were included between 2004 to 2008. Received rituximab (375 mg/m^2) D1 + cyclophosphamide (750 mg/m^2)D1 + vincristine (1.4 mg/m^2; max. 2 mg)D1 + prednisone (100 mg/d D1 and D5) and non-pegylated liposomal doxorubicin (50 mg/m^2) every two weeks. Response was assessed at cycle 3, and patients with complete or partial response received 5 additional courses. Granulocyte colony-stimulating factor (G-CSF). Pegfilgrastim was administered on day 2. The primary efficacy endpoint was (CR) and objective response rate (ORR). Survival follow-up data were updated. **Results:** 59 evaluable patients with a median age of 50 years (21-65) were analyzed. Clinical Characteristics: 22 Pts stage I-II (aaIPI≥1 (37%), 17 (29%) stage III, and 19 (32%) in stage IV. aaIPI=1 41(67%), aaIPI2/3= 18(33%).LVEF basal: 65,5[50-93]. Extra-nodal disease: 42%. B symptoms: 44.1%. The mean calculated dose intensities of cyclophosphamide, non-pegylated liposomal doxorubicin, vincristine and rituximab were 98,7%, 98,7%, 76,1% and 98,3% respectively. Among 60 eligible patients (96,7% completed six cycles and 74,4% completed all eight cycles. ORR was 81%, and CR rate of 54,2%. IC 95% [40,7-67,8]. The main toxicity was neutropenia Gr=III-IV/ and febrile neutropenia in 20% of patients. Neurotoxicity Gr=III-IV in 3,4%. No cardiac toxicity Gr: III-IV was reported. No toxic deaths. After a median follow-up of 25-64m(44m) the 5-year overall survival (OS), event-free survival, (EFS) and disease free survival (DFS) were 80%, 67%, and 77% respectively. Forty two patients (71%) had (<60 y) and med. OS(p=0,017) and med EFS(p=0,014) was 72,3% and 68,1 in aaIPI=1 and 50,4% and 33,8 in aaIPI>1. **Conclusions:** Dose dense R-COMP-14 is an effective regimen in patients with (DLBCL) comparable o R- CHOP-14. Good tolerability profile with no Gr: III-IV cardiac toxicity or reduction of LVEF.

8063 General Poster Session (Board #34D), Mon, 1:15 PM-5:15 PM

Progression-free survival for subsequent relapses in patients with peripheral T-cell lymphoma (PTCL).

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Background: In B-cell lymphoma, overall response (ORR) is lower and progression free survival (PFS) is often shorter with each subsequent progression. However, this has not been described for PTCL. **Methods:** We undertook a retrospective analysis in two U.S. centers (MSKCC and UNMC) and in GELA studies. All data for PTCL were reviewed to collect data for each line of therapy: treatment, response, PFS, date of next treatment, and survival. When date of progression could not be defined we calculated PFS as the time to next treatment. Pts who did not progress, died during first line, or were untreated at progression 1 were excluded. Data were collected for 4 lines of treatment, front line and 3 progressions. **Results:** 254 pts were identified. 205 were analyzed (49 excluded for missing data): GELA 116, MSKCC 51, and UNMC 37. Diagnoses were PTCL NOS in 34% and 60%, AITL in 49% and 35%, ALCL Alk- in 3% and 5%, and others in 15% and 18% for GELA and US centers respectively. 67% were male, median age was 51 vs 58 y. Advanced stage was more frequent in GELA (79% vs. 56% for US); baseline IPI was ≥2 in 90% vs 71%. Multidrug regimens were given in 99% and 80% for front line, 67% and 66% for 2nd line, 61% and 50% for 3rd line, 53% and 54% for 4th line, for GELA and US. Significantly fewer pts received each subsequent line of therapy with 205 pts receiving 2nd line, 96 pts 3rd line and 38 pts 4th line. No pt ≥65 y received 4th line treatment. Responses and PFS are listed in the table. **Conclusions:** For pts with PTCL, similar to B-cell lymphomas, ORR and PFS decrease with each line of therapy. When evaluating the activity of therapies in relapsed PTCL, line of therapy is a consideration and this series provides a benchmark for comparison. Based on this dataset, it is possible that better responses will be seen as new agents are moved into earlier treatment paradigms.

	GELA data	U.S. data	All
1st line (front line)	.	.	.
- ORR	71%	64%	68%
- CR	57%	43%	51%
2nd line	.	.	.
- ORR	44%	52%	47%
- CR	35%	28%	32%
- Median PFS	13 m	27 m	15 m
- 6-m event-free	74%	66%	71%
3rd line	.	.	.
- ORR	23%	32%	27%
- CR	13%	18%	15%
- Median PFS	Not reached	2 m	8 m
- 6-m event-free	63%	36%	50%
4th line	.	.	.
- ORR	6%	38%	24%
- CR	6%	9%	8%
- Median PFS	6 m	NA	NA
- 6-m event-free	38%	NA	NA

Abbreviation: NA: not available.

8064 General Poster Session (Board #34E), Mon, 1:15 PM-5:15 PM

MLN9708, an investigational proteasome inhibitor, in patients (pts) with relapsed/refractory lymphoma: Emerging data from a phase I dose-escalation study.

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Background: MLN9708 is a reversible, orally bioavailable, specific 20S proteasome inhibitor. This study (NCT00893464) studied the safety and determined the MTD of IV MLN9708 in pts with relapsed/refractory lymphoma, and characterized pharmacokinetics (PK) and pharmacodynamics (PD). **Methods:** Pts aged ≥18 yrs who had failed ≥2 chemotherapeutic regimens received IV MLN9708 on days 1, 8, and 15 of 28-day cycles until disease progression or unacceptable toxicity. One pt was enrolled at the 0.125 mg/m^2 starting dose; dose doubling proceeded with 1 pt at each dose up to 1.0 mg/m^2. Dose escalation occurred in ≤40% increments using a standard 3+3 scheme based on DLT occurrence in cycle 1. Blood samples were collected at multiple time points after dosing on days 1 and 15 of cycle 1 for PK/PD analyses. **Results:** At data cut-off (Dec 1 2011), 21 pts had been enrolled and treated: 1 each at 0.125, 0.25, 0.5 and 1 mg/m^2, 4 at 1.4 mg/m^2, 7 at 1.76 mg/m^2, and 6 at 2.34 mg/m^2. Median age was 57 yrs (range 23–78); 57% were male. Median number of prior therapies was 5; 29% had prior radiation, 24% prior stem cell transplant. Histologies included T-cell lymphoma (n=5), Hodgkin lymphoma (n=3), follicular lymphoma (n=2), DLBCL (n=1) and other indolent B-cell lymphoma (n=7). Pts had received a median of 2 cycles (range 1–22); 2 DLTs were seen (neutropenia at 1.76 and 2.34 mg/m^2). All pts experienced drug-related AEs, including fatigue (48%), nausea (29%), diarrhea (29%), pyrexia, thrombocytopenia, and vomiting (each 24%). 43% had drug-related grade ≥3 AEs, 1 pt discontinued due to drug-related grade 3 neutropenia (2.34 mg/m^2). Three pts had drug-related peripheral neuropathy (1 grade 1, 2 grade 2). There were no on-study deaths. Of 18 response-evaluable pts, 3 achieved PR (including 2 who remain in response and on-study for >1 yr) and 4 SD. PK analyses showed linear PK (0.5–2.34 mg/m^2) and a terminal half-life of ~6–9 days. There was a dose-dependent increase in maximal whole blood 20S proteasome inhibition. **Conclusions:** These data suggest IV MLN9708 is generally well tolerated, with infrequent PN, and is clinically active in pretreated lymphoma pts. The trial is ongoing and updated data will be presented.

8065 General Poster Session (Board #34F), Mon, 1:15 PM-5:15 PM

Phase I/II study of MEDI-551, a humanized monoclonal antibody targeting CD19, in subjects with relapsed or refractory advanced B-cell malignancies.

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Background: Novel B-cell targeting agents, including monoclonal antibodies such as rituximab, are among recent advances in treatment of B-cell malignancies. New approaches are needed for patients progressing after rituximab-based therapies. MEDI-551 is an afucosylated monoclonal antibody targeting CD-19, a B-cell restricted transmembrane protein with enhanced affinity and antibody-dependent cellular cytotoxicity. **Methods:** Pts with relapsed or refractory follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), chronic lymphocytic leukemia, or multiple myeloma received single agent MEDI-551 at dosages ranging from 0.5 mg/kg to 12 mg/kg via intravenous infusion over 28-day cycles; cohorts 1-6 received 0.5, 1, 2, 4, 8, and 12 mg/kg, respectively. **Results:** 25 pts were enrolled in the phase I portion Jun 2010–Aug 2011. No maximum tolerated dose (MTD) was achieved. Most AEs were grade 1/2 with dose-independent frequency and severity (Table). Six pts had grade 3 toxicities including tumor lysis syndrome, infusion reaction, thrombocytopenia, and neutropenia, or grade 4 neutropenia. No grade 5 AEs were seen. All pts recovered. Three partial responses (PR) and 2 complete responses (CR) were seen in DLBCL and FL pts at 0.5, 4, and 8 mg/kg. Activity included a CR lasting 9 mo. in a FL pt in cohort 1, who is currently being retreated with MEDI-551 on relapse. **Conclusions:** MEDI-551 demonstrated a safety profile warranting further study and showed no MTD reached at the highest dose studied. Anti-tumor activity is suggested by the responses achieved across dose levels. Phase II is currently enrolling subjects. This study is funded by MedImmune, LLC.

Frequency of treatment emergent Medi-551-related adverse events.

Preferred term	Total events (N=37)
Infusion-related reaction	6 (16.2%)
Anaemia	3 (8.1%)
Nausea	3 (8.1%)
Thrombocytopenia	3 (8.1%)
Aspartate aminotransferase increased	2 (5.4%)
Blood immunoglobulin M decreased	2 (5.4%)
Chills	2 (5.4%)
Fatigue	2 (5.4%)
Headache	2 (5.4%)
Hypertension	2 (5.4%)
Hypotension	2 (5.4%)
Neutropenia	2 (5.4%)
Pyrexia	2 (5.4%)
Alanine aminotransferase increased	1 (2.7%)

8066 General Poster Session (Board #34G), Mon, 1:15 PM-5:15 PM

Dose- and time-intensified ABVD without radiotherapy (RT) for advanced-stage Hodgkin lymphoma (HL) with mediastinal bulky disease (MBD).

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Background: The role of consolidation RT on MBD after upfront chemotheraphy for advanced HL is debated, also given the supradditive iatrogenic risk. We present the results achieved in the subset of patients (pts) with MBD (max width > 1/3 of thoracic diameter) accrued in a phase II study of an intensified ABVD program without RT. **Methods:** The current analysis derives from the final evaluation of our trial for advanced HL (stage IIXB-IV) conducted from 06/2004 to 03/2010 (Russo et al, ASH 2009 abst 715). Pts were scheduled to 6 cycles of a 'time-densified' ABVD (3-week intercycle, drugs on days 1 and 11) with the first 4 cycles being also 'dose-intensified': doxorubicin (ADM) 35 mg/m^2, days 1 and 11 and G-CSF on days 6-8 and 17-19. **Results:** Of 82 accrued pts, 39 had BMD at presentation. Median age was 29yrs (r 16-58); male 46%; stage IIB 48%, III 8%, IV 43%; B-sympt 87%, E-disease 53%; IP Score ≥3 51%. All pts completed the intensified program. Median actual dose intensities for ADM, bleomycin, vinblastine and dacarbazine were 23.12, 6.69, 3.96 and 245 mg/week, respectively; the increase over conventional ABVD was 85% for ADM and averaged 32% for the other agents. PET2 negativity was achieved in 36/39 (92%; 95% CI 79-98), complete responses (CR) in 37/39 [94%; 95% CI 82-99]. At a median f.u. of 54 mo.s (r 20-91) all pts are alive with an event-free survival of 89% (95% CI, 80-98). Events were: <CR (n=1, CS IVB), progression (n=1, CS IIIA), relapse [n=2; at 10 (CS IVA) and 15 (CS IIB) months after treatment]; all these pts had isolated mediastinal recurrence. CTCAE v3.0 toxicity: Grade (G) 2 nail changes (31%), G2-G3 hemorrhoids (12%-3%), G3 infection (13%) and constipation (5%), G3-G4 stomatitis (7%-2%). No acute or delayed G3-G4 cardiac events, nor G3-G4 decline in pulmonary function ($FEV_{1,}$ DL_{CO},FEF25-75) were seen. **Conclusions:** Intensified ABVD can achieve PET2 negativity in a very high proportion of pts with MBD and ensure a long-term disease-free status even without RT. While results need confirmation on a randomized basis, the low mediastinal failure rate seems in line with recent suggestions that RT could be omitted in MBD when CR is achieved upon intensified chemotheraphy.

8067 General Poster Session (Board #34H), Mon, 1:15 PM-5:15 PM

Comparison of the international prognostic factors index (IPI) with the absolute monocyte and lymphocyte prognostic index (AMLPI) for patients (Pts) with diffuse large b-cell lymphoma (DLBCL) receiving R-CHOP.

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Background: We studied the value of a proposed prognostic index (PI) generated by baseline absolute monocyte (AMC) and lymphocyte (ALC) counts for pts with DLBCL, using values as previously reported (Leukemia 25:1502-9, 2011). **Methods:** From 03/07 to 01/09, 245 consecutive pts with untreated DLBCL receiving standard R-CHOP from the MDACC database were evaluated. Baseline AMC and ALC were retrospectively recorded. High AMC ($\geq$610/uL) and a low ALC ($\leq$1000/uL) were examined as dichotomized variables for progression-free (PFS) and overall survival (OS). An AMLPI was generated, stratifying pts into 3 risk groups (RGs): low-(AMC $<$610/uL and ALC $>$1000/uL), intermediate-(AMC $\geq$610/uL or ALC $\leq$1000/uL), and high-risk(AMC $\geq$610/uL and ALC $\leq$1000/uL). The prognostic effect of the AMLPI and the IPI were examined by multivariate analysis (MVA). **Results:** Ninety (37%) had high AMC and 71 (29%) had low ALC. By univariate analysis, a high AMC was associated with inferior PFS ($p=0.01$) and OS ($p=0.03$). The frequencies of AMLPI RGs were: low-105 pts (43%), intermediate-119 (48%), and high risk-21 (9%). With a median follow-up of 22 months (range $<$1-42), 3-year PFS and OS rates for these RGs were 80%, 61%, and 46% ($p=0.007$) and 92%, 76%, and 60% ($p=0.006$), respectively. Three-year PFS rates for IPI 0-2 and 3-5 RGs were 73% and 58%, respectively ($p=0.0004$); comparable OS rates were 88% and 68%($p<0.0001$). For pts with IPI 0-2, 1-year PFS rates for AMLPI low, intermediate, and high RGs were 92%, 89% and 80% ($p=0.022$); comparable 1-year OS rates were 96%, 95% and 80% ($p=0.049$). By MVA, AMLPI effect (low vs. high RGs) on PFS was significant ($p=0.046$) as was IPI effect (0-2 vs 3-5, $p=0.005$); similar results were observed for OS ($p=0.052$ and $p=0.003$, respectively). **Conclusions:** Baseline AMC and AMLPI are significant variables for PFS and OS for pts with DLBCL receiving R-CHOP. AMLPI can identify pts with low, intermediate, and high-risk disease for PFS and OS, particularly for those with IPI 0-2. AMLPI may also add prognostic value beyond that of the IPI.

8068 General Poster Session (Board #35A), Mon, 1:15 PM-5:15 PM

Prognostic value of etoposide area under the curve (AUC) in lymphoma patients treated with BEAM regimen and ASCT: Multicenter study of Groupe d'Etudes des Lymphomes de l'Adulte (GELA).

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Background: The prospective LYMPK study primary objective was to assess the impact of etoposide pharmacokinetic (PK) parameters on toxicity and efficacy in lymphoma patients receiving the BEAM regimen (carmustine, cytarabine, etoposide and melphalan) followed by autologous stem cell transplant (ASCT). We previously showed the high inter-individual variability in etoposide PKs, defined by area under the curve (AUC) and trough concentration (Cmin), among study patients treated with the same doses /m^2 (You B et al, Proc. ASCO 2008). **Methods:** Ninety-six patients with malignant lymphoma at 1st line (n=52) or relapse (n=44) were enrolled in 5 centers. All received BEAM regimen, including high-dose etoposide (100 to 200 mg/m^2 bid for 4 days), followed by ASCT. Individual etoposide AUC and Cmin were estimated by population PK approach using NONMEM program. The impact of PK parameters on toxicity and survival was assessed using linear regression and univariate/multivariate analyses. **Results:** Data from 90 patients were assessable after a 4.2-year median follow-up. The bi-compartment model previously reported was used to characterize PK parameters (You B et al, Proc. ASCO 2008). Etoposide AUC and Cmin correlated with mucositis duration, especially for grade 3-4 toxicity ($p < 0.05$), but not with other toxicities. Cmin had significant prognostic value regarding 5 year progression free survival ($p=0.03$). Five year overall survival (OS) was longer in patients with higher AUC (76% vs 56%, if AUC > median, $p=0.04$) as it was in patients with higher Cmin (78% vs 54%, if Cmin > median, $p=0.02$). When assessed with available IPI prognostic factors (age; performance status; LDH and stage) using Cox analysis, the only independent prognostic factors of OS and disease specific survival were etoposide AUC (HR= 0.39, 95% CI = 0.16-0.94) and Cmin (HR = 0.32, 95% CI = 0.12-0.80). **Conclusions:** LYMPK study results suggest that individual etoposide systemic exposure has a strong impact on survival in lymphoma patient receiving BEAM regimen and ASCT. Given the high variability in patient AUCs, plasma concentration-based adjustment of etoposide dose may be considered in future studies.

8069 General Poster Session (Board #35B), Mon, 1:15 PM-5:15 PM

Central nervous system involvement in T-cell lymphomas: A single center experience.

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Background: Large experiences have reviewed the risk of central nervous system (CNS) involvement in diffuse large B-cell lymphoma (DLBCL), but there are limited data on CNS involvement by peripheral T cell lymphomas (PTCL). We characterized the incidence of CNS involvement, risk factors and outcome in a large single institution dataset of PTCL. **Methods:** Retrospective review of the T-cell lymphoma database at Memorial Sloan Kettering Cancer Center. We identified 232 patients with any subtype of PTCL between 1994-2011 with a minimum 6 months of follow-up or an event defined as relapse or death. We excluded indolent forms of cutaneous T cell lymphoma. **Results:** Histologies included PTCL-NOS (31%), angioimmunoblastic (16.8%), anaplastic (ALCL), ALK negative (12%), ALCL, ALK positive (6%), extranodal NK/T cell lymphoma (7.3%), adult T cell leukemia/lymphoma (ATLL) (7.3%), and transformed MF (8.6%). Median age was 58 years with 59.9% men. CNS disease was found in 17 patients (7.32%). 8 (47%) had pathologic confirmation and 7 (41.2%) were clinically diagnosed. Two had other diagnoses at biopsy: DLBCL and glioblastoma. Median time to CNS involvement was 2.33 months (range, 0.16 to 103.1). CNS prophylaxis was given to 24 (10.34%), primarily intrathecal methotrexate. There was no difference in CNS involvement in patients who received prophylaxis vs. those who did not: 3/24 (12.5%) vs. 12/208 (5.77%) ($p=0.192$) respectively. Univariate analysis identified: stage III-IV ($p=0.03$), bone marrow involvement ($p=0.018$), >1 extranodal site ($p<0.001$), and ATLL vs. all other subtypes, 23.5% vs. 6.4% ($p=0.003$) as risk factors for CNS disease. On multivariate analysis, >1 extranodal site ($p=0.004$) and high intermediate (H-I) and high (H) IPI (IPI 3-5 & 4-5) were predictive for CNS involvement ($p<0.05$). The median survival of patients with CNS involvement was 2.628 months. **Conclusions:** Despite high relapse rates, PTCL carries a low risk of CNS involvement other than the ATLL subtype. As with other aggressive lymphomas, survival of patients with CNS involvement is poor and risk factors include: >1 extra nodal site and H-I-H IPI. In this dataset, prophylactic intrathecal chemotherapy does not appear to reduce the risk of CNS disease.

8070 General Poster Session (Board #35C), Mon, 1:15 PM-5:15 PM

Brentuximab vedotin for relapsed or refractory non-Hodgkin lymphoma: Preliminary results from a phase II study.

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Background: Brentuximab vedotin is a CD30-directed antibody-drug conjugate approved for the treatment of Hodgkin lymphoma and systemic anaplastic large cell lymphoma (ALCL) after failure of other therapies. Based on the high objective response rate observed in patients with systemic ALCL, a type of non-Hodgkin lymphoma that is characterized by homogeneous CD30 expression, a study was initiated in other non-Hodgkin lymphomas that express the CD30 target. **Methods:** A phase 2 open-label single-arm study is underway in patients with relapsed or refractory CD30-positive non-Hodgkin lymphoma, excluding ALCL (NCT01421667). Brentuximab vedotin is administered IV at 1.8 mg/kg every 3 weeks until disease progression or unacceptable toxicity. The primary endpoint is objective response rate assessed by the Revised Response Criteria for Malignant Lymphoma (Cheson 2007). Tumor specimens are assessed by central lab in order to characterize the relationship of CD30 expression with antitumor activity. **Results:** Ten patients (age range 28–83; 5 M, 5 F) have enrolled to date. Diagnoses include diffuse large B-cell lymphoma (DLBCL, n=2), EBV-positive DLBCL of the elderly (n=3), primary mediastinal B-cell lymphoma (n=2), peripheral T-cell lymphoma NOS (n=2), and angioimmunoblastic T-cell lymphoma (AITL). Patients had received 1–6 prior chemotherapy regimens; 3 patients had prior stem cell transplants. Of 6 patients who have completed the cycle 2 response assessment, 2 attained complete remission, 1 with DLBCL (90% CD30+) and 1 with AITL (8% CD30+), 1 had stable disease, and 3 had progressive disease. Treatment-related serious adverse events observed to date were rash, febrile neutropenia, and mastoiditis. **Conclusions:** Preliminary results suggest that brentuximab vedotin may have antitumor activity in patients with relapsed or refractory CD30-expressing non-Hodgkin lymphomas, in addition to the efficacy previously observed in systemic ALCL. Updated study results will be presented.

8071 General Poster Session (Board #35D), Mon, 1:15 PM-5:15 PM

Ocular adnexal lymphoma (OAL)-outcomes for 82 patients (pts) treated at a single center.

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Background: OALs comprise 1-2% of NHL and are extranodal marginal zone (EMZL) in 80% of cases. We present a retrospective review of 82 pts with OAL managed at the Cleveland Clinic between January 2004 and November 2011. **Methods:** 82 pts with NHL of the OA were identified. All biopsies were performed/reviewed at the Cleveland Clinic. Survival and relapse were estimated using the Kaplan-Meier method. Risk factors for relapse and survival were identified using Cox proportional hazards analysis. Risk factors included age at diagnosis (dx), gender, prior autoimmune disease, prior lymphoma history (hx), hx of other malignancy, bilateral disease, and ocular disease site. **Results:** The table lists pt characteristics. Median follow-up was 25.8 months (range 0.3-307.4). Age at dx (HR=1.45, CI 1.04-2.02) and prior lymphoma hx (HR=3.35, CI 1.33-8.46) were predictive of relapse in a multivariate analysis. There was no difference in relapse rates between pts with EMZL and other lymphoma types (p=0.82). Relapse occurred in 26 (31.7%) pts with most common sites being ipsilateral eye (n=8), contralateral eye (n=3), distant lymph node (n=11), and other organs (n=11). Most common organ was breast (n=4). Of the 10 pts who had eye-only relapses, 8 received rituximab (R) and 2 were observed. Of the 16 with extraocular relapse, 9 received radiation (RT), 2 received R, 3 received other therapies, and 2 were observed. 7 deaths were recorded with a 5 year overall survival of 84.2%. Survival was similar to a matched healthy population (p=0.69). Causes of death were lymphoma in 4, another cancer in 1, and unknown in 2. **Conclusions:** OAL relapse patterns differ depending on initial treatment. Initial RT was more likely to relapse at distant sites; where as initial R was more likely to relapse in the OA. RT should be used for localized OAL. With bilateral ocular or systemic disease, R results in a high rate of long-term disease control.

Pt characteristics	n (%)
Median age at Dx (range)	64 (24-91)
Male	45 (54.9)
Bilateral involvement	22 (26.8)
Stage IE (n=73)	48 (69.5)
Pathologic Dx (n=80)	
ENMZ	56 (70.0)
Follicular	9 (11.3)
DLBCL	3 (3.8)
Mantle	2 (2.5)
Other lymphoma	7 (8.8)
Non-dx	3 (3.8)
Initial Rx (n=73)	
RT	43 (58.9)
R	13 (17.8)
Chemo	5 (6.8)
Combination	8 (11.0)
Observation	4 (5.5)

8072 General Poster Session (Board #35E), Mon, 1:15 PM-5:15 PM

The impact of race, age, and sex in follicular lymphoma (FL): A comprehensive SEER analysis in the pre- and post-rituximab (R) eras.

Chadi Nabhan, Briseis Aschebrook-Kilfoy, Brian C-H Chiu, Kimberly R. Kruczek, Angelo Clemenzi-allen, Anand Patel, Sonali M. Smith, Andrew M. Evens; Advocate Lutheran General Hospital and Oncology Specialists, S.C., Park Ridge, IL; University of Chicago, Chicago, IL; Department of Health Studies, Division of Epidemiology, University of Chicago, Chicago, IL; Advocate Lutheran General Hospital, Park Ridge, IL; University of Massachussetts, Worcester, MA; The University of Chicago, Chicago, IL; University of Massachusetts Medical School, Worcester, MA

Background: While racial disparity has been well documented in a number of cancers, the impact of race in FL outcomes is not well defined. Further, the importance of gender in FL has not been fully explored. **Methods:** We examined population-based FL overall survival (OS) data from SEER 13 (1993-2008) regarding race, sex, age, and socioeconomic status (SES) over two consecutive 8-year (yr) periods: Era 1 (1993-2000, n=7,409) and Era 2 (2001–2008, n=9,083). **Results:** We identified16,492 FL patients (pts) (white (W): n=13,441; Hispanic (H): n=1,417; Asian/Pacific Islander (A/PI): n=887; and Black (B): n=747). Median ages at diagnosis differed significantly according to: (in yrs, W: 62.1, H: 57.3, A/PI: 60.5, B: 56.6; P<0.01 for each race vs. W). For all pts, OS was superior in Era 2 vs. Era 1 (5-yr OS: 77% vs. 68%, respectively, P<0.0001). Further, OS was significantly improved for all age groups (<50, 50-59, 60-69, and 70-79 yrs) as well as for males (P=0.0019) and females (P<0.0001) across eras. Interestingly, females had superior OS compared with males in Era 1 (P=0.004), but not in Era 2 (P=0.83). We subsequently compared OS within and across races (Table). All races, except A/PI, had improved 5-yr OS rates (age adjusted) from Era 1 to Era 2 (W: <0.001, H: 0.049, A/PI: 0.15, B: 0.003). Notably, A/PIs had the highest OS in Era 1, while H had the poorest OS in Era 2. These differences were more evident in males compared with females within each race. Finally, pts with higher SES had better OS in both eras, although OS was improved across eras for lower and higher SES populations. **Conclusions:** Collectively, we identified improved OS across eras, which was apparent for all ages, both sexes, and all races. We did not find superior outcome for females in the modern era as has been recently noted. However, several racial disparities persist, including inferior OS for H and superior OS A/PIs in the contemporary era. The disproportionate improvement in outcomes for some, but not all races, warrants continued study of racial disparities in FL.

OS across eras based on race.

				P values		
5-yr OS				**W vs. H**	**W vs. A/PI**	**W vs. B**
Era 1						
W	B	H	A/PI			
68%	64%	68%	73%	0.20	0.85	0.007
Era 2						
W	B	H	A/PI			
77%	75%	73%	79%	<0.0001	0.019	0.11

8073 General Poster Session (Board #35F), Mon, 1:15 PM-5:15 PM

Phase I trial of fenretinide (4-HPR) intravenous emulsion in hematologic malignancies: A California Cancer Consortium study (PhI-42).

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Background: Fenretinide (4-HPR) is a cytotoxic retinoid with broad anticancer activity in preclinical studies. Due to limited bioavailability of a capsule formulation an intravenous intralipid-like emulsion formulation (4-HPR ILE) was developed to increase systemic exposures. **Methods:** 4-HPR was administered as a continuous intravenous infusion for 120 hrs every 21 days. Systemic toxicities, responses, and pharmacokinetics were assessed. Accelerated Simon design proceeded until moderate or dose-limiting toxicities (DLT) were scored on Course 1. Doses were 80 mg/m^2/day to 1810 mg/m^2/day. Patients with asymptomatic hypertriglyceridemia were scored separately. All patients were heavily pretreated. **Results:** Toxicity-evaluable patients = 25. At 1810 mg/m^2/day, two patients experienced DLT hypertriglyceridemia, one with transient Grade 2 pancreatitis; at 1280 mg/m^2/day (8 pts), two had asymptomatic Grade 4 hypertriglyceridemia, one experienced DLT pleural effusions; at 905 mg/m^2/day (6 pts) 2 experienced asymptomatic Grade 4 hypertriglyceridemia; All 5 pts at 640 mg/m2/day tolerated treatment. Pharmacokinetics showed a dose-to-plasma level relationship with mean steady-state 4-HPR levels of ~mid-20's μM (640 mg/m^2); ~mid-30's μM (905 mg/m2/day); and ~mid-50's μM (1280 mg/m^2). Responses to date include a 64% CR+PR+SD response rate (36% CR+PR response rate) in 11 relapsed T-cell lymphomas which included histone deacetylase inhibitor-refractory patients, and a PRu response in a NHL B-cell lymphoma. Reversible hypertriglyceridemia related to the intralipid vehicle accounted for 6/7 DLTs. **Conclusions:** MTD = 1280 mg/m^2/day x 5 days, every three weeks. 4-HPR ILE was safely administered and obtained 4-HPR plasma levels 6 -7 times higher than previously obtained using oral capsules. Durable complete responses were observed in T-cell lymphomas from 905 – 1810 mg/m^2/day. An expanded cohort is accruing to a dosing schedule modified to decrease asymptomatic hypertriglyceridemia of 600 mg/m^2 on Day 1 (to allow for induction of serum lipases) followed by 1200 mg/m^2 Days 2-5. Supported by NCI U01 CA062505 and CPRIT RP10072.

8074 General Poster Session (Board #35G), Mon, 1:15 PM-5:15 PM

Use of exon-based transcriptome profiling to identify novel signaling pathways and survival-associated genes in diffuse large B-cell lymphoma.

Sirpa Leppa, Minna Taskinen, Satu Koivula, Ping Chen, Riku Louhimo, Jan Delabie, Marja-Liisa Karjalainen-Lindsberg, Magnus Bjorkholm, Oystein Fluge, Lars Moeller Pedersen, Karin Rydstrom, Mats Jerkeman, Mikael Eriksson, Sampsa Hautaniemi, Harald Holte, Nordic Lymphoma Group; Helsinki University Central Hospital, Helsinki, Finland; University of Helsinki, Helsinki, Finland; Oslo University Hospital, Oslo, Norway; Karolinska University Hospital, Stockholm, Sweden; Haukeland University Hospital, Bergen, Norway; Roskilde University Hospital, Roskilde, Denmark; Lund University Hospital, Lund, Sweden

Background: Identification of biological prognostic factors that could be used to define poor risk diffuse large B-cell lymphoma (DLBCL) patients is a main concern. **Methods:** Study population consisted of 38 de novo high risk DLBCL patients less than 65 years old. The patients were treated in the Nordic phase II protocol with six courses of R-CHOEP14 followed by systemic central nervous system prophylaxis with one course of high dose methotrexate and one course of high dose cytarabine. Exon array-based profiling was used to screen signaling pathways and differentially expressed genes between the clinically high risk patients, who had relapsed or remained in remission in response to dose dense chemoimmunotherapy. At the time of the analysis, median follow up was 34 months, progression free survival (PFS) 78% and overall survival (OS) 78%. **Results:** The screen between relapsed patients and the patients in remission using criteria of $p \leq 0.05$ and fold change ≥ 1.6 revealed 566 differentially expressed genes (131 protein coding), of which 24 were likely to be involved in conventional signaling pathways, including those regulating antigen processing and presentation (*CIITA, HLA-DQA2, HLA-DQB1, RFXAP*), Jak-STAT signaling (*SOCS3*), Notch signaling (*NOTCH1*) and Toll-like receptor signalling (*IRF5*). In cox univariate analysis, 12 of 24 genes were found to associate with PFS ($p<0.05$). Of these, high expression of *CIITA, DLL4, HLA-DQA2, HLA-DQB1, IRF5, NOTCH1, PER1, RFXAP, SEMA4D* and *ZFP36* had a favorable impact on PFS, whereas high levels of *ENPP3* and *PRKAR2B* were associated with adverse outcome. Differential expression of four genes was confirmed by quantitative PCR, and prognostic value of six genes validated using Lymphoma/Leukemia Molecular Profiling Project microarray data set. Immunohistochemical validation of the findings in a larger patient cohort is ongoing. Germinal centre B-cell signature did not predict survival in this cohort. **Conclusions:** The results provide evidence that exon-based transcriptome profiling can identify biologically relevant signaling pathways and genes that discriminate the outcome of homogenously treated young high risk DLBCL patients.

8075 General Poster Session (Board #35H), Mon, 1:15 PM-5:15 PM

Phase I trial of temsirolimus and lenalidomide in pts with rel/ref lymphomas.

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Background: The PI3K/Akt/mTOR axis is deregulated in lymphomas and is an emerging therapeutic target. We previously reported activity of temsirolimus (TEM) in DLBCL and FL (JCO 2010 28(31); however, the response duration was short. Lenalidomide (LEN) is an immunomodulatory agent with multiple anti-tumoral and microenvironmental effects, with activity across lymphoma subtypes. We are thus conducting a phase I/II study of TEM plus escalating doses of LEN. The phase I portion is completed. **Methods:** Patients (pts) had rel/ref lymphoma after >1 cytotoxic regimen. Other criteria: ANC > 1000/mL, platelets > 75,000/mL, nl renal and hepatic function, no VTE within 3 months, non-pregnant. A standard "3 + 3" design was used with dose levels (DL) listed (Table). TEM was given IV weekly and LEN was dosed orally on D1-D21, q28 days. Dose-limiting toxicity (DLT) was defined as cycle 1 grade 3 or 4 non-hematologic toxicity not responsive to standard supportive care, grade 4 thrombocytopenia > 7 days (or associated with bleeding or requiring more than 1 platelet transfusion), ANC < 500/mL > 7 days despite growth factors, or any thromboembolic event. **Results:** 18 pts (13M, 5F), med age 64 y (range, 42-80 y) were enrolled. 3 pts are ineval for DLT evaluation: one withdrew consent before starting treatment, 1 withdrew consent after a single dose, and 1 died of rapid disease progression after 1 dose. There was 1 DLT at DL1 and 2 DLTs at DL3 (Table). Adverse effects that did not meet DLT criteria: hypokalemia, hypertriglyceridemia, vomiting, urinary tract infection, skin infection, nausea, hypoxia, hyponatremia, diarrhea, and hyperglycemia (each occurring in one pt). There are 5 partial responses, 4 stable disease, 3 progressive disease, 2 not adequately assessed, and 4 still on active treatment. **Conclusions:** The combination of weekly intravenous TEM plus oral LEN is well-tolerated in a heavily pretreated group of pts with rel/ref lymphomas. The recommended phase II doses are TEM 25mg weekly plus LEN 20mg (D1-D21, q28d).

Dose level	Dose: TEM (flat dose in mg)	Dose: LEN (flat dose in mg)	No. Pts	DLT
-1	25 mg	10 mg	n/a	n/a
1	25 mg	15 mg	8 (2 ineval for DLT)	Grade 4 hypokalemia
2	25 mg	20 mg	4 (1 ineval for DLT)	No DLT
3	25 mg	25 mg	6	Grade 3 diarrhea, grade 3 HSV mucositis

8076 General Poster Session (Board #36A), Mon, 1:15 PM-5:15 PM

Efficacy and safety of bexarotene combined with psoralen/ultraviolet A light (PUVA) compared to PUVA treatment alone in stage IB-IIa mycosis fungoides (MF): Final results from EORTC cutaneous lymphoma task force (CLTF) phase III clinical trial 21011.

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Background: Skin-directed treatment with methoxsalen (PUVA) is the current treatment standard in stage IB-IIA MF. A combination of PUVA and bexarotene might be of additional clinical benefit for MF stage I/II patients (pts). **Methods:** EORTC 21011 was a randomised, open label phase III study comparing combined bexarotene and PUVA versus PUVA alone in pts with stage IB and IIA MF. Study primary endpoint was response (complete clinical + partial response, CCR+PR) rate; secondary endpoints: cumulative dose of UVA and number of PUVA sessions necessary to achieve a CCR, duration of CCR, time to relapse, safety and percentage of drop-outs. **Results:** The study recruited stage IB/IIA MF pts and was prematurely closed due to low accrual after 93/145 required pts (65%) were randomized; 45 to PUVA, 48 to PUVA+bexarotene. Median number of PUVA weeks were 12 (1-17) in PUVA vs. 10.5 (1-16) in combination arm. Total UVA doses were 107J/cm2 (1.4-489.9) in PUVA vs. 101.7J/cm2 (0.2-529.9) in combination arm. Few grade 3-4 toxicities were observed in both arms (liver enzyme elevation, neutropenia, anemia, increased cholesterol, photosensitivity, pruritus, rash, hypertriglyceridemia). Best overall response (CCR/PR) rate was 71.1% (33/45) for PUVA alone and 77.1% (37/48) for combination arm (p-value=0.57). The median of duration of response was 9.6 for PUVA vs 5.8 months for combination arm (p value=0.33). CCR was seen in 25 pts, 10 in PUVA (CCR 24%) and 15 in combination therapy (CCR 33%) (pvalue=0.45). Similarily, a lower UVA dose was required to achieve a CCR in the combination arm (median of 55.8 J/cm2) compared to the PUVA arm (median of 117.58 J/cm2) (p value=0.5). **Conclusions:** No significant difference in response rate was observed in this study. There was a trend towards fewer PUVA sessions and lower UVA dose to achieve CCR in the PUVA/bexarotene combination arm (median of 27.5 vs. 22,p-value = 0.11) but this did not achieve statistical significance due to insufficient power. The safety profile was acceptable, as there were only few grade 3-4 toxicities observed in both arms.

8077 **General Poster Session (Board #36B), Mon, 1:15 PM-5:15 PM**

Dual-point FDG-PET: A novel scanning technique in Hodgkin lymphoma with bulky disease.

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Background: Interim ^{18}F-FDG-PET (iPET) is the most important prognosticator in advanced-stage ABVD-treated Hodgkin Lymphoma (HL), but in early stage w/ or w/o bulky lesion a low PPV of iPET was reported. Dual-point PET scan (2P-PET) has been used to discriminate unspecific inflammatory from neoplastic FDG uptake. At the Tx end, with a single FDG-avid mass (SFAM), the specificity of PET in Tx response evaluation was sub-optimal. We report here preliminary results from a cohort of HL patients (p) presenting with bulky lesions, scanned with 2P-PET with the aim to increase specificity and PPV. **Methods:** From 12.2008 till 01.2012 24 HL bulky p from Italian, French and Polish centers underwent 2P-PET at baseline (2P-PET-0), after 2 ABVD (2P-PET-2) and at Tx end (2P-PET-end). 2P-PET scanning technique consisted in 2 consecutive image acquisitions +60' (EaS) and +120'(LaS) after single, standard-dose FDG injection. Tx was ABVD (x4 or x6) ± consolidation RxT. No Tx change was done based on iPET results. Scans were reviewed by 2 expert readers in a consensus session. Standardized-Uptake Value $(SUV)_{MAX}$ was calculated both in EaS and LaS using Volume of Interest Regions (VOIs) in sites of residual FDG uptake already recorded in PET-0. ΔSUV_{MAX} and FDG retention index (RI) were calculated from SUVs in the same VOIs of both scans. **Results:** In 24 p (1 stage I,12 II, 4 III, 7 IV), 34 2P-PET were done.10 p underwent 2P-PET-0: in 10/10 SUV_{MAX} increased from EaS to LaS (ΔSUV_{MAX} 1-4.3). 15 p had a 2P-PET-2: 12 with a mean-follow-up of 18.36 months were evaluable, 3 too short (+1, +5, +6 months). 7/12 p showed a RI reduction of 55% (200-14): all are in continuous CR (CCR). 5/12 p. showed a 20% (11-26) RI increase: all progressed +1 to +9 months after Tx end. Overall 3/12 cases (1 false +, 2 false- with a Deauville score 4 and 2,3 respectively) were correctly classified after 2P-PET. 9 p with a SFAM had a 2P-PET-end: in the 5/9 with an increased RI of 23% (9-43) a biopsy proved HL relapse. In 4/9 a reduced RI of -29% (9-45) was found: in 2 biopsy disclosed presence of residual thymic along with inflammatory tissue and 2 were in CCR +2 to+8 after Tx end. **Conclusions:** DSUV Max increased at baseline and in all relapsing patients, and decreased in patients in CCR. The PPV and a PNV of 2P-PET were 100%.

8078 General Poster Session (Board #36C), Mon, 1:15 PM-5:15 PM

Association of tumor-associated macrophages of M2 subtype with outcome in follicular lymphoma.

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Background: Current methods used to prognosticate patients with follicular lymphoma (FL) include the Follicular Lymphoma International Prognostic Index (FLIPI) and tumor grade. However, they do not provide information on the biological and molecular features of FL. Recent data suggest that high tumor-associated macrophages (TAM) content may be an adverse prognostic factor in FL. However, TAM consists of two main subtypes, M1 and M2, with the former related to pro-inflammatory properties while the latter, anti-inflammatory functions. Currently, the prognostic impact of each individual subtype has not been elucidated and this may be more important than looking at TAM alone. **Methods:** Tumor specimens of 98 patients with FL diagnosed between 2005 and 2009 were investigated using immunohistochemistry and fluorescence in-situ hybridization (FISH) using break-apart FISH probes targeting BCL2, BCL6, MYC and IgH genes. Tumor specimens expressing a higher proportion of CD68+/CD163- in one high power field were defined as M1 subtype and those that expressed a greater proportion of CD68+/CD163+ were denoted as M2 subtype. **Results:** Amongst the 98 patients, 60 (61%) were of the M2 subtype, 59% presented with advanced disease, 47% were grade 3 and the median age was 59 years (21 – 88 years). Baseline characteristics including grade, stage and recurrent translocations did not significantly differ between the M1 and M2 groups. Similarly, there was also no difference in terms of treatment received (both Rituximab and chemotherapy) between the two groups. Despite these similarities, with a median follow-up of 3.2 years, the 3-year overall survival (OS) was significantly different (M1, 100% vs M2, 85%; $p < 0.01$). All 11 patients who died were of the M2 subtype ($p=0.009$). **Conclusions:** Our findings show that despite similar patient characteristics and treatment, there was, however, a statistically significant difference in OS, with the M2 subtype demonstrating an inferior outcome. The M2 TAM subtype rather than TAM alone may be a more important prognostic marker in FL, which could possibly be explained by its known biological anti-inflammatory function.

8080 General Poster Session (Board #36E), Mon, 1:15 PM-5:15 PM

The incorporation of rituximab (R) and liposomal doxorubicin (LD) into CODOX-m/IVAC for untreated Burkitt lymphoma (BL): Final results of a prospective multicenter phase II study.

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Background: Two-year survival rates remain <65-70% for adult BL. Further, there is a paucity of data examining the addition of R with CODOX-M/IVAC. **Methods:** 25 patients (pts) with classic BL enrolled onto this phase II study (3/07-4/11). Pts were classified as low risk (LR) or high risk (HR); LR received 3 CODOX-M, while HR had 4 alternating CODOX-M/IVAC (Mead et al, Blood 2008). LD (40 mg/m^2) was used in lieu of doxorubicin, while intravenous R (500 mg/m^2) was given days 0 + 8 of CODOX-M and days 0 + 6 of IVAC cycles. Ejection fraction (EF) was assessed at baseline, s/p 2 cycles and completion. **Results:** Median age was 44 years (yrs) (23-70). There were 20 HR and 5 LR pts; 3 HR and 1 LR pt were HIV+. 15% of HR pts had + CNS disease. In addition, 35% of HR pts had bulk >10 cm and 40% had bone marrow involvement. 24/25 pts were evaluable for toxicity and response. Therapy was completed at a median of 13 weeks (11-20) for HR pts and 10 weeks for LR (9-12). Myelosuppression (62% grade 4 thrombocytopenia, 4% grade 4 anemia) and mucositis (33% grade 3, 13% grade 4) appeared comparable with prior CODOX-M/IVAC data. Other grade 3 toxicities were infection (38%), neutropenic fever (29%), transaminitis (33%), diarrhea (8%), creatinine (8%), seizure (4%), vomiting (4%). Notably, there was no grade 3 or 4 neuropathy. Two grade 2 and three grade 3 cardiac events occurred (all depressed EF, no clinical CHF). Two of the three grade 3 cardiac events occurred in pts age >65 yrs. Among all pts, the median change in EF at baseline vs study end was -2% (-22% to +11%). The overall response rate (modified Cheson with FDG-PET) after 2 cycles was 100% with a 67% complete remission rate. At a median follow-up of 2.3 yrs, 2-year PFS and OS rates for all pts were 86% and 86%, respectively (LR 2-yr PFS and OS: both 100%; HR 2-yr PFS and OS: both 82%). Furthermore, 2-yr PFS and OS for HR, HIV-negative BL were 91% and 91%, respectively (disease-specific survival: 100%). **Conclusions:** The integration of R and LD into CODOX-M/IVAC for adult BL is feasible and associated with similar tolerability compared with prior reports. Moreover, this regimen was associated with excellent survival rates, especially for HIV-negative BL.

8081 General Poster Session (Board #36F), Mon, 1:15 PM-5:15 PM

Efficacy of ocaratuzumab (AME-133v) in relapsed follicular lymphoma patients refractory to prior rituximab.

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Background: Ocaratzumab, previously known as AME-133v, is a humanized next-generation anti-CD20 monoclonal antibody. It has been optimized with a 13 to 20-fold increase in binding affinity to CD20 and improved binding to the low-affinity (F/F and F/V) polymorphisms of FcγRIIIa (CD16), which are thought to predict lower response rates and shorter duration of responses to rituximab. **Methods:** In a phase I dose escalation study in relapsed follicular lymphoma (FL) patients, ocaratuzumab was well-tolerated at doses up to 375 mg/m^2 (Forero-Torres et al. CCR 2012). In a follow-on phase II trial, 44 patients with relapsed FL following prior rituximab and the low-affinity FcγRIIIa polymorphism (F-carriers) received 375 mg/m^2 of ocaratuzumab weekly for 4 doses. In this study, overall response rate (ORR) was 36% and median progression free survival (PFS) was 91 weeks (Ganjoo et al. Haematologica 2011). **Results:** Amongst the 56 patients receiving 100 and 375 mg/m^2 of ocaratuzumab, 8 patients had a previous time to progression of $\leq$ 180 days following their last rituximab treatment. These patients had a median of 2 prior rituximab treatments, (range 1-6 treatments), and median PFS following last treatment of 159 days. Five of the 8 patients showed a longer PFS after ocaratuzumab administration, compared with last rituximab treatment. All 5 patients expressed the homozygous low-affinity genotype of FcγRIIIa (F/F). At the time of study closure, 3 of the patients were still in remission (indicated by * in the table). **Conclusions:** This retrospective analysis suggests that ocaratuzumab may be non-cross-resistant to rituximab in patients with the low-affinity FcγRIIIa polymorphism. Prolonged PFS in selected patients following ocaratuzumab suggests that the increased binding affinity to CD16 and improved antibody-dependent cell-mediated cytotoxicity (ADCC) of this antibody is clinically relevant. As a single agent, ocaratuzumab may provide prolonged clinical benefit in relapsed FL patients and a clinical trial comparing ocaratuzumab to rituximab is in preparation.

No. of prior RTX treatments	PFS after RTX (days)	PFS after ocaratuzumab (days)
1	172	826*
2	159	636
1	97	434*
2	163	357*
3	103	257
6	180	168
2	116	119
2	176	91

8082 General Poster Session (Board #36G), Mon, 1:15 PM-5:15 PM

Disruption of the eIF4F translation initiation complex as a determinant of diffuse large B-cell lymphoma responsiveness to enzastaurin (LY317615.HCl) and its primary metabolite (LY326020).

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Background: Enzastaurin (enza) is in ph 3 registration trials for DLBCL patients at high risk of relapse following R-CHOP therapy. In a phase 2 DLBCL study, 4 of 55 treated patients were progression- free after prolonged, continuous oral enza therapy with 3 of these 4 confirmed as complete responders (Robertson et al., JCO, 2007). The molecular mechanism for this differential response is unclear. **Methods:** In clinical trials, Enza yields 2-4 μM total circulating drug, comprised of ~50% enza, ~50% primary metabolite, LY326020. We therefore evaluated the sensitivity of a DLBCL cell panel representing both Activated B Cell (ABC) and Germinal Center (GC) subtypes to enza and LY326020. Gene expression analyses, western blotting to explore intracellular signaling and mRNA cap analogue co-capture assays were used to identify the critical effectors of drug sensitivity. **Results:** For the first time, we show the profound biological activity of LY326020, the primary metabolite that accounts for ~ 50% of circulating drug in patients. Like Enza, though more potently, LY326020 inhibits PKC and PI3K-AKT-TOR pathway signaling and robustly induces apoptosis in both ABC and GC DLBCL cells. In both sensitive and resistant cells, enza and LY326020 reduced phosphorylation of numerous proteins in the PI3K-AKT-TOR pathway (e.g. pGSK3β^{ser9}) in a dose and time-dependent manner. However, only sensitive DLBCL cells showed reduced 4EBP1^{ser65} phosphorylation. Accordingly, we show a dose and time-dependent increase in 4EBP1: eIF4E binding. This increase is most pronounced by LY326020. Moreover, cells selected for resistance to enza show reduced 4EBP1 expression and cells lacking 4EBP1 are insensitive to the pro-apoptotic effects of enza and LY326020. **Conclusions:** These data demonstrate that sensitivity of DLBCL to both enza and LY326020 is critically dependent upon 4EBP1 modulation and subsequent disruption of the eIF4F translation complex. Moreover, these data are the first to show the potent biologic activity of LY326020, the primary metabolite of enza that accounts for ~50% of total circulating drug in patients and in preclinical models.

8083 General Poster Session (Board #36H), Mon, 1:15 PM-5:15 PM

Use of the cumulative amount of serum-free light chains (sFLC) at diagnosis and PET2 for the early identification of high risk of treatment failure in Hodgkin lymphoma (cHL).

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Background: Since early identification of patients (pts) at risk of failure is the mainstay of a risk-adapted therapy, we explored the prognostic impact of the sFLC assay in cHL, whose biology involves ongoing activation of polyclonal B-cells. **Methods:** Serum samples from 248 untreated cHL pts were tested by the Freelite assay. Median age was 32 yrs (r 15-85), males 47%, stages: I (5%), II (51%), III (17%), IV (27%); B-sympt. 60%, E-disease, 38%; bulky >10 cm, 44%; ESR > 65, 42%; IPS ≥3, 39%. Early unfavorable disease (GHLSG/ EORTC) was respectively found in 33% and 42% of cases. ABVD was given to 89% of pts. **Results:** Absolute FLC levels were summed into a sFLC($\kappa+\lambda$) variable and ROC analysis indicated 57.1 mg/mL as the threshold to discriminate outcomes. CR rates were 96% and 67% for pts below and above the cutoff, respectively ($p<.0001$). Cox univariate analysis disclosed a HR of 16.70 (95% CI, 8.5-32.9) of events for sFLC($\kappa+\lambda$) ≥ 57.1 mg/mL, by far higher than for PET2 positivity (HR 10.8), PS >1 (HR 4.2), IPS ≥3 (HR 2.8) and all other predictors (HR 0.54-2.4). In a multivariaye model only sFLC($\kappa+\lambda$) and PET2 remained independent predictors. A dismal 8-yrs EFS characterized pts with sFLC($\kappa+\lambda$) above threshold (20% vs 89%; X^2 119, $p<.0001$). Pts with sFLC($\kappa+\lambda$) below cutoff and a negative PET2 had an EFS of 93% as compared to 36% of those with sFLC($\kappa+\lambda$) above cutoff or a positive PET2. Pts with sFLC($\kappa+\lambda$) above cutoff and positive PET2, had the worse outcome with an EFS <10% and a median survival <12 mo.s (X^2 65.4; $p<.0001$). sFLC assay was even more valuable in identifying poor risk pts within the early unfavorable category (5-yrs EFS <25%, X^2 51 $p<.0001$). By immunoistochemistry small B cells and plasmacytoid lymphocytes were identified as the main source of sFLC in HL tissues while a strong sFLC uptake by mast cells was documented. **Conclusions:** A cumulative amount of sFLC ≥57.1 mg/mL, is the strongest independent predictor of failure in cHL. Combining sFLC($\kappa+\lambda$) and PET2 outcomes can timely discriminate poor risk pts subsets, who may benefit from upfront treatment escalation or early salvage. Our data also support that sFLC might endorse immunobiologic activities relevant to cHL pathobiology.

8084 General Poster Session (Board #37A), Mon, 1:15 PM-5:15 PM

An update on gemcitabine, rituximab, and oxaliplatin in combination for relapsed/refractory non-Hodgkin lymphomas.

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Background: Relapsed/refractory non-Hodgkin lymphomas (NHL) have no standard of care. A variety of salvage chemotherapy options are available. We previously reported results of our phase II trial using gemcitabine, rituximab and oxaliplatin (GROC) in the salvage setting for relapsed/refractory NHL in which we observed an overall response rate of 58% with an incidence of grade 3-4 thrombocytopenia of 9% and neutropenic fever of 3.5%, but no grade 3-4 non-hematologic toxicities. Here we update progression free survival (PFS) and overall survival (OS) data. **Methods:** This phase II, single-arm, multicenter study evaluated safety and efficacy of GROC in patients with relapsed/refractory NHL. Patients were treated on a 14 day cycle. On day 1, patients with CD20+ NHL received rituximab (375 mg/m^2). On day 2, patients received gemcitabine (1000 mg/m^2) and oxaliplatin (100 mg/m^2). Granulocyte colony stimulating factor was given. Stem cell transplant (SCT) was considered after a minimum of 6 cycles. **Results:** A total of 58 patients were enrolled from the H. Lee Moffitt and the Auxilio Mutuo Cancer Centers. Ages ranged from 24 to 88 years (median 72 years). The majority of patients had an ECOG performance status of 0-1 (89%). Lymphoid neoplasms included large B-cell (79%), follicular (7%), lymphoblastic (1.8%), Burkitt (1.8%), primary mediastinal large B-cell (3.5%), and peripheral T-cell lymphoma (7%). Eighty-one percent of patients had stage III-IV disease, median IPI was 3, 40% had B-symptoms, 43% had bulky disease and 74% had an elevated LDH. Anthracycline-based therapy had been used in 91% of patients and 66% had received rituximab. Median PFS was 134 days (95% CI 115-153) and median OS was 296 days (95% CI 164-428). No difference in response was observed based on age $>$60, IPI, LDH or albumin levels. Prior therapy with rituximab ($p=0.02$) and initial response to front-line therapy ($p=0.04$) appear to correlate with improved outcomes. Nine patients went on for SCT. **Conclusions:** GROC is a useful salvage regimen for relapsed/refractory NHL with minimal toxicities and good clinical efficacy. Several patients were able to be successfully mobilized, collected and transplanted post GROC therapy.

8085 General Poster Session (Board #37B), Mon, 1:15 PM-5:15 PM

Prevention of adverse events during treatment of HIV-associated Hodgkin lymphoma with ritonavir and zidovudine.

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Background: In response to very high rates of neurologic and hematologic adverse events (AE) when ABVD was used in combination with ritonavir (RTV) or zidovudine (AZT) in HIV-associated Hodgkin (HL) we instituted a policy to use alternative antiretroviral agents during HL therapy in our HIV patients. In this study, we examined all AE in HIV-HL since the exclusion of RTV and AZT over 2 years ago. We also evaluated the AEs when HAART and chemotherapy for NHL were taken together in an expanded cohort of 52 pts. **Methods:** A screen of pharmacy and hospital databases between 1998-2012 identified all HIV-associated HL and NHL patients. Adverse events during chemotherapy were assessed by chart review and graded per the NCI Common Terminology Criteria for Adverse Events. Statistics: Fisher's exact test was used to examine the differences in AE incidence associated with use of specific antiretrovirals. **Results:** HAART use during chemotherapy was identified in 35/36 (96%) pts with HL and 52/108 (48%) of pts with NHL. Before RTV and AZT were prohibited, G3/4 neuropathy, neutropenia, and anemia developed in 31, 68, and 57% of 23 pts with HIV-HL respectively. Since then, 12 patients were treated with non-RTV and AZT based HAART. 0% neuropathy and only 20% G3/4 neutropenia and 10% anemia was observed, each statistically significant ($p<0.01$). Of the 54 patients with NHL, 64% received CHOPR like, HYPERCVADR (18%), and daEPOCHR (11%). All AEs for each NHL regimen were similar to historical controls and no anti HIV medication was found to correlate with any AE, despite 28% of the HAART regimens containing RTV. **Conclusions:** No relationship between any AE and anti HIV medications was identified during treatment for NHL. But, excluding RTV or AZT-based HIV therapy during HL treatment, decreased neuropathy, neutropenia, and anemia by 100%, 38%, and 28% respectively. We suggest that exclusion of ritonavir and zidovudine from HAART regimens used with ABVD become the standard.

8086 General Poster Session (Board #37C), Mon, 1:15 PM-5:15 PM

Hematologic safety data from four phase II studies of single-agent carfilzomib in relapsed and/or refractory multiple myeloma

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Background: Carfilzomib (CFZ) is a next-generation proteasome inhibitor that is currently being evaluated in patients (pts) with multiple myeloma (MM). Given that the majority of pts with MM exhibit either disease- or therapy-related myelosuppression sometime in the course of their disease, detailed evaluation of treatment-emergent hematologic safety data with CFZ is of significant interest. In the following analysis, we report the hematologic safety profile for single-agent CFZ from 526 pts treated in four phase 2 studies. **Methods:** Pts treated with CFZ in trials 003-A0, 003-A1, 004, and 005 were included in the analysis. Pts with preexisting hematologic abnormalities of Grade (G) 0–2 (G0–3 for 005) were eligible to enroll. CFZ was dosed in all studies on Days 1, 2, 8, 9, 15, and 16 of a 28-day cycle (C). Doses were 20 mg/m^2 in C1 for all studies escalating to 27 mg/m^2 in C2 per individual protocol, except 005 (15 mg/m^2 in C1, 20 mg/m^2 in C2, and 27 mg/m^2 in C3). Incidence, frequency, and severity of thrombocytopenia, lymphopenia, neutropenia, and anemia were analyzed in terms of adverse events (AEs) of interest. Laboratory data were analyzed for trends over time. **Results:** See table below for summary of hematologic events. In general, platelet counts trended down, reached a nadir by Day 8 of a 28-day treatment cycle, and normalized before the start of next cycle. There was no evidence of cumulative thrombocytopenia or clinically significant episodes of bleeding associated with thrombocytopenia. Febrile neutropenia was reported in 1% of pts. No mortality due to hematologic events was reported. **Conclusions:** Hematologic AEs, although common with CFZ treatment, were infrequently dose limiting. Clinically significant G3/4 cytopenias were both infrequent and transient. In summary, the hematological safety profile of CFZ was similar to or better than currently approved MM therapies, providing further evidence of its acceptable safety profile in heavily pretreated MM pts. Summary of hematologic events.

Total population N=526, n (%)	Thrombocytopenia	Lymphopenia	Neutropenia	Anemia
Any AE	199 (37.8)	136 (25.9)	119 (22.6)	246 (46.8)
G3/4 AE	131 (24.9)	104 (19.8)	63 (11.9)	118 (22.4)
Dose reductions	6 (1.1)	0	6 (1.1)	2 (0.4)
Discontinuations	5 (1.0)	0	1 (0.2)	3 (0.6)

8087 General Poster Session (Board #37D), Mon, 1:15 PM-5:15 PM

Natural killer (NK) cell activation, cytokine production, and cytotoxicity in human PBMC/myeloma cell co-culture exposed to elotuzumab (Elo) alone or in combination with lenalidomide (Len).

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Background: Elo is a monoclonal IgG1 antibody targeting CS1, a cell surface glycoprotein highly expressed on >95% of myeloma cells. In preclinical models Elo exerts anti-myeloma activity via NK cell-mediated antibody-dependent cellular cytotoxicity. Len is an immunomodulatory agent that may activate NK cells. The combination of Elo + Len synergistically enhanced anti-tumor activity in myeloma xenograft models. We investigated the mechanism of enhancing NK cell activation and myeloma cell killing with Elo + Len. **Methods:** Human PBMC/OPM-2 co-cultures were treated for 24-72h with Elo, Len, or Elo + Len. Activation markers and adhesion receptors were evaluated by flow cytometry. Cytokines were measured by Luminex and ELISpot assays. Cytotoxicity was assessed by cell counting. **Results:** Elo + Len increased IFN-γ secretion significantly more than Elo or Len alone. IFN-γ elevates ICAM-1 expression, and ICAM-1 surface expression on OPM-2 target cells increased synergistically with Elo + Len. Elo, Elo + Len but not Len increased expression of CD25 (IL-2Rα) on NK cells. Len increased the levels of IL-2, but those were decreased in the presence of Elo due to increased consumption by CD25 expressing NK cells. Blocking uptake of IL-2 with anti-CD25 resulted in higher IL-2 levels than with Len. ELISpot assays confirmed that Elo + Len significantly increased the number of IL-2-producing cell colonies compared with Elo or Len. Elo induced NK dependent myeloma cell killing, and the effect was significantly higher with Elo + Len. **Conclusions:** Elo alone activated NK cells and mediated the killing of myeloma cells in PBMC/OPM-2 co-cultures. Elo + Len synergistically enhanced myeloma cell killing and increased expression/production of IFN-γ, ICAM-1, IL-2, and CD25.

	No blocking (control mAb) ave n=6			Anti-CD25 blocking mAb ave n=6			
Treatment	IFN-γ (pg/mL) ave n=8	ICAM-1 on OPM-2 (MFI) n=4	CD25 on NK cells (MFI) n=8	IL-2 (pg/mL) (Luminex)		# IL-2 positive colonies (ELISpot) n=9	OPM-2 killing (%) n=4
*Control	48	427	155	21	-	30	1
**Len	94	2040	131	50	-	71	15
Elo + Len	386	42,259	1546	14	134	191	67
Elo	65	3068	975	7.8	52	80	39

*cIgG1 (isotype); **plus cIgG1.

8088 General Poster Session (Board #37E), Mon, 1:15 PM-5:15 PM

A prospective clinical study evaluating current models for risk of progression from smoldering multiple myeloma (SMM) to multiple myeloma (MM).

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Background: The updated (2010) International Myeloma Working Group criteria emphasize individual follow-up and development of early treatment trials for high risk SMM patients. To facilitate these goals, it is important to have reliable models for risk of progression to MM derived from prospective clinical studies. Current clinical risk models by the Mayo Clinic and the Spanish PETHEMA group stratify SMM patients as low (LR), intermediate (IR), or high risk (HR) of progression using bone marrow plasma cell fraction and protein levels (Mayo) and abnormal plasma cell fraction on flow cytometry with or without immunoparesis (Spanish). We report the first comparison of these models in a prospective natural history study. **Methods:** We evaluated 70 patients with SMM and determined the risk classifications of each using the Mayo and Spanish models. P values of comparisons between risk groups were calculated using Fisher's exact test. **Results:** Among SMM patients classified as HR by the Spanish model (n=31), 2 patients (6%) were HR by the Mayo model; the remaining 17 (55%) and 12 (39%) patients were classified as IR and LR by the Mayo model, respectively. Among 2 SMM patients classified as HR by the Mayo model, both patients (100%) were HR by the Spanish model. There was significant disagreement between the models in identifying HR patients (HR v. non-HR, $p<0.0001$). Similarly, of SMM patients classified as LR by the Spanish model (n=17), 11 patients (65%) were LR by the Mayo model; 6 (35%) were IR and 0 (0%) were HR by the Mayo model. Among SMM patients classified as LR by the Mayo model (n=36), 11 (31%) patients were classified as LR by the Spanish model; 13 (36%) were IR and 12 (33%) were HR by the Spanish model. There was significant disagreement between the models in identifying LR patients (LR v. non-LR, $p=0.0016$). **Conclusions:** The significant discordance between the Mayo Clinic and Spanish PETHEMA clinical risk models underscores the urgent need for biologically derived models that rely on molecular markers to predict disease progression. Such models are critical for counseling individual patients and for the development of early treatment studies that seek to prevent or delay progression to MM.

8089 General Poster Session (Board #37F), Mon, 1:15 PM-5:15 PM

Costimulatory molecule profiles and NK cell recovery after autologous hematopoietic cell transplantation (HCT) in multiple myeloma (MM) patients.

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Background: Increased immune responses post autologous HCT may be of benefit in long term disease control. Responses may be mediated by NK cell function and possibly other alternate pathways, including costimulatory molecule pathways. This pilot study assesses the expression of inhibitory (PD-1 and CTLA-4) and stimulatory (OX-40, ICOS, 4-1BB, and CD28) molecules on NK cells after auto-HCT in MM patients and evaluates the effect of lenalidomide treatment on these pathways. **Methods:** 17 patients with MM undergoing HCT, median age 56.7 years (36 – 67), were included in the study. Peripheral blood samples were taken 3 days prior to HCT and 14, 30, 60, 90, 180 days after HCT. At d180 post-HCT, 13/17 patients were receiving lenalidomide with d91 as median start date. NK cells and their costimulatory molecules were evaluated by flowcytometry using 2 six color panels of antibodies. One way ANOVA test and Kruskal-Wallis test (non-parametric) were applied to analyze the data using the Graphpad Software. **Results:** See table below. NK cell number was highest (median: 26% of total lymphocytes) at d14 ($p: < 0.0001$) compared to pre and post HCT levels. At d180, TNF-R OX40 expression was significantly increased in ≤PR group (n=5) (median: 9.5% of NK cells) compared to ≥VGPR (n=12) (0.8%; $p=0.0084$). In addition, NK cell number was higher in the lenalidomide group (n=13) (median: 15.15 % of total lymphocytes) compared to the no lenalidomide group (n=4) (6.74%; $p=0.0108$) at d180 post HCT. Significantly lower level of CTLA-4 expression was also found in the lenalidomide group (0.33% vs. 2.54%; $p=0.0362$). **Conclusions:** We observed NK cell recovery to baseline values at 60 days after HCT. At d180 post-HCT, OX-40 expression in NK cells was higher in ≤PR group than ≥VGPR group. Lenalidomide treatment was associated with higher NK cells number and decreased expression of CTLA-4. This observation could be a possible marker of enhanced host NK cell immune response against MM. Future clinical trials will explore therapies that increase NK cell responses.

	Pre-HCT	d180
Very good partial response or better (≥ VGPR)	6	12
Partial response or worse (≤ PR)	11	5

8090 General Poster Session (Board #37G), Mon, 1:15 PM-5:15 PM

Retrospective analysis of second malignancies in patients with multiple myeloma.

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Background: Recent data from patients with multiple myeloma (MM) enrolled in randomized clinical trials have shown an increased incidence of second malignancies after treatment with lenalidomide, but the prevalence of second malignancies in the overall MM population is uncertain. **Methods:** We retrospectively analyzed the medical records of 320 consecutive MM patients followed at the Penn State Hershey Cancer Institute between 2006 and 2010. We excluded from the analysis basocellular and squamocellular carcinomas of the skin. **Results:** Forty-three patients (13%) were found to have second malignancies, and 5 of them had a third cancer. One pt had 4 cancers. They included cancers of the prostate (8 pts), breast (8), MDS/leukemia (6), colon/rectum (5), melanoma (5), lung (4), uterus (4), bladder (3), kidneys (2), pancreas (2), testicle (1), myeloproliferative disorders (1), and sarcoma (1). Of 50 cancers, 36 (72%) developed before the diagnosis of MM, at a median of 65 months (range, 1-372), and 14 after that, at a median of 37 months (range, 3-104). Lenalidomide was used in 239 (75%) patients, and in 9 of 14 cases of post-MM second malignancies. **Conclusions:** Second malignancies usually develop before the diagnosis of MM, i.e., MM is the second malignancy for the majority of patients. The use of lenalidomide could not be indicated as a possible carcinogenic factor for the majority of MM patients with second malignancies.

8091 General Poster Session (Board #37H), Mon, 1:15 PM-5:15 PM

Predictive value of baseline serum MIP-1α and CRP on symptom burden and tumor response to induction therapy in patients with multiple myeloma.

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Background: Macrophage inflammatory protein-1α(MIP-1α) is a growth factor for human multiple myeloma (MM) cells. As an osteoclastic factor, its presence provides pathophysiological evidence of the development of lytic bone lesions in MM. C-reactive protein (CRP) indicates systemic inflammation. The relationship between disease-driven inflammatory markers and both patient-experienced symptoms and tumor response to induction therapy is unknown. **Methods:** MM patients (N=39) who were either newly diagnosed or had received fewer than 2 cycles of chemotherapy, and who also were to receive induction therapy, were enrolled. To test concentrations of MIP-1α and CRP, serum samples were collected before and after induction and assayed by Luminex. Multiple symptoms were measured twice a week via the M. D. Anderson Symptom Inventory MM module (MDASI-MM) from -8 to +112 days of induction. The MM-specific items of the MDASI-MM are bone aches, constipation, muscle weakness, diarrhea, sore mouth or throat, rash, and difficulty paying attention. Correlation between symptom severity and inflammatory markers at baseline was examined by linear regression modeling. Kruskal-Wallis significance test and Wilcoxon test were used to examine association between MIP-1α and tumor response. **Results:** Patients received either bortezomib-based (89%) or lenalidomide-based induction therapy. Baseline MIP-1α and CRP were significantly inversely related to the mean severity component score of the 5 most-severe symptoms (fatigue, pain, bone aches, poor sleep, drowsiness) (p=.03; p=.02), and significantly inversely related to the severity of a component score of the module-specific symptoms (p=0.04; p=.002). Change over time in MIP-1α differed significantly by tumor response category (p=.04), with the partial response group having a higher median score than the complete response group (1.483 vs. 0.016, p=.01). **Conclusions:** Our data suggest that higher baseline levels of serum MIP-1α and CRP predict effective chemotherapy-induced reduction of disease-related symptoms in MM patients. Higher serum MIP-1α expression after induction therapy was related to less-ideal tumor response.

8092 General Poster Session (Board #38A), Mon, 1:15 PM-5:15 PM

Second autologous stem cell transplantation as a strategy for management of relapsed multiple myeloma.

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Background: High dose therapy and autologous stem cell transplant (SCT) remain an integral part of the treatment of multiple myeloma (MM). Despite the introduction of several new drugs, disease relapse remains inevitable and a second SCT often allows continued disease control. **Methods:** We examined the outcomes in 105 patients (pts) undergoing a second SCT (SCT2) for relapsed MM, from among 1033 pts receiving initial transplant between 1994 and 2009. Patients receiving an allogeneic SCT post SCT2 were not included in the survival analysis. **Results:** Median (range) age at SCT2 was 60 yrs (35-74) and the time between SCTs was 46 mos (10-130). The median follow-up was 5 yrs from SCT2. The median (range) number of regimens between the two SCTs and from diagnosis was 2 (0-7) and 3 (1-11), respectively. Conditioning regimen was Mel 200 in 85 (81%) pts. Median (range) CD34 cells infused was 4.6 (2.5-25 million/kg). Hospitalization was required for 53 pts (50%), median hospital stay was 7 days.. Median time to ANC of 500 and platelets of 50,000 were 13 and 16 days, respectively. Treatment related mortality was seen in 5 (5%) pts. A partial response or better was seen in 95 (90%) pts, including a stringent CR in 10%, CR in 19%, and VGPR in 21%. Stable disease or progression was seen in 7 pts and 3 pts died prior to disease assessment. The median (95% CI) PFS and OS after SCT2 were 10.4 (8, 14) and 33 (28, 51) mos, respectively. The median OS was not reached and 33 mos respectively, for those obtained a CR and those with $<$CR, P$=$0.03. FISH pre-SCT2 was available for 73 pts; the PFS and OS were not affected by the presence of high-risk MM. In multivariate analyses, shorter duration of response to SCT1, higher plasma cell (PC) labeling index at SCT2, more regimens used prior to SCT2 all predicted shorter PFS and OS post SCT2. Lack of CR to SCT2 was also significantly associated with shorter PFS. **Conclusions:** Second SCT is an effective therapy for eligible pts relapsing after other treatments. It provides a meaningful duration of response and appears to be well tolerated. Pts with longer duration of response to first transplant and those achieving a CR appear to have maximum benefit.

8093 General Poster Session (Board #38B), Mon, 1:15 PM-5:15 PM

Prognostic value of serum lactate dehydrogenase in symptomatic multiple myeloma.

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Background: In patients with symptomatic multiple myeloma, the clinical features, responses to treatment, and survival times vary. Well established predictors of survival include the International Staging System (ISS), cytogenetic abnormalities, and response to therapy. Long recognized has been the association of high serum lactate dehydrogenase (LDH) with advanced disease and shorter survival. We focused here on the impact of high LDH on staging and prognosis in order to guide the role of recent advances in therapy. **Methods:** We evaluated 1,247 patients with newly diagnosed, symptomatic myeloma from 10/74 to 7/11. Our goal was to determine the prognostic value of high LDH (>300 IU/L) in relation to ISS stage. We also compared the frequencies of anemia, hypercalcemia, and response to therapy in patients with high LDH with those of patients with Stage III disease and normal LDH values. **Results:** All 1,139 patients with normal LDH lived significantly longer than the 108 patients with elevated values (47 vs. 16 months, p <.01). LDH was elevated in 9% of all patients, but in 2%, 6%, and 18% of patients with ISS-I, II, and III disease, respectively. Their survival times were also significantly shorter than those of comparable patients in each stage with normal LDH (table). Among the 108 patients with high LDH, the frequencies of hemoglobin <8.5 g/dl (54 vs. 41%, p=.03), and serum calcium>11.5 mg/dl (41 vs. 27%, p<.01) were significantly higher than those of 292 patients with Stage III disease and normal LDH, and the frequency of response to therapy was less (40 vs. 62%, p<.01). **Conclusions:** Serum lactate dehydrogenase provides a convenient and dependable prognostic indicator in patients with multiple myeloma. An elevated LDH value indicates a poor prognosis regardless of ISS stage, confirming the report by Gkotzamanidou, Terpos, and Dimopoulos et al, and should be included in the definition of stage III disease. Such patients require rapid control of disease with sequential combinations of effective drugs and intensive therapy in order to improve their outcome.

Effect of elevated LDH on survival according to ISS stage (median months).

ISS Stage	≤ 300 IU/L	>300 IU/L	p
I	56	16	.09
II	49	21	<.01
III	35	16	<.01

8094 General Poster Session (Board #38C), Mon, 1:15 PM-5:15 PM

Predicting bortezomib-related severe neurologic adverse events by measuring proteasome activity in PBMCs.

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Background: Although a proteasome inhibitor bortezomib (BOR) is one of the backbone drugs for the treatment of multiple myeloma, severe neurologic adverse event (sNE) is a major obstacle for continuing the treatment. As there is no clinically available biomarker for predicting the occurrence of sNAE, we measured the proteasome activity (PrsAtv) in peripheral blood mononuclear cells (PBMCs). **Methods:** Patients (Pts) were treated by either standard Q3wks or weekly (BOR 1.3mg/m^2: day 1, 8, 15, 22; Q5wks) schedule depending on physician's decision. PBMCs were collected from 21 Pts and 99 healthy volunteers. Pts' samples were collected before treatment, 1 hour after the 1st injection of BOR, and at the end of the 1st course. PrsAtv in PBMCs was measured by using a specific substrate SUC-LLVY-AMC, which becomes fluorescent upon cleavage by proteasome. **Results:** Levels of PrsAtv among volunteers were highly variable with no certain correlation with age and sex. Pretreatment levels of PrsAtv among Pts were also variable, and didn't correlate with the occurrence of sNAE. After 1 hour of BOR injection, PrsAtv decreased to 33.2±20.5% (mean ± SD) of the pretreatment level, and it generally recovered (112.5±77.6%) at the end of the 1st course. However, in 12 out of 21 Pts, it didn't recover to ≥ 100%. Among these Pts, 5 manifested with sNAE (≥G3) during the 2nd or 3rd course of the chemotherapy. In a sharp contrast, no patients whose PrsAtv recovered to ≥100% manifested with sNAE. Pts who manifested with sNAE (5 Pts) showed the lower levels of PrsAtv at the end of the 1st course than those without sNAE (16 Pts) (67.4±11.8 vs 126.6±83.8%, p=0.075). It should be also strengthened that all the Pts who manifested with sNAE were treated by the standard Q3wks schedule, although levels of PrsAtv at the end of the 1st course were not significantly different between Q3 and Q5wks groups (109.0±68.3 vs 121.1±96.4 %, p=0.38). Contrary, there was no significant difference of the bortezomib response between these two treatment groups. **Conclusions:** Pts whose PrsAtv does not recover to ≥100% at the end of the 1st course are at high risk of manifesting with sNAE, and these Pts should not be treated by the standard Q3wks schedule in the subsequent courses.

8095 General Poster Session (Board #38D), Mon, 1:15 PM-5:15 PM

Regional differences in the treatment approaches for relapsed multiple myeloma: An IMF study.

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Background: Multiple myeloma (MM) remains incurable and invariably relapses after initial therapy. There is no uniform approach to management of relapsed MM and is dictated by type of initial therapy and the response seen, and availability of new drugs. The outcomes associated with current approaches have not been systematically examined. **Methods:** We enrolled 383 patients (pts) with myeloma who had a documented relapse between Jan 2007 and June 2010, including 220 from Europe, 106 from Asia, and 31 from South America and 26 from North America. Time Zero (T_0) was defined as date of treatment after first relapse. **Results:** Across the study, 61% were male and 49% were over 65 years at T_0. ISS stage distribution at diagnosis included 26, 40 and 33% of patients in stages 1, 2 and 3, respectively. Among regimens used at first relapse; bortezomib (Btz) containing regimens were most common (54%), followed by lenalidomide (Len, 25%) and cyclophosphamide (21%). The overall response rate (>=PR) to first therapy after relapse was 58% including 14% with a CR. There was a progressive decrease in the response rates with successive regimen; 45%, 30% and 15% for regimens 2, 3 and 4 respectively. Len use was considerably lower in the Asian cohort, while Btz use was comparable across the regions. The median PFS from T_0 was 13 mos and OS was 35 mos, for the entire cohort. The PFS to first salvage regimen was similar across the regions, while OS was shorter for the Asian and South American cohorts. In a univariate analysis, ISS stage 3, presence of cytogenetic abnormalities, history of plasma cell leukemia or extramedullary disease (EMD), bone marrow PC% > 33% and presence of renal insufficiency were all associated with a shorter PFS as well as shorter OS (P<=0.01). In a multivariate model, ISS stage 3 and presence of EMD were most associated with short OS. **Conclusions:** Median PFS for current second line regimens, typically containing Btz or Len appear to be 1 yr with an OS from first relapse of about 3 yrs. The OS from first relapse is nearly double that seen in a cohort of patients in first relapse prior to introduction of new drugs. Clear-cut regional differences can be seen in terms of patterns of drug use and likely reflect drug availability and healthcare costs.

8096 General Poster Session (Board #38E), Mon, 1:15 PM-5:15 PM

Long-term outcome with lenalidomide and dexamethasone therapy for newly diagnosed multiple myeloma.

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Background: The combination of lenalidomide and dexamethasone (Len-Dex) is a commonly used initial therapy for newly diagnosed multiple myeloma. While the short-term outcomes with respect to response and toxicity is well-known, long-term outcome with this combination as initial therapy is not well described. **Methods:** We studied 286 consecutive patients with newly diagnosed MM seen at our institution, who received initial therapy with Len-Dex, and who had complete follow up records. Data regarding the clinical course was obtained from medical records. **Results:** The median (range) age at diagnosis was 63 (28-92) yrs; 166 (58% were $\leq$ 65 yrs and175 (61%) were male. The median estimated follow-up was 3.9 yrs (95% CI, 3.4, 4.2) and 203 (71%) pts were alive at the time of last follow up. The median estimated duration on Len-Dex was 5.3 mos (95% CI, 4.6, 6.4). The best overall response ($\geq$PR) was 72%, including 26% with VGPR or better and 14 (5%) not being evaluable for a response. At last follow up, 41 (14%) patients were continuing on therapy. There were 93 pts (32%) who stayed on therapy for 12 months or more. Among these patients, the ORR was 86%, including 45% with VGPR or better. The median overall survival (OS) for the entire cohort from diagnosis was 7.4 yrs (95% CI; 5.8, NR) and the estimated 5-yr survival was 67%. There were 16 (5.5%) pts who died within a year of diagnosis. The median time to first disease progression, irrespective of transplant status, was 30.2 mos (95% CI, 25, 42). Overall, 143 (50%) of the patients have gone to stem cell transplant. Censoring those patients who proceeded to SCT prior to relapse at the time of BMT, the median TTP was 25.5 mos (95% CI, 22, 29). The median OS was 7.4 yrs for those $\leq$65 yrs, compared with 6.2 yrs for the older patients (P=0.01). The 5-yr OS estimate for patients in ISS stage 1, 2 and 3 were 82, 65, and 44 months respectively. **Conclusions:** The current study provides long-term estimates of responses and survival in a series of patients treated initially with lenalidomide and dexamethasone. The median survival of nearly 8 years reflects the efficacy of the novel agents both at diagnosis and at relapse and confirms the survival improvements seen in MM in the last decade.

8097 **General Poster Session (Board #38F), Mon, 1:15 PM-5:15 PM**

Clinical profile of multiple myeloma in Asia: An Asian Myeloma Network (AMN) study.

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Background: The incidence of multiple myeloma (MM) is known to be variable according to ethnicity. However the difference of clinical characteristics between ethnic groups is not well-defined. In Asian countries the incidence of MM has been lower compared with Western countries. However, there are growing evidences that MM is increasing very rapidly in this region. Until now, only few data of Asian patients has been reported. Asian myeloma network (AMN) decided to analyze the first multinational project to explore clinical characteristics of Asian MM patients and clinical practice performed in Asian countries. **Methods:** Data were collected from 21 centers from 7 countries and regions were collected retrospectively. Clinical characteristics of 2969 symptomatic MM patients at diagnosis were described. Overall survival (OS) and prognostic factors were analyzed for 2273 patients who have survival data. **Results:** Median OS was 54 months (95% CI 48.0-60.0). Patients who were diagnosed before 2000 were shorter survival. Transplantation was performed to 513 patients with better survival (84 vs. 45 months, $p<0.001$). First line treatment of 2339 evaluable patients was analyzed. Overall response rate was 71% with 30%, VGPR or better. New drugs including bortezomib, thalidomide or lenalidomide were combined for 32.5% of all 2339 patients without difference in response rate or OS according to combination. **Conclusions:** We successfully described clinical characteristics of Asian MM patients and this project will be the base for future studies or clinical trials for Asian MM patients. Updated analyses and comparison with Western data will be presented. AMN, supported by the International Myeloma Foundation (IMF) IMWG initiative.

8098 General Poster Session (Board #38G), Mon, 1:15 PM-5:15 PM

A phase I/II study of carfilzomib (CFZ) as a replacement for bortezomib (BTZ) for multiple myeloma (MM) patients (Pts) progressing while receiving a BTZ-containing combination regimen.

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Background: Recent data has shown that single-agent CFZ can produce responses among MM pts refractory to previous treatment regimens including those containing BTZ. We conducted an intrapatient Phase 1/2 trial investigating the safety and efficacy of CFZ as a replacement for BTZ in BTZ-containing regimens to which pts have progressed. **Methods:** Eligible pts had to have progressed while receiving their most recent BTZ-containing regimen after at least 4 doses of BTZ at $>$ 1.0 mg/m^2 in $<$ 4 weeks per cycle. Combination regimens containing an alkylating agent, anthracycline, or a glucocorticosteroid were eligible. CFZ replaced BTZ in each regimen via intravenous administration over 30 min on days 1, 2, 8, 9, 15, and 16 of each cycle. Treatment continued using the same dose(s) and schedule(s) of each drug administered in the BTZ-containing regimen. CFZ doses were escalated on each of the first 4 cycles from 20 to 27, 36, and 45 mg/m^2 or until a maximum tolerated dose (MTD) was reached for that regimen. **Results:** Of 19 enrolled pts 13 are evaluable to date and 6 have recently started treatment. Pts received a median of 7 (range, 1-18) prior treatments and 5 (range, 1-5) different BTZ-containing regimens. Pts were treated with CFZ and the following different combinations: bendamustine (BEND) alone, BEND + methylprednisolone, dexamethasone (DEX) alone, DEX + pegylated liposomal doxorubicin, ascorbic acid + cyclophosphamide, and melphalan alone. Pts have completed a median of 3 cycles. Clinical benefit was seen in 10 (77%) pts (complete response = 8%; very good partial response = 8%; partial response = 31%; minor response = 31%) with another 23% showing stable disease. The median time to progression (range: 2-8 months) has not been reached and only 2 pts have progressed. The most common grade 3/4 adverse events were thrombocytopenia occurring in 5 pts (all = grade 3 except 1 event) and fever occurring in two pts (grade 3). Four pts experienced a serious adverse event but no regimen has reached a MTD. **Conclusions:** These early results suggest that CFZ is an effective and tolerable replacement for BTZ for pts who are refractory to BTZ-containing combination regimens.

8099 **General Poster Session (Board #38H), Mon, 1:15 PM-5:15 PM**

Effect of matrix metallopeptidase 13 (MMP13) on multiple myeloma (MM) cells, osteoclast (OCL) activity, and bone resorption.

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Background: MM cells produce OCL-activating factors that induce excessive bone resorption resulting in lytic lesions. The role of MMPs in invasion/progression of solid tumors is well-known, but its function in MM has not been well elucidated. Our group has shown that MMP13 is highly expressed in primary MM cells and in sera of MM patients. Levels of MMP13 significantly correlate with the extent of bone disease. MMP13 is induced by IL-6 via AP-1 activation in MM cells and enhances fusion of OCL precursors resulting in excessive bone resorption. OCL formation using MNCs of *mmp-13*$^{-/-}$ mice resulted in a fusion defect, significantly decreased OCL size and activity, which could be reversed by exogenous MMP13 *(ASH 2009, IMW 2011)*. **Methods:** Methods will be presented in the Results section. **Results:** RT-PCR and western blotting revealed that IL-6 treatment of MM cells induced MMP13 transcription (30-fold) and secretion (>1000-fold). Protein expression of the AP-1 members c-Jun and c-Fos was induced by IL-6, which correlated with MMP13 upregulation. Our data further indicate that the catalytic activity of MMP13 is not required to enhance OCL formation and bone resorption. To prove this, we generated the MMP13 activity-dead mutation MMP13-E223A construct by site-directed mutagenesis PCR-based cloning. The mutated protein was overexpressed in HEK293 cells and purified from the supernatant to confirm whether loss of catalytic activity blocks MMP13 function. To further investigate the in vivo role of MMP13 in MM bone disease, MMP13 expression was knocked down (KD) in murine 5TGM1-MM cells by pKLO. 1 puro lentiviral infection containing sh-RNA targeting mouse MMP13 sequence. MMP13-KD 5TGM1-MM cells or WT-5TGM1-MM cells were intratibially injected into RAG2$^{-/-}$ mice. Development of lytic bone lesions are monitored by micro-QCT and data will be available at the time of presentation. **Conclusions:** Our data suggest that MMP13, secreted by MM cells, plays a critical role in the development of lytic lesions. Targeting MMP13 represents a promising approach to treat or to prevent bone disease in MM.

8100 General Poster Session (Board #39A), Mon, 1:15 PM-5:15 PM

Survival outcomes of early autologous stem cell transplant (ASCT) followed by lenalidomide, bortezomib, and dexamethasone (RVD) maintenance in patients with high-risk multiple myeloma (MM).

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Background: Despite markedly improved survival rates for MM pts in the last decade, 15-20% of pts with high risk genetics continue to have dismal outcomes with a median PFS of 18.5 months (Kapoor P et al). In this subset of pts, efforts are needed to improve response rates and prolong the response duration, but doing so without genotoxic therapy as this has been shown not to improve outcomes (Barlogie et al). **Methods:** We evaluated 37 pts with high risk features [del17p (n=16), t(4;14) (n=1), t(14;16) (n=4) by FISH/CTG; hypodiploidy (n=9), del 13 (n=16); complex karyotype (n=14) by CTG; PCL (n=7) and atypical presentation (n=4)]. After completing induction therapy, all pts underwent ASCT followed by RVD maintenance. 60 days after ASCT following hematological recovery, pts began maintenance [lenalidomide 10 mg/day (days1–21), bortezomib 1.3 mg/m2 and dexamethasone 40 mg once a week (days 1, 8, 15) every 28 days]. **Results:** The response rates are summarized in the table. 7/36 pts progressed while on RVD maintenance. The median PFS and OS for pts on RVD maintenance has not been reached. Pts with <VGPR pre-ASCT and with <VGPR on RVD maintenance have median PFS of 28 months and 11 months, respectively. 4 pts with prior h/o DVT received anticoagulation, while all others received ASA for DVT prophylaxis. No thrombotic events were seen. There were no grade 3/4 toxicities or treatment-related mortality. The most common toxicities during maintenance schedule were: PN-40% (G1: 26%; G2:14%); G1 rash-10% and G1 fatigue in 78% pts. Cytopenias were seen in 25% pts and dose reductions were made in 50% pts. There is no report of secondary malignancies. **Conclusions:** Early ASCT followed by RVD maintenance delivers superior response rates in this high risk segment achieving sCR in 47% and ≥VGPR in 73% pts and prevents early relapses. The median PFS and OS have not been reached. RVD maintenance regimen is well tolerated and promising.

Response rates.

	Pre-ASCT response		Post-ASCT response		Best response with RVD maintenance	
	n	%	n	%	n	%
sCR	3	8	8	22	17	47
CR	3	8	8	22	5	14
sCR + CR	6	16	16	44	22	51
VGPR	13	35	16	43	8	22
≥VGPR	19	51	32	77	30	73
PR	15	41	5	14	3	8
≥PR	34	92	37	91	33	81
SD	1	3				
PD	2	6			3	8

8101 General Poster Session (Board #39B), Mon, 1:15 PM-5:15 PM

Efscalefect of lenalidomide, bortezomib, and dexamethasone (RVD) induction therapy in transplant-eligible patients (Pts) with newly diagnosed multiple myeloma (MM) on CR rates and survival.

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Background: Addition of lenalidomide to bortezomib and dexamethasone (RVD) demonstrated to be an effective and well tolerated regimen in phase II trials with overall response rate (ORR) >95% (Richardson P et al). Given the lack of phase III data, we have evaluated our institutional experience of pts treated with RVD induction therapy, to support this triplet combination. **Methods:** 286 transplant-eligible pts with newly diagnosed MM were treated with RVD induction therapy [R - 25 mg/day (days1–14), V - 1.3 mg/m2 (days 1, 4 8, 11) and D - 40 mg once/twice weekly as tolerated every 21 days] from January 2008 until January 2012. 148 pts underwent ASCT and 138 pts opted for delayed transplant. Post-ASCT 56% pts are on maintenance therapy tailored to their risk (R-40%; RVD-10%; V-6%). Demographic and outcomes data for the pts that underwent ASCT were collected and responses were evaluated per IMWG Uniform Response Criteria. **Results:** Median age of the pts is 60 years (range 32-77). Other pt characteristics include: M/F 55%/45%; ISS I/II/III 40%/30%/30%; Isotype IgG/IgA/FLC/IgM 61%/20%/18%/1%; high risk/standard risk 13%/87%. Pts received a median of 4 cycles (2-9) of RVD. Median CD34+ stem cell collection was 11.24 x 10^6/kg. 18% pts required dose reductions (R/V/D-5%/9%/2%) and discontinuation in 2% pts for progressive disease. 49%/8% pts had G1-2/G3-4 PN. Median estimated PFS is 47 months and median OS has not been reached. Response rates are included in the table. **Conclusions:** RVD is an active induction regimen with superior response rates of > 80% ≥VGPR rates post-ASCT and is well tolerated in newly diagnosed MM pts. Incorporation of lenalidomide did not impact the stem cell collection. Until phase III data are available, our institutional experience could provide a perspective in the choice of RVD as an effective induction regimen in improving ORR and prolonging survival.

	Post-induction response		Post-ASCT response		Best response	
	N (148)	%	N (146)	%	N (142)	%
sCR	27	18	50	35	81	57
CR	10	7	18	12	8	6
nCR	15	10	12	8	10	7
sCR + CR + nCR	52	35	80	55	99	70
VGPR	40	27	36	25	26	18
≥VGPR	92	62	116	80	125	88
PR	48	33	25	17	13	9
≥PR	140	95	141	97	138	97
MR	3	2				
PD	5	3	5	3	4	3

8102 General Poster Session (Board #39C), Mon, 1:15 PM-5:15 PM

Association of bone marrow plasma cell infiltration pre-auto transplant with adverse outcomes in multiple myeloma.

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Background: Auto-stem cell transplantation (SCT) has become the standard of care for eligible patients (pts) with multiple myeloma (MM). However, the impact of bone marrow (BM) plasma cell (PC) percentage before SCT is not yet known. **Methods:** Retrospective review of 1489 MM pts who underwent auto-SCT from 7/8/98 – 12/31/2010 with post-induction, pre-SCT BM biopsy information available. Pts were divided into 2 groups: $<$10% PC infiltration ("PC low") and $>$10% PC infiltration ("PC high"). Progression-free (PFS) and overall (OS) survivals were estimated by the Kaplan-Meier method. Log-rank test was performed to test differences in survival. **Results:** 1489 pts were studied. 1174 pts had $<$10% involvement of BM by PCs and 315 had $>$ 10% involvement. For pts in the PC low group, 32% had a CR, 20% had a VGPR, 31% had a PR, 13% had $<$PR and 3% had progressive disease (PD) after SCT. For pts in the PC high group, 11% had a CR, 14% had a VGPR, 48% had a PR, 21% had $<$PR and 5% had PD after SCT. Median PFS was significantly shorter for the PC high group vs the PC low group (24.8 vs 29.5 months, $p=0.05$), as was median OS (52.5 vs 79.4 months respectively, $p<0.001$). When only pts who had a PR to induction were examined, there was a significant difference in both PFS (24.4 vs 33.2 months, $p=0.04$) and OS (58.3 vs 81.2 months, $p=0.002$) for the PC high vs PC low groups, respectively. For the 1299 (87%) pts treated in the era of novel therapeutics (after 2000), the differences between the PC high and PC low groups were maintained for both PFS (24.4 vs 29.5 months respectively ($p=0.029$)) and OS (54.8 vs 88.4 months respectively, $p<0.001$). Chemo-mobilization before SCT did not improve PFS or OS but this was done in only 44 (14%) of PC high pts. **Conclusions:** PC BM infiltration before auto-SCT is associated with a worse outcome. This finding persists in pts with a PR before SCT. Thus BM disease burden may further stratify pts with a PR. Though additional therapy did not significantly change the outcome for pts with high PC burden, this was done only in a minority of pts. Additionally, differences between PC high and PC low groups are maintained despite new salvage agents over the last 10 years. Further prospective study is warranted to determine the true impact of BM PC infiltration.

8103 General Poster Session (Board #39D), Mon, 1:15 PM-5:15 PM

Patterns of nonhematologic malignancies in a population of African American veterans with monoclonal gammopathy of unknown significance (MGUS).

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Background: Monoclonal Gammopathy of Unknown Significance (MGUS) is characterized by the presence of a monoclonal immunoglobulin in the serum or the urine with no evidence of hematologic malignancy. A possible relationship between MGUS and increased incidence of NHM has been suggested in Caucasian populations. However, data in African Americans with MGUS are lacking. **Methods:** Non-MGUS controls were selected randomly from patients who did not have a paraprotein detected on electrophoresis (NMGUS) and were matched 2-to-1 to MGUS cases. Descriptive statistics and comparisons are presented to compare MGUS and NMGUS groups. **Results:** 492 male patients with MGUS patients were matched with 984 male NMGUS patients. 451 patients had abnormal serum protein studies (91.6%) and 40 had light chain disease (8.4%). Median age at diagnosis of MGUS was 68 years (28-81). 144 MGUS patients (29.2%) and 296 NMGUS patients (30%) had 1 or more NHM. The median age of diagnosis of 1st NHM was 70 (25-94) in the MGUS group and 68.4 in the NMGUS group (34.5-94.4). 19 MGUS patients (3.8%) and 27 NMGUS patients had 2 different types of NHM (2.7%). 1 MGUS patient (0.2%) and 3 NMGUS patients (0.3%) had 3 NHM. 57 patients had MGUS before NHM (11.5%) and 69 patients were diagnosed with MGUS after the diagnosis of NHM (14%), and median differences between diagnosis of MGUS and 1st NHM were 4 years (1-12 years) and 5 years (1-38 years) respectively. Types of NHM were comparable, and prostate cancer was the most prevalent NHM in both groups (15% of MGUS patients and 17% of NMGUS patients). Median time of follow up was 49.3 months for MGUS patients and 35.2 months for NMGUS patients 140 of the MGUS patients (28.4%) and 214 non-MGUS patients (21.75%) had died at data cut-off. **Conclusions:** Based on these observational data, prevalence and types of NHM appear to be comparable in MGUS and NMGUS African American patients. All cause mortality appears to be higher for NHM patients if they had MGUS. This pattern will need to be verified prospectively in a larger group of patients.

8104 General Poster Session (Board #39E), Mon, 1:15 PM-5:15 PM

Role of immune-related conditions in smoldering myeloma and MGUS.

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Background: Recent guidelines emphasize tailored follow-up and the need for clinical trials for high-risk smoldering myeloma (SMM). Emerging evidence from epidemiological studies suggests that immune-related conditions play a role in the causation of myeloma precursor disease (SMM and monoclonal gammopathy of undetermined significance; MGUS) and are of clinical importance for the risk of developing multiple myeloma. The aim of our study is to assess whether there is an altered biology in SMM/MGUS patients with preceding immune-related conditions. **Methods:** From our ongoing prospective SMM/MGUS natural history study, we evaluated 56 SMM and 60 MGUS patients. Information on autoimmunity was identified at baseline. All patients underwent extensive clinical and molecular characterization. At baseline, all patients underwent bone marrow biopsy evaluation using immunohistochemistry and multi-color flow cytometry of plasma cells. We assessed expression patterns of adverse plasma cell markers (CD56 and CD117), and applied risk models based on serum immune markers and bone marrow findings. **Results:** Among enrolled SMM and MGUS patients, 7 (12%) and 9 (15%) had a preceding autoimmune disorder. We found SMM patients with (vs. without) a preceding autoimmune disorder to have a substantially lower rate of CD56 (28% vs. 61%) and CD117 (28% vs. 61%) expressing plasma cells. When we compared the same markers in MGUS patients, CD56 and CD117 expression patterns were similar among patients with vs. without preceding autoimmunity (10% vs. 17%, and 50% vs. 48%). Using the Mayo Clinic risk model, none of the SMM patients with a preceding autoimmune disorder had high-risk features; in contrast, 3/41 (7%) of those without a preceding autoimmune disorder were high-risk SMM. Using the Mayo Clinic risk model, none of the MGUS patients were high-risk independent of autoimmune status. **Conclusions:** Our prospective clinical study found SMM patients with preceding immune-related conditions to have less adverse biology, supportive of epidemiological studies suggesting the risk of developing multiple myeloma is substantially lower in these patients.

8105 General Poster Session (Board #39F), Mon, 1:15 PM-5:15 PM

Does stage migration exist in active multiple myeloma (MM)?

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Background: Tumor stage migration can artifactually inflate cancer survival rates and overestimate benefits of newer therapies. We have previously shown a favorable impact of widely used novel agents in MM patients. However, it is not known whether use of well tolerated and easily administrable novel agents results in their introduction at lower levels of MM burden (and therefore add to improved outcome). Our goal was to assess for stage migration in newly diagnosed active MM patients. **Methods:** We reviewed records of 1,467 patients with active MM at Mayo Clinic, at initiation of therapy from 3 consecutive 5-year intervals: 01/1996-12/2000 (Group 1), 01/2001-12/2005 (Group 2), 01/2006- 12/2010 (Group 3). These intervals reflect the practice changing approaches at our center transitioning from the use of alkylator-based to novel agent-based initial therapy. Traditional parameters and staging systems were used to estimate tumor burden. We performed one way analysis of variance (ANOVA) to assess for differences in these parameters among the groups. A p-value of <0.05 was considered significant. **Results:** Group 3 shows an upward trend for hemoglobin (Hgb), and lower creatinine and bone marrow plasma cell (BMPC) percent. Compared to other groups, a greater proportion of Group 3 patients are assigned to lower Durie Salmon (DS) stages (Table) suggesting reduced tumor burden at therapy initiation. In contrast, the International Staging System (ISS) which is not used for decisions regarding therapy initiation divides cohorts in similar proportions. **Conclusions:** Stage migration is evident in our cohort of active MM patients presenting in the time periods of evolving initial therapeutic strategies. Future studies should take into account the bias introduced by this phenomenon in interpreting survival analysis of MM patients.

	Group 1 (N=432) 1996-2000		Group 2 (N=480) 2001-2005		Group 3 (N=555) 2006-2010		
Parameters	**Median**	**IQ range**	**Median**	**IQ range**	**Median**	**IQ range**	**P value**
Hgb (g/dL)	10.9	9.6-12.1	10.9	9.5-12.1	11	9.8-12.6	0.01
Creatinine (mg/dL)	1.3	1-1.6	1.2	1-1.6	1	0.8-1.3	<0.0001
BMPC (%)	37	17-59	32	14-57	29	13-51	0.02
Calcium (mg/dL)	9.5	9.1-10.2	9.6	9-10.1	9.6	9.1-10.1	NS
DS stage				(%)			
1	10		13			17	0.0003*
2	06		14			12	
3	84		73			71	
ISS				(%)			
1	25		32			24	NS*
2	45		37			43	
3	30		31			33	

* Chi square.

8106 General Poster Session (Board #39G), Mon, 1:15 PM-5:15 PM

Participation of BTK in MYD88 signaling in malignant cells expressing the L265P mutation in Waldenstrom's macroglobulinemia, and effect on tumor cells with BTK-inhibitor PCI-32765 in combination with MYD88 pathway inhibitors.

Guang Yang, Lian Xu, Yangsheng Zhou, Xia Liu, Yang Cao, Christina Tripsas, Christopher J Patterson, Zachary R Hunter, Yu-Zu Tai, Kenneth Carl Anderson, Steven P. Treon; Dana-Farber Cancer Institute, Boston, MA

Background: Bruton's tyrosine kinase (BTK) promotes B-cell receptor signaling along with B-cell expansion and survival through NF-κB and MAPK. MYD88 L265P is a widely expressed somatic mutation in tumor cells from WM patients. MYD88 L265P promotes enhanced tumor cell survival through IRAK 1/4 mediated NF-κB and MAPK signaling. We therefore sought to clarify the role of BTK signaling in MYD88 L265P expressing WM cells, and the impact of BTK and MYD88/IRAK inhibition on WM cell signaling and survival. **Methods:** Western blot analysis was performed using total and phospho-specific BTK antibodies in MYD88 L265P expressing primary WM patient cells, BCWM.1 and MCWL-1 WM cell lines following MYD88 knockdown by lentiviral transduction, and/or use of MYD88 or IRAK signal inhibitors. Cells were also treated with the BTK inhibitor PCI-32765, in the presence or absence of MYD88 homodimerization or IRAK1/4 inhibitors. Annexin V / PI staining was used to assess cell survival, and synergism assessed with CalcuSyn software. **Results:** BTK was phosphorylated in MYD88 L265P expressing WM cells. Knockdown of MYD88 by lentiviral transduction, and/or use of MYD88 or IRAK 1/4 kinase inhibitors led to decreased BTK phosphorylation. Phosphorylation of BTK, TIRAP, a major TLR adapter protein for MYD88 signaling, IRAK1, IKBα, ERK1/2 and STAT3 were significantly reduced following treatment with PCI-32765. Treatment with PCI-32765 also induced apoptosis of MYD88 L265P expressing WM cells, and showed synergistic tumor cell killing in the presence of either MYD88 homodimerization or IRAK 1/4 kinase inhibitors. **Conclusions:** BTK activation is facilitated by MYD88 pathway signaling in L265P expressing WM cells, and participates in MYD88 downstream signaling. Inhibition of BTK by PCI-327625 led to robust tumor cell killing of MYD88 L265P expressing WM,cells, which was potentiated by MYD88 pathway inhibitors. These studies provide the framework for the investigation of BTK inhibitors in WM, as single agents and in combination with MYD88 pathway inhibitors.

8107 General Poster Session (Board #39H), Mon, 1:15 PM-5:15 PM

Use of whole genome sequencing to identify highly recurrent somatic mutations in Waldenström's macroglobulinemia.

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Background: Waldenstrom's Macroglobulinemia (WM) is an IgM secreting lymphoplasmacytic lymphoma. The genetic basis for this disease remains to be clarified. **Methods:** We performed whole genome sequencing (WGS) using $CD19^+$ selected bone marrow lymphoplasmacytic cells (LPC) from 30 WM patients. For 10 of these patients, paired $CD19^+$ depleted peripheral blood samples were used for WGS as normal controls. **Results:** The most common somatic variants identified and validated by Sanger sequencing included MYD88 L265P, an activating mutation for IRAK/TRAF6/NFKB and MAPK signaling, which was observed in 27/30 (90%) patients; the N-terminal domain of CXCR4, which included mutations associated with WHIM syndrome and confer constitutive CXCR4 signaling resulting from dysfunctional receptor endocytosis, a finding observed in 8/30 (27%) patients, and ARID1A (5/30; 17%), a tumor suppressor gene. Less common somatic variants were also identified in MUC16 (4/30; 13%), TRAF2 (3/30; 10%), TRRAP (3/30; 10%) and MYBBP1A (2/30; 7%). **Conclusions:** Using WGS and confirmatory Sanger sequencing, we have identified several somatic variants with oncogenic function, the most common of which include MYD88 L265P, the N-terminal domain of CXCR4, and ARID1A.

8108 General Poster Session (Board #40A), Mon, 1:15 PM-5:15 PM

miRNA expression profiling of CD20+ plasma cell myeloma (PCM): Upregulation of miR-155 shedding new insight into disease biology and clinicopathologic behavior.

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Background: Up to15-20% of patients with PCM have expression of CD20, although the significance of this remains unclear. The prognostic significance of CD20 expression in PCM is unclear. Recently, a class of noncoding RNAs, miRNAs, were identified as critical gene regulators in cell growth, disease, and development. Our study investigates importance of miRNAs in cases of CD20+ PCM and correlates them with clinicopathological parameters. **Methods:** The miRNA expression profile of CD20+ PCM (n=6), diffuse large B cell lymphoma (DLBCL) (n=6), and CD20 negative PCM (n=8) were evaluated using the Affeymertrix miRNA microarray platform on GeneChip miRNA 2.0 array in paraffin-embedded samples. After hybridization and data acquisition, we used Partek Genomics Suite software for RMA normalization and to determine statistically significant differences in miRNA expression between experimental groups by ANOVA and pairwise comparisons (two-sided α=0.05). **Results:** miRNA expression profiles of CD20+ PCM, show upto >4 times upregulation of 7 miRNAs and downregulation of 8 miRNAs. miR-155, the miRNA upregulated in various B cell lymphomas and plays a key role in the lymphomagenesis, was amongst the highest miRNAs that were upregulated. **Conclusions:** miR-155 is known to repress SH2-domain containing inositol-5-phosphatase-1 (SHIP-1), which is a critical phosphatase that negatively down modulates AKT pathway and has functions during normal B-cell development. Physiologically, miR-155 is upregulated during B-cell activation upon antigen stimulation and so plays a role in antibody class switching and plasma cell formation. We propose that this overexpression of miR-155 in CD20+ PCM unblocks AKT activity, inducing cell proliferation and may explain some of the immunophenotypic behavior of CD20+ PCM. This work is intriguing for the new information it provides about the role of miR-155 in CD20+ PCM. Furthermore, the phenotype of miR-155+ve CD20+ PCM might ultimately provide new insights into regulation of poorly understood steps in B cell differentiation and maturation into plasma cell and more importantly the clinicopathological behavior of this entity.

TPS8109 **General Poster Session (Board #40B), Mon, 1:15 PM-5:15 PM**

Phase I/II study of investigational agent MLN8237 (alisertib) plus rituximab with or without vincristine in patients (pts) with relapsed/refractory (rel/ref) aggressive diffuse large B-cell lymphoma (DLBCL)/transformed follicular lymphoma (TFL).

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Background: DLBCL and TFL are aggressive subtypes of non-Hodgkin lymphoma (NHL), with poor prognosis in the rel/ref setting. Alternatives to standard rituximab-based treatments are needed. MLN8237 is an oral, selective inhibitor of Aurora A kinase – a key mitotic regulator overexpressed/amplified in various human cancers, including lymphomas (Hamada et al, 2003; Yakushijin et al, 2004; Qi et al, 2011). Emerging data from a phase 2 study suggest that MLN8237 has single agent activity in aggressive NHL (Friedberg et al, ASH 2011). MLN8237 + rituximab (MR) ± vincristine (MRV) has also shown activity in preclinical B-cell NHL models (Mahadevan et al, ASH 2011). Further clinical evaluation of these regimens in rel/ref B-cell NHL is warranted. **Methods:** This single-arm phase 1/2 study (ClinicalTrials.gov #NCT01397825) aims to assess the safety, efficacy, and pharmacokinetics of, and determine a recommended phase 2 dose (RP2D) and schedule for, MR and MRV in adults with CD20+ rel/ref DLBCL/TFL after 1–4 prior regimens (including ASCT) and ECOG PS 0–2. Pts with other aggressive B-cell lymphomas may also enroll in phase 1. ~100 pts will be recruited at 22 sites in the US, UK, Italy, and Spain, and study duration will be ~2 years. In part 1, a safety lead-in cohort will receive MR (table), with the RP2D determined as when <2 dose limiting toxicities (DLT) occur in 6 pts in cycle 1. MRV dose escalation (part 2) will then follow a 3+3 design. Phase 2 enrollment (part 3) will follow a Simon optimal 2-stage design, with pts receiving MRV at the RP2D determined in part 2. The primary phase 2 objective is overall response rate by IWG criteria. Responders may continue MLN8237 if clinical benefit is seen and if the regimen is tolerable. Enrollment as of 20 Jan 2012 is 6 evaluable pts.

	Starting doses: repeating 21-day cycles		
	MLN8237	**Rituximab**	**Vincristine**
Phase 1 (part 1)	50 mg ECT BID, days 1–7*	375 mg/m^2 IV, day 1	–
(part 2)	~50% of MR RP2D, days 1–7†	as above	1.4 mg/m^2 IV, days 1, 8†
Phase 2 (part 3)	RP2D from part 2		

ECT, enteric coated tablet; BID, twice daily; *dose reduction permitted; †dose/schedule adjustments based on cycle 1 DLT.

TPS8110 General Poster Session (Board #40C), Mon, 1:15 PM-5:15 PM

Phase III study of investigational MLN8237 (alisertib) versus investigator's choice in patients (pts) with relapsed/refractory (rel/ref) peripheral T-cell lymphoma (PTCL).

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Background: PTCL is a rare form of aggressive non-Hodgkin lymphoma (NHL), accounting for 5–20% of NHL diagnoses. Standard NHL therapies developed primarily for B-cell lymphomas are not optimal for PTCL and early relapse is common. Current treatments for rel/ref PTCL include pralatrexate, romidepsin, and gemcitabine; however, outcomes remain poor. The oral, investigational drug, MLN8237, is a selective inhibitor of Aurora A kinase (AAK) – a key mitotic regulator that is overexpressed or amplified in various human tumors. Emerging clinical data from a phase II study of single agent MLN8237 in rel/ref aggressive T-cell lymphoma (Friedberg et al, ASH 2011) support further clinical evaluation in this indication. **Methods:** In this open-label, randomized, phase III study, a maximum of 354 adults with rel/ref PTCL after $\geq$1 prior systemic cytotoxic therapies will be enrolled at approximately 140 centers worldwide. Pts will be randomized 1:1 to MLN8237 50 mg twice daily as an enteric coated tablet on days 1–7 of 21-day cycles, or to investigator's choice of: pralatrexate 30 mg/m^2 IV once weekly for 6 weeks in 7-week cycles; romidepsin 14 mg/m^2 IV on days 1, 8, and 15 of 28-day cycles; or gemcitabine 1000 mg/m^2 IV on days 1, 8, and 15 of 28-day cycles. Pts with disease response/stabilization will be able to continue treatment provided that clinical benefit is demonstrated and treatment is tolerable. The expected study duration is 44 months. Primary endpoints are overall response rate (complete response [CR] + partial response) and progression free survival by International Working Group criteria (Cheson et al, 2007). Secondary endpoints include CR rate, overall survival, time to progression, time to response, duration of response, safety, and quality of life. Exploratory endpoints include an evaluation of candidate biomarkers (such as AAK protein expression levels and gene amplification, and the tumor proliferative marker Ki-67) in tumor biopsies. This study is registered at ClinicalTrials.gov: #NCT01482962.

TPS8111 General Poster Session (Board #40D), Mon, 1:15 PM-5:15 PM

Pilot study of MAGE-A3 protein vaccination and autologous stem cell transplantation (autoSCT) as consolidation therapy for multiple myeloma (MM).

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Background: MAGE-A3 is a cancer-testis antigen (CT Ag) commonly expressed in MM but not in normal non-gonadal tissues. MAGE-A3 inhibited p53-dependent and independent apoptosis in MM cells (Clin Cancer Res 2011;17:4309), and spontaneous immunity against CT Ags in MM patients was associated with favorable clinical outcomes (Blood 2007;109:1103; Blood 2008;112:3362), making it a rational target for immunotherapy. In this study (NCT01380145), we are examining if a recombinant (rec) MAGE-A3 protein vaccine + adjuvant combined with vaccine-primed peripheral blood lymphocytes (PBL) can safely stimulate antigen-specific immunity in MM patients undergoing autoSCT for consolidation therapy. **Methods:** Patients meeting the following criteria are eligible: within 12 months of diagnosis; MAGE-A+ MM cells by immunohistochemistry; achieving at least a very good partial response with induction therapy; and meeting institutional criteria for autoSCT. One patient of a planned cohort of sixteen has been enrolled. Six weeks before SCT, subjects will receive their first vaccination (300 μg IM) and three weeks later undergo leukopheresis to collect vaccine-primed PBL. They then undergo stem cell mobilization followed by a standard melphalan-conditioned autoSCT. On day 3 after stem cell infusion, the unmanipulated, primed PBL will be re-infused followed by the second recMAGE-A3 vaccination on day 10. An additional six vaccinations will be administered on days 31, 52, 73, 94, 180, and 270 after autoSCT. The primary objectives are safety and tolerability. The secondary objectives of cellular and humoral immune responses and lymphocyte reconstitution will be assessed by a validated series of quantitative assays using established response criteria (PNAS 2008;105:1650). Success criteria based on immune response have not been specified for this pilot study, though induction of MAGE-A3 immunity in at least 50% of patients would merit consideration for further evaluation of clinical efficacy.

TPS8112 General Poster Session (Board #40E), Mon, 1:15 PM-5:15 PM

ELOQUENT-2: A phase III, randomized, open-label trial of lenalidomide/dexamethasone (Len/Dex) with or without elotuzumab (Elo) in relapsed or refractory multiple myeloma (RR MM) (CA204-004).

Sagar Lonial, Paul Gerard Guy Richardson, Philippe Moreau, Robert Z. Orlowski, Jesùs F. San-Miguel, Meletios A. Dimopoulos, Antonio Pierangelo Palumbo, Thierry Facon, Ravi Vij, Darrell White, Donna Ellen Reece, Anil Singhal, Glenn Scott Kroog, Justin Kopit, Kenneth Carl Anderson; Multiple Myeloma Research Consortium, Norwalk, CT/Winship Cancer Institute of Emory University, Atlanta, GA; Dana-Farber Cancer Institute, Boston, MA; University Hospital, Nantes, France; University of Texas M. D. Anderson Cancer Center, Houston, TX; Hospital Universitario de Salamanca, Salamanca, Spain; Hellenic Cooperative Oncology Group, Athens, Greece; University of Torino, Torino, Italy; Hôpital Claude Huriez, Lille, France; Multiple Myeloma Research Consortium, Norwalk, CT; Washington University School of Medicine, St. Louis, MO; Queen Elizabeth II Health Sciences Centre, Halifax, NS, Canada; Program for Multiple Myeloma, Princess Margaret Hospital, Toronto, ON, Canada; Abbott Biotherapeutics, Redwood City, CA; Bristol-Myers Squibb Global Clinical Research--Oncology, Princeton, NJ; Bristol-Myers Squibb, Princeton, NJ

Background: MM remains incurable and patients (pts) typically relapse or become refractory to current treatments. Novel regimens are needed to improve pt outcomes. Elo is a humanized monoclonal IgG1 antibody targeting the cell surface glycoprotein CS1, which is highly expressed on >95% of MM cells. Len/Dex is approved for treatment of relapsed MM and an objective response rate (ORR) of ~60% was reported in phase III trials of this combination in RR MM. In a phase II study (N=73) of Elo (10 or 20 mg/kg) in combination with Len/Dex in pts with RR MM, the 10 mg/kg group (n=36) demonstrated an ORR of 92% and median progression-free survival (PFS) that was not reached after a median follow-up of 14.1 months. Encouraging activity was seen in patients with high-risk cytogenetics and/or stage 2-3 disease. Based on these data, a randomized, open-label phase III trial has been initiated to determine if the addition of Elo to Len/Dex will improve PFS in patients with RR MM compared with Len/Dex alone. **Methods:** Pts (N=640) with RR MM and 1-3 prior therapies are eligible, including pts with mild or moderate renal impairment. Pts are randomized in a 1:1 ratio to receive 28-day cycles of Len 25 mg PO (days 1-21) and Dex 40 mg PO (days 1, 8, 15 and 22) with or without Elo. Elo dose and schedule is 10 mg/kg IV on days 1, 8, 15, 22 in the first 2 cycles and on days 1 and 15 in subsequent cycles. Dex 8 mg IV + 28 mg PO is used during the weeks with Elo. Treatment will continue until disease progression, death, or withdrawal of consent. Patients will be followed for tumor response every 4 weeks until progressive disease and then survival every 12 weeks. The primary endpoint is PFS (90% power for a hazard ratio [experimental to control arm] of 0.74) and the secondary endpoints are ORR and overall survival. Exploratory endpoints are safety, time to response, duration of response, time to subsequent therapy, health-related quality of life, and pharmacokinetics and immunogenicity of Elo. Potential biomarkers will also be assessed. As of January 10th, 2012, 107 pts were enrolled and 68 pts were treated. NCT01239797.

TPS8113 General Poster Session (Board #40F), Mon, 1:15 PM-5:15 PM

ELOQUENT-1: A phase III, randomized, open-label trial of lenalidomide/dexamethasone with or without elotuzumab in subjects with previously untreated multiple myeloma (CA204-006).

Meletios A. Dimopoulos, Thierry Facon, Paul Gerard Guy Richardson, Robert Z. Orlowski, Jesùs F. San-Miguel, Sagar Lonial, Kenneth Carl Anderson, Philippe Moreau, Donna Ellen Reece, Anil Singhal, Ronald L. Shazer, Justin Kopit, Antonio Pierangelo Palumbo; Hellenic Cooperative Oncology Group, Athens, Greece; Hôpital Claude Huriez, Lille, France; Dana-Farber Cancer Institute, Boston, MA; University of Texas M. D. Anderson Cancer Center, Houston, TX; Hospital Universitario de Salamanca, Salamanca, Spain; Multiple Myeloma Research Consortium, Norwalk, CT/Winship Cancer Institute of Emory University, Atlanta, GA; University Hospital, Nantes, France; Program for Multiple Myeloma, Princess Margaret Hospital, Toronto, ON, Canada; Abbott Biotherapeutics, Redwood City, CA; Bristol-Myers Squibb, Wallingford, CT; Bristol-Myers Squibb, Princeton, NJ; University of Torino, Torino, Italy

Background: Elotuzumab (Elo) is a humanized monoclonal IgG1 antibody targeting the cell surface glycoprotein CS1, which is highly expressed on >95% of MM cells. In a MM xenograft mouse model, the combination of Elo + lenalidomide (Len) significantly reduced tumor volume in a synergistic manner compared with either agent alone. In a phase 2 study (N=73) of Elo (10 or 20 mg/kg) in combination with Len and low-dose-dexamethasone (Dex) in pts with RR MM, the 10 mg/kg dose group (n=36) demonstrated objective response rates (ORR) of 92% in all pts, and 100% in pts who had received only 1 prior therapy (n=16). The higher response rate in pts with fewer prior lines of therapy provides a rationale for investigating this combination earlier in the disease course. This randomized, open-label, phase 3 trial will determine if the addition of Elo to Len/Dex improves progression-free survival (PFS) in pts with newly diagnosed, untreated MM. **Methods:** Pts (N=750) with newly diagnosed symptomatic MM ineligible for stem cell transplant will be randomized in a 1:1 ratio to receive 28-day cycles of Len 25 mg PO (days1-21) and Dex 40 mg PO (days 1, 8, 15 and 22) with or without Elo. Elo dose and schedule is 10 mg/kg IV on days 1, 8, 15, 22 in the first 2 cycles and on days 1 and 15 of cycles 3-18 followed by 20 mg/kg on day 1 of cycle 19 onward. Dex 8 mg IV + 28 mg PO is used during the weeks with Elo. Treatment will continue until disease progression, death, or withdrawal of consent. Pts will be followed up for response every 4 weeks until progressive disease and for survival every 16 weeks. The primary endpoint is PFS (90% power for a hazard ratio [experimental to control arm] of 0.74) and the secondary endpoints are ORR and overall survival. Exploratory endpoints are safety, time to response, duration of response, time to subsequent therapy, health-related quality of life, and pharmacokinetics and immunogenicity of Elo. Potential biomarkers will also be assessed. As of January 1, 2012, 13 pts were enrolled and 9 pts were treated. NCT01335399.

TPS8114 **General Poster Session (Board #40G), Mon, 1:15 PM-5:15 PM**

A phase II randomized study of bortezomib/dexamethasone (Bort/Dex) with or without elotuzumab (Elo) in patients (pts) with relapsed/refractory multiple myeloma (RR MM) (CA204-009).

Andrzej J. Jakubowiak, Darrell White, Philippe Moreau, Thierry Facon, Ravi Vij, Glenn Scott Kroog, Justin Kopit, Anil Singhal, Antonio Pierangelo Palumbo; University of Chicago Medical Center, Chicago, IL; Queen Elizabeth II Health Sciences Centre, Halifax, NS, Canada; University Hospital, Nantes, France; Hôpital Claude Huriez, Lille, France; Multiple Myeloma Research Consortium, Norwalk, CT; Washington University School of Medicine, St. Louis, MO; Memorial Sloan-Kettering Cancer Center, New York, NY; Bristol-Myers Squibb, Princeton, NJ; Abbott Biotherapeutics, Redwood City, CA; University of Torino, Torino, Italy

Background: MM is rarely curable and pts typically relapse or become refractory to current treatments. Elo is a humanized monoclonal IgG1 antibody targeting the cell surface glycoprotein CS1, which is highly expressed on >95% of MM cells with little to no expression on normal tissues. The mechanism of action of Elo is primarily natural killer (NK) cell-mediated antibody-dependent cellular cytotoxicity (ADCC) against myeloma cells. Elo + Bort significantly enhanced antimyeloma activity in a mouse xenograft model vs either agent alone. The addition of Bort enhanced the ADCC activity of Elo in preclinical studies. In a phase I study of Elo + Bort in pts with RR MM, objective response rate (ORR) was 48%, median progression-free survival (PFS) was 9.5 months, and activity was observed in 2/3 patients (67%) refractory to Bort (Jakubowiak et al. J Clin Oncol, in press). This study will assess if the addition of Elo to Bort/Dex improves PFS and, if so, whether magnitude of the improvement is linked to FcγRIIIa polymorphism. **Methods:** Pts (N=150) with RR MM after 1 or 2 prior therapies will be randomized in a 1:1 ratio to receive Bort 1.3 mg/m^2 IV or SQ (Cycles 1-8: days 1, 4, 8, and 11; Cycles ≥9: days 1, 8, and 15) and Dex with or without Elo. Elo dose and schedule is 10 mg/kg IV (Cycles 1-2: days 1, 8, and 15 [21-day cycles]; Cycles 3-8: days 1 and 11 [21-day cycles]; Cycles ≥9: days 1 and 15 [28-day cycles]). In the arm without Elo, Dex 20 mg PO is scheduled for Cycles 1-8: days 1, 2, 4, 5, 8, 9, 11, and 12; and Cycles ≥9: days 1, 2, 8, 9, 15, 16. In the arm with Elo, Dex 20 mg PO is scheduled for Cycles 1-2: days 2, 4, 5, 9, and 11; Cycles 3-8: days 2, 4, 5, 8, 9, 12; Cycles ≥9: days 2, 8, 9, and 16) on weeks without Elo, and on weeks with Elo, Dex 8 mg PO and 8 mg IV is scheduled on the same day as Elo. Treatment will continue until disease progression, unacceptable toxicity, or withdrawal of consent. Patients refractory or intolerant to Bort will be excluded. Efficacy will be assessed on day 1 of each cycle by IMWG criteria. The primary endpoint is PFS. Secondary endpoints include ORR and PFS/ORR in pts with ≥1 FcγRIIIa V allele. As of February 1, 2012, 1 pt was enrolled. NCT01478048.

TPS8115 **General Poster Session (Board #40H), Mon, 1:15 PM-5:15 PM**

A single-arm, open-label, multicenter phase I/II study of the combination of panobinostat (pan) and carfilzomib (cfz) in patients (pts) with relapsed/refractory multiple myeloma (RR MM).

Jesus G. Berdeja, Joseph Mace, Ruth E. Lamar, Victor Gian, Patrick Brian Murphy, Manish R. Patel, Lowell L. Hart; Tennessee Oncology, PLLC/Sarah Cannon Research Institute, Nashville, TN; Florida Cancer Specialists/Sarah Cannon Research Institute, St. Petersburg, FL; Florida Cancer Specialists/Sarah Cannon Research Institute, Sarasota, FL; Florida Cancer Specialists, Fort Myers, FL

Background: Despite novel therapies, MM remains an incurable disease. Changes in histone modification are commonly found in human cancers including MM. Preclinical studies demonstrate synergistic anti-MM activity with histone deacetylase inhibitors (HDACi) and proteasome inhibitors (PI) through the dual inhibition of the proteasome and aggresome pathways. Pan is an oral pan-HDACi which has shown synergy with bortezomib in clinical studies. Cfz is a 2nd generation PI which has shown marked anti-MM activity with an improved safety profile. In this trial we evaluate the safety and efficacy of the combination of pan and cfz in pts with RR MM. **Methods:** This multi-center US study plans to enroll up to 52 adults with RR MM. The phase I study will determine the MTD of the combination of cfz and pan and follow a standard dose escalation design. Pan will be administered orally three times weekly during weeks 1 and 3 of each 28-day cycle (Days 1, 3, 5, 15, 17, 19) at a starting dose of 20 mg. Cfz will be administered intravenously on Days 1, 2, 8, 9, 15, and 16 of each 28-day cycle. Cfz starting dose will be 20mg on days 1,2 of cycle 1 with escalation to the corresponding dose level beginning at 27 mg , if well tolerated. Dose modifications will not be permitted during cycle 1 unless a pt experiences a DLT. A maximum of four dose levels will be evaluated. Approximately 24 pts will be enrolled during the phase I portion to establish the MTD. In the phase II portion of this study, pts with RR MM will receive treatment with the optimal dose of pan and cfz established during phase I. Pts will be assessed for response to treatment after each cycle (4 weeks). Pts with objective response or stable disease will continue treatment until disease progression or unacceptable toxicity occurs. The primary endpoint is to establish the optimal doses of cfz and pan that can be administered to pts with RR MM (phase I) and to evaluate the overall response rate (phase II). Secondary endpoints include time-to-progression, progression-free survival, overall survival and safety. Approximately 25 pts are planned for the phase II portion. Current status: As of 1/27/12 3 patients have been enrolled.

TPS8116 General Poster Session (Board #41A), Mon, 1:15 PM-5:15 PM

Phase I/II open-label, multiple-dose, dose-escalation study to evaluate the safety and tolerability of SNS01T administered by intravenous infusion in patients with relapsed or refractory multiple myeloma.

John Anthony Lust, Charles Barranco, Martha Lacy, Angela Dispenzieri, Morie A. Gertz, David Dingli, Stephen J. Russell, Francis Buadi, Steven R. Zeldenrust, Suzanne R. Hayman, S. Vincent Rajkumar, Shaji Kumar, Saad Zafar Usmani, John Thompson, Catherine Taylor, Richard Dondero; Mayo Clinic, Rochester, MN; Senesco Technologies, Bridgewater, NJ; Myeloma Institute for Research and Therapy, Little Rock, AR; University of Waterloo, Waterloo, ON, Canada; Senesco Technologies Inc., New Brunswick, NJ

Background: Eukaryotic translation initiation Factor 5A (eIF5A) has been implicated in the regulation of apoptosis and is the only known protein to be modified by hypusination. Hypusinated eIF5A is the predominant form of eIF5A in cancer cells. However, in its unhypusinated form, eIF5A is pro-apoptotic. SNS01-T, designed to treat myeloma, consists of two components: a plasmid DNA expressing $eIF5A^{K50R}$ (human eIF5A containing a lysine to arginine substitution at position 50) which remains pro-apoptotic because it cannot be hypusinated, and an siRNA against an untranslated region of native eIF5A mRNA. When these two components are combined with linear polyethyleneimine (PEI), the nucleic acids are condensed into nanoparticles for protection from degradation in the blood and enhanced delivery to tissues. The $eIF5A^{K50R}$ transgene is under the control of the B29 promoter and enhancer, which restricts expression to B cells. The mode of action of SNS01-T is to use an eIF5A-specific siRNA to deplete the pool of hypusinated eIF5A in myeloma cells while simultaneously adding pro-apoptotic $eIF5A^{K50R}$. In vitro cell studies and in vivo xenograft studies have demonstrated the efficacy of this approach. **Methods:** Eligible patients are enrolled sequentially into four cohorts of increasingly higher doses. Each cohort will receive SNS01-T by intravenous infusion twice weekly for 6 consecutive weeks and then be observed every 4 weeks during a 24-week follow-up period. Eligible patients must have been diagnosed with multiple myeloma according to IMWG criteria, have measurable disease, have relapsed disease after two or more prior treatment regimens, have a life expectancy of at least 3 months, and not be eligible to receive any other standard therapy known to extend life expectancy. The primary objective is to evaluate the safety and tolerability of multiple escalating doses of SNS01-T. Secondary objectives include pharmacokinetics, immunogenicity studies, proinflammatory cytokine quantitation, and therapeutic efficacy. Two of the planned 15 patients have been enrolled. (Clinical Trials.gov Identifier: NCT01435720.)

TPS8117 General Poster Session (Board #41B), Mon, 1:15 PM-5:15 PM

Recruitment in a randomized, double-blind, placebo-controlled study to assess siltuximab (CNTO 328), an anti-IL-6 monoclonal antibody, in patients with multicentric Castleman's disease.

Frits Van Rhee, Marcelo Capra, Raymond Wong, Jessica Vermeulen, Karim Safer, Marija Todorovic, Patricia Rhoten, Helgi Van De Velde; University of Arkansas for Medical Sciences, Little Rock, AR; Hospital Mãe de Deus, Porto Alegre, Brazil; Prince of Wales Hospital, NT, Hong Kong; Janssen Research & Development, Leiden, Netherlands; Janssen Research & Development, Spring House, PA; Johnson & Johnson SE, GCO Serbia, Belgrade, Serbia; Janssen Research & Development, Bridgewater, NJ; Janssen Research & Development, Beerse, Belgium

Background: Multicentric Castleman's disease (MCD) is a rare lymphoproliferative disorder in which dysregulated production of interleukin (IL)-6 results in lymph node enlargement and debilitating symptoms, including systemic inflammatory manifestations (eg, fever, fatigue, weight loss), autoimmune phenomena, and markedly abnormal laboratory findings (eg, anemia, hyper-γ-globulinemia, hypoalbuminemia, thrombocytosis, increases in acute-phase proteins such as CRP, ESR, fibrinogen). There is currently no approved systemic treatment for MCD in the US or EU. Siltuximab (CNTO 328) is a chimeric mAb with high affinity for soluble IL-6. In a previous phase 1 study, high objective tumor response rate (64%) has been observed in patients with MCD (van Rhee F et al. Blood 2008;112:1008), and the long-term safety profile looks favourable (Kurzrock R et al. Blood 2011;118:3959). These results have prompted a randomized, double-blind, placebo-controlled study to definitively assess the efficacy and safety of siltuximab in combination with best supportive care (BSC) compared with BSC in patients with MCD. **Methods:** Eligibility includes HIV- and HHV-8-negative, symptomatic, measurable MCD patients. Patients with prior lymphoma or prior exposure to treatment targeting IL-6 or its receptor are excluded. Patients can be enrolled when receiving stable doses of corticosteroids (<1 mg/kg/d of prednisone or equivalent). Patients will be randomized in a 1:2 ratio to placebo + BSC or to 11 mg/kg siltuximab + BSC and will receive siltuximab/placebo in a 1-hour IV infusion every 3 weeks. The primary objective is to evaluate durable tumor and symptomatic response in the intent-to-treat population. Secondary objectives include additional efficacy measures, safety, patient reported outcomes, and pharmacologic assessment. Status: 67/78 patients have been randomly assigned. This is the first randomized, placebo-controlled study to be conducted in MCD. The rarity of the disease has posed unique challenges, and various enrollment strategies have been successfully implemented, with projected completion of enrollment in March 2012.

TPS8118 General Poster Session (Board #41C), Mon, 1:15 PM-5:15 PM

PILLAR-2: A randomized, double-blind, placebo-controlled, phase III study of adjuvant everolimus in poor-risk diffuse large B-cell lymphoma (DLBCL).

Tongyu Lin, Jun Zhu, Kamal Bouabdallah, Michinori Ogura, Masayuki Hino, Jin Seok Kim, Cassandra Wu, Claudia Corrado, Thomas E. Witzig; Department of Medical Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China; Department of Lymphoma, Peking University School of Oncology, Beijing Cancer Hospital and Institute, Beijing, China; Department of Hematology, Hôpital du Haut Lévêque, Centre François Magendie, Pessac, France; Department of Hematology and Oncology, Nagoya Daini Red Cross Hospital, Cancer Chemotherapy Center, Nagoya, Japan; Department of Clinical Hematology and Diagnostics, Osaka University Graduate School of Medicine, Osaka, Japan; Division of Hematology, Department of Internal Medicine, Yonsei University College of Medicine, Severance Hospital, Seoul, South Korea; Oncology Clinical Development, Novartis Pharmaceuticals Corporation, Florham Park, NJ; Oncology Clinical Development, Novartis Pharma AG, Basel, Switzerland; Division of Hematology, Mayo Clinic, Rochester, MN

Background: Effective DLBCL adjuvant therapy after first-line chemotherapy is needed as high-risk DLBCL is associated with a poor 4-year overall survival (OS) rate (Sehn et al, *Blood* 2007;109:1857-61). In a phase II study of the oral mammalian target of rapamycin inhibitor everolimus in relapsed, aggressive non-Hodgkin lymphoma, DLBCL patients (n=47) had a 30% overall response rate (Witzig et al, *Leukemia* 2011;25:341-7). **Methods:** PILLAR-2 is an ongoing international, randomized, double-blind, phase 3 study designed to compare everolimus efficacy and safety with that of placebo in poor-risk DLBCL patients who achieved complete response (CR) with first-line rituximab-based chemotherapy (R-chemo) (ClinicalTrials-.gov: NCT00790036; sponsor: Novartis Pharmaceuticals). Eligibility criteria include age ≥18 years; confirmed stage II bulky, III, or IV DLBCL and International Prognostic Index 3-5 at diagnosis; confirmed CR per revised International Workshop Response Criteria for malignant lymphoma (Cheson et al, *J Clin Oncol* 2007;25:579-86) after first-line R-chemo regimen completed 6-14 weeks before study drug start; Eastern Cooperative Oncology Group performance status ≤2; no ongoing or post–R-chemo radiation; and no myelosuppressive chemotherapy or biologic therapy within 3 weeks. Patients are randomized 1:1 to everolimus 10 mg once daily or matching placebo and treated for 12 months or until disease relapse, unacceptable toxicity, or death. Radiologic tumor assessment is performed at baseline, every 12 weeks during years 1 and 2, every 24 weeks during years 3 and 4, and annually thereafter until start of new anticancer therapy or 5 years after last patient randomization. The primary endpoint is disease-free survival (DFS). Secondary endpoints are OS, lymphoma-specific survival, and safety. Expected enrollment is 687 patients. Final analysis will be performed when 279 DFS events occur; survival follow-up will continue until 338 deaths occur and the last randomized patient has been followed for ≥5 years. Currently, 422 patients are enrolled. The data monitoring committee last reviewed the trial in July 2011 and recommended that it continue as planned.