The outcome of Multiple Myeloma (MM) patients has significantly improved over the last decade, and this is mainly due to the efficacy of novel drugs, such as Thalidomide, Lenalidomide, and Bortezomib. Nevertheless, most patients relapse and become eventually refractory to all available treatments. Therefore, drugs with novel mechanisms of action are urgently needed in order to improve the outcome of relapsed MM patients. The investigation of these novel therapies is currently focusing in agents aiming at specific targets essential for MM emergence and progression. In this sense, some of the molecular events responsible for the transformation of a normal into a malignant Plasma Cell represent potential therapeutic targets. Thus, the (4;14) translocation induces the constitutive activation of the oncogenic receptor tyrosine kinase (RTK) FGFR3, and several IGH translocations lead to Cyclin D deregulation representing a common pathogenic event in MM. Therefore, the use of inhibitors of cyclin dependent kinases as well as inhibitors of the FGFR3 tyrosine kinase could be attractive therapeutic targets against MM. The second area of MM pathogenesis with important implications for treatment intervention is the interaction between the malignant cell and the bone marrow microenvironment through soluble molecules and membrane receptors. This interaction promotes MM cell growth and proliferation involving different signalling pathways. In this area several targeted oriented drugs are already at early phases of clinical investigation, including: 1. Agents acting against surface receptors present in plasma cells, such as IL-6-R, CD56, C5a1, or CD41. 2. Agents designed to block RTKs, like, the already mentioned FGFR3, VEGFR, IGE-R or c-Kit. and 3. Drugs interfering with the activated signalling pathways, including Farnesyl Transferase (Tipifarnib), RAF (RAF-653), MAPK (GSK-690), STAT3 (Attirapimod), MTOR (RAD001) or AKT (Perineser). Other mechanism which has been demonstrated to be critical for MM survival is the unfolded protein response (UPR). Three classes of agents have been designed to target this system: Hsp90 inhibitors, novel proteasome inhibitors (NPI-0052 and Carfilzomib) and inhibitors of aggresome formation (tubacin). Finally, epigenetic is emerging as a relevant player in tumor progression, therefore the use of histone deacetylase (HDAC) inhibitors or demethylating agents seems to be promising for the treatment of MM patients. Unfortunately, the expectations raised by some of these agents have not been so far confirmed in the clinic. It is probable that these targeted directed drugs will be more effective in science based combinations with other agents which have already shown clear efficacy in MM.

133 NEW DRUGS FOR T-CELL LYMPHOMA

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Purpose: The T-cell lymphomas represent a very heterogeneous and challenging group of hematologic malignancies. Given the rarity of these diseases, there is little to no consensus regarding the management of patients either in the front line or relapsed state. One of the major difficulties with the management of these malignancies is the fact that there have been very few new drugs or agents that have been introduced into the standard treatment regimen. Most treatments used in T-cell lymphomas have been adopted based on the use of drugs active in the treatment of B-cell lymphomas (i.e. CHOP or ICE based). Over the past 15 years, there has been a number of major breakthroughs in the identification of novel targets and agents with activity in T-cell lymphoma. Gemcitabine, a deoxycytidine analogue, has proven to be a very active drug in a variety of T-cell lymphomas including cutaneous T-cell lymphoma (CTCL) and peripheral T-cell lymphoma (PTCL). Another promising small molecule with activity in T-cell lymphoma is pralatrexate, a 10-deazaaminopterin. This drug was designed to have very high affinity for the reduced folate carrier (RFC), and thus is rapidly internalized into malignant tissue. In ongoing clinical trials, this compound has demonstrated an overall response rate of 50% or more in patients with relapsed or refractory disease. In addition, preclinical studies have demonstrated that pralatrexate is synergistic when administered in a schedule dependent manner with gemcitabine. This observation has been extended to ongoing Phase 1 studies of the combination. Another class of drugs with unusual activity in T-cell lymphomas are the histone deacetylase inhibitors. Interestingly, there seems to be a class effect with regard to these compounds. Vorinostat (previously known as SAHA), has been approved for CTCL. Desipramide, a naturally occurring HDAC inhibitor has demonstrated an overall response rate of about 30% in patients with CTCL and PTCL with very durable responses despite their chemotherapy refractory nature. At this time, both depsipeptide and PXD, another hydroxamic acid derivative, are both in registration directed phase 2 trials for patients with CTCL. Another agent, LBH589, a potent hydroxamic acid derivative, has similarly demonstrated marked activity in patients with CTCL. It is now clear there are a number of very exciting agents, and promising targets, that offer the opportunity to develop more T-cell centric based treatment programs. As these agents mature in the clinic, there is enormous hope that more effective upfront treatment programs for T-cell lymphomas will emerge in the very near future.

135 ALL B LYMPHOMA SUBTYPE DO NOT SHARE SIMILAR OUTCOME AFTER FRONT-LINE R-CHOP PLUS BORTEZOMIB TREATMENT: A RANDOMIZED PHASE 2 TRIAL FROM THE GROUPE D’ETUDE DES LYMPHOMES DE L’ADULTE (GELA)

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Background: Bortezomib is the first proteasome inhibitor that showed promising activity in hematologic malignancies. In Jan 2005, we initiated a phase II randomized trial to evaluate front-line R-CHOP + bortezomib in various pathological B lymphoma subtypes.

Methods: 6 cycles of standard R-CHOP-21 were planned, pts were randomized between 2 schedules of bortezomib (A: 1mg/m2 wk 1-2-3; B: 1.3 mg/m 2 wk 1-2-3-4-5-6). Patients were randomized into 2 arms: 1. arm A (4 pts), 2. arm B (6 pts). In arm A, bortezomib was administered at 1 mg/m2 in week 1 and 1.3 mg/m2 in week 2. For the next 4 weeks (steps 2-6), the dosage was increased at 1.3 mg/m2 and 1.6 mg/m2 respectively. Primary endpoint was CR rate after 6 cycles.

Results: 49 pts were included. Sex ratio M/F: 28 /21. Median age : 63 years [32-76]. IPI 2: 3-18 pts. 3 Lymphoplasmocytic, 6 small lymphocyt, 8 MZL, 2 MALT, 1 FL, 3 MCL, 5 FL with histological transformation and 1 DLBCL without adverse factor. Although their single agent activity is likely to be limited, they enhance the efficacy of chemotherapeutic agents or monoclonal antibodies. Inhibitors of histone deacetylase and mTOR are also active. New monoclonal antibodies include a new generation of drugs with activity in T-cell lymphomas and PTCL, such as: 1. Bortezomib, currently rituximab plus pralatrexate: Rational development of combinations of these various agents, guided by correlative laboratory science, will increase the cure of pts with B-NHL.
Panobinostat (LBH589) is a novel cinnamic acid hydroxamate DACi which induces cell death in multiple hematopoietic tumor cell lines in vitro at nanomolar levels and has demonstrated objective responses in CTCL in ongoing clinical trials.

Methods: In an ongoing Phase I trial, panobinostat is administered orally, once/day, on Mon/Wed/Fri (MWF), every week (Arm 1) or every other week (Arm 2), in 28-day cycles, to adult patients (pts) with advanced hematologic malignancies including HL.

Results: To date, 86 pts have been enrolled: 45 pts in Arm 1 at doses of 20, 30, 40, 60, and 80 mg; 41 pts in Arm 2 at doses of 30, 45, 60, and 80 mg. The maximum tolerated dose has not yet been determined for either arm. Four dose-limiting toxicities (DLTs), none in pts with HL, have been reported in Arm 1: G3 fatigue at 40 mg (2 pts) and 60 mg (1 pt); and G3 QT prolongation at 80 mg (1 pt). No DLTs have been reported in Arm 2. To date, 8 pts with relapsed/refractory HL have been enrolled across arms and dose levels: median age 26 yrs (range 16–41), 3 female, 5 male, median 5 prior therapies (range 4–15), all had prior stem cell transplant. Among HL pts, the most common dose-limiting toxicities (DLTs) included diarrhea, thrombocytopenia, and fatigue. Thrombocytopenia was the only G3/4 AE experienced by >1 HL pt (4 pts). The median number of cycles was 5 (range 2–10) with 6 of 8 pts ongoing. Metabolic PR was observed in 6 of 7 HL pts evaluable for PET response.

Conclusions: Panobinostat appears to be well tolerated and has shown evidence of activity based on PET and CT studies in pts with HL.

137 ISOTYPE-SELECTIVE HISTONE DEACETYLASE (HDAC) INHIBITOR MGCD0103 DEMONSTRATES CLINICAL ACTIVITY AND SAFETY IN PATIENTS WITH RELAPSED/REFRACTORY CLASSICAL HODGKIN LYMPHOMA (HL)

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Background: MGCD0103 is an oral isotype-selective inhibitor of histone deacetylases (HDACi) with significant preclinical and clinical activity in hematopoietic cancers.

Methods: Open-label, Phase II trial in adults with relapsed/refractory HL (Trial 010); 13 pts with prior transplant. Ps received MGCD0103 at 110 or 85 mg 3x per week in 4-week cycles. Plasm Thymus and Activation Regulated Chemokine (TARC) levels were determined by ELISA. Responses were assessed by CT and PET.

Results: 33 pts have been enrolled to date (median age, 31 yrs; range, 19-62 yrs) of which 29 (88%) had prior transplant. Among 23 pts in the 110 mg cohort, 21 were evaluable, of whom 2 (10%) had a complete response (CR) and 6 (29%) had a partial response (PR) for an overall response (OR) rate of 38% (median time to response, 2 cycles). The 2 pts CR had progression free survival lasting >270 and >420 days with both responses ongoing. One additional pt (5%) had SD >6 cycles. Among 10 pts in the 85 mg cohort, 5 were evaluable for efficacy, all of whom had tumor reductions of 20% including 1 PR and 2 SDs (45% and 49% tumor reduction). Comparison between 85 and 110 mg revealed 20% and 39% of pts respectively with ≥2 grade 3 non-hematological toxicities. Decrease in Day 8 plasma TARC levels correlated with clinical response (PR+CR).

Conclusion: MGCD0103 demonstrated significant anti-tumor activity in relapsed/refractory post-transplant HL. The 85 mg dose exhibited meaningful activity and may be better tolerated.