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ONGOING TRIALS

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A PHASE 2 STUDY OF GS-9973 IN HEMATOLOGIC MALIGNANCIES

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Background: Spleen tyrosine kinase (Syk) is a non-receptor cytoplasmic tyrosine kinase that is an important mediator of immunoreceptor signaling in macrophages, neutrophils, mast cells, and B cells.Recent studies have suggested a role for the dysregulation of the tyrosine kinase Syk in B-cell malignancies.GS-9973 is a highly specific Syk inhibitor.In B-cells, GS-9973 effectively blocked BCR-mediated activation and proliferation.Syk activation has been implicated in the pathogenesis of several common B-cell malignancies, including CLL, DLBCL, FL, MCL, MZL, and B-ALL.
Methods: Phase 2 study evaluating the efficacy, safety, tolerability, and pharmacodynamics (PD) of GS-9973 in subjects with relapsed or refractory CLL, iNHL, MCL, or DLBCL.Bayesian, continuous data review approach will be used to monitor for lack of activity. A maximum of 40 subjects in each cohort will be studied.
Treatment: All subjects will receive treatment with 800 mg GS-9973 BID under fasted conditions and evaluated for safety and efficacy. Drug levels and PD monitoring will occur at multiple time points during the study.
Major Inclusion Criteria: Previously treated adults with B-cell iNHL, DLBCL, MCL, or CLL; Radiographically measureable disease; KPS >60; Life expectancy > 3 months; Adequate hematologic, hepatic and renal function.
Major Exclusion Criteria: Known history of Richter's transformation; Known active CNS lymphoma; Current therapy with agents that reduce gastric acidity; History of most non-lymphoid malignancies; Evidence of ongoing systemic infection;Unless approved in advance, prior therapy with any inhibitor of B-cell signaling pathways.
Correlative studies: PD monitoring to assess activation of B-cell receptor mediated signaling.
Current enrollment: Enrollment to begin by March 2013.
Clinical trial registry number: NCT01799889

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MLN8237 (ALISERTIB), AN INVESTIGATIONAL AURORA A KINASE INHIBITOR, + RITUXIMAB ± VINCRISTINE IN RELAPSED/REFRACTORY (REL/REF) AGGRESSIVE DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)/TRANSFORMED FOLLICULAR LYMPHOMA (T-FL): PHASE 1/2 STUDY

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Background: Despite advances in treatment for aggressive lymphoma, outcomes remain poor for patients (pts) with aggressive subtypes of non-Hodgkin lymphoma (NHL) relapsing after primary treatment. The investigational, oral drug, MLN8237 is a selective inhibitor of Aurora A kinase, a key mitotic regulator that is overexpressed/amplified in various malignancies, including lymphomas. Single-agent activity of MLN8237 in aggressive NHL has been shown in a recent phase (Ph 2) study (Friedberg et al, ASH 2011) and rationale for combination with rituximab (MR) ± vincristine (MRV) is supported by preclinical evaluation in B-cell NHL models (Mahadevan et al, ASH 2011). Here we outline an open label, single-arm, Ph 1/2 study (NCT01397825) of MR and MRV in pts with rel/ref DLBCL and t-FL.
Methods: Up to100 adult pts with CD20+ rel/ref DLBCL/t-FL (pts with other aggressive B-cell lymphomas may enroll in Ph 1), 1 to 4 prior regimens (including ASCT) and ECOG PS 0-2 will be enrolled at 22 sites in the US, UK, Italy, and Spain. Study design is shown in the table. The Ph 1 portion of this study is divided into two parts: Part 1, a safety lead-in cohort will receive MR to determine the doublet recommended Ph 2 dose RP2D; Part 2, vincristine will be added to the MR doublet, with dose escalation following a 3+3 design. The primary endpoint of the Ph 1 study is safety; secondary endpoints include pharmacokinetics and response. In the Ph 2 portion of the study, pts will receive MR and MRV at the triplet RP2D determined in the Ph 1 study and enrollment will follow a Simon optimal 2-stage design. The primary Ph 2 objective is overall response rate by IWG criteria. The expected study duration is 2 years; responders may continue to receive MLN8237 if treatment is tolerated and clinical benefits are seen.

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PHASE I TRIAL OF THE BASE – EXCISION REPAIR BLOCKER METHOXYAMINE COMBINED WITH FLUDARABINE IN RELAPSED/REFRACTORY HEMATOLOGIC MALIGNANCIES.

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Introduction: Methoxyamine binds covalently to intermediary structures generated during removal of Fludarabine – induced DNA lesions by base excision repair (BER). CLL cells have increased BER activity; in vitro and animal studies demonstrate Methoxyamine augments the cytotoxicity of Fludarabine against CLL cells but not normal bone marrow cells.

Abstract 549 Table

	21-day cycles		
	Ph 1		Ph 2
	Part 1	Part 2	Part 3
MLN8237	50 mg* ECT BID, days 1 to 7**	Around 50% of MR RP2D**, days 1 to 7†	RP2D from part 2
Rituximab	375 mg/m^2 **, IV day 1	375 mg/m^2 **, IV day 1	
Vincristine	X	1.4 mg/m^2 IV, days 1, 8† (max, 2mg)	

ECT, enteric coated tablet; *dose reduction permitted; †dose/schedule adjustments based on cycle 1 DLT **starting dose

We are conducting a phase I trial to determine the maximum tolerated dose and dose limiting toxicities (DLT) of Methoxyamine combined with Fludarabine.
Methods: Eligible patients were older than 18 years of age, with relapsed /refractory hematologic malignancies. Fludarabine, 25mg/m^2 was given IV daily for 5 days; Methoxyamine doses were 15, 30, and 60mg/m,^{2} in a 3+3 escalation design, given IV on day 2 of cycle 1 and day 1 of cycles 2 - 6. Treatment was given every 28 days for a maximum of 6 cycles. DNA damage was assessed with the single cell Comet assay.
Results: 11 patients have enrolled; median age is 64 years (range 46 – 82). The diagnoses include CLL (n = 6), non Hodgkin lymphoma (NHL) (n = 3), and plasma cell myeloma (PCM) (n = 2). Median number of prior therapies is 3 (range 1 to 5). All CLL patients had previously received Fludarabine.

No DLTs have been observed. The only grade 3 – 4 adverse events (AE) were hematologic (neutropenia, 72.7%; lymphopenia, 63.6%; leukopenia 54.5%; anemia 27.3%; thrombocytopenia, 9.1%); fatigue was the most common grade 1 – 2 AE (100%). 3 subjects presented low serum haptoglobin without overt hemolysis or positive DAT.

Three patients developed progressive disease within the first 2 cycles (NHL = 1, PCM = 2). Partial response was observed in 1 CLL patient, while 7 subjects had stable disease after 2-5 cycles (CLL = 5; NHL = 2). All CLL patients with lymphocytosis (n = 4) had normal or low lymphocyte counts after 5 days of treatment (n = 4). We observed a consistent trend of increasing DNA damage after exposure to Fludarabine which was further elevated after Methoxyamine treatment.
Conclusions: The combination of Methoxyamine and Fludarabine is well tolerated, with toxicities comparable to Fludarabine alone. Notably, the combination has activity in CLL patients who have relapsed after Fludarabine – containing regimens. This trial continues accrual at higher methoxyamine doses.

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PHASE 2 STUDY OF GS-9973 AND IDELALISIB IN HEMATOLOGIC MALIGNANCIES

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Background: Interfering with B-cell receptor (BCR)-signaling has promising activity in treating B-cell malignancies including CLL, DLBCL, FL, MCL, MZL, and B-ALL.Combination treatment with agents that inhibit different points in targeted pathways may help overcome resistance and improve efficacy.In circulating malignant cells obtained from patients with CLL, there was decreased cell viability upon in vitro exposure to idelalisib, a PI3K delta inhibitor, and GS-9973, a spleen tyrosine kinase inhibitor, compared to either drug alone.
Methods: Phase 2 study evaluating the efficacy, safety, tolerability of GS-9973 in combination with idelalisib for subjects with relapsed or refractory CLL, iNHL, MCL, or DLBCL.Five cohorts will be studied concurrently with a maximum of 40 subjects in each.
Treatment: All subjects will receive treatment with GS-9973 and idelalisib BID under fasted conditions and be evaluated for safety and efficacy. A maximum tolerated dose level will be determined for each subject using an inter-patient dose escalation scheme. In the absence of dose limiting toxicity dosing will be continuous without interruption. Drug levels and pharmacodynamic (PD) monitoring will be assessed.
Major Inclusion Criteria: Previously treated adults with B-cell iNHL, DLBCL, MCL, or CLL; Measurable disease; KPS $>$ 60; Life expectancy $>$ 3 months; Adequate hematologic, hepatic and renal function
Major Exclusion Criteria: Known history of Richter's transformation; Known active CNS lymphoma; Concurrent therapy with agents that reduce gastric acidity; History of most non-lymphoid malignancies; Evidence of ongoing systemic infection; Unless approved in advance, prior therapy with inhibitor of B-cell signaling.
Correlative studies: PD monitoring to assess activation of BCR mediated signaling.
Current Enrollment: Enrollment to begin April, 2013.
Clinical trial registry number: NCT01796470

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A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY EVALUATING THE EFFICACY AND SAFETY OF IDELALISIB (GS-1101) IN COMBINATION WITH RITUXIMAB FOR PREVIOUSLY TREATED CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

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Background: PI3K-delta is critical for the activation, proliferation and survival of B cells and plays a role in homing and retention of B cells in lymphoid tissues. PI3Kδ signaling is hyperactive in many B-cell malignancies. Idelalisib is a first-in-class, selective, oral inhibitor of PI3Kδ that reduces proliferation, enhances apoptosis, and inhibits homing and retention of malignant B cells in lymphoid tissues (Lannutti et al, 2011). Phase 1 trials demonstrated that idelalisib is highly active in heavily pretreated pts with CLL as a single agent or in combination with rituximab (R), bendamustine (B), or BR: pts experienced reductions in disease-associated chemokines, improvement of organomegaly and cytopenias, profound and rapid reductions in lymphadenopathy, and durable clinical benefit with an acceptable safety profile (Coutre et al, 2012; Sharman et al, 2011).
Methods: Study will enroll 160 pts with previously treated CLL who have measurable lymphadenopathy, have experienced CLL progression $<$24 months since the completion of the last prior therapy, and are currently not sufficiently fit to receive cytotoxic therapy. Pts are randomized in a 1:1 ratio to Arm A or B. On Arm A, pts receive idelalisib at 150 mg BID continuously + rituximab at 375 mg/m^2 (1st dose) and then 500 mg/m^2 q2 wks x 5, after that q4 wks x 3 (8 doses total). On Arm B, pts receive placebo BID instead of idelalisib. In a companion extension study, pts who are tolerating primary study therapy but experience definitive CLL progression are eligible to receive idelalisib therapy at the standard dose (previously Arm B) or a higher dose (300 mg BID, previously Arm A) with the dose levels remaining blinded. The primary endpoint is PFS and secondary endpoints include ORR, lymph node response rate, CR rate, and OS. For the primary efficacy analysis, the difference in PFS between the treatment arms will be assessed in the ITT analysis set. The main study was initiated in April 2012 and a data monitoring committee has begun regular review of data (NCT01539512, NCT01539291).

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A PHASE III, RANDOMIZED, CONTROLLED STUDY EVALUATING THE EFFICACY AND SAFETY OF IDELALISIB (GS-1101) IN COMBINATION WITH OFATUMUMAB FOR PREVIOUSLY TREATED CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

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Background: PI3K-delta is critical for activation, proliferation and survival of B cells and plays a role in homing and retention in lymphoid tissues. PI3Kδ signaling is hyperactive in many B-cell malignancies. Idelalisib is a first-in-class, selective, oral inhibitor of PI3Kδ that reduces proliferation, enhances apoptosis, and inhibits homing and retention of malignant B cells in lymphoid tissues (Lannutti et al, 2011). Ofatumumab (O) is an anti-CD20 monoclonal antibody approved for the treatment of pts with CLL refractory to fludarabine and alemtuzumab. Phase 1 studies demonstrated that idelalisib, as monotherapy or combined with O, is highly active in pts with heavily pretreated CLL: pts experienced profound and rapid regression of lymphadenopathy, reductions in disease-associated chemokines, and durable clinical benefit with an acceptable safety profile (Furman et al, 2012).
Methods: This study will enroll 210 pts with CLL previously treated with a purine analog and/or bendamustine, with measurable lymphadenopathy who require treatment for CLL and have disease that is not refractory to ofatumumab, and are expected to benefit from a change in therapy because of CLL progression <24 months since completion of their last prior treatment. Pts are randomized in a 2:1 ratio (Arm A:Arm B). In Arm A, pts receive idelalisib at 150 mg BID continuously in combination with 12 infusions of O at 1000 mg over ~24 weeks (weekly x 8 then monthly x 4). In Arm B, pts receive 12 infusions of O at 2000 mg over ~24 weeks. Stratification factors address IGHV mutational status, del(17p)/p53 mutation status, and refractory vs relapsed disease. The primary study endpoint is PFS. Secondary endpoints include ORR, lymph node response rate, CR rate, and OS. This is an event-driven trial and primary endpoint evaluation will be based on independent central review. For the primary efficacy analysis, the difference in PFS between the treatment arms will be assessed in the ITT analysis set using Kaplan-Meier methods and the stratified log-rank test. The study opened for enrollment in December 2012 (NCT01659021).

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A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY EVALUATING THE EFFICACY AND SAFETY OF IDELALISIB (GS-1101) IN COMBINATION WITH RITUXIMAB FOR PREVIOUSLY TREATED INDOLENT NON-HODGKIN LYMPHOMAS (INHL)

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Background: PI3K-delta is critical for activation, proliferation and survival of B cells and plays a role in homing and retention in lymphoid tissues. PI3Kδ signaling is hyperactive in many B-cell malignancies. Idelalisib is a first-in-class, targeted, highly selective, oral inhibitor of PI3Kδ that reduces proliferation, enhances apoptosis, and inhibits homing and retention of malignant B cells in lymphoid tissues (Lannutti et al, 2011). Phase 1 trials demonstrated that idelalisib is highly active in pts with heavily pretreated iNHL: pts experienced reductions in disease-associated chemokines, profound and rapid reductions in lymphadenopathy, and durable clinical benefit with acceptable safety profile (de Vos et al, 2011).
Methods: 375 pts with previously treated iNHL, who have measurable lymphadenopathy, have received prior anti-CD20-antibody-containing therapy, and who have iNHL that is not refractory to rituximab (R) are randomized in a 2:1 ratio into Arm A or Arm B. In Arm A, pts receive idelalisib at 150 mg BID continuously + R at 375 mg/m^2 (weekly x 4 then every 8 weeks x 4). In Arm B, pts receive placebo BID instead of idelalisib. Stratification factors include tumor type (follicular lymphoma vs others), tumor burden (high vs low), and time since completion of last prior therapy for iNHL (<18 months vs ≥18 months). The primary endpoint is PFS and key secondary endpoints include ORR, lymph node response rate, CR rate, and OS. This is an event-driven trial and primary endpoint evaluation will be based on independent central review. For the primary efficacy analysis, the difference in PFS between the treatment arms will be assessed in the ITT analysis set using Kaplan-Meier methods and the stratified log-rank test. The study opened for enrollment in Dec 2012 (NCT01732913).

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A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY EVALUATING THE EFFICACY AND SAFETY OF IDELALISIB (GS-1101) IN COMBINATION WITH BENDAMUSTINE AND RITUXIMAB FOR PREVIOUSLY TREATED CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

J. C. Barrientos,[1] S. E. Coutre,[2] K. R. Rai,[1] H. A. Eradat,[3] C. M. Farber,[4] P. Hillmen,[5] J. P. Sharman,[6] P. Ghia,[7] B. Coiffier,[8] J. A. Walewski,[9] Z. N. Berneman,[10] S. M. O'Brien,[11] J. R. Brown,[12] S. Peterman,[13] R. D. Dansey,[13] T. M. Jahn,[13] P. Cramer,[14] M. J. Hallek.[14]

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

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AN OPEN-LABEL, SINGLE-ARM, PHASE 2 STUDY OF IBRUTINIB IN PATIENTS WITH REFRACTORY FOLLICULAR LYMPHOMA

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Background: Follicular lymphoma (FL) is the second most common non-Hodgkin lymphoma (NHL) and comprises approximately 22% of all NHL cases. Most patients treated eventually relapse andsubsequent responses and duration of responses become shorter. Patients ultimately become resistant to chemoimmunotherapy and repeated treatment-related toxicity commonly outweighs the benefit of treatment. Ibrutinib is a potent inhibitor of BTK (downstream of the B-cell receptor, BCR) that binds covalently to Cys-481 in the active site, abrogating intrinsic survival pathways (eg, ERK1/2, NF-kB, AKT) as well as survival signals from the microenvironment (eg, TNF family members: BAFF, CD40L; cytokines from T-cells: IL4, IL6, IL10, TNFα). Irish et al (2010) have also shown that up to 60% of FL patients display BCR signaling addiction. Early indications from study PCYC-04753 suggest activity of the BTK inhibitor ibrutinib in FL. Three CR and 3 PR were observed in 11 patients at a dose of 2.5 mg/kg or higher that achieved full BTK occupancy (Fowler, ASH 2012).
Methods: The DAWN study, PCI-32765FLR2002, is a phase 2, single-arm study of ibrutinib in refractory FL. The study aims to enroll 110 patients with chemoimmunotherapy-resistant FL. Patients will receive an oral daily dose of 560 mg ibrutinib. Patients must have been treated with at least 2 prior lines of therapy, at least 1 rituximab-containing combination chemotherapy regimen, and the last prior line of therapy included an anti-CD20 monoclonal antibody-containing chemotherapy regimen. The primary objective of the study is to evaluate the ORR (CR PR), with secondary objectives of duration of response, progression-free survival, overall survival, and safety. To better understand the mechanism of action of ibrutinib, blood and tumor samples will be collected and, where feasible, characterized by GEP, SMA, IHC, or other technology as applicable. These evaluations aim to identify biomarkers associated with response or resistance to ibrutinib in subjects with FL and results may assist in the development of this drug in this and potentially other indications. Approximately 64 sites in the US and Europe will enroll patients. Enrollment began in 1Q of 2013.

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A PHASE 3 STUDY OF IBRUTINIB VERSUS TEMSIROLIMUS IN PATIENTS WITH RELAPSED OR REFRACTORY MANTLE CELL LYMPHOMA (MCL) WHO HAVE RECEIVED AT LEAST 1 PRIOR THERAPY

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Introduction: MCL is a rare and incurable subtype of non-Hodgkin lymphoma (NHL) for which existing chemotherapeutic options are suboptimal and relapse is common. Temsirolimus (an inhibitor of the mammalian target of rapamycin, mTOR) is approved in the EU for the treatment of relapsed or refractory MCL, but additional treatment options are still required for this patient population. Ibrutinib, an oral inhibitor of Bruton's tyrosine kinase (BTK), shows promise as a single-agent therapy based on an observed overall response rate of 68% in a phase 2 study of patients with relapsed or refractory MCL (PCYC-1104; Wang ASH 2012). The aim of the current study is to compare the efficacy and safety of ibrutinib versus temsirolimus for the treatment of relapsed or refractory MCL.
Methods: The RAY study (PCI-32765MCL3001) is a randomized, controlled, open-label, phase 3 trial of ibrutinib versus temsirolimus in patients with relapsed or refractory MCL. The study aims to enroll 280 patients (140 per arm), who have received 1 prior rituximab-containing chemotherapy regimen, with documented relapse or disease progression following the last anti-MCL treatment. Key exclusion criteria include prior treatment with BTK or mTOR inhibitor, known CNS lymphoma, requirement for treatment with warfarin or equivalent vitamin K antagonists, and treatment with strong CYP3A4/5 inhibitors. Patients will be randomized to receive either oral ibrutinib 560 mg QD on a 21-day cycle, or intravenous temsirolimus 175 mg on Days 1, 8, and 15 of the first cycle, followed by 75 mg on Days 1, 8, and 15 of each subsequent 21-day cycle. The primary objective of the study is to evaluate whether treatment with ibrutinib, compared to temsirolimus, will result in prolongation of progression-free survival, with key secondary objectives of overall response rate, overall survival, 1-year survival rate, duration of response, and safety. Pharmacokinetic and biomarker evaluations will also be conducted. Approximately 114 sites outside the US will enroll patients. Enrollment began in 2012.

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RANDOMIZED, MULTICENTER, OPEN-LABEL, PH 3 STUDY OF THE BTK INHIBITOR IBRUTINIB VS. CHLORAMBUCIL IN PATIENTS 65 YEARS OR OLDER WITH TREATMENT-NAïVE CLL/SLL (RESONATE™-2, PCYC-1115-CA)

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Background: There is an unmet need for safer and more effective therapies for CLL patients who are older/have comorbidites. Ibrutinib, a small molecule inhibitor of BTK, has demonstrated single-agent activity in CLL in the Ph 1b/2 study, PCYC-1102-CA. Treatment-naïve (TN) patients aged >= 65 yrs (n=31) experienced an estimated PFS and OS of 96% at 26 months; ORRs per iwCLL were: 10% CR, 58% PR, and 13% PR with lymphocytosis (Byrd, ASH 2012). AEs were generally Grade 1/2, most commonly diarrhea. Incidence of Grade 3/4 hematologic toxicities was low. These findings support a phase III study of ibrutinib in older patients with treatment-naïve CLL/SLL.
Methods: The ongoing study is a randomized, multicenter, open label Ph 3 study comparing safety and efficacy of ibrutinib vs. chlorambucil in TN patients aged >= 65 yrs with CLL/SLL. Approximately 272 patients will be randomized in 1:1 ratio to receive either chlorambucil or ibrutinib, stratified for ECOG PS and Rai stage. Oral chlorambucil will be administered at 0.5 mg/kg on Days 1 and 15 of each 28-day cycle, for up to 12 cycles. Ibrutinib 420 mg q.d. will continue until PD or unacceptable toxicity. Key incl. criteria include age >= 65 yrs, active disease requiring treatment per iwCLL, measurable nodal disease by CT, ECOG performance status 0-2, and adequate organ function (ANC ≥1,000/μL, platelets ≥50,000/μL, creatinine clearance ≥30 mL/min). Key excl. criteria include Richter's transformation, del(17p13.1) or previous treatment for CLL/SLL.

The primary endpoint of the study is PFS, assessed by Independent Review Committee (IRC). Secondary endpoints include ORR, MRD-negative CRs, fatigue by FACIT-F, hematological improvement, safety, and tolerability. Subjects who relapse on PCYC-1115 will be enrolled on PCYC-1116 for long term follow up. Second line therapy is investigator choice; ibrutinib will be made available for patients who experience IRC-confirmed PD ≤12 months of completing chlorambucil therapy, if they meet the treatment criteria. Approximately 85 sites will enroll patients in North America, Europe, Israel, Australia/New Zealand and China.Enrollment began in Q1 2013.

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PHASE II RANDOMIZED STUDY WITH RITUXIMAB-DHAP +/- BORTEZOMIB AS INDUCTION THERAPY IN RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) PATIENTS BEFORE HIGH-DOSE CHEMOTHERAPY WITH STEM CELL TRANSPLANTATION (SCT): AN ONGOING TRIAL OF THE FONDAZIONE ITALIANA LINFOMI (FIL)

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Introduction: DLBCL patients failing first line rituximab-containing regimens show dismal prognosis. Bortezomib had proven activity in different lymphoma

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subtypes and promising activity in non-germinal center derived DLBCL in association with chemotherapy.
Methods: On this basis, FIL designed VERAL12 study, a prospective, multicenter, two-arm randomized phase II screening trial with the aim to assess whether the addition of Bortezomib to R-DHAP (BR-DHAP) is more active in term of PET-defined complete response (CR) than standard R-DHAP, as induction therapy before high dose chemotherapy with SCT. According to a one-sided test with an alpha-error of 0.10 and a beta-error of 0.20, and assuming a 30% CR for the standard arm R-DHAP and an expected CR rate in experimental arm of 50%, a sample size of 54 patients for each arm is required. Inclusion criteria are: young patients (18-65 years) affected by relapsed/refractory DLBCL after first line R-CHOP, eligible to high-dose therapy. Patients will be randomized between: a) the standard salvage therapy R-DHAP every 28 days for 4 cycles and b) subcutaneous 1.5 mg/sqm Bortezomib on days 1 and 4 of each 4-week cycle in addition to the same regimen (BR-DHAP). Restaging, mobilization and harvesting of peripheral stem cell will be performed after the second course. The main efficacy variable will be the response to treatment, defined as the proportion of CR assessed by PET-scan after 4 cycles of chemotherapy. The rate of non-hematologic toxicity of grade 3 or greater will be the principal measure of safety. All relapsed patients will be re-biopsied for centrally histological review and classification according to cell of origin profile.
Results: Enrollment started on January 2013. At now, two patients with refractory disease and non-germinal center DLBCL have been enrolled.
Conclusions: Study is ongoing. A result of this screening trial in favor of the experimental combination should be interpreted as a promising result to support the rationale of a next confirmatory phase III randomized trial.

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EVALUATION OF ADJUVANT EVEROLIMUS IN POOR-RISK PATIENTS (PTS) WITH DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL): A RANDOMIZED, PLACEBO-CONTROLLED, PHASE 3 STUDY (PILLAR-2)

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Introduction High-risk DLBCL is associated with poor overall survival (OS), with most relapses occurring in the first 12 mo following immunochemotherapy. The oral mTOR inhibitor everolimus demonstrated a 30% overall response rate and acceptable tolerability in 47 pts with relapsed DLBCL enrolled in a phase 2 study. We hypothesized that using everolimus for 1 year after completion of conventional therapy would reduce relapse risk and prolong survival.
Methods: PILLAR-2 is an ongoing international, randomized, double-blind, phase 3 study comparing the efficacy and safety of everolimus versus placebo in poor-risk pts with DLBCL who achieved complete response (CR) after first-line rituximab-based chemotherapy (R-chemo) (ClinicalTrials.gov NCT00790036). Eligibility criteria include age ≥18 years; confirmed bulky stage II or stage III or IV DLBCL; IPI 3-5 at diagnosis; confirmed CR per revised IWRC for malignant lymphoma after first-line R-chemo; last R-chemo cycle completed 6-14 weeks before study drug start; ECOG performance status ≤2; no ongoing post–R-chemo radiation; and no myelosuppressive chemotherapy or biologic therapy within 3 weeks. Pts are randomized 1:1 to receive everolimus 10 mg once daily or matching placebo for 12 months or until 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 pt randomization. Primary study endpoint is disease-free survival (DFS). Secondary endpoints are OS, lymphoma-specific survival, and safety. Planned enrollment is 687 pts. Final analysis will be performed when 279 DFS events occur. Survival follow-up will continue until 338 deaths occur and the last randomized pt has been followed for ≥5 years.
Results:As of 28 February 2013, 590 pts are enrolled. Per the recommendation of the data monitoring committee (last review, June 2012), enrollment is continuing as planned.
Conclusions: PILLAR-2 will evaluate the efficacy and safety of adjuvant everolimus in poor-risk DLBCL following CR on first-line R-chemo.

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A PHASE 3 TRIAL COMPARING GA101 (OBINUTUZUMAB) + CHEMOTHERAPY FOLLOWED BY GA101 MAINTENANCE VS RITUXIMAB + CHEMOTHERAPY FOLLOWED BY RITUXIMAB MAINTENANCE IN ADVANCED FL AND MZL

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Introduction: Standard therapy for FL is induction rituximab + chemotherapy followed by rituximab maintenance, yielding a median PFS of 6 y. It is not curative: most patients (pts) die from recurrent disease. Given rituximab's efficacy in CD20+ lymphomas, novel anti-CD20 mAbs are being developed. The type II, glycoengineered anti-CD20 mAb GA101 induces increased direct cell death, increased ADCC, and decreased CDC vs rituximab. Trials are assessing whether GA101's distinct mechanism of action translates to improved clinical efficacy. Phase 1/2 data show GA101 alone or combined with chemotherapy to be well tolerated and effective in previously treated CD20+ lymphoma.
Methods: GALLIUM (NCT01332968) is a randomized open-label international trial comparing induction GA101 + chemotherapy followed by GA101 maintenance vs induction rituximab + chemotherapy followed by rituximab maintenance. Eligibility requires previously untreated advanced stage FL or MZL needing treatment. Pts (FL=1200; MZL=200) will be randomized 1:1 and stratified by chosen chemotherapy backbone (CHOP, CVP, bendamustine), FLIPI or IPI risk group, and geographic region. A total of 6-8 induction cycles will be delivered. GA101 1000 mg will be given on days 1, 8, and 15 of cycle 1 and day 1 of subsequent cycles. Rituximab 375 mg/m^2 will be infused on day 1 of each cycle. Responders will receive bimonthly maintenance therapy until progression or for ≤2 years. The primary efficacy endpoint is investigator-assessed PFS in the FL cohort. Response rates at induction end, OS, and safety are secondary endpoints. The predictive value of MRD and ^{18}FDG-PET status at induction end on PFS in FL will be explored.
Results: Enrollment began in July 2011. Pts will be followed until trial end in 2022: ≈11.7 y after inclusion of the first pt.
Conclusions: Given encouraging data from single-arm studies of GA101 in B cell lymphomas, GALLIUM will compare the efficacy and safety of induction followed by maintenance with GA101 vs rituximab in FL and MZL.

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A PHASE I STUDY OF RITUXIMAB, LENALIDOMIDE, AND IBRUTINIB IN PREVIOUSLY UNTREATED FOLLICULAR LYMPHOMA: ALLIANCE STUDY A051103

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Traditional chemoimmunotherapy regimens for advanced stage follicular lymphoma (FL) are associated with acute and long-term toxicity. Targeted therapy is favored to improve efficacy and tolerability in this incurable, multiply relapsing disease. In CALGB 50401 (Alliance) in recurrent FL, lenalidomide (L) produced an ORR of 49%, while L with concurrent rituximab (LR) had an ORR of 75% and median EFS of 2 years. In the front-line setting LR produced an ORR of 98% (CR 87%) and estimated 2-year PFS of 89% (Fowler, ASH 2012). In CALGB 50803 (Alliance) with LR in previously untreated FL, preliminary data are promising with an ORR $> 90\%$. These data support the Relevance study of R^2 vs. R-chemo in untreated FL. Ibrutinib (I) is an inhibitor of Bruton's tyrosine kinase (BTK), a mediator of B-cell receptor signaling and B-cell development. In a phase I study the ORR was 55% (27% CR) in recurrent FL. In patients who received at least 5 mg/kg, the median PFS was 20 months. We are conducting a phase I combination of R, L, and I. By targeting the B-cell through multiple pathways, we believe this regimen will produce superior antitumor efficacy with excellent tolerability. Based on preliminary data from our 50803 trial, we designed this study to further evaluate this combination as a front-line regimen for FL.

Methods: Patients must have previously untreated, grade 1-3a FL, Stage III, IV, or bulky Stage II disease, performance status < 2, and adequate organ function. All FLIPI risk groups are eligible. This phase I study has a 3 3 cohort design with a fixed dose of R and escalating doses of L and I. Patients will receive R 375 mg/m^2 on Cycle 1 D 1, 8, 15, 22 and at week 13, 21, 29, and 37 for 8 doses. L and I will be given as per cohort dose on D1-21 for 18 months and D1-28 until progression, respectively, of each 28-day cycle. The starting dose level is L 15 mg and I 420 mg. Once the MTD is determined, there will be a 10-patient expansion cohort. The primary endpoint is the recommended phase II doses of L and I for combination with R in previously untreated FL. The secondary endpoints are toxicity, pharmacokinetics, and preliminary efficacy data. Correlative studies will include ibrutinib occupancy of BTK. The recommended phase II doses will be incorporated into a subsequent phase III study of LR with or without I.

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ALLIANCE A051202: A PHASE I TRIAL OF LENALIDOMIDE, RITUXIMAB AND GS-1101 (IDELALISIB) IN RECURRENT FOLLICULAR LYMPHOMA

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Background: Lenalidomide (L) and rituximab (R) are active single agents in follicular (FL) and other B-cell lymphomas.CALGB 50401 demonstrated an ORR of 73% and median EFS of 2 years with acceptable safety for the LR combination in patients with recurrent FL, and efficacy of LR appeared greater than that with L alone.GS-1101 (idelalisib, I) is a selective inhibitor of the p110 delta isoform of phosphatidylinositol-3-kinase (PI3K).In a single agent phase I trial of I, ORR was 45% in FL, and toxicities were manageable, principally liver enzyme abnormalities, GI issues, rash and fatigue. In our effort to further develop effective and well tolerated chemotherapy-free treatment approaches, we report the design of Alliance A051202, a multicenter cooperative group phase I trial of the combination of L, R and I in patients with recurrent FL.

Methods: Subjects with FL (grades 1, 2, 3a) who have received prior rituximab (with time to progression of ≥ 6 months from last rituximab dose) and with adequate hematologic, hepatic and renal status will be eligible.Prophylactic ASA or anticoagulants will be recommended for subjects at high risk of thrombosis.L will be administered orally days 1-21 of 28 days x 12 cycles with R 375 mg/m2 weekly x 4 total doses and idelalisib 150 mg orally twice daily x 12 cycles.Following a 3 + 3 design: cohort 1 will include L 10mg; cohort 2 L 15 mg; cohort 3 L 15 mg cycle 1/20 mg cycle 2+; and cohort 4 L 15 mg cycle 1/20 mg cycle 2/25 mg cycle 3+.If required for dose limiting toxicity, cohorts with dose-de-escalations of L and I will be included.An additional 10 patients will be treated at the MTD for more data.Primary endpoint of the study is determination of the MTD of L in this combination, and secondary endpoints include efficacy and toxicity.Based on findings of this trial, a follow-up randomized study of L+ R vs the 3 drug L+R+I combination will be considered for development.

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ROCHOP STUDY: A PHASE III RANDOMIZED STUDY OF CHOP COMPARED TO ROMIDEPSIN-CHOP IN UNTREATED PERIPHERAL T-CELL LYMPHOMA

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Peripheral T-cell lymphomas (PTCL) account for 10-15% of lymphomas. They share an aggressive clinical behaviour and a poor prognosis when treated by CHOP-like regimen which is nevertheless consider as a standard because others regimens failed to demonstrate survival advantage. Romidepsin is a histone deacetylase inhibitor with promising results in PTCL. First trials showed a response rate of 38% in heavily pre-treated PTCL patients. These results were confirmed with 15% of patients reaching a CR/CRu, 89% of them without disease progression at 13 months. Adverse events include gastrointestinal, hematologic and asthenic conditions. A phase I study of romidepsin combined with CHOP was conducted by LYSA. A total of 18 patients were included. The recommended dose was 12 mg/m^2 administered at day 1 and day 8 of each cycle.

Ro-CHOP study is an international phase III study comparing 6 cycles of CHOP21 with 6 cycles of romidepsin-CHOP21 (EUDRACT 2012-001580-68). Primary endpoint is Progression-Free Survival assessed independently. Secondary objectives include overall survival, other efficacy parameters, analysis of response rate according to ^{18}FDG-PET, safety, quality of life and biological ancillary studies. A total of 420 subjects aged from 18 to 80 years will be enrolled in the study. Main inclusion criteria are untreated PTCL whatever Ann Arbor stage and a performance status of 0-2. Main exclusion criteria are other subtypes of lymphoma, HTLV1 positivity, any cardiac abnormality, poor renal, hepatic and marrow functions unless related to lymphoma. Patients are randomized 1:1 between the two regimens. A stratification is performed with IPI score, age and histology. The first patient has been included in January 2013. A recruitment of 10.5 patients per month is anticipated, with a total duration of the study of 60 months. An update on enrollment will be presented at the meeting.

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INVESTIGATIONAL AGENT MLN8237 (ALISERTIB) VS INVESTIGATOR'S CHOICE IN PATIENTS (PTS) WITH RELAPSED/REFRACTORY (REL/REF) PERIPHERAL T-CELL LYMPHOMA (PTCL): RANDOMIZED PHASE 3 STUDY

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Background: Outcomes in patients with rel/ref PTCL remain poor. The development of chemotherapy refractory disease or early relapse is common. Aurora A kinase (AAK) is a key mitotic regulator that is overexpressed/amplified in various malignancies, including lymphomas, making it a potential therapeutic target. MLN8237 (alisertib) is an investigational oral AAK inhibitor. MLN8237 is being evaluated in preclinical (Qi et al, 2011 Br J Haematol) and clinical (Friedberg et al, ASH 2011) studies in patients with hematologic and non-hematologic malignancies that have shown preliminary antitumor activity in lymphomas, including PTCL.

Methods: The ongoing, international, open label, phase 3 study (C14012; NCT01482962) was designed to evaluate MLN8237 as a single agent versus investigators' choice of either pralatrexate, gemcitabine, or romidepsin. Up to 354pts with rel/ref PTCL and ECOG PS 0–2 are being enrolled at approximately 180 sites in 30 countries. Pts are randomized (1:1) to receive either MLN8237 (50 mg BID for 7 days in 21-day cycles) or investigator's choice: pralatrexate (30 mg/m^2 IV, Q1W for 6 weeks in 7-week cycles); gemcitabine (1000 mg/m^2 IV on days 1, 8, and 15 in 28-day cycles); or romidepsin (USA only, 14 mg/m^2 IV on days 1, 8, and 15 of 28-day cycles). Treatment may continue for up to 2 years in patients with stable disease or better. The primary endpoints of this study are overall response rate (ORR=complete response [CR] + partial response [PR]) and progression-free survival (PFS). ORR and PFS evaluations will be based on independent review committee assessment using the IWG criteria. Secondary endpoints include CR rate, overall survival, time to progression, time to response, duration of response, safety, and quality of life. Evaluation of candidate biomarkers in tumor biopsies (including gene amplification and protein expression levels of AAK and Ki-67), and health

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utilization (defined as all resources consumed by patients during the study such as inpatient/outpatient visits and medication usage) assessments are exploratory objectives.

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FIRST INTERIM ANALYSIS OF THE NORDIC LYMPHOMA GROUP PHASE II STUDY WITH DOSE-DENSE CHEMOIMMUNOTHERAPY AND EARLY CENTRAL NERVOUS SYSTEM PROPHYLAXIS IN PATIENTS LESS THAN 65 YEARS WITH HIGH-RISK DIFFUSE LARGE B-CELL LYMPHOMA

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Introduction: Despite the advent of rituximab (R)-based chemoimmunotherapy, outcome for patients with high-risk diffuse large B-cell lymphoma (DLBCL) continues to be suboptimal, and the risk of central nervous system (CNS) relapse is high. In a previous Nordic phase II study with dose-dense chemoimmunotherapy followed by systemic CNS prophylaxis, the CNS relapse rate was lower than expected (4.5%), but all events occurred within 6 months after initiation of therapy. The primary aim of the present study is to determine if moving systemic CNS prophylaxis to the beginning of the therapy and addition of intrathecally administered liposomal cytarabine further reduce the incidence of CNS relapse. A secondary aim is to elucidate if cerebrospinal fluid (CSF) cytology (C)-/flow cytometry (FC) + cases carry an increased risk of CNS relapse with the present regimen.
Methods: Inclusion criteria are age 18-65 years, primary DLBCL or grade 3B follicular lymphoma without clinical signs of CNS disease and CSF C-, aaIPI 2-3, WHO performance score 0-3, and/or site specific risk factors for CNS recurrence. 170 patients will be included. Treatment consists of two courses of HD-Mtx in combination with R-CHOP14, four courses of R-CHOEP14 and a course of HD-cytarabine with R. In addition, liposomal cytarabine is administered intrathecally in courses 1, 3 and 5. Primary endpoints are failure-free survival at 3 years, and CNS relapse rate at 18 months.
Results: The first interim analysis was performed in Oct 2012 after 40 patients had completed treatment. Median age of patients was 54 years (range 28-64). The majority presented with DLBCL, advanced-stage disease, and elevated LDH, and 48% with more than one extranodal site. Five (9%) CSF-samples were FC+. No toxic deaths have been reported. Grade 3-4 infections were observed in 42%, mucositis in 23%, gastrointestinal toxicity in 30%, and grade 3 arachnoiditis in 2.5% of the patients. CR, CRu, PR and PD at the end of therapy are 73%, 15% and 9% and 3%, respectively. Three patients have relapsed, one of whom with a CNS manifestation.
Conclusions: Preliminary results indicate a reasonable toxicity despite intensive therapy, and highly satisfactory remission rates.

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A PHASE I TRIAL OF PANOBINOSTAT IN COMBINATION WITH IGEV (IFOSFAMIDE, GEMCITABINE, VINORELBINE) IN RELAPSED/REFRACTORY HODGKIN LYMPHOMA (HL): PRELIMINARY RESULTS

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Introduction: The gold standard for refractory/relapsed HL pts is chemotherapy (CT) followed by autologous stem cell transplant (ASCT). The IGEV regimen is characterized by high response rate, and low toxicity. Panobinostat is a pan-DAC inhibitor active in pretreated HL. We suggest that the combination of IGEV plus panobinostat (pIGEV) could improve the overall response and CR rate. We are conducting a phase 1, multi-centric trial to find the maximum tolerated dose (MTD) and assess the safety of this combination.
Methods: adult patients with relapsed/refractory classical HL, treated with no more than 2 prior lines, are eligible. Cohorts of at least 3 pts are treated with panobinostat at increasing dose level (20-30-35mg) on days 1,3,5,8,10,12 in combination with IGEV(Ifosfamide 2 g/m^2 days 1-4, Gemcitabine 800 mg/m^2 on days 1 &4, Vinorelbine 20 mg/m^2 day 1, prednisone 100 mg days 1-4) as part of a 21-days cycle. Planned treatment is 4 pIGEV followed by ASCT.
Results: This preliminary analysis include 8 pts (3 male; median age 40 years, range 20-56); 3 pts have been enrolled in 20 mg, 3 pts in 30 mg and 2 in 35 mg cohorts.All pts received at least the first cycle, required for MDT evaluation. A total of 24 cycle have been performed: 4 pts completed the planned therapy, 2 pts discontinued after 2 cycles (1 due to PD, 1 due to TVP and syncope and 2 are ongoing. No DLTs have been observed. The panobinostat dose have been reduced in 1 patient (cohort 20 mg) due to hematological toxicity. 9/24 cycles have been postponed 7 due to toxicity and 2 for logistic reasons; as expected the most frequent AEs were neutropenia and thrombocytopenia. Transfusions support (PRBC and PLT) were required in 2/24 cycles in the same patient. QTc prolongation was observed in 1/24 cycle. Serious AEs, regardless of causality, were reported 3/24 cycles: 1 febrile neutropenia, 1 TVP, 1 syncope. The same patient had TVP and syncope and discontinued panobinostat. Six pts are evaluable for response: 4 achieved CR, 1 PRand 1 PD.
Conclusions: pIGEV showed no unexpected toxicities, the most common AEs are related to myelosuppression without DLT. Preliminary results demonstrate clinical activity of the combination and the study accrual continues.

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POST-AUTHORISATION SAFETY STUDY (PASS) MA25101: AN OBSERVATIONAL COHORT STUDY OF THE SAFETY OF BRENTUXIMAB VEDOTIN IN THE TREATMENT OF RELAPSED OR REFRACTORY (RR) CD30+ HODGKIN LYMPHOMA (HL) AND RR SYSTEMIC ANAPLASTIC LARGE CELL LYMPHOMA (SALCL). THE ARROVEN STUDY.

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Introduction: Brentuximab vedotin (ADCETRIS®), a novel antibody drug conjugate directed against the CD30 surface antigen, is indicated for treatment of RR CD30+ HL and RR sALCL. During clinical development the safety of brentuximab vedotin was evaluated in more than 300 patients, and analyses indicate a manageable and tolerable safety profile in approved indications. As is common with new therapies for rare conditions, the European Commission granted a conditional marketing authorization in the EU for which the PASS is a required study to further evaluate the safety profile of brentuximab vedotin.
Methods: The objectives of the ARROVEN study are to evaluate the occurrence of serious adverse events (SAEs) and specified adverse events of special interest (AESI), both serious and non-serious, in patients actively treated for RR CD30+ HL or RR sALCL in routine practice with brentuximab vedotin; to also identify and describe potential risk factors for peripheral neuropathy. Target enrolment of approximately 500 patients (~50 with sALCL) treated with brentuximab vedotin at around 75-100 sites in Europe will occur over 3 years. Study duration will be 5 years from first patient enrolled. Patients will remain under follow-up until death, withdrawal of consent, loss of follow-up or study closure, whichever comes first. Data will be collected from the routine medical record. No study visits, examinations, laboratory tests or procedures are mandated by the study. Baseline patient and disease characteristics, relevant medical history and all initial and subsequent treatment for RR CD30+ HL or RR sALCL will be recorded. Follow-up and safety data will be collected at all routine visits, typically every 3 months.
Results: The ARROVEN study is open and enroling as of March 2013. Initial patient enrolment includes sites in Austria, Denmark, and Germany with enrolment projected in additional European countries over the next 3 years as brentuximab vedotin becomes commercially available.

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Conclusions: ARROVEN is an observational cohort study to further evaluate the safety profile of brentuximab vedotin.

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A PHASE I-II TRIAL OF BRENTUXIMAB VEDOTIN PLUS RITUXIMAB AS FRONTLINE THERAPY FOR PATIENTS WITH CD30+ AND/OR EBV + LYMPHOMAS

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Rationale: Chronic immunosuppression increases the risk of lymphoid malignancies, termed post-transplant lymphoproliferative disorder (PTLD).Up to 86% of PTLD cases are EBV-associated; roughly 70% express CD30; and over 80% of PTLD express CD20.Although the PTLD population is heterogenous, outcomes are generally poor; recent studies reporting median overall survival (OS) of 2-4 years.Rates of treatment-related mortality (TRM) of 13-50% are striking when these patients are treated with early cytotoxic chemotherapy, and high rates of graft rejection have also been reported. A recent risk-stratified sequential treatment strategy for PTLD patients yielded a 93% ORR, with 32% of patients able to avoid cytotoxic chemotherapy, and low rates of TRM (1/40 patients). We hypothesize that the combination of brentuximab vedotin (Bv) and rituximab (R) for the upfront treatment of EBV-related lymphoid malignancies would optimize efficacy by A) improving response rates as compared to single-agent rituximab; B) reducing exposure to cytotoxic therapy, and thereby reduce rates of TRM; and C) ultimately improving progression-free survival (PFS) and OS.
Methods: A Phase I/II trial combining Bv with R in patients with newly-diagnosed lymphoid malignancies that are CD20+ plus either CD30+ or EBV+ (or both) is actively enrolling. Subjects receive Bv 1.2 mg/kg weekly x 3, and R 375 mg/m^2 weekly x 4, followed by early assessment of response. Those with good response proceed to maintenance therapy, while those with suboptimal response may be treated with another course of induction at discretion of the local investigator. The Phase II primary endpoint is response rate; secondary endpoints include PFS, OS, and time to first cytotoxic chemotherapy.
Results/Conclusions: Phase I patients have been enrolled and treated, with no unexpected or dose-limiting toxicities. Excellent early responses have been observed, though follow-up remains short. Phase II of the trial will open shortly at three centers. We remain optimistic that this will provide a new therapeutic strategy for PTLD that optimizes efficacy and toxicity in this difficult-to-treat population.

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PHASE 3 STUDY OF BRENTUXIMAB VEDOTIN PLUS DOXORUBICIN, VINBLASTINE AND DACARBAZINE (A+AVD) VS DOXORUBICIN, BLEOMYCIN, VINBLASTINE AND DACARBAZINE (ABVD) AS FRONTLINE TREATMENT FOR ADVANCED STAGE CLASSICAL HODGKIN LYMPHOMA (CHL). THE ECHELON-1 STUDY

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Background: Brentuximab vedotin (ADCETRIS®), a CD30-targeted antibody-drug conjugate, has demonstrated effectiveness and a manageable safety profile when used for relapsed/refractory (RR) CD30-positive HL following autologous stem cell transplant (ASCT). In pts with RR CHL post-ASCT, single-agent brentuximab vedotin yields an objective response rate of 75% (complete response (CR), 34%; Younes, J Clin Oncol 2012;30:2183). ABVD, a frequently employed front-line regimen for advanced stage CHL, achieves CR rates of 70-80%. However, front-line ABVD fails to cure 20-30% of patients. In a phase 1 study in treatment-naïve CHL patients, A+AVD was associated with manageable toxicity and a CR rate of 96% whereas brentuximab vedotin + ABVD induced unacceptable pulmonary toxicity (Ansell, ASH 2012, abstract 798). Replacing bleomycin with brentuximab vedotin may improve disease control compared to standard ABVD and at the same time eliminate bleomycin-associated pulmonary toxicity.
Clinical Trial: ECHELON-1, an ongoing, open-label, randomized, multicenter study (NCT01712490), will compare A+AVD vs ABVD in 1040 patients with stage III/IV CHL. Major inclusion criterion: histologically-confirmed previously untreated stage III/IV CHL. Patients will be randomized 1:1 to receive A+AVD (brentuximab vedotin 1.2 mg/kg with each dose of AVD) or ABVD administered intravenously on days 1 and 15 in 28-day cycles, for up to 6 cycles. The primary endpoint is modified progression-free survival (mPFS) (events defined as progression/relapse, or receipt of subsequent anticancer therapy for residual disease after completion of planned front-line therapy for HL, or death). The key secondary endpoint is overall survival. Disease status and survival will be evaluated regularly until study closure. Safety assessments include incidence and severity of adverse events, plus changes to physical and laboratory tests. Pharmacokinetic and biomarker studies will be performed. The final analysis may lead to a new standard treatment for advanced stage CHL.

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PHASE 3 STUDY OF BRENTUXIMAB VEDOTIN VERSUS PHYSICIAN'S CHOICE OF METHOTREXATE OR BEXAROTENE IN PATIENTS (PTS) WITH CD30-POSITIVE (CD30+) CUTANEOUS T-CELL LYMPHOMA (CTCL). THE ALCANZA STUDY

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Introduction: Brentuximab vedotin (ADCETRIS®) is a CD30-targeted antibody-drug conjugate. Clinical activity and a manageable safety profile have been noted in phase 2 studies in relapsed/refractory CD30+ mycosis fungoides (MF; overall response rate [ORR] 70%; Krathen ASH 2012) and CD30+ CTCL and cutaneous lymphoproliferative disorders (ORR 67.3%; Duvic ASH 2012). In the former study, the most common (≥20%) treatment-emergent adverse events (TEAEs) were peripheral neuropathy, fatigue, decreased appetite, nausea, alopecia, dyspepsia, and skin eruption. In the latter study, the most common (≥20%) TEAEs were peripheral neuropathy, fatigue, drug rash, and diarrhea.
Methods: This randomized, open-label, multicenter study (NCT01578499) will assess the efficacy of brentuximab vedotin in 124 CD30+ CTCL pts, including primary cutaneous anaplastic large-cell lymphoma (pcALCL) and MF. Primary endpoint: ORR lasting ≥4 months. Key secondary endpoints: complete response (CR) rate, progression-free survival, and changes in burden of symptom domain per Skindex-29 questionnaire. All randomized pts will be followed for survival. Key inclusion criteria: histologically-confirmed CD30+ (≥10% total lymphocytes or neoplastic cells) pcALCL or MF and ≥1 prior systemic therapy. Pts will be stratified by diagnosis and randomized to receive brentuximab vedotin 1.8 mg/kg every 3 weeks (wks) for up to 16 cycles (48 wks), or physician's choice (methotrexate or bexarotene) up to 48 wks. Pts with partial response or CR at cycle 3 may continue study drug for up to 48 wks. Pts with stable disease and evidence of benefit may continue for a further 3 cycles. Pts with increasing skin score (modified severity weighted assessment tool; mSWAT) prior to cycle 3 may continue until cycle 3 if it is due to tumor flare. Response assessments: skin (mSWAT), nodal and visceral radiographic assessments, and detection of circulating Sézary cells (MF only). ORR will be evaluated until disease progression or study closure. Safety assessments: incidence and severity of AEs, and changes to physical and laboratory tests. Enrollment into this study is ongoing.

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