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Complete Remissions Observed in a Subset of Pediatric Patients With CD30-expressing Malignant Lymphomas Treated in Clinical Studies of Brentuximab Vedotin (SGN-35)

M. Fanale¹, A. Franklin², R. Radhakrishnan³, A. Termuhlen⁴, A.K. Gopal⁵, A. Shustov⁶, D.A. Kennedy⁷, E.L. Sievers⁷. ¹University of Texas MD Anderson Cancer Center, Department of Lymphoma and Myeloma, Houston TX, ²University of Texas MD Anderson Cancer Center, Department of Pediatrics Patient Care, Houston TX, ³Karmanos Cancer Institute, Hematology/Oncology, Detroit MI, ⁴Miller Children's Hospital, Department of Pediatrics, Long Beach CA, ⁵University of Washington Medical Center, Medical Oncology Division, Seattle WA, ⁶University of Washington Medical Center, Hematology Division, Seattle WA, ⁷Seattle Genetics Inc, Clinical Affairs, Bothell WA, USA

Background: Brentuximab vedotin (SGN-35) consists of an anti-CD30 antibody conjugated by a plasma-stable linker to the potent antimicrotubule agent, monomethyl auristatin E (MMAE). Brentuximab vedotin selectively induces apoptotic death of CD30-expressing cells by binding to cells, followed by internalization and release of MMAE. Brentuximab vedotin has shown encouraging anti-tumour activity in adult patients with relapsed or refractory Hodgkin lymphoma (HL) and systemic anaplastic large cell lymphoma (sALCL).

Methods: A subset of pediatric patients (12–17 yrs) was enrolled in two phase 1 and two phase 2 multicenter studies. Patients with CD30-expressing hematologic malignancies received intravenous brentuximab vedotin as a 30-minute outpatient infusion in weekly treatment cycles (3 out of 4 weeks) at doses of 0.8 or 1.2 mg/kg (1 pt each) or every 3 weeks at doses of 1.2 mg/kg (1 pt) or 1.8 mg/kg (6 pts). Informed consent and assent were obtained for all patients. Clinical response was assessed by the investigator using the Revised Response Criteria for Malignant Lymphoma (Cheson 2007).

Results: Across the 4 studies, 9 pediatric patients were enrolled, ranging in age from 12–17 yrs. Diagnosis was HL for 5 patients and sALCL for 4 patients. Baseline Karnofsky performance was 0 (5 pts) or 1 (4 pts). The 5 male and 4 female patients all had at least 1 prior systemic chemotherapy regimen (range, 2–7) and 4 patients had prior autologous stem cell transplantation. Patients received 3–16+ cycles of brentuximab vedotin. The most frequent treatment-emergent adverse events (TEAEs) were fatigue, nausea, and peripheral neuropathy. Treatment-related Grade 1–2 peripheral neuropathy was reported in 7 patients. Three of 9 patients experienced related TEAEs ≥ Grade 3 (hyperesthesia, leukocytopenia, and neutropenia). Six of 9 patients obtained complete remission (CR; 2/5 HL pts and 4/4 sALCL pts) and the remaining 3 HL patients achieved best response of stable disease. Duration of CR to date has been approximately 3–12 months and 5/6 patients remain in CR after 6–12+ months of follow up.

Conclusions: Consistent with findings in the adult population, treatment with brentuximab vedotin induced CR in 6 of 9 pediatric patients with relapsed/refractory HL or sALCL, of which 5/6 patients remain in CR, and adverse events were manageable. HL and sALCL are relatively common pediatric lymphomas and further study in children and young adults is planned.

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MRC Myeloma IX Trial – Characterizing the Biologic and Temporal Basis of Efficacy of Long-term Bisphosphonate Treatment in Patients With Multiple Myeloma

G. Morgan¹, F.E. Davies¹, W.M. Gregory², A.J. Szubert², S.E. Bell², M.T. Drayson³, R.G. Owen⁴, J.A. Child². ¹Royal Marsden Hospital, Institute of Cancer Research, London, ²University of Leeds, Clinical Trials Research Unit, Leeds, ³University of Birmingham, Birmingham, ⁴St. James's University Hospital, Leeds, United Kingdom

Background: Myeloma IX examined the effect of thalidomide-based induction and maintenance and 2 different bisphosphonates (BPs), intravenous zoledronic acid (ZOL) and oral clodronate (CLO), in patients with multiple myeloma (MM). In 1960 evaluable patients, ZOL improved overall survival (OS) by 5.5 mo ($P = 0.04$) and significantly reduced the risk of skeletal-related events (SREs) vs CLO (Morgan et al. *Lancet*. 2010). However, there has been little previous investigation into the effects of BPs by MM prognostic variables and treatment duration.

Methods: Patients with newly diagnosed MM were assigned to intensive or non-intensive treatment pathways and then randomized to concurrent ZOL or CLO, each of which was continued at least until disease progression. The effects of ZOL vs CLO on OS were assessed in subgroup analyses (demographics, biologic disease characteristics, and duration of BP therapy). Baseline bone disease (BD+ or BD-) was screened

using axial skeletal surveys. FISH analysis was performed using standard methodology in a substudy ($n \approx 1000$).

Results: In subgroup analyses, ZOL OS benefit vs CLO was not affected by sex, ISS stage, or specific myeloma genotypes. BD+ patients had significantly shorter OS (median = 45.5 mo, $n = 1401$) vs BD- patients (median = 51.6 mo, $n = 540$; $P = 0.009$). OS benefit with ZOL vs CLO was most profound in BD+ patients ($n = 1401$; ~71% of total) and in patients receiving BPs for ≥ 2 years ($n = 582$; ~30% of total). In the latter subset, ZOL improved OS vs CLO from randomization (median not reached for either; log-rank $P = 0.02$) and from first on-study disease progression (median = 34 mo [ZOL] vs 27 mo [CLO]; log-rank $P = 0.03$). Additional efficacy and tolerability analyses are ongoing in this subset.

Conclusions: OS benefits with ZOL vs CLO are independent of demographic and baseline disease characteristics evaluated except for BD (benefit restricted to BD+ patients). OS improvements with ZOL were most profound in patients receiving BPs for ≥ 2 years, and suggest continued benefits despite disease progression.

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Targeting Pro-survival Bcl-2 Proteins in Haematological Malignancies Driven by Activated Mutant JAK2

M. Waibei¹, V.S. Solomon¹, R. Ralli¹, E. Vidacs¹, S.K. Kim¹, K.M. Banks¹, R.W. Johnstone¹. ¹Peter MacCallum Cancer Centre, Cancer Immunology Program, Melbourne Victoria, Australia

Background: Oncogenic mutations and translocations of JAK2 are frequently detected in myelo- and lymphoproliferative disorders. One example is the fusion of the transcription factor TEL (ETV6) to the kinase domain of JAK2 identified in human T cell acute lymphocytic leukemia (ALL). Furthermore, different activating point mutations of JAK2 have recently been identified in pediatric acute pre-B cell lymphoblastic leukemias (pre B-ALL). Using a TEL-JAK2-driven mouse model of T-ALL, this project aims to identify the critical downstream effectors of oncogenic JAK2 signalling to discover novel strategies to treat JAK2-driven malignancies.

Material and Methods: EμTEL-JAK2-transgenic mice develop a rapid onset T-ALL which is transplantable into C57Bl/6 mice. Using Western Blot, FACS analysis and cell death assays we studied molecular pathways and survival in EμTEL-JAK2 T-ALL cells *ex vivo*. Furthermore, we analysed the therapeutic efficacy of the JAK2 inhibitor TG101209, the BH3-mimetic ABT-737, the chemotherapeutic drugs Etoposide and Cyclophosphamide, or combinations of these drugs in cohorts of mice with secondary EμTEL-JAK2 T-ALL.

Results: When cultured *ex vivo*, EμTEL-JAK2 T cell leukemic cells exhibited resistance to common chemotherapeutics, but were sensitive to the JAK2 inhibitor TG101209. Consistent with our understanding that chemotherapeutic drugs induce tumour cell apoptosis via the intrinsic apoptotic pathway, we demonstrated that these cells express high levels of anti-apoptotic Bcl-2 and Bcl-xL. When treated with the Bcl-2/Bcl-xL antagonist ABT-737, EμTEL-JAK2 T-ALL cells underwent rapid apoptosis. Moreover, mice bearing secondary EμTEL-JAK2 leukemias displayed prolonged survival following treatment with ABT-737 or TG101209 concomitant with robust tumour cell apoptosis *in vivo*. Furthermore, combination therapies involving ABT-737, TG101209 and Etoposide or Cyclophosphamide eradicated disease.

Conclusions: We hypothesise that TEL-JAK2 expression induces Bcl-2/Bcl-xL expression through constitutive activation of STAT5, and posit that Bcl-2/Bcl-xL upregulation may be a common feature of JAK2-driven haematological malignancies. Therapeutic regimens using ABT-737 in combination with JAK2 inhibitors or standard chemotherapeutic drugs may therefore be a rational approach to treating these diseases. We are currently testing this hypothesis in a xenotransplantation model using human pre-B ALL cells expressing constitutively active mutant JAK2.

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Telomerase Inhibition Affects Fludarabine Sensitivity in Primary Chronic Lymphocytic Leukemia Lymphocytes

M. Shaw¹, L. Amrein², S.M. Gryaznov³, C. Autexier¹, R. Aloyz¹. ¹McGill University, Experimental Medicine, Montréal, ²Segal Cancer Center, Oncology, Montréal, Canada; ³Geron, Oncology, Menlo Park, USA

Background: B-cell chronic lymphocytic leukemia (CLL) is clinically very heterogeneous and has a highly variable clinical course. Different studies have demonstrated that telomere length and telomerase activity are good prognostic factors in CLL. These studies have prompted the assessment of Imetelstat, a telomerase inhibitor which targets the telomerase RNA component hTR, and is currently in phase I-II clinical trial in CLL as a single agent.