Phase I study of intravenous Decitabine in combination with oral Vorinostat in patients with advanced solid tumors and Non-Hodgkin's Lymphomas (NHL).

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Background: Decitabine (D), a hypomethylating agent, and Vorinostat (V), a histone deacetylase inhibitor, belong to two different classes of drugs with an epigenetic effect. The ideal dose scheduling of these drugs remains controversial. This phase I study aims to determine the recommended phase II dose (RPTD) of the combination, their toxicity profile, pharmacokinetic (PK) interaction and preliminary clinical activity.
Methods: Patients (pts) with advanced solid tumors or relapsed/refractory NHL are eligible. Two different schedules of D and V are being evaluated: sequential administration of D followed by V and concurrent administration of D and V. Dose escalation of D and V on the sequential schedule is described in Table.
Results: To date, 27 pts have been entered into dose levels 1, -1, 1a, 1b, -1b, -2b of the sequential schedule. Demographics: median age 61 (range 31-76), F:M = 13:14, ECOG 0:1:2 = 8:16:3, tumor types: 24 solid tumor and 3 NHL. Pts received a total of 77 cycles with a median of 2 cycles (range 1-8). Adverse events (AE) of grade 3 or higher of at least possible attribution to the study treatment were neutropenia (16 pts), thrombocytopenia (4), febrile neutropenia (2), fatigue (2), and 1 pt each for constipation, dehydration, nasal bleeding, elevated alanine aminotransferase, and hyponatremia. Dose limiting toxicities (DLT) consisted mainly of myelosuppression, constitutional and gastrointestinal symptoms occurred in 7/27 (26%) of pts so far. Disease stabilization for 4 or more cycles was observed in 7 out of 22 (31.8%) evaluable pts (two with breast and one each of thymus, colon, pancreatic, appendix and non-small cell lung cancers).
Conclusions: The sequential combination of D and V seems to be tolerable after some adjustments in the doses and duration of drug administration. Prolonged disease stabilization has been observed in multiple tumor types. Accrual is ongoing and RPTD will likely be dose level -1b or -2b.

Dose level	D (mg/m^2) d1-5	V (mg)	Total no. of cycles	No. of pts with DLT/ Total no. of pts	Nature of DLT
1	20	100 mg BID d6-21	11	2/6	• Gr 4 PLT, Gr 4 ANC $\geq$ 7 days • Gr 2 intolerable fatigue, anorexia, dehydration
-1	15	100 mg BID d6-21	10	0/3	
1a	20	100 mg BID d6-12	14	2/3	• Gr 4 PLT • Gr 4 ANC $\geq$ 7 days
1b	15	200 mg BID d6-12	10	2/4	• Febrile neutropenia • Gr 3 constipation, febrile neutropenia, Gr 4 PLT
-1b	10	200 mg BID d6-12	27	0/7	
-2b	10	200mg TID d6-12	5	1/3	• Gr 3 fatigue
Cycles delivered every 28d					

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